COVID-19 Management in Pediatrics

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a deadly global pandemic, with scientific efforts improving our understanding of this novel coronavirus. No proven disease-specific therapies exist, although 2 vaccines have been recently approved by the United States Food and Drug Administration under emergency use authorization, and several others are in development or phase III clinical trial testing. COVID-19 presents in greater severity in the medically fragile, obese, elderly, and socially disadvantaged, and children in general are less affected. All children are at risk, but those with comorbidities and neonates are more susceptible. The multisystem inflammatory syndrome is a severe version which can present in any child with a recent COVID-19 infection. The face of the pandemic has been changing in the last few months, with recent increasing cases, virus mutations, and onset of vaccination. This article provides COVID-19 management for children and adolescents and implications for nursing and advanced practice providers.

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Introduction

Coronavirus disease 2019 (COVID-19) has prompted global responses to recognize and treat this deadly virus, engendered rapid development of testing, and facilitated research. The severe acute respiratory syndrome-2 coronavirus (SARS-CoV-2) is the same virus in adults as in children. This novel coronavirus appeared in the Wuhan region of China as a viral pneumonia in late 2019. Initially named 2019-new Coronavirus, it was renamed by the World Health Organization (WHO) as coronavirus disease-2019, thus COVID-19. While early warnings indicated that elderly individuals were at greatest risk for death or disability due to existing comorbidities, it has become evident that children can be affected by the virus. This article reviews the most common effects of COVID-19 on pediatric patients, differential diagnosis, and treatment options.

Epidemiology

At the time of this writing, COVID-19 has affected > 87 million people globally, resulting in 1.9 million deaths.[1] The United States (US) recorded > 21 million cases and > 360,000 deaths as of January 9, 2021.[2] As of November 12, 2020, the American Academy of Pediatrics and the Children's Hospital Association reported that 1,039,464 total children have tested positive for COVID-19 since the onset of the pandemic.[3] Children represent 11.5% of all cases in states that are reporting cases by age. By the end of 2020, a 22% increase in pediatric cases had occurred in the US.[3] Children have comprised 1.2% to 3.3% of total hospitalizations (adult and pediatric cases), and of all child COVID-19 cases, 0.5% to 6.1% were

hospitalized; in states reporting, 0.00% to 0.15% pediatric cases have resulted in death.[3]

Etiology

Coronaviruses are human and animal pathogens. Bats are the suspected main source of SARS CoV-2, but the exact transmission path is unknown. Transmission of COVID-19 occurs via exposures to respiratory droplets and aerosolization from coughing, sneezing, singing, heavy breathing, or talking. Larger expelled droplets fall to the ground within seconds to minutes, while smaller ones remain circulating in the air.[4] Proximity and duration of exposure have been speculated to be greatest within 6 feet from the source and duration > 15 minutes; however, prolonged durations at greater distances have resulted in positive transmissions.

COVID-19 can survive on human skin for 9 hours and various surfaces (glass, polymer currency, stainless steel, vinyl, and paper currency) for up to 28 days[5]; however, the virus loses potency once it leaves the host. Time of exposure to symptoms ranges from 5 to 11 days.[6] Viral shedding can occur 2 to 3 days before symptom onset; therefore, asymptomatic and presymptomatic individuals are considered infectious carriers. Asymptomatic transmission is important to guide screening and family education, and the Centers for Disease Control and Prevention (CDC) and WHO recommend wearing masks, frequent hand washing/sanitizing, and social distancing of at least 6 feet to reduce transmission.

Screening for COVID-19

For infants 3 months old, presentations of fever, cough, myalgia, and fatigue are common in viral infections and require testing[7]: influenza, parainfluenza, adenovirus, metapneumovirus, respiratory syncytial virus, and COVID-19.[8] Accurate COVID-19 screening requires real-time polymerase chain reaction (RT-PCR), immunoglobulin (Ig) G and IgM via enzyme-linked immunosorbent assay or antigen test. The RT-PCR is the most commonly used and reliable test. The nasopharyngeal area, throat, or nares are usually swabbed, but the virus can be detected in saliva, blood, urine, and stool.[9] The PCR value provides the viral RNA cycle threshold, or the number of viral replications needed to elicit a detectable signal.[9]

The COVID-19 virus is detectable at day 1 in the nasopharynx, peaks during the first week, and declines until undetectable over 3 to 6 weeks. A PCR of < 40 indicates clinical COVID-19 positivity.[10] Lower PCR results equate to higher viral loads and sicker presentations. To illustrate, the PCR result for a severely ill patient will be much less than that of one who is asymptomatic. Reported values do not always reflect the clinical picture, because viral load is not indicative of viral viability, and a positive test still can be detected beyond the expected onset of symptoms.[11] Sampling from the buccal cavity has resulted in false-negative cases because lower viral loads were detected,[12] particularly in children with mild COVID-19 symptoms.[13]

Antibody Screening

COVID-19 antibody screening assesses antibody presence/absence after COVID-19 infection. This is primarily done upon the request of the parents. Serology detects IgG and IgM as early as the fourth day after exposure. Although IgM is almost untraceable in the blood by 7 weeks after symptom onset, IgG may still be present.[12] Further, elevated cytokine levels have been reported in asymptomatic infants (n = 6) born to symptomatic mothers diagnosed after delivery.[13] Longitudinal antibody testing found seroconversion, with 2 neonates positive for IgG with IgM antibodies. Contact tracing is initiated after a positive PCR test.

Areas of Controversy

It was thought that vertical transmission of COVID-19 from mother to baby did not occur, as evidenced by various birth cohorts[14]; however, recent cases of perinatal transmission have been reported, with neonates developing severe symptoms requiring intensive care.[15] Transmission is thought to have been via placental transfer based on immunohistochemistry, very high viral load, placental inflammation, maternal viremia, and neonatal viremia. While transmission sources are still being identified for all variant mutations of COVID 19, it is now clear that children can transmit COVID-19 as easily as adults, thus warranting ongoing precautions for school and sporting activities.[16] The CDC recommends wearing a mask to minimize the viral load that can be inhaled; note that cloth masks are not recommended for children younger than 2 years old for fear of suffocation. Use of alcohol-based sanitizers for handwashing pose no threat to children who lick their hands after the hand sanitizer has fully dried. However, small amounts of liquid hand sanitizer can cause alcohol poisoning and hypoglycemia in children. Thus, children younger than 6 years old should be supervised when using alcohol-based sanitizer, and it should be kept out of the reach and sight. Hand sanitizers made of isopropyl alcohol may be more toxic than those made of ethanol.

Pathophysiology

Milder presentations in children have prompted exploration into pathophysiological differences from adult cases. Table 1 presents some observed differences.[17] One hypothesis for the differences in severity observed between pediatric and adult patients related to cytokine release,[17,18] because children may elicit a decreased response. Simply, by releasing less cytokines, less lung damage ensues.[19] There have been measured lower viral load responses in the respiratory tract of children once COVID-19 invades it (Table 1).

Another distinction is that the angiotensin converting enzyme 2 (ACE-2) receptor used by COVID-19 to enter cells is expressed differently in children and that pediatric lungs may have fewer or less mature ACE-2 receptors than adult counterparts.[14,19,20] Another factor is that the endothelium of children's blood vessels is less susceptible to inflammation and clotting than adult endothelium, which is prone to thrombosis resulting in myocardial infarctions and cerebral events.[14,21,22] Of note, COVID-19 presentations of entirely gastrointestinal (GI) symptoms, such as nausea, vomiting, diarrhea, abdominal pain, and decreased appetite, occur primarily in adults. However, computed tomography (CT) scanning reveals abnormalities consistent with those observed in COVID-19 pneumonia. It is postulated that the virus induces GI bacterial translocation to lung parenchyma, thereby causing increased capillary permeability and the observed CT pulmonary abnormalities.[22]

Differential Diagnosis

A thorough evaluation is vital when a child presents with mild GI or respiratory symptoms, with or without fever.[8] The differential diagnosis is broad and includes other viruses, urinary tract infections, intra-abdominal infections, viral and bacterial pneumonia, sepsis, and soft tissue infections (Table 2). Viral and bacterial pneumonia tend to be indistinguishable because signs and symptoms often overlap. Dyspnea, anosmia, or myalgia are more typical of viral pneumonia, whereas pleuritic chest pain and purulent expectoration are more common for bacterial pneumonia. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are common in school aged children and should be considered. Once pneumonia is diagnosed, antibiotics should be initiated to cover the suspected organism. The CDC and the WHO have advocated for children to continue to receive their regular immunizations during this pandemic (Table 3).[23,24]

Presentation

Most pediatric case presentations initially were milder and appeared to only be severe in those with comorbidities. However, the multisystem inflammatory syndrome in children (MIS-C) is a life-threatening complication, even after mild illness; further, those developing MIS-C often do not have preexisting comorbidities.[23,25]. A child presenting with persistent fever > 24 hours, without obvious source or from possible coronavirus exposure, should be tested for COVID-19. Any pediatric death in association with COVID-19 should be considered linked to MIS-C.[21,22]

Dry cough and fever are the most common symptoms in children aged 0 to 9 years (Table 4).[22] Additional symptoms include myalgia (15%), rhinorrhea (13%), nausea/vomiting (10%), abdominal pain (7%), diarrhea (14%), and anosmia/ageusia (1%). Symptoms for children aged 10 to 19 years include fever (35%), cough (41%), dyspnea (16%), myalgia (30%), rhinorrhea (8%), diarrhea (14%), and anosmia/ageusia (10%).[22] Children < 12 months old may present feeding difficulties and fever without a source. Abdominal pain,

Table 1
Differences Between Pediatric and Adult Physiology and Responses to COVID-19[17]

Pediatric	Adult
Less severe illness	More severe illness
Few infections	Prolonged infections
Strong innate immune response due to trained immunity (live vaccines, frequent viral infections)	Immune senescence; suppressive adaptive immunity
Higher number but immature ACE-2 Receptors	ACE-2 numbers decrease with age
In lungs leading to less inflammation	
Infants have more severe illness compared to adult	Dysfunctional overactive response to severe infection

ACE-2 = angiotensin converting enzyme 2.

diarrhea, and vomiting are the most common GI symptoms in children, but no GI bleeding has been reported. Rashes are common in viral presentations. COVID-19 rashes are macular, papular (painful, purple or red), vesicular, and urticarial, leading to the term "COVID toes" being coined for patients with reddish-purple nodules of the extremities.[25]

MIS-C, also termed pediatric multisystem inflammatory syndrome, pediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2, pediatric hyperinflammatory syndrome, or pediatric hyperinflammatory shock, awoke the medical community to the reality that COVID-19 could severely affect and kill children.[23] This syndrome develops 2 to 4 weeks after an acute SARS-CoV-2 infection. The constellation of symptoms resembles pediatric variants of Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome, which produce fever and systemic and mucocutaneous inflammation (Table 5).[23,24] Symptoms include fever, bilateral nonexudative conjunctivitis, lip/oral mucosa erythema (cracked red lips, strawberry tongue), rash, and cervical lymphadenopathy. Children who develop MIS-C tend to be older, sicker, and display greater elevations of inflammatory markers and more cardiac involvement. The CDC and WHO have developed MIS-C diagnostic criteria[21,23,24] (Table 3).

Children and adolescents with MIS-C typically present with prolonged fever of 4 to 6 days (100%), GI symptoms (abdominal pain, vomiting, diarrhea; 60%-100%), rash (45%-76%), conjunctivitis (30%-81%), mucous membrane involvement (27%-76%), headache, lethargy (29%-58%), tachypnea and dyspnea (21%-65%), sore throat, myalgias, swollen feet/hands, and lymphadenopathy (6%-16%). Clinically, they may present with an arrhythmia (12%), in shock (32%-76%), respiratory failure (28%-52%), acute renal failure or insufficiency (<52%), hepatitis/hepatomegaly (20%), or central nervous system dysfunction, including encephalitis, seizures, coma, or meningoencephalitis (6%-7%).[24]

Because children with MIS-C tend to present with elevated markers of inflammation (C-reactive protein, erythrocyte sedimentation rate, D-dimer), they run the risk of coronary artery aneurysms.[26] The myriad signs and symptoms, along with hemodynamic compromise, that a child or adolescent presents with in the presence or upon suspicion of COVID-19 should alert the clinician to the possibility of MIS-C (Tables 3-5).

Diagnostics

Imaging Studies

Chest radiography is typically not required unless the child presents with fever, cough, abnormal results on a pulmonary examination, or suspicion of pneumonia. Chest x-ray imaging has exhibited limited sensitivity and specificity in detecting pulmonary lesions in pediatric patients with mild COVID-19; therefore, pulmonary CT scanning is a better diagnostic and monitoring tool.[13] Small nodular or speckled ground-glass opacities are visualized on pulmonary CT, even in resolved cases with negative serology.[27]

Laboratory Tests

Most pediatric COVID-19 patients do not require laboratory testing aside from the rapid COVID-19 test or a PCR. Zhu et al[28] found 94% (n = 157) of patients with mild-moderate COVID-19 presentations had increased T- and B-cell lymphocytes and decreased neutrophils. The neutrophil-to-lymphocyte ratio was negatively associated with abnormal alanine aminotransferase, aspartate aminotransferase, creatine kinase-MB, and lactate dehydrogenase results. However, Mussap[14] reviewed 12 research studies reporting abnormal laboratory results, finding many inconsistencies in collection times, sampling methods, and tests used, resulting in a lack of homogeneity for laboratory interpretation. Laboratory testing is, however, essential in the child presenting with signs and symptoms of MIS-C.

MIS-C Diagnostics

The best approach to detect MIS-C is to screen a very ill child or adolescent for the most common symptoms and perform a detailed physical examination. Being a multisystemic illness, diagnosis and treatment of MIS-C requires a multidisciplinary team involving infectious disease, rheumatology, cardiology, intensive care, and hematology. Imaging is selectively used based on presentation.[26]

Echocardiography should be performed within 24 hours in the child with myocardial depression to rule out coronary aneurysms, mitral regurgitation, or pericardial effusion; this is repeated within 24 hours and as needed to monitor illness progression. Chest radiographs may be normal or may display pleural effusions, patchy consolidations, and atelectasis. Chest CT is performed for those with abnormal result on the chest examination or chest x-ray imaging or those in respiratory distress and may demonstrate presence of nodular ground-glass opacification.[13,27] Severe GI symptoms and abnormal abdominal examination may prompt an ultrasound or CT of the abdomen and pelvis; results may vary from nonspecific findings to free fluid, ascites, bowel and mesenteric adenopathy/adenitis, or ileitis.

In addition to laboratory tests monitored for severe illnesses, specific abnormalities include hematologic abnormalities, such as lymphopenia, neutropenia, mild anemia, and thrombocytopenia, and elevated markers of inflammation, including C-reactive

Table 2
Differential Diagnosis in CoVID-19

Other viruses
Urinary tract infection
Viral and bacterial
Pneumonia
Intra-abdominal infection
Sepsis
Soft tissue infection
Meningitis

Table 3
Centers for Disease Control and Prevention and World Health Organization Case Definitions of Multisystem Inflammatory Syndrome in Children[23,24]

CDC Case Definition	WHO Case Definitions
All 4 criteria must be met 1. Age < 21 years old 2. Clinical presentation consistent with MIS-C, including all of the following • Fever • Documented fever > 38.0°C (100.4°F) for ≥ 24 hours or • Report of subjective fever lasting ≥ 24 hours 3. Laboratory evidence of inflammation • Included but not limited to any of the following: • Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, elevated ferritin, LDH, IL-6 level • Neutrophilia • Lymphocytopenia • Hypoalbuminemia • Multisystem involvement • 2 or more organ systems involved • Cardiovascular (eg, Shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia) • Respiratory (e,. pneumonia, ARDS, pulmonary embolism) • Renal (eg, acute kidney injury, renal failure) • Neurologic (eg, seizure, stroke, aseptic meningitis) • Hematologic (eg, coagulopathy) • Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding) • Dermatologic (eg, erythroderma, mucositis, other rash) • Severe illness requiring hospitalization • No alternative plausible diagnosis 4. Recent or current SARS-C0V-2 infection or exposure • Any of the following: Positive SARS-CoV-2 RT-PCR, Positive serology, Positive antigen test • COVID-19 exposure within the 4 weeks prior to the onset of symptoms.	All 6 criteria must be met. The 6 criterias are: 1. Age 0 to 19 years 2. Fever for ≥ 38.0°C (100.4°F) for > 3 days 3. Clinical signs of multisystem involvement (at least 2 of the following): • Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet), hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP • Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) 4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin) 5. No other obvious microbial cause of inflammation including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes 6. Evidence of SARS-CoV-2 infection • Any of the following: Positive SARS CoV-2 RT-PCR, positive serology, antigen, positive antigen test and contact with an individual with COVID-19

ARDS = acute respiratory distress syndrome; BNP = brain natriuretic peptide; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin 6; LDH = lactate dehydrogenase; MIS-C = multisystem inflammatory syndrome in children; PT = prothrombin time; PTT = partial thromboplastin time; RT-PCR = real-time polymerase chain reaction; SARS-COV-2 = severe acute respiratory syndrome-2 coronavirus; WHO = World Health Organization.

protein, erythrocyte sedimentation rate, D-dimer, fibrinogen, pro-calcitonin, and interleukin 6.[19,24]

Guidelines for Management

COVID-19 can be prevented with hand hygiene, environmental decontamination, personal protective equipment, elimination of second-hand smoke, social distancing, and isolation of those infected.[29-31] Providers should teach caregivers that fever should be reported: either subjective fever (feeling feverish) or measured temperature > 100.4°F (38°C).[30]

Nurse practitioners (NPs) should ensure use of reliable communication links and telehealth. Indications for immediate medical assistance include children with poor oral intake, persistent fever, worsening dyspnea, especially at rest, and lethargy, especially in infants or children with comorbidities. WHO guidelines for management of pediatric COVID-19 respiratory symptoms are summarized in Table 4.

Management

Management of COVID-19 is generally supportive, yet may require progressive complex interventions, ranging from oxygen therapy via nasal cannula to endotracheal intubation. Outpatient management is recommended for children with mild symptoms and stable vital signs; appropriate follow-up via telehealth or clinic encounter should occur within 48 hours for repeat

laboratory testing and imaging for persistent or worsening symptoms.

Hospitalization is required for children presenting with unstable vital signs, shock, respiratory distress, and signs of cardiovascular dysfunction, including coronary artery aneurysm, left ventricular depression, elevated troponins and brain natriuretic peptide, arrhythmia, MIS-C, and other end-organ dysfunction, including altered mental status, seizures, dehydration, acute kidney injury, underlying immunodeficiency, and cardiac or lung abnormalities.

The inability to return for follow-up is an important consideration in the socially disadvantaged, such as a homeless child, and can be used as a basis for admission.[30,31]

MIS-C

Patients suspected of having MIS-C should be isolated and tested for COVID-19; a repeat PCR should be performed within 24 hours if the initial test is negative. The management of children with MIS-C is dependent upon the presentation. Hypotension and shock should be approached in the usual manner, and if refractory to intravenous fluid, epinephrine or norepinephrine should be used. Intravenous immune globulin, aspirin, and glucocorticoids may be indicated if there is any sign of coronary dilation or aneurysm or persistent shock. If hemodynamic instability due to left ventricular dysfunction or arrhythmias is present, intravenous diuretics and inotropic agents, such as milrinone, dopamine, or dobutamine, can be added. Extracorporeal membrane oxygenation

Table 4
Pediatric COVID-19 Respiratory Symptom Management

Symptom Severity	Management
Suspected infections	• Immediately isolate suspected individuals. • Remain "under investigation" until confirmed negative. • Isolate for at least 10 days from symptom beginning, to 3 days after symptom resolution.
Mild: pneumonia	• Isolation with caretaker at home or selected facility required. • Case-by-case management. • Antibiotic therapy not advised.
Moderate: pneumonia	• Isolation at designated location/home. • Provide empiric antibiotic treatment. • Monitor for complications (chest pain, shortness-of-breath, etc) • Complications/progression require hospitalization.
Severe: pneumonia	• Hospitalization, airborne precautions, isolation required. • Oxygenation via nasal cannula, air-entrainment mask, non-rebreather mask • Provide fluid resuscitation, antibiotics. • Avoid bag-valve mask due to droplet exposure. • Goal: O_2 saturation $\geq$ 94% but 90% acceptable in stable patients.
Critical: mild ARDS	• Hospitalization, airborne precautions, isolation required. • Stable patients may benefit from high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV), or bi-level positive airway pressure. • HFNO: up to 25 L/min gas flow with F_{IO_2} of 1.0; some may function at adult capacity of up to 60 L/min. • Mechanical ventilation for decompensation
Critical: severe ARDS	• Hospitalization, airborne precautions, isolation required. • Progressive hypoxemia unresponsive to NIV demands intubation: Oxygenate 100% F_{IO_2} for 5 minutes preintubation. • Keep plateau pressure <28 cm H_2O and pH 7.15-7.30. • Adjust tidal volumes to disease acuity: 3-6 mL/kg predicted body weight (PBW) for poor lung compliance; 5-8 mL/kg PBW for lung compliance. • For moderate-severe ARDS, provide positive-end expiratory pressure up to 15 cm H_2O; titrate to avoid harm.
Critical symptoms: COVID-19−Septic Shock	• Septic shock symptoms: hypotension, bradycardia/tachycardia, tachypnea, hyper/hypothermia, altered mental status, rash, high lactate. • Administer empiric broad-spectrum antibiotics • Taper with clinical improvement but Continue in immune compromised • Direct treatment based on infection site • Limit fluid resuscitation: 10-20 mL/kg crystalloid bolus over 30-60 minutes; avoid fluid overload. • Initiate vasopressors for persistent shock.
Other recommendations	• Avoid antiviral administration with plasma therapy to prevent cardiac, gastrointestinal, liver enzyme impairments. • Corticosteroid therapy is not recommended. • Positive mother and child may isolate together. • Test and isolate neonates of confirmed/suspected mothers. • If separation is not feasible, mother should wear mask, social distance, perform hand hygiene. • Nasal cannula should be used in young children; avoid face mask on children $\leq$ 2 years-old for fear of suffocation.

ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; F_{IO_2} = fraction of inspired oxygen.
Adapted from WHO, 2020.[24]

(ECMO) or even a ventricular assist device may be in order in extreme hemodynamic compromise. Continuous cardiac monitoring for arrhythmias, serial echocardiography, and laboratory assessments (troponins, brain natriuretic peptide) should be performed.

Antibiotic therapy is indicated in the case of septic shock or toxic shock syndrome. Ceftriaxone plus vancomycin or ceftaroline plus piperacillin-tazobactam can be administered after cultures are obtained. The clinician must keep an index of suspicion for other infections, such as acute appendicitis, cellulitis, or intra-abdominal abscess as the source of shock. Antiviral therapy is limited to children with severe MIS-C.[29-31]

Pharmacology Management

Currently, drugs with promising in vitro antiviral activity, such as remdesivir, and lopinavir/ritonavir have some proven clinical efficacy. Antivirals should be considered only in severe or critical cases and on a case-by-case basis, preferably as part of a clinical trial.[32] Remdesivir, a treatment for Ebola, is a nucleoside analog prodrug. When activated, it binds to viral RNA-dependent RNA polymerase, resulting in premature RNA chain termination and blocking viral replication. Potent antiviral activity has been demonstrated in several in vitro studies against SARS-CoV-2, as well as SARS-CoV-1 and Middle East respiratory syndrome.[33]

Remdesivir is administered intravenously using weight-based dosing. Baseline hepatic function and serum creatinine should be tested.[34] Day 1 loading dose and subsequent daily dosing comprise treatment: 5 days for patients not requiring mechanical ventilation and/or ECMO; 10 days for patients on mechanical ventilation and/or ECMO.[34]

Guidelines for remdesivir include (1) patients aged > 28 days old to < 1 year must have an estimated glomerular filtration rate = 0.45 × (height in cm)/(serum creatinine mg/dL) or (2) patients aged from 1 to 18 years must have an eGFR = 0.413 × (height cm)/serum creatinine mg/dL).[33,34] Remdesivir is not recommended in pediatric patients > 28 days old with a serum creatinine level $\geq$ 1 mg/dL unless the potential benefit outweighs the potential risk.[33] Infusion-related reactions during administration have been observed, including hypotension, nausea/vomiting, diaphoresis, and shivering. Alanine aminotransferase elevations have been reported. On November 5, 2020, the final report on remdesivir was published by the *New England Journal of Medicine* after a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in COVID-19−positive patients with a lower respiratory infection showed superiority to placebo in shortening the time to recovery.[34]

Lopinovir/retronivir is an oral protease inhibitor approved for pediatric HIV.[32] The mechanism of action is interference with the maturation of viral particles by inhibiting protease enzymes. The

Table 5
Kawasaki and Toxic Shock Syndrome[23,24]

Kawasaki disease (KD)
- Complete KD: Unexplained fever for $\geq$ 4 days PLUS at least 4 of the 5 criteria
- Incomplete KD: Unexplained fever for $\geq$ 5 days PLUS 2 to 3 of the 5 criteria

Clinical criteria:
- Bilateral bulbar conjunctival injection
- Oral mucous membrane changes, including injected or fissured lips,
- Peripheral extremity changes, including erythema of palms or soles, erythema and periungual desquamation (convalescent phase)
- Polymorphous rash
- Cervical lymphadenopathy (at least 3 lymph nodes > 1.5 cm in diameter

Toxic shock syndrome (TSS)
A probable case is defined by all 5 of the following criteria:
- Fever ($\geq$ 38.9°C [102.0°F])
- Rash (diffuse macular erythroderma)
- Hypotension
- Multisystem involvement (> 3 organ systems involved)
- Negative results on microbiologic and/or serologic testing for other causes
- A confirmed case is defined by all 5 of the above criteria PLUS desquamation

ritonavir component inhibits the metabolism of lopinavir, thereby increasing plasma levels of lopinavir.[32,35] The most common adverse reactions in children include vomiting and rash; less common is diarrhea. This treatment is contraindicated in children with jaundice because lopinovir/retronivir may increase free bilirubin and exacerbate jaundice.[35]

An alternative management strategy, hyperbaric oxygen therapy (HBOT), is designed to increase blood oxygen levels. Severe COVID-19 revealed a decreased ratio of arterial oxygen partial pressure to fractional inspired oxygen with concomitant hypoxia and tachypnea. Low carbon dioxide levels were also observed, with the median partial pressure of carbon dioxide level 34 mm Hg. In HBOT, the patient is enclosed in the chamber, the pressure is raised, and 100% oxygen is administered. Administering 100% oxygen at ambient pressure increases oxygen delivery in blood 5-fold, equating to 1.5 mL/dL. HBOT may provide a novel means of treating and/or mitigating respiratory conditions associated with COVID-19.

In July 2020, the FDA approved expanded access to remestemcel-L for MIS-C. It is an investigational allogeneic mesenchymal stem cell product taken from the bone marrow of an unrelated donor. It is administered via a series of intravenous infusions to candidates aged 2 months to 17 years with severe MIS-C. The drug is an immunomodulator that interferes with the inflammatory process induced by the virus and stimulates the production of anti-inflammatory cytokines at the affected tissues.

Heparin is another potential regimen for asymptomatic patients.[36] Heparin has a very strong bonding to the same protein that the coronavirus attaches to in human cells, thereby competing for the receptor and precluding the sequelae of inflammation that contributes to morbidity and death. It is not known at this point how this research will apply to the pediatric population.[36]

Glucocorticoids have decreased mortality in adults, but trials in children are ongoing.[37] In an ongoing phase 2 trial administering LY-CoV555 (bamlanivimab), a potent antispike neutralizing monoclonal antibody, initial results indicate reduction in viral load by day 11 in mild-moderate COVID-19 cases.[38] To date, pediatric patients have not yet been enrolled.

Vaccines

As of December 11, 2020, the FDA approved the use of the Pfizer-BioNTech COVID-19 vaccine under emergency use authorization, followed by the Moderna vaccine, for ages > 16 years old. Both vaccines are messenger (m-)RNA engineered and boast strong efficacy (Pfizer, 95%; Moderna, 94.5%) across age groups and ethnicities. The COVID-19 m-RNA—type vaccines use the coronavirus spike protein to enter human cells and attach to the ACE-2 receptor to stimulate the immune response. As the m-RNA—type vaccine eliminates the need for the cell DNA to create the m-RNA, it is more efficient in creating the desired immune response, less likely to incite long-long lasting effects, and does not cause infection.[39] Several vaccine developers (ie, Pfizer, Moderna, and Jansen) have ongoing clinical trials enrolling children ages 12 to 16 years old, while AstraZeneca is enrolling children 5 to 12 years old in the United Kingdom. Both US FDA-approved vaccines require 2 injections administered 21 days (Pfizer) and 28 days (Moderna) apart (±4 days), and are not interchangeable. Current debates involve providing only 1 of the 2 doses as a means to provide partial immunity to more people while vaccine distribution continues to remain limited due to supply.

Commonly reported adverse vaccine reactions include localized injection reaction, chills, pyrexia, headache, myalgia, and arthralgia. Contraindication exists for those with previous vaccine reaction. Lactation and pregnancy or planned pregnancy currently are not absolute contraindications to the 2 current vaccines; however, pediatric and obstetrical inputs are advised before administering. Vaccine recipients should be routinely monitored for 15 minutes after vaccination and for 30 minutes if a history of anaphylactic reaction to previous vaccination exists. To date, it is recommended to stagger administering the COVID-19 vaccine by 14 days either before or after other vaccines to be given. Pediatricians are advised to adhere to the routine vaccination schedule of children.[40,41]

Psychological Effects and Social Disparities

The growing prevalence of pediatric mental and behavioral health disorders coupled with scarce psychiatric resources have resulted in a substantial increase in the number of youths waiting in emergency departments and medical units for in-patient psychiatric care[42]; this has been exacerbated from the effects of lockdown and social distancing. Because children and adolescents depend on friendships to maintain self-worth and manage anxiety and depression, the pandemic lockdown has increased feelings of isolation and depression among them despite their being adept at using social media platforms and gaming technology. A study of adolescents at the University of Amsterdam and Emma Children's Hospital found a profound increase in severe anxiety and sleep problems during the country's lockdown, and this problem was intensified when the children or the family knew personally someone who had COVID-19. Further, adolescents reported sadness, loneliness, isolation, inability to make friends, and feeling abandoned, especially if they had to quarantine.[43]

Since the pandemic, the National Alliance on Mental Illness has reported many young adults experiencing anxiety and depression attributed partly to social isolation. The group cautions for teachers and parents to look for warning signs, including severe risk-taking behavior, significant weight loss, excessive use of drugs and alcohol, and drastic mood swings. The American Psychiatric Association Council on Children, Adolescents and their Families recommends that schools put in place a lesson plan to teach students on how to share their emotions; further, the National Alliance on Mental Illness emphasizes that "kids need to be kids."

Pandemic challenges for health care providers to deliver mental health services to clients and their families at physical locations has prompted use of telehealth.[44] However, language and literacy barriers, limited access to internet technology, as well as socio-economic disadvantages and limited income have negatively contributed toward mental health disparities that have arisen during the pandemic.[45] This pandemic has deeply affected families economically. Among low-income households, 93.5% report food insecurity, use of food pantries, economic instability, lack of health care access, and fear of contracting COVID-19.[44] The US has observed significantly greater ratios of hospitalizations and deaths from COVID-19 in diverse racial and ethnic populations than non-Hispanic Whites.[46] Native Americans, African Americans, and Hispanics had hospitalization rates approximately 5 times that of non-Hispanic Whites.[42] Likewise, the pandemic has negatively affected the mental health of these diverse groups as businesses closed, social relationships changed, and jobs were lost.[47]

Both African Americans and Hispanics (24%) recently reported higher rates of stress, anxiety, or emotional disturbances compared with non-Hispanic Whites (17%) in a cross-sectional, descriptive study (n = 1,226).[47] Nearly half of Hispanics (44%) and African Americans (42%) further reported work loss, reduced work hours, or cuts in income related to the COVID-19 crisis.[47] These factors could potentially play a role in US health care disparities among diverse and vulnerable groups, particularly during a global pandemic. Telehealth, however, could fulfill the medical and psychiatric needs of Americans of all ethnic groups by increasing access to health care and controlling COVID-19 rates.[45]

Follow-up, Practice, Education, and Research

After recovery, the provider needs to assess the patient's infectivity because reinfection and reactivation may occur. Ye et al[42] found 5 patients with previous COVID-19 infection presenting with reactivation weeks later. Postinfection immunity is an active topic that is fascinating the public and has boosted antibody testing; however, the clinical significance of the antibody response remains unclear. NPs can raise awareness and create public health campaigns to reduce the spread of this infection.

Conclusion

COVID-19 has serious health effects on pediatric patients. This review has focused on pediatric COVID-19 presentation and treatment because the long-term psychological and physical effects are yet to be known. The last few months have shown that the pandemic does inflict psychological wounds on children and adolescents as well as on adults. Asymptomatic individuals found in contact tracing weeks later present to clinic with vague lingering effects from the illness. Our knowledge has continued to grow and change as new case studies of variant symptom presentations, responses to treatment, vaccination responses and its immunity, and lingering or reactivated presentations are reported. It is incumbent upon NPs to stay abreast of evidence-based practices to prevent and mitigate COVID-19 and its mutations, while guiding the public in making safe decisions regarding schooling, sporting, and social activities that affect the participation of children.

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