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LITERATURE REVIEW

A Pediatric Infectious Diseases Perspective of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Novel Coronavirus Disease 2019 (COVID-19) in Children

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Understanding the role that children play in the clinical burden and propagation of severe acute respiratory syndrome coronavirus 2, responsible for coronavirus disease 2019 (COVID-19) infections, is emerging. While the severe manifestations and acute clinical burden of COVID-19 have largely spared children compared with adults, understanding the epidemiology, clinical presentation, diagnostics, management, and prevention opportunities and the social and behavioral impacts on child health is vital. Foremost is clarifying the contribution of asymptomatic and mild infections to transmission within the household and community and the clinical and epidemiologic significance of uncommon severe post-infectious complications. Here, we summarize the current knowledge, identify resources, and outline research opportunities. Pediatric infectious diseases clinicians have a unique opportunity to advocate for the inclusion of children in epidemiological, clinical, treatment, and prevention studies to optimize their care as well as to represent children in the development of guidance and policy during pandemic response.

Key words. children; COVID-19; pediatrics; novel coronavirus; SARS-CoV-2.

EPIDEMIOLOGY

In December 2019, coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, and the etiology was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By the end of January 2020, the World Health Organization (WHO) declared COVID-19 a public health emergency of international concern, and by mid-March 2020, the outbreak was declared a pandemic. Initially, children comprised between 1% and 2% of the laboratory-confirmed SARS-CoV-2 detections among people in China [1], Italy [2], and the United States [3]. Initial reports from the Centers for Disease Control and Prevention (CDC) noted the following age distributions: 15–17 years (32%), 10–14 years (27%), 5–9 years (15%), 1–4 years (11%), and <1 year (15%), with a median age of 11 years [3]. As access to diagnostic testing increased, subsequent assessments demonstrated that children, defined in this cohort as birth to age 19 years, comprised 5.2% of the laboratory-confirmed test results submitted from 22 January 2020 through 30 May 2020 [4]. In a subsequent surveillance

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effort, specimens from children from birth through age 9 years comprised 1.5% of the total positive results, while those from age 10 through 19 years comprised 3.7% of the total 5.2%.

Internationally, most children who met either a laboratory or clinical definition for detection of SARS-CoV-2 or having COVID-19 have been school-aged and adolescents. The small proportion of confirmed infections in infants and younger children probably results from the propensity of infants and young children to have mild symptoms and thus remain undetected [5]. A retrospective cohort study of contacts of patients with COVID-19 in Shenzhen, China, found similar infection attack rates across pediatric age groups. Among children aged 0–9 years, the secondary attack rate was 7.4% (95% confidence interval [CI], 4.2–12.8), and among those aged 10–17 years, the secondary attack rate was 7.1% (95% CI, 3.3–14.6) [6]. In a household transmission study in Guangzhou, China, researchers reported that the risk of household infection was lower in the youngest age group (<20 years; odds ratio, 0.23; 95% CI, .11–.46) compared with household contacts aged >60 years [7]. Challenges with interpretation of epidemiological studies in children include the variation among upper limit age parameters for classification as a child, varying clinical and laboratory parameters for classifying as a related infection, and a lack of representative samples from both symptomatic and asymptomatic children. These factors likely impact differences in the descriptive epidemiology of children with COVID-19.

Estimates of the basic reproduction number (R_0) have varied across studies. As with factors that impact epidemiological classification, the setting, degree of crowding, adherence to controls measures, and extent of diagnostic testing affect R_0 estimates. Data from China early in the epidemic that suggest a median R_0 of 2–3 are widely accepted [8]; however, recent modeling suggests that the R_0 value may be much higher at 5.7 (95% CI, 3.8–8.9) [9].

The incubation period of SARS-CoV-2 is estimated to be 5.2 days (95% CI, 4.1–7.0), with a range of 2 to 14 days [10, 11]. Failure to account for transmission from mildly symptomatic individuals makes defining the incubation period in children more challenging. Transmission is primarily through respiratory droplets or close contact [12]. The contribution of transmission via aerosolized particles remains controversial. Transmission from presymptomatic (within 48–72 hours before signs and symptoms appear) [13, 14] and asymptomatically [15] infected children have been suggested [16]. This has also been observed with influenza [17] and other respiratory viral infections, when asymptomatic or subclinically infected children elude case detection. Case series suggest that the majority (80%–84%) of infected children have a symptomatic adult household or other direct epidemiologic close contact [18].

There are reasons to suspect that children may represent an important reservoir of infection within the community, especially those with higher viral loads who escape recognition because they manifest less severe disease [19, 20]. Although symptomatic children have demonstrated higher viral loads from nasopharyngeal specimens than asymptomatic children [21], an understanding of how viral load corresponds with transmission is evolving. Detectable SARS-CoV-2 from the nasopharynx for up to 22 days following symptom onset and from pediatric fecal samples for up to 30 days following symptom onset demonstrates the challenge of interpreting the significance of prolonged and variable shedding from different anatomical sites [18, 22, 23]. The association seen in adults of a greater severity of disease with higher viral loads and longer shedding of SARS-CoV-2 may not hold in children [24]. Moreover, polymerase chain reaction (PCR) detection of viral RNA may not represent infectious virus particles. The ongoing accumulation of information related to serological correlates of protection following both symptomatic and asymptomatic infections will add to our understanding of transmissibility in recovered children [25].

UNDERLYING CONDITIONS AND CLINICAL FEATURES

Underlying health conditions, including chronic respiratory insufficiency, obesity, and neurodevelopmental conditions, are common in hospitalized children with acute COVID-19, [4, 26–28]. It is unclear whether the increased hospitalization rate among children with underlying medical conditions is due to a lower threshold for hospitalization, concern for complications, or more severe manifestations of a SARS-CoV-2 infection.

Several case series have described the clinical features of SARS-CoV-2 infection in children from the perspective of disease severity, presenting symptoms, and in comparison with those described in adults. A consistent picture of a generally mild disease in children has emerged from settings in Asia, North America, and Europe. More than 96% of children reported to the equivalent of the Chinese CDC with laboratory-confirmed SARS-CoV-2 infections had mild or moderate illness (fever, respiratory symptoms, or radiographic pneumonia without hypoxemia). Less than 3% had severe disease that required oxygen supplementation, and <1% (3 children) were considered to be critically ill [29]. In several case series, most children were identified based on symptoms, making rates of infection in asymptomatic children unknown. Among 17 877 children who had symptoms reported to the US CDC, the most common symptoms were fever (46%), cough (37%), headache (15%), diarrhea (14%), and sore throat (13%) in children aged ≤9 years and headache (42%), cough (41%), fever (35%), myalgia (30%), sore throat (29%), shortness of breath (16%), and diarrhea (14%) in children aged 10–19 years. Other less commonly reported symptoms included rhinorrhea, nausea/vomiting, abdominal pain, and anosmia and dysgeusia [4]. Among a cohort of 50 hospitalized children (aged ≤21 years) in New York City, the median time from symptom onset to hospitalization was 2 days,

with a median length of hospitalization of 3 days. Forty (80%) had fever and 32 (64%) had respiratory symptoms, with infants less likely to have respiratory symptoms compared with older children. Sixteen (32%) required respiratory support and 9 (16%) required assisted ventilation [30]. A cohort of 65 children who received care in a New York City area health system demonstrated similar demographics, with 35% of patients requiring care in an intensive care unit. Severity was lowest in infants aged <60 days and highest in chronically ill children; 79% of immunocompromised children had mild disease. One death was reported [28]. In comparison, a multinational systematic review of clinical information from 1780 children noted fever (52%), cough (47%), sore throat (18%), and severe illness (0.6%) [26].

As the pandemic progressed, the ability of SARS-CoV-2 infection to result in a broad spectrum of pathological conditions with varying clinical manifestations became apparent. In April 2020, several European countries noted increasing numbers of children with systemic inflammation and clinical features that resembled both Kawasaki disease and toxic shock syndrome. Simultaneously, reports from the United States began to describe the clinical characteristics, treatment, and outcomes of previously healthy SARS-CoV-2–infected children and adolescents with inflammation in multiple systems [31]. Initially termed "the pediatric multisystem inflammatory syndrome potentially associated with COVID-19" [32], the CDC developed a case definition for what is now referred to as "multisystem inflammatory syndrome in children (MIS-C)" in North America. Publicized in a health alert disseminated in the United States [33], the clinical and laboratory parameters of children who meet the criteria for MIS-C differ from those with Kawasaki disease. Children with MIS-C are usually older, have more symptoms consistent with clinical shock, have involvement of their gastrointestinal and cardiovascular systems, and have lymphopenia with notably elevated inflammatory markers. Coronary artery aneurysms have been noted both in children aged <5 years who were more likely to have presentations similar to those seen with Kawasaki disease as well as in older children [34, 35]. One of the first case series to be described in the United States consisted of 6 critically ill children with fever, diarrhea, and shock, with variable skin lesions, conjunctivitis, extremity edema, and mucous membrane changes [34]. A more recently studied cohort of 186 children who presented with MIS-C had a mean age of 8.3 years; the majority (73%) were previously healthy and 130 (70%) had laboratory evidence of a SARS-CoV-2 infection via PCR and/or serum antibody testing. In the US cohort, gastrointestinal (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%) symptoms were reported; 80% required intensive care and there were 4 deaths [36]. A cohort of children identified in New York had similar findings, with an increase in MIS-C cases noted 1 month following a peak of SARS-CoV-2 infections in the state [35]. A case series from a single center in London, United Kingdom, described 4 (15%) children with MIS-C who had new neurological symptoms that involved both the central and peripheral nervous systems, with splenial changes on imaging in the absence of respiratory symptoms. Complete neurological recovery was noted in 2 of the children, with ongoing monitoring of the improving neurological status of the other 2 children. Three of the 4 children received intravenous immunoglobulin (IVIG); 2 of whom also received biologics [37]. Guillain-Barré syndrome has been associated with COVID-19 in 2 case reports. The first occurred 3 weeks following a mild febrile and respiratory SARS-CoV-2 infection in an 11-year-old male [38], and a second was coincident with a SARS-CoV-2 presentation in a 15-year old male [39]. Neurotropism of the SARS-CoV-2 virus may explain these manifestations with a temporal relationship to COVID-19 infections in children.

Unusual symptoms have been recognized as likely related to COVID-19. Children and young adults have presented with painful purple and red papules on their fingers and toes, similar to pernio, which has been termed "COVID toes," as their only manifestation of COVID-19 [40]. Anosmia with or without dysgeusia has recently been incorporated into the list of symptoms associated with COVID-19 [41], but both are less commonly reported in children [28], possibly due to lack of appreciation, lack of reporting, or true absence. Several children's hospitals in the United States have collaboratively developed a registry for the standardized collection of clinical and epidemiologic information from children with COVID-19. This centralized source of information will help to characterize many aspects of COVID-19 disease manifestations in children [42].

LABORATORY AND RADIOGRAPHIC FINDINGS

Early reports from China noted leukopenia (19%), lymphopenia (31%), transaminitis (6%), elevated myocardial enzymes (31%), and elevated C-reactive protein (3%) among children with SARS-CoV-2 infections [43]. Cytokine abnormalities have been described in children with severe manifestations of COVID-19, including elevated levels of interleukin (IL)-6, IL-10, and interferon-gamma [44]. A European systematic review of 655 children with mild to moderate clinical manifestations of COVID-19 noted lymphopenia or neutropenia in 13% and elevated inflammatory markers in 31% [26]. Among 2 cohorts of hospitalized children aged ≤21 years in the New York City area with laboratory-confirmed SARS-CoV-2 detected via PCR, between 44% and 72% had lymphopenia and inflammatory marker abnormalities; coagulopathy was correlated with a more severe disease presentation [28, 30].

The most common imaging abnormalities noted among Chinese children with both symptomatic and asymptomatic COVID-19 were pulmonary ground-glass opacities or consolidation [45]. In a case series of 171 children from whom

SARS-CoV-2 was detected, 56 (33%) had ground-glass opacities, 32 (19%) had local patchy shadowing, 21 (12%) had bilateral patchy shadowing, and 2 (1%) had interstitial abnormalities [46]. Another series found that bilateral infiltrates were more common than unilateral infiltrates; 4 (20%) children had normal initial chest computerized tomography imaging [47]. Although children with more severe manifestations of disease were more likely to have imaging abnormalities [43], this association may be due to ascertainment bias, as children with severe manifestations may be more likely to undergo imaging. Additionally, imaging abnormalities have been described in children with minimal to no recognized symptoms.

OUTCOMES

Most children with severe manifestations of COVID-19 recover completely. Accounting for access to diagnostic testing, children with underlying conditions appear to be most at risk for adverse outcomes. The spectrum of outcomes was described among 48 children cared for in pediatric intensive care units (PICUs) in North America; 40 (83%) had an underlying medical condition. Although 18 (38%) of these children required mechanical ventilation and 1 patient required extracorporeal membrane oxygenation, the overall mortality was 4% among this North American PICU cohort [27]. In a case series from New York City, obesity and asthma were prevalent in the cohort but not significantly associated with PICU admission [48]. Prolonged courses of critical care have been reported in China for children with acute lymphocytic leukemia, hydronephrosis, and intussusception [44, 46, 49, 50].

These generally favorable outcomes among children who experience clinically significant COVID-19 is an area of active exploration. Hypotheses that may explain the decreased severity of disease in children compared with adults include the lower expression of the angiotensin-converting enzyme 2 viral entry receptor in the lungs and nasal epithelia of children compared with adults [51, 52], differences in innate immune responses that control viral killing and expression of inflammatory regulators involved in the acute respiratory distress syndrome pathway [53, 54], cross-protection from nonnovel coronaviruses, exposure to vaccines with immunomodulating properties [55], and the lower prevalence of underlying chronic medical conditions compared with adults and the elderly with COVID-19 [56].

SPECIAL POPULATIONS

Pregnant Women

While developing an understanding of the impact of SARS-CoV-2 on pregnant women and their neonates, professional societies, including the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, have issued joint guidance [57], and registries have been developed to track outcomes of infected pregnant women and their infants [58]. The American Academy of Pediatrics (AAP) issued guidance for the care of newborns born to women with suspected or confirmed COVID-19 [59].

Routine testing for SARS-CoV-2 in women in a high-prevalence city in the United Stated at the time of delivery of their infants showed that 1 in 8 women from whom SARS-CoV-2 was detected at the time of delivery were asymptomatic [60]. Initial reports did not suggest a higher mortality or increased rates of complications among pregnant women from whom SARS-CoV-2 was detected [61–63]. Subsequently, ongoing CDC surveillance has noted that pregnant women in the United States with SARS-CoV-2 infections were more likely to be hospitalized than nonpregnant women for nonobstetric indications. Adjusting for cofounders, pregnant women were more likely to be cared for in an intensive care unit and to receive mechanical ventilation than nonpregnant women of childbearing age. Among 81% of 11 312 pregnant women with SARS-CoV-2 detection for whom information was available, 50% were of Hispanic or Latino ethnicity, 23% were of white race and non-Hispanic ethnicity, 20% were of black race and non-Hispanic ethnicity [64]. A high rate of acute respiratory distress syndrome was observed among a cohort of 64 pregnant women with severe or critical COVID-19 in the United States. Half of the women delivered during their third trimester; most of the infants born to the critically and severely ill women were premature. However, there were no maternal or perinatal deaths in this cohort [65].

Evidence for vertical transmission of SARS-CoV-2 has been sought from maternal–neonatal pairs. A case series of 33 SARS-CoV-2–infected mothers identified 3 (9%) neonates in whom SARS-CoV-2 was detected from nasopharyngeal and stool specimens on day of life 2 and 4 and who had symptoms of early-onset sepsis with initial fever and pneumonia. Rapid clinical improvement and lack of persistent viral detection made the significance of vertical transmission unclear [66].

Probable congenital infection has been reported in an infant born via cesarean section with SARS-CoV-2 detected via PCR from neonatal nasopharyngeal swabs on day of life 0, 2, and 7; from blood on day of life 4; and from stool on day of life 7; umbilical cord tissue was negative for SARS-CoV-2. The neonate had an uneventful post-natal course and was reportedly well at a day-of-life 30 follow-up assessment [67]. From a case series of women diagnosed with COVID-19, their third trimester placentas were more likely to show at least 1 feature of maternal vascular malperfusion, although rates of acute and chronic inflammation were not increased compared with the placentas of women without COVID-19 [68].

One can speculate that the endovascular effects of SARS-CoV-2 infection result in placental thrombosis and insufficiency, affecting the fetus even in the absence of transplacental infection.

Neonates

Preliminary analyses have suggested that in utero vertical transmission is possible from SARS-CoV-2–positive pregnant women. SARS-CoV-2 has been detected in placentae, umbilical cord blood, and vaginal mucosa of pregnant women and in expressed human milk [69]. Other researchers have provided evidence that supports probable congenital transmission from women without active infection at the time of delivery [67]. Guidance regarding the management of the infant born to a woman with known or suspected COVID-19 or asymptomatic detection of SARS-CoV-2 virus has evolved. The initial suggestion of mother–infant separation was subject to debate, with the AAP [70], US CDC [71], and WHO [72] all suggesting different approaches. Recent revisions by the AAP, based on accumulated data and experience, have harmonized guidance [59]. Between 2% and 5% of more than 1500 infants registered in the Perinatal COVID-19 Registry tested positive in the 24–96 hours following birth [59]. Noting that the risk for neonatal acquisition of SARS-CoV-2 appears to be equivalent when rooming-in with maternal adherence to infection prevention guidance vs physical separation of women and their neonates, post-partum women may be offered the choice of rooming-in. Infants who require hospitalization before 1 month of age have been found to have symptoms consistent with COVID-19, and SARS-CoV-2 has been detected in their nasopharyngeal specimens. The relationship between maternal and caregiver exposure and neonatal acquisition of infection is an area of ongoing investigation.

Although SARS-CoV-2 nucleic acid has been detected in expressed human milk, the viability of the virus and the presence and role of antibodies to SARS-CoV-2 is currently unknown. To date, SARS-CoV-2 transmission has not been documented via human milk ingestion; therefore, expressed human milk or direct breastfeeding is supported for women with COVID-19. Hand and breast hygiene along with maternal masking is also recommended to decrease opportunities for transmission of SARS-CoV-2 from mother to neonate.

The AAP continues to recommend diagnostic testing of all asymptomatic newborns at 24 hours of age and, if still hospitalized, at 48 hours of age [59, 70]. While the results of universal testing of asymptomatic neonates may have utility for in-hospital isolation and for understanding the epidemiology of COVID-19 in this low-risk population, the implications of test results for post-hospital pediatric care should be considered. Additional guidance regarding hospital visitation and discharge of neonates born to mothers with COVID-19 may be found on the AAP COVID-19 Clinical Guidance page [73].

Immunocompromised Individuals

Our current understanding of the risk for SARS-CoV-2 acquisition and subsequent COVID-19 in immunocompromised children reflects limited epidemiologic data. Assumptions about the elevated risk for infection and adverse outcomes in immunocompromised children are based on extrapolation from experience with other respiratory viruses [74]. The duration of viral shedding may be prolonged in those who receive immunosuppressive therapies.

Considerations relevant to the care of children with cancer [75], children who have undergone hematopoietic cell transplant [76, 77], or children who have undergone solid organ transplants [78] are emerging but are mostly adult-focused. Accumulating evidence suggests that mild to moderate immunosuppression may not be a risk factor for more severe manifestations of COVID-19 in children [28, 79, 80].

Given the current pandemic, a high level of clinical suspicion for COVID-19 in immunocompromised children is needed. Societies dedicated to the care of immunocompromised persons recommend that children with fever or respiratory symptoms (cough, shortness of breath, hypoxemia) be considered for SARS-CoV-2 PCR testing. If children have respiratory symptoms, multiplex respiratory panels should also be considered. An immunocompromised child with symptoms consistent with COVID-19 with a negative SARS-CoV-2 PCR may be considered for repeat testing if clinical suspicion for COVID-19 remains high, given variability in screening test sensitivity and specificity. Last, children positive for SARS-CoV-2 with lower respiratory tract symptoms should be considered for chest imaging if the result of the imaging study will impact their management. Given the heterogeneity of the immunocompromised pediatric population and the rapidly evolving nature of the COVID-19 pandemic, a list of organizations and their associated COVID-19 websites is provided as a reference for the most updated information regarding management (Table 1).

DIAGNOSTICS

Diagnosis of acute SARS-CoV-2 infection is a rapidly evolving field. Most assays utilize specific real-time reverse-transcription PCR techniques [81, 82]. Numerous PCR assays approved only under the US Food and Drug Administration (FDA) emergency use authorization (EUA) have been extensively used in children [18, 29, 43, 66]. Although the nucleocapsid gene has been the primary target, some assays have included other viral target sequences [77, 82]. Molecular testing is the optimal diagnostic test for detection of SARS-CoV-2 in a person suspected of having acute COVID-19.

For diagnostic testing for SARS-CoV-2, the CDC recommends collecting and testing an upper respiratory tract specimen, preferably a nasopharyngeal specimen [83]. The diagnostic utility of saliva specimens, antigen testing, and self-collected

Table 1. Resources for Lay and Medical Caregivers for Coronavirus Disease 2019 from Organizations and Societies Involved in the Care of Immunocompromised Pediatric Patients

Organization or Society	URL for Resources, Including Guidelines, Newsletters, and Educational Materials
American Association of Blood Banks (AABB)	http://www.aabb.org/advocacy/regulatorygovernment/Pages/AABB-Coronavirus-Resources.aspx
American Red Cross (ARC)	https://www.redcrossblood.org/donate-blood/dlp/coronavirus--covid-19--and-blood-donation.html
American Society of Hematology (ASH)	https://hematology.org/covid-19
American Society of Pediatric Hematology/Oncology (ASPHO)	http://aspho.org/covid-19-resources-for-pediatric-hematologists-oncologists
American Society of Transplantation (AST)	https://nam03.safelinks.protection.outlook.com/?url = https%3A%2F%2Fwww.myast.org%2Fcovid-19-information&data = 02%7C01%7Cashane%40emory.edu%7C880396cd6b8f4b17cada08d83ac09447%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637323946089322541&sdata = pr1Ka0SweWpRS%2FJfL4oherv0LRSMKwRxXPSftI5ReMU%3D&reserved = 0
American Society for Transplantation and Cellular Therapy (ASTCT)	https://www.astct.org/communities/public-home?CommunityKey = d3949d84–3440–45f4–8142–90ea05adb0e5
Center for International Blood & Marrow Transplant Research (CIBMTR)	https://www.cibmtr.org/Covid19/Pages/default.aspx
Children's Oncology Group (COG)	https://childrensoncologygroup.org/
Emerging Infections Task Force (EITaF), European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	https://www.escmid.org/research_projects/emerging_infections_task_force/eitafoutbreak_news/
European Society for Blood and Marrow Transplantation (EBMT)	https://www.ebmt.org/covid-19-and-bmt
European Society for Organ Transplantation (ESOT)	https://www.hivma.org/globalassets/idsa/news-and-publication/covid-19-special-considerations-final-.pdf
Federation for the Accreditation of Cellular Therapy (FACT)	http://www.factwebsite.org/News.aspx#news-id2014
Human Immunodeficiency Virus Medicine Association (HIVMA)	*Directs to* Infectious Diseases Society of America *COVID-19 Resource Center*
Immunodeficiency Foundation (IDF)	https://primaryimmune.org/coronavirus
Infectious Diseases Society of America (IDSA)	https://www.idsociety.org/public-health/COVID-19-Resource-Center/
International AIDS Society (IAS)	https://www.iasociety.org/covid-19-hiv
International Pediatric Transplant Association (IPTA)	Directs to TTS and TID COVID-19 websites
International Society for Heart and Lung Transplantation (ISHLT)	https://ishlt.org/covid-19-information
Jeffrey Modell Foundation (JMF)	https://www.jmf-melbourne.org.au/news-and-events/2020/3/12/covid-19-update
Leukemia & Lymphoma Society (LLS)	https://www.lls.org/public-health/coronavirus
National Cancer Institute (NCI)	https://www.cancer.gov/contact/emergency-preparedness/coronavirus
National Comprehensive Cancer Network (NCCN)	https://www.nccn.org/covid-19/
National Marrow Donor Program (NMDP)	https://network.bethematchclinical.org/news/nmdp/be-the-match-response-to-covid-19/
Organ Procurement and Transplant Network (OPTN)	https://optn.transplant.hrsa.gov/governance/policy-notices/
Pediatric Infectious Diseases Society (PIDS)	http://www.pids.org/resources/covid-19.html
Pediatric Transplantation and Cellular Therapy Consortium (PTCTC)	None
The Transplantation Society (TTS)	https://tts.org/index.php?option = com_content&view = article&id = 692&Itemid = 115
Transplant Infectious Diseases (TID) Section, The Transplantation Society (TTS)	https://tts.org/tid-about/tid-presidents-message/23-tid/tid-news/657-tid-update-and-guidance-on-2019-novel-coronavirus-2019-ncov-for-transplant-id-clinicians
United Network for Organ Sharing (UNOS)	https://unos.org/covid/
World Marrow Donor Association (WMDA)	https://share.wmda.info/display/LP/COVID-19+-+Impact + on + Registry + Operations#/

On-line search performed on 13 April 2020 using the search terms "coronavirus," "COVID-19," and "SARS-CoV-2." Updated 5 August 2020

nasal specimens are being assessed in adults and will need to be validated in children. Nonrespiratory samples, including stool, have been evaluated in infants and children using research-based assays to detect SARS-CoV-2 RNA, but FDA EUA, commercially available assays are currently not available for stool specimens. To conform to EUA guidance, users should note the anatomical sites for which an approved SARS-CoV-2 assay is validated.

Antibody assays that detect immunoglobulin M and immunoglobulin G may be reactive as early as 4 days after symptom onset [56] and until as late as 11–14 days from the date of infection [84], impacting the utility of serology as a diagnostic modality. Serological assays approved under the FDA EUA [85] have largely used adult specimens for validation and raise the question of applicability in children, especially with respect to cross-reactivity to the nonnovel coronaviruses [86]. Serologic assays may be helpful to describe the epidemiology of SARS-CoV-2 retrospectively, but population samples will be a key factor in interpreting the results.

Although detection of another respiratory virus does not eliminate the possibility of SARS-CoV-2 coinfection, at the beginning of the pandemic, many public health entities suggested that detection of a non–SARS-CoV-2 respiratory organism was enough evidence to exclude COVID-19. In part, this triage system was based on limited access to acute diagnostic capability at the time, which also coincided with an end to the respiratory viral season. Among 161 hospitalized children (aged ≤14 years) with positive respiratory virus PCR assays enrolled in a retrospective study,

2 (1%) were coinfected with human respiratory viruses and *Mycoplasma pneumoniae* in China. These organisms were detected in the bronchoalveolar lavage fluids from both patients [87]. Another case series from China suggested that 17 (50%) children had nasopharyngeal codetection of SARS-CoV-2 with other respiratory viruses [88]. Understanding coinfection and codetection of organisms with SARS-CoV-2 in children is of ongoing interest. Particularly as the pandemic extends into the winter viral season in the Northern Hemisphere, consideration of other respiratory viruses may inform management decisions.

Consideration of the sensitivity, specificity, and positive and negative predictive values of diagnostic assays is essential. Despite low limits of detection of viral RNA in most commercially available PCR assays, false-negative and discordant results have been noted [89]. As with any assay, timing of collection with respect to the illness course, intermittent shedding, variability of sample collection, degradation of viral RNA during shipping or storage of samples, the specimen acquisition site, and host and epidemiological factors must be considered in the interpretation of diagnostic test results.

TREATMENT AND PREVENTION

Management of children with acute SARS-CoV-2 infection and post-infectious sequelae such as MIS-C is rapidly evolving, with guidance available from the CDC [90], WHO [91] National Institutes of Health [92], and Infectious Diseases Society of America [93]. The Pediatric Infectious Diseases Society developed guidance that focuses on the rationale and indications for the use of antivirals for known or suspected COVID-19 in children [94]. Supportive care remains the mainstay of management for most children. A summary of relevant candidate therapies is provided in Table 2. Additional investigational COVID-19 therapeutics with ongoing or upcoming planned human trials can be found on ClinicalTrials.gov. Following the finding that the antiviral remdesivir was superior to placebo in shortening the time to recovery and in reducing mortality in adults hospitalized with lower respiratory tract involvement from COVID-19 [91], a phase 2/3, single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of remdesivir (GS-5734) in children from birth to age < 18 years with COVID-19 was initiated (NCT04431453) and is ongoing. An evaluation of the management of children using immunomodulatory therapies such as IVIG, corticosteroids, IL-6, and IL-1Ra inhibitors is ongoing for children with inflammatory (MIS-C) or severe presentations [36]

There is currently no medical evidence to support the use of chemoprophylaxis for SARS-CoV-2 infections in children. A recent randomized, controlled trial showed no efficacy in the prevention of COVID-19 in adults who took hydroxychloroquine for COVID-19 as a post-exposure prophylaxis [118]. There is one ongoing trial for prevention of thromboembolism in children with COVID-19 (NCT04354155). It is not clear whether the burden of disease warrants trials of monoclonal antibody prophylaxis in immunocompromised children who may not respond adequately to a vaccine.

There are currently no licensed vaccines available to prevent COVID-19. More than 140 vaccine candidates targeted at COVID-19 prevention are in development, with many in ongoing clinical trials. Assessment of a variety of vaccine platforms including adjuvanted and nonadjuvanted protein-based, DNA-based, inactivated viral, mRNA-based, viral-like particles, and viral vector-based, has resulted in the selection of candidates with promising phase 1 and 2 performances to be evaluated in phase 3 clinical trials. Most vaccine trials currently exclude the enrollment of children in initial stages; however, plans are in place to extend trials of promising vaccine candidates to pregnant women and children.

INFECTION PREVENTION AND CONTROL

SARS-CoV-2 is spread by respiratory droplets or close contact [119], facilitating transmission in grouped care arrangements. Person-to-person transmission as well as healthcare-associated transmissions have been described. The extent of transmission by aerosols remains controversial. The virus is not believed to be spread by food. Emerging data that support lack of infectivity with prolonged shedding after 9 to 10 days has helped to guide isolation and quarantine guidance within healthcare settings and in the community [120, 121]. As with all infectious diseases, the principles of *i*dentify, *i*solate, and *i*nform may be applied to the management of children with known or suspected COVID-19. The unique aspects related to care of children with known or suspected COVID-19 center on maintaining a balance between family-centered care and healthcare worker safety (Table 3).

As the epidemiology of SARS-CoV-2 and COVID-19 unfolds, the mild and varied spectra of illness in most children makes identification challenging. Unique to children is the important consideration of parental presence during care. To prevent transmission in facilities, screening, triage, and isolation strategies implemented at all points of entry should involve accompanying family members. A high level of clinical suspicion, well-equipped triage stations, routine objective and subjective screening, and signage in public areas that promotes masking with child-sized masks and child-accessible hand hygiene efforts are recommended [122]. Environmental controls, including child-friendly floor markings, to encourage social distancing, partitioning, and physical distancing are recommended. Several unique aspects for care of children during an infectious disease pandemic are reviewed in Table 3.

Table 2. Status of Therapeutic Options and Ongoing Clinical Trials for Specific Antiviral Agents for Treatment of Coronavirus Disease 2019

Therapeutic	Possible Mechanism of Action	Evidence for Anti-Coronavirus Activity	Evidence for Anti- Severe Acute Respiratory Syndrome Coronavirus 2 Activity	Additional Considerations	Current Status
Remdesivir	Prodrug of an adenosine analog that leads to impairment of viral replication via delayed chain termination [96]	In vitro, remdesivir demonstrates inhibitory activity against multiple human coronavirus strains [97–100] In a MERS-CoV mouse model, remdesivir improved lung function, decreased pulmonary viral loads, and decreased lung pathology compared with untreated mice [99, 100] In a MERS-CoV nonhuman primate model, remdesivir treatment decreased clinical disease scores, decreased pulmonary viral loads, and decreased lung pathology compared with untreated controls [101]	Inhibition of viral replication demonstrated in vitro [102] Significantly shortened recovery time in a randomized controlled trial of hospitalized adults [95]	Limited data on pediatric use from Ebola treatment trials and individual case reports of pediatric use [103, 104]	Recent FDA emergency use authorization for hospitalized adult and pediatric patients who require oxygen, mechanical ventilation, or extracorporeal membrane oxygenation Phase 2/3 pediatric trial enrolling (NCT04431453)
Corticosteroids	Generalized antiinflammatory activity	Widely used among critically ill patients with severe acute respiratory syndrome and Middle East respiratory syndrome	Rates of acute respiratory distress syndrome, shock, and need for respiratory support were higher in patients on steroids, but steroids were only used for those with more severe illness; unclear if there was benefit [105] Dexamethasone reduced deaths by one-third in adults who required mechanical ventilation and by one-fifth in adults who received supplemental oxygen [106]	Limited pediatric data	Currently available for use for multiple conditions
Convalescent plasma	Human convalescent plasma is available from people who have recovered and can donate high-titer neutralizing immunoglobulin-containing plasma	Antiviral activity may result from passive transfer of antibodies, promoting viral clearance	In a randomized trial of 103 patients, convalescent plasma did not provide statistically significant improvement. Trial ended early and may have been underpowered [107]	Available for children via a national expanded access protocol (https://www.uscovidplasma.org)	Multiple trials in progress
Chloroquine/ Hydroxychloroquine +/– azithromycin	Altered glycosylation of the angiotensin-converting enzyme 2 receptor [102, 108] Decreased viral entry due to impaired acidification of endosome [108, 109] Modulation of the host immune response	In vitro, chloroquine inhibits viral replication of multiple coronavirus strains, although the effect may be lost if the drug is added several hours post-infection [108, 110–113] Hydroxychloroquine inhibits severe acute respiratory syndrome coronavirus and MERS-CoV in vitro [114, 115]	A large observational study showed neither overall benefit nor harm [116]	FDA warns against use in unmonitored settings due to the potential for arrhythmias, especially with QT prolonging medications	Currently available for use in treating malaria and rheumatologic disorders Currently recommended to be administered only as part of a clinical trial due to lack of efficacy against severe acute respiratory syndrome coronavirus 2 in studies to date [117]

Updated 10 July 2020.

Abbreviations: FDA, US Food and Drug Administration; MERS-CoV, Middle East respiratory syndrome coronavirus.

Table 3. Unique Aspects of Pediatric Infection Prevention and Management for Children Known or Suspected of Having Coronavirus Disease 2019

	Ambulatory	Inpatient
Identify	Prescreen for symptoms prior to visit to assist with triage upon arrival Limit family members present Screen accompanying family members as well as patient Mask symptomatic, if not subject to universal masking Emphasize hand hygiene	Limit family members to essential caregivers Screen accompanying family members daily for symptoms and fever Universal masking Emphasize hand hygiene
Isolate	Isolate family in examination room with patient Limit activities in clinic to essential services Limit aerosol-generating procedures to those that are essential for care Healthcare workers to wear PPE including a fit-tested N95 respirator for aerosol-generating procedures Parents and patients aged >2 years to wear face coverings	Isolation based on symptom and diagnostic test result (if done) considering patient and essential parent Limit to asymptomatic essential caregiver(s), unless end-of-life care Healthcare workers to wear PPE including a fit-tested N95 respirator for aerosol-generating procedures Parents and patients aged >2 years to wear face coverings Asymptomatic caregiver may remove PPE in child's room but should replace with entrance of healthcare personnel Cancel congregate events and close or strictly limit access to family lounges
Inform	Query diagnostic testing status of patient and accompanying family members to assist with triage Place isolation status indicator on door of examination room Have PPE available exterior to room	Isolation status should consider both patient and symptoms of essential caregiver(s) Place isolation status indicator on door of patient's room Have PPE available exterior to room
Manage	Label and decorate PPE if decorations do not interfere with function	Utilize remote programing for: - Music and art therapy - Behavioral therapy - Hospital school programming - Child life therapy and instruction - Pet therapy Label and decorate PPE if decorations do not interfere with function

Abbreviation: PPE, personal protective equipment.

PREPAREDNESS AND COMMUNITY IMPACT

As part of the preparedness response, many pediatric healthcare entities have provided resources to adult healthcare systems, given the greater clinical impact of COVID-19 among adults. While the burden of clinical disease has been notably less in children, the psychosocial impact has been profound. Accustomed to socialization and interaction, children separated from their peer group have experienced the adverse effects of physical and social distancing manifest as depression, anxiety, and loss of developmental milestones. An estimated 188 countries imposed countrywide school closures that affected more than 1.5 billion children [123]. While a systematic review estimated that school closures may contribute a 2% to 4% reduction in COVID-19–associated deaths [124], emerging evidence supports the hypothesis that children are not the primary propagators of infection [125, 126] and that reopening schools provides an essential service to children and their communities [127]. The timing and extent of school reopening are multidisciplinary decisions that should consider local epidemiology and resources, while engaging pediatric infectious diseases clinicians. The CDC [128] and AAP [129] have developed guidance to assist policymakers with strategies to safely open schools by optimizing infection prevention and surveillance and developing inclusion and exclusion approaches in collaboration with local public health authorities.

In addition to disruption of their peer groups, some children may have 1, both, or all caregivers debilitated by illness, resulting in interruption of delivery of care. In many instances, preventive care, including immunization delivery, has been delayed [130].

Nonhospital institutional systems that house or provide care to children and adolescents may be adversely impacted by ill residents or staff. Many ambulatory group and chronic care facilities for children have been unable to continue operations due to their inability to comply with requirements related to social distancing in the provision of care [131], resulting in discontinuation of essential services. Transmission of SARS-CoV-2 at an overnight summer camp resulted in high attack rates among persons in all age groups. Asymptomatic infection potentially contributed to undetected transmission; the assessment of clinical impact is ongoing. Use of face coverings and other preventive strategies were not universal [132]. This report also questions the utility of preattendance, asymptomatic SARS-CoV-2 PCR testing, collected up to 12 days in advance of participation in a congregate activity.

CONCLUSIONS AND OPPORTUNITIES

As we learn more about the impact of SARS-CoV-2 on children, the adults who care for them, and the impact of management and containment strategies, questions related to the management of children during a pandemic have emerged (Table 4). While we gain a greater understanding of the clinical impact and epidemiology of SARS-CoV-2, we must continue to advocate

Table 4. Research Opportunities Related to Children and Coronavirus Disease 2019

Category	Question/Topic	Population	Approach
Epidemiology	Immunologic basis of relative sparing of younger children	Children of all ages	Collect serological data pre- and post-COVID-19; compare immunologic biomarkers in COVID-19 hospitalized, mildly asymptomatic, and asymptomatic children
Diagnostics	Understand the variable detection of viral nucleic acid from nasopharyngeal, oropharyngeal, nasal, and stool specimens in children	Children of all ages	Colonization studies of various sites correlated with clinical presentation and symptoms
Clinical manifestations	Understand the varying infectious and post-infectious clinical manifestations associated with infection, including multisystem inflammatory syndrome in children	Children of all ages; comparison with adults	Analyze registries assembled by compiling descriptive and epidemiologic data
Treatment	Engagement of children with their unique pathophysiology and limited severity in treatment and vaccine trials from the development stage	Older adolescents with progression to younger age groups	Enroll and engage older adolescents in early phase trials
Infection prevention	Role of asymptomatic or mildly symptomatic children in COVID-19 propagation in the population	Children of all ages	Household and community transmission studies; design vaccine trials with consideration of herd protection
Preparedness and impact	Understand the impact of social isolation and abrupt economic changes on physical and social development, food security, and behavioral health	Children of all ages	Compare cohorts of different ages and from different communities
	Distribute public health messaging, optimize engagement, and subsidize systems to optimize uptake of routine pediatric vaccines and monitor for disease outbreaks	Children all ages	Engage pediatric infectious disease clinicians with public health professionals in the assessment of immunization uptake; collaborate with clinicians to develop safe and effective outreach strategies to immunize children during the stages of pandemic response; engage the media in propagating productive messaging

Abbreviation: COVID-19, coronavirus disease 2019.

for the inclusion of children in clinical research, treatment, and prevention trials. Pediatric infectious diseases clinicians and researchers are uniquely poised to partner with pediatricians, health departments, and policymakers to develop guidance that incorporates the unique needs of children and the communities in which they reside.

Notes

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