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Managing COVID-19 disease in pediatric patients

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■ ABSTRACT

Children are less likely to be infected with SARS-CoV-2 than adults and often have a milder course of COVID-19 disease and a lower case fatality rate. Children account for an estimated 1% to 8% of those diagnosed with COVID-19. Even so, preschool-aged children, infants, and children with underlying health conditions may still be at risk for severe disease and complications. Unique aspects of COVID-19 presentation and disease course in children and possible vertical transmission to newborns from COVID-19–positive mothers are discussed.

■ WORLD EXPERIENCE WITH COVID-19 IN CHILDREN

Thus far, studies have shown that children are less likely to be infected with SARS-CoV-2 than adults and often have a milder course of COVID-19 disease and a lower case fatality rate. As of October 2020, children account for an estimated 1% to 8% of those diagnosed with COVID-19.¹ Children of preschool age, infants, and those with underlying health conditions may still be at risk for severe disease and complications.²

A large retrospective study of 2,135 confirmed or suspected COVID-19 cases in children reported to the Chinese Center for Disease Control and Prevention showed milder clinical manifestations in this population.³ Patients were classified as being asymptomatic (4.4%) or as having mild (51.0%), moderate (38.7%), severe (5.2%), or critical disease (0.6%) based on clinical features, laboratory testing, and imaging. Severe disease was defined as the presence of dyspnea, central cyanosis, and an oxygen saturation

of less than 92%. Critical disease was defined as the presence of acute respiratory distress syndrome, respiratory failure, or shock. Younger children were more at risk for severe illness than older children—half of the children with critical disease were less than 1 year old. There was no significant difference in cases between boys and girls.

Current morbidity data available in the United States as of October 2020, show that children make up 11.1% of all COVID-19 cases. Children were 1% to 3.5% of total reported hospitalizations and 0% to 0.2% of all COVID-19 deaths. The Centers for Disease Control (CDC) estimates that 45% of pediatric COVID-19 infections are asymptomatic.⁴

CDC morbidity and mortality data from February 12 – April 2, 2020, reported median age of patients was 11 years, and infants younger than 1 year of age made up 15% (398) of the pediatric cases at that time.⁵ Among the 184 (7.2%) children for whom exposure information was available, 168 (91%) were infected by a positive close contact within the household or community.⁵ Signs and symptoms of fever, cough, and shortness of breath were less commonly reported in children than in adults (56% vs 71%, 54% vs 80%, and 13% vs 43%, respectively). Among 345 pediatric patients with information on underlying comorbidities, 80 (23%) had at least 1 underlying health condition, most commonly chronic lung disease (including asthma), cardiovascular disease, or immunosuppression. This subset of patients and infants is more likely to require hospitalization, including intensive care.

This continues to remain the case as of September 2020. An analysis of clinical outcomes and trends in school-aged children in the United States from March 1 to September 19, 2020 demonstrated that incidence among adolescents 12 to 17 years was twice that of children aged 5 to 11 years (37.4 vs 19). Children with at least one underlying health condition

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were more likely to develop severe outcomes: hospitalized (16%), admitted to an intensive care unit (27%) or death (28%).⁶

Similarly to adults, data trends have also shown that racial and ethnic minorities have been disproportionately affected in the United States. Hispanic and non-Hispanic black children had higher cumulative rates of COVID-19 associated hospitalizations (16.4 and 10.5 per 100,000 respectively) than did non-Hispanic white children (2.1).⁷

There are reports from Europe and the United States of children and teenagers who developed a multisystem inflammatory condition with features similar to those of Kawasaki disease and toxic shock syndrome with temporal association to COVID-19, termed *Multisystem Inflammatory Syndrome in Children* (MIS-C).⁸ These patients typically require hospitalization and, at times, intensive care. Please refer to World Health Organization scientific brief on MIS-C related to COVID-19.

There are scarce data on children from Italy, Iran, and South Korea. One case series of 9 children from Iran reported a high probability of direct transmission from a family member.⁹ All children presented with fever and respiratory symptoms such as cough, tachypnea, and chest wall retractions. None presented with gastrointestinal symptoms. This case series reported an overall good prognosis of COVID-19 in children. Similarly, case reports from South Korea of children with COVID-19–positive familial close contacts reported no critical complications or mortality in pediatric patients.¹⁰

It is also important to note that COVID-19 diagnoses in children may be underreported due to varying testing prioritization as well as cases being largely asymptomatic or with mild symptoms at the time of presentation.

■ UNIQUE ASPECTS OF COVID-19 PRESENTATION AND COURSE IN CHILDREN

Signs and symptoms in children are usually less severe than those in adults and are similar to those seen with respiratory tract infections, including fever, cough, shortness of breath, and pharyngeal erythema.⁷ Although gastrointestinal symptoms have been described in adult patients, diarrhea and vomiting are less commonly reported in children.^{2,5,11}

One anecdotal report described pernio-like lesions or acro-ischemic lesions on the toes and sometimes on the fingers of asymptomatic older children.¹² These round, painful lesions were a few millimeters in size with a clear demarcation at the metatarsal-

phalangeal level. The lesions can initially have a reddish-purple color and become bullous, black, or both over the ensuing weeks.

Coinfection with other respiratory pathogens has been described in children with COVID-19 (eg, influenza, mycoplasma, respiratory syncytial virus, and cytomegalovirus), and providers should consider these when ordering tests. During winter and influenza season it is recommended that children who are tested for COVID-19 generally also be tested for influenza as the clinical symptoms overlap.¹³ Results of chest radiography are usually normal in pediatric patients or may show patchy infiltrates similar to that seen with viral pneumonias. Computed tomography scans generally show unilateral or bilateral subpleural ground-glass opacities and consolidations with surrounding halo sign. The consolidation with surrounding halo sign was seen in 50% of pediatric patients in 1 study and is a unique finding described in children with COVID-19.¹⁴

Laboratory findings vary. In one study of 20 pediatric cases,¹⁴ the white blood cell count was normal in 14 patients and lymphopenia (< 45% of lymphocyte) was noted in 7 patients. Procalcitonin levels were elevated (> 0.05 mg/L) in 16 patients whereas C-reactive protein levels were elevated (> 3 mg/L) in 7 patients. Only 5 patients had elevated levels of transaminase (> 40 IU/L) and creatine-kinase myocardial band (CK-MB > 25 IU/L).

A meta-analysis of laboratory findings in 66 pediatric patients aged 2 weeks to 17 years also reported that most had normal leukocyte counts (69.6%), neutrophil counts (89.4%), and normal C-reactive protein (86.4%) and procalcitonin (89.4%) levels.¹⁵ Only 2 infants had lymphopenia (3%).

The reasons why children are not as severely ill as adults when infected with COVID-19 are largely unknown, but there are multiple theories. First, children are generally well taken care of by caregivers and, hence, may have a smaller chance of being exposed to the pathogen itself. Second, it is possible that children have higher levels of antibodies against viruses due to higher rates of respiratory infections during winter. Third, their immune systems are less mature than those of adults, which may lead to a less robust cytokine response to the pathogen. Finally, the binding ability of angiotensin converting enzyme II—which is a known cell receptor for COVID-19—is reduced in children.^{3,16}

Because most pediatric cases are mild, treatment with supportive care is usually sufficient. As of October 22, 2020, the US Food and Drug Administration

(FDA) has approved only the use of remdesivir, an antiviral agent, in children 12 and older weighing at least 40 kg to treat COVID-19. For those hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or children younger than 12 who weigh at least 3.5 kg, the drug may still be used under an emergency use authorization. Clinical trials in this patient population are still ongoing.¹⁷ The National Institutes of Health has also suggested that dexamethasone may be beneficial in pediatric patients with COVID-19 infection on mechanical ventilation based on adult data however additional pediatric studies are needed.¹⁸

Although most manifestations of COVID-19 in children are benign and self-limiting, there have been increasing reports of a small subset of older children and young adults with multisystem inflammatory syndrome, which emphasizes the need to detect and report these cases early as they are often sick and require intensive care with a multidisciplinary approach. Please see the World Health Organization commentary on MIS-C for full diagnostic criteria and treatment guidelines.⁸

Given our current knowledge of COVID-19 infection in children — that they are more likely to be asymptomatic or have mild clinical presentation — there is growing evidence and studies into the role children play on transmission of the infection. This is especially important at this time in the United States with school re-entry and creation of re-opening policies. There are few studies currently that suggest children younger than 10 may be less likely to be infected and less likely to spread infection to others, while those older than 10 may spread the virus as efficiently as adults.^{19,20} However further in-depth studies are needed.

■ IS THERE A RISK OF VERTICAL TRANSMISSION?

A few studies (case reports and series) have described possible vertical transmission to newborns from COVID-19–positive mothers. Of 33 neonates delivered at Wuhan Children's Hospital to COVID-19–positive mothers, 3 (9%) were clinically symptomatic and tested positive via nasopharyngeal and anal swabs at day 2 of life.²¹ Strict infection prevention procedures were followed during delivery and, thus, vertical transmission was suspected.

Another series from China reported elevated IgM antibody and cytokine levels at birth in infants born to COVID-19–positive mothers. The infants remained asymptomatic and tested negative via nasopharyngeal swab and serum PCR.²²

A study from China retrospectively reviewed 9 pregnant women with COVID-19 nasopharyngeal swab-positive disease who gave birth and reported negative viral detection in cord blood, placental tissue, serum, vaginal mucus, amniotic fluid, and breast milk,^{23,24} providing evidence against vertical transmission.

Even though overall vertical transmission seems less likely due to low viremia rates, leading to a small chance of placental seeding, all studies are limited by their small sample sizes. Further studies are needed to better understand the risk of perinatal transmission.

To date, there is no clear evidence of intrauterine vertical transmission. However, there is a plausible risk of infection occurring during and after delivery. The US Centers for Disease Control and Prevention and the American Academy of Pediatrics currently recommend that newborns born to COVID-19–positive mothers or those who are suspected to be positive should be considered persons under investigation and tested using nasal and throat swabs via molecular assays at 24 hours of age and again at 48 hours if they are still in the care facility.²⁵

Current recommendations regarding room-in practices have changed based on National Perinatal COVID-19 Registry. Among the over 3000 mother-infant dyads the likelihood that an infant has a positive COVID-19 PCR test was similar for infants separated from their mothers and for those who room-in with mothers using appropriate infection prevention measures. Mothers and newborns may now room-in according to usual center practice. Mothers should maintain a reasonable distance from the infant when possible and wear a mask and perform hand hygiene when providing hands on care and breastfeeding. Use of an isolette may be an added measure of protection from respiratory droplets.²⁰

The American Academy of Pediatrics strongly supports breastfeeding and no studies have detected viable infectious virus particles in breast milk. It is not established whether protective antibody is found in breast milk.^{23,24,25} After discharge, COVID-19–positive mothers are encouraged to maintain a 6-foot distance from their newborn infants, as possible, and use proper hand hygiene and masks while providing care to their newborn until they are afebrile for 72 hours and 7 days out from symptom onset.²⁵ Providers should continue optimal newborn care and prioritize immunizations of infants and young children, after discharge, while following measures of social distancing.²⁶

VISITORS IN HEALTHCARE SETTINGS

Many pediatric healthcare systems, including Cleveland Clinic Children's Hospital, have instituted strict visitor restrictions to both inpatient and outpatient locations. Many limit visitors to 1 parent each day during the hospital stay (except for end-of-life situations), visitors are screened and temperature taken prior to entering the facilities. All visitors are encouraged to wear cloth masks at all times, respect social distancing, and practice hand hygiene. If visitors are for patients with COVID-19, they are typically required to wear personal protective equipment.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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