Special Considerations in Children

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Key Considerations

| SARS-CoV-2 infection is generally milder in children than in adults, and a substantial proportion of children with the infection are asymptomatic. |
| Most nonhospitalized children with COVID-19 will not require any specific therapy. |
| Observational studies describe associations between severe COVID-19 and the presence of ≥1 comorbid conditions, including cardiac disease, neurologic disorders, prematurity (in young infants), diabetes, obesity (particularly severe obesity), chronic lung disease, feeding tube dependence, and immunocompromised status. Age (<1 year and 10–14 years) and non-White race/ethnicity are also associated with severe disease. |
| Most children hospitalized for severe COVID-19 have not been fully vaccinated or are not eligible for COVID-19 vaccination. |
| Data on the pathogenesis and clinical spectrum of SARS-CoV-2 infection are more limited for children than for adults. |
| Vertical transmission of SARS-CoV-2 appears to be rare, but suspected or probable cases of vertical transmission have been described. |
| A small subset of children and young adults with SARS-CoV-2 infection may develop multisystem inflammatory syndrome in children (MIS-C). Many patients with MIS-C require intensive care management. The majority of children with MIS-C do not have underlying comorbid conditions. |
| Data on the prevalence of post-COVID conditions in children are limited but suggest that younger children may have fewer persistent symptoms than older children and adults. |

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = One or more randomized trials without major limitations; Ila = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

This section provides an overview of the epidemiology and clinical spectrum of disease, including COVID-19, multisystem inflammatory syndrome in children (MIS-C), and post-COVID conditions. This section also includes information on risk factors for severe COVID-19, vertical transmission, and infants born to a birth parent with SARS-CoV-2 infection. Throughout this section, COVID-19 refers to the acute, primarily respiratory illness due to infection with SARS-CoV-2. MIS-C refers to the postinfectious inflammatory condition.

For information on the prevention, treatment, and management of severe complications of COVID-19 in children, see:

- Prevention of SARS-CoV-2 Infection
- Therapeutic Management of Hospitalized Children With COVID-19
- Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A])
- Introduction to Critical Care Management of Children With COVID-19

Epidemiology

Data from the Centers for Disease Control and Prevention (CDC) demonstrate that SARS-CoV-2 infection and severe disease and death due to COVID-19 occur less often in children than in adults.1-4
However, the true burden of pediatric SARS-CoV-2 infection remains unclear, as children with mild symptoms are seldom systematically tested, and contact tracing and seroprevalence studies are not generally conducted. Seroprevalence data have suggested that, as of mid-2021, most children did not have evidence of prior SARS-CoV-2 infection. However, among children and adolescents, the estimated number of SARS-CoV-2 infections that occurred through May 2021 was 4.7 to 8.9 times greater than the number of COVID-19 cases. In a report from the CDC, by February 2022, approximately 75% of children and adolescents had serologic evidence of prior SARS-CoV-2 infection.

Data on the pathogenesis and disease severity of SARS-CoV-2 infection in children are increasing but are still limited compared to the adult data. Although only a small percentage of children with COVID-19 will require medical attention, the percentage of intensive care unit (ICU) admissions among hospitalized children is comparable to that for hospitalized adults with COVID-19.

Children from some racial and ethnic groups experience disproportionate rates of COVID-19-related hospitalization, which may be a result of barriers to accessing health care and economic and structural inequities. From 2020 to 2021, Black/African American children with COVID-19 in the United States were 2 times more likely to be hospitalized and 5 times more likely to be admitted to the ICU than White children.

A U.S. study of children with COVID-19 who were hospitalized between April and September 2020 reported an association between race/ethnicity and disease severity. In a large United Kingdom study, admission to critical care was independently associated with hospitalized children who self-reported as being of Black ethnicity. A study in England reported that children who identified as Asian were more likely than children who identified as White to be hospitalized for COVID-19 and to be admitted to an ICU. The study also found that children who identified as Black or as mixed or other races/ethnicities had significantly more hospitalizations than children who identified as White.

**Clinical Manifestations of COVID-19**

The signs and symptoms of SARS-CoV-2 infection in symptomatic children may be similar to those in adults; however, a greater proportion of children may be asymptomatic or have only mild illness when compared with adults. Although the true incidence of asymptomatic SARS-CoV-2 infection is unknown, a small study reported that 45% of children who underwent surveillance testing at the time of hospitalization for a non-COVID-19 indication had asymptomatic infection. The most common signs and symptoms of COVID-19 in hospitalized children are fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms. The signs and symptoms of COVID-19 may overlap significantly with those of influenza and other respiratory and enteric viral infections. Critical disease, including respiratory failure, acute respiratory distress syndrome, and, less commonly, shock, may occur in children with COVID-19. The overall incidence of SARS-CoV-2 infection and, by extension, COVID-19-related hospitalizations among children has increased substantially with the emergence of recent variants of concern (VOCs), particularly Omicron.

**Risk Factors for Severe COVID-19**

Risk factors for severe COVID-19 identified by observational studies and meta-analyses include having ≥1 comorbidities, such as cardiac disease, neurologic disorders, prematurity (in young infants), diabetes, obesity (particularly severe obesity), chronic lung disease, feeding tube dependence, and immunocompromised status. Demographic factors, such as age (<1 year and 10–14 years) and non-White race/ethnicity, have also been associated with severe disease. However, many studies did not assess the relative severity of underlying medical conditions.

Many published studies reported an increased relative risk of severe disease in children with
comorbidities, but the absolute risk of severe COVID-19 among children remains low. However, protocolized admissions for certain populations (e.g., febrile young infants) may confound the association between comorbid conditions and severe COVID-19. Most children who have been hospitalized for severe COVID-19 have not been fully vaccinated—many were not eligible for COVID-19 vaccination because of their age. The CDC has additional information on the underlying conditions that are risk factors for severe COVID-19.

The children most likely to benefit from treatment are nonhospitalized patients with mild to moderate COVID-19 who are at the highest risk for severe COVID-19 (e.g., those with severe comorbidities). For a description of children considered at high risk for severe COVID-19 and the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations for their treatment, see Therapeutic Management of Hospitalized Children With COVID-19.

Age
Among all children, infants and adolescents have the highest risk of COVID-19-related ICU admission or death. From March 2020 to mid-August 2021, U.S. children aged <5 years had the highest cumulative COVID-19-related hospitalization rates, followed closely by adolescents.27 Children aged 5 to 11 years had the lowest hospitalization rates. From July to August 2021, when the Delta variant was the dominant VOC, 25% of 713 children admitted to 6 U.S. hospitals were aged <1 year, 17% were aged 1 to 4 years, 20% were aged 5 to 11 years, and 38% were aged 12 to 17 years.28 From March 2020 to mid-June 2021, 26.5% of 3,116 U.S. children hospitalized for COVID-19 were admitted to an ICU.27

An individual patient data meta-analysis reported that patients aged <1 year and those aged 10 to 14 years had the highest risks of ICU admission and death among hospitalized children with COVID-19.20 Another meta-analysis reported that neonates, but not infants aged 1 to 3 months, had an increased risk of severe COVID-19 compared with other pediatric age groups.30 When Omicron was the dominant circulating VOC, hospitalization rates among children and adolescents were higher than when the Delta VOC was dominant, and they were highest for children aged <5 years.26,31 However, the proportion of hospitalized children requiring ICU admission was significantly lower when the Omicron VOC was dominant.

Comorbidities
Several chronic conditions are prevalent in hospitalized children with COVID-19. When the Delta variant was the dominant VOC in the United States, 68% of hospitalized children had ≥1 underlying medical condition, such as obesity (32%), asthma or reactive airway disease (16%), or feeding tube dependence (8%). Obesity was present in approximately a third of hospitalized children aged 5 to 11 years, 60% of whom had a body mass index (BMI) ≥120% of the 95th percentile. For adolescents, 61% had obesity; of those patients, 61% had a BMI ≥120% of the 95th percentile.28

Meta-analyses and observational studies identified risk factors for ICU admission, mechanical ventilation, or death among hospitalized children with COVID-19.30,32,33 These risk factors included prematurity in young infants, obesity, diabetes, chronic lung disease, cardiac disease, neurologic disease, and immunocompromising conditions. Another study found that having a complex chronic condition that affected ≥2 body systems or having a progressive chronic condition or continuous dependence on technology for ≥6 months (e.g., dialysis, tracheostomy with ventilator assistance) was significantly associated with an increased risk of moderate or severe COVID-19.34 The study also found that having more severe chronic disease (e.g., active cancer treated within the previous 3 months or asthma with hospitalization within the previous 12 months), when compared with less severe conditions, increased the risk of critical COVID-19 or death. The CDC has additional information on the underlying
conditions that are risk factors for severe COVID-19.

Having multiple comorbidities increases the risk of severe COVID-19 in children. A meta-analysis of data from children hospitalized with COVID-19 found that the risk of ICU admission was greater for children with 1 chronic condition than for those with no comorbid conditions, and the risk increased substantially as the number of comorbidities increased.29

**COVID-19 Vaccination Status**

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. Most children hospitalized for COVID-19 were not fully vaccinated or were not eligible to receive COVID-19 vaccination because of their age.16,18,28,35 With the wider availability of COVID-19 vaccines for younger children, the number of COVID-19 cases among children may decrease over time.

**Mortality**

Death from COVID-19 is uncommon in children. Risk factors for death include having chronic conditions, such as neurologic or cardiac disease, and having multiple comorbidities. Among children aged <21 years in the United States, deaths associated with COVID-19 have been higher for children aged 10 to 20 years, especially for young adults aged 18 to 20 years, and for those who identify as Hispanic, Black, or American Indian/Alaskan Native.36,37

A systematic review and meta-analysis reported that neurologic or cardiac comorbidities were associated with the greatest increase in risk of death among hospitalized children with COVID-19.29 In the same study, an individual patient data meta-analysis reported that the risk of COVID-19-related death was greater for children with 1 chronic condition than for those with no comorbid conditions, and the risk increased substantially as the number of comorbidities increased.

**Vertical Transmission and Infants Born to People With SARS-CoV-2 Infection**

A systematic review and meta-analysis reported that confirmed vertical transmission of SARS-CoV-2 appears to be rare, and severe maternal COVID-19 has been associated with SARS-CoV-2 infection in babies.38 In two large, combined cohorts of pregnant individuals from the United States and United Kingdom, SARS-CoV-2 infection was reported in 1.8% and 2% of the babies born to people with SARS-CoV-2 infection.39

Case reports have described intrauterine fetal demise during the third trimester of pregnancy in individuals with mild COVID-19 due to infection with the Delta VOC.40,41 These individuals had evidence of placental SARS-CoV-2 infection, placental malperfusion, and placental inflammation. One case report described a person with asymptomatic SARS-CoV-2 infection and severe preeclampsia who gave birth at 25 weeks of gestation by emergency cesarean delivery. The neonate died on Day 4, and evidence of SARS-CoV-2 infection was found in placental tissues and in the infant’s lungs and vascular endothelium at autopsy.42 Evidence of placental SARS-CoV-2 infection was reported in 5 stillbirths and for 1 live-born neonate in Sweden.43

A systematic review of neonatal SARS-CoV-2 infections reported that 70% were due to postpartum transmission, and 30% were due to vertical transmission from an infected birth parent.44 Another systematic review reported that newborn infants rooming-in with the birth parent did not have an increased risk of SARS-CoV-2 transmission when compared with newborns who were isolated from the birth parent.45

Detection of SARS-CoV-2 RNA in the breast milk of individuals with confirmed cases of COVID-19 is
very uncommon.\textsuperscript{46} Currently, there is no evidence of SARS-CoV-2 transmission through breast milk.\textsuperscript{47} Breast milk from people with SARS-CoV-2 infection can contain antibodies to SARS-CoV-2.\textsuperscript{48,49}

**Multisystem Inflammatory Syndrome in Children**

A small subset of children and young adults with SARS-CoV-2 infection, including those with asymptomatic infection, may develop MIS-C. This syndrome is also called pediatric multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 (PMIS-TS). Although the case definitions for these syndromes differ slightly, they are likely the same disease. The syndrome was first described in Europe, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified as having current or recent infection with SARS-CoV-2.

The clinical spectrum of MIS-C has been described in the United States and is similar to that described for PMIS-TS. MIS-C is consistent with a postinfectious inflammatory syndrome related to SARS-CoV-2.\textsuperscript{50,51} Most patients with MIS-C have serologic evidence of previous SARS-CoV-2 infection, but only a minority have had a positive reverse transcription polymerase chain reaction (RT-PCR) result for SARS-CoV-2 at presentation.\textsuperscript{52,53}

The peak population-based incidence of MIS-C lags about 4 weeks behind the peak of acute pediatric COVID-19-related hospitalizations. Emerging data suggests that adults may develop a similar syndrome, multisystem inflammatory syndrome in adults (MIS-A), although it is not clear if this postinfectious complication is similar to MIS-C.\textsuperscript{52-54} Published data that characterize the condition are limited.

Although risk factors for the development of MIS-C have not been established, an analysis of MIS-C cases in the United States found that ICU admission was more likely for patients aged 6 to 12 years than for younger children, and it was more likely for children who identified as non-Hispanic Black than for those who identified as non-Hispanic White.\textsuperscript{55} Unlike most children who present with severe COVID-19, the majority of children who present with MIS-C do not seem to have common underlying comorbid conditions other than obesity.\textsuperscript{55} In addition, children whose deaths were related to MIS-C were less likely to have underlying medical conditions than children who died of COVID-19.\textsuperscript{37}

Emerging evidence suggests that COVID-19 vaccination protects against the development of MIS-C.\textsuperscript{56,57} The development of MIS-C after COVID-19 vaccination is very rare.\textsuperscript{56,58}

**Clinical Manifestations of Multisystem Inflammatory Syndrome in Children**

The current CDC case definition for MIS-C is an individual aged <21 years who:

- Presents with fever,\textsuperscript{a} laboratory evidence of inflammation,\textsuperscript{b} and evidence of clinically severe illness requiring hospitalization, with multisystem (i.e., >2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); and
- Has no alternative plausible diagnoses; and
- Is positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or serology results; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.\textsuperscript{59}

\textsuperscript{a} Fever >38.0°C for $\geq$ 24 hours or report of subjective fever lasting $\geq$ 24 hours

\textsuperscript{b} Including, but not limited to, $\geq$ 1 of the following: elevated levels of C-reactive protein, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin (IL)-6; an elevated erythrocyte sedimentation rate or neutrophil count; or a reduced lymphocyte count or albumin level

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but the presence of persistent fever, multisystem manifestations, and laboratory abnormalities could help early recognition.\textsuperscript{60} The clinical spectrum of hospitalized cases has included younger children with
mucocutaneous manifestations that overlap with Kawasaki disease, older children with more multiorgan involvement and shock, and patients with respiratory manifestations that overlap with COVID-19.

Patients with MIS-C are often critically ill, and up to 80% of children require ICU admission. Most patients with MIS-C have markers of cardiac injury or dysfunction, including elevated levels of troponin and brain natriuretic protein; higher levels of these markers are associated with ICU admission, myocardial dysfunction, and shock. In these cases, echocardiographic findings may include impaired left ventricular function, coronary artery dilations, and, rarely, coronary artery aneurysms. The reported mortality in the United States for hospitalized children with MIS-C is 1% to 2%. Longitudinal studies to examine the long-term sequelae of MIS-C are currently ongoing.

The pathogenesis of MIS-C is still being elucidated and may include distinct humoral immune responses, innate immune activation, or a superantigen effect. Differences between MIS-C and typical Kawasaki disease have been demonstrated in terms of epidemiology, cytopenias, cytokine expression, and elevation of inflammatory markers. Immunologic profiling has also shown differences in cytokine expression (tumor necrosis factor alpha and IL-10) between MIS-C and COVID-19 in children.

For the Panel’s recommendations on the treatment of MIS-C, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

Post-COVID Conditions

Persistent symptoms after COVID-19 have been described in adults and are an active area of research in children, although data on the incidence of post-COVID sequelae in children are limited and somewhat conflicting (see Clinical Spectrum of SARS-CoV-2 Infection). Cardiac imaging studies have described myocardial injury in young athletes who had only mild disease; additional studies are needed to identify long-term cardiac sequelae.

The reported clinical manifestations and duration of post-COVID conditions in children are highly variable. Not all studies included controls without SARS-CoV-2 infection, which makes determining the true incidence a challenge. The incidence of post-COVID symptoms appears to increase with age. The most common symptoms reported include persistent fatigue, headache, shortness of breath, sleep disturbances, and altered sense of smell.

Among children, health care utilization increases following COVID-19. A Norwegian study of 10,279 children with and 275,859 without SARS-CoV-2 infection reported that primary care visits for children aged 6 to 15 years increased for up to 3 months after a positive SARS-CoV-2 test result when compared with controls. For preschool-age children, visits increased for up to 6 months.

In a study of 6,804 adolescents in England, 30% of the 3,065 participants who tested positive for SARS-CoV-2 infection reported ≥3 symptoms at a 3-month follow-up visit. Common symptoms included tiredness (39%), headache (23%), and shortness of breath (23%). In the same study, only 16% of the 3,739 participants who tested negative for SARS-CoV-2 infection reported ≥3 symptoms at the 3-month follow-up visit.

A study in Denmark examined persistent symptoms among 16,836 children with and 16,620 children without SARS-CoV-2 infection. The number of children with SARS-CoV-2 infection who reported symptoms that persisted for >4 weeks increased as age increased. Among the preschool-age children, more children in the control arm than in the SARS-CoV-2 arm reported experiencing symptoms that persisted for >4 weeks.
Additional research is needed to define the incidence, spectrum, and severity of post-COVID conditions in children and to identify optimal strategies for prevention, diagnosis, and treatment of those conditions.

References


