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. • Children with ≥1 of the following comorbidities are at increased risk of severe COVID-19: 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. • 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. • 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 comorbidities. • 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.
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

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. It 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, the term "COVID-19" refers to the acute, primarily respiratory illness due to infection with SARS-CoV-2. MIS-C refers to the postinfectious inflammatory condition.

Epidemiology

Data from the Centers for Disease Control and Prevention (CDC) demonstrate that severe disease and death due to COVID-19 occur less often in children than in adults.[1-4] However, weekly hospitalization rates for children aged <6 months are high, exceeded only by the rates for adults aged ≥75 years.[5] The overall incidence of SARS-CoV-2 infection and, by extension, COVID-19–related hospitalizations among children increased substantially with the emergence of newer variants, particularly the Omicron variant and its subvariants.[6,7] According to the CDC, by December 2022, an estimated 96% of children and adolescents had serologic evidence of prior SARS-CoV-2 infection.[8] The high infection rate among children makes the overall burden substantial despite the low rate of severe outcomes.[9]

Data on the pathogenesis and clinical spectrum of SARS-CoV-2 infection in children are still limited compared to the data for adults. 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.[6,10-18]

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.[19]

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.[20] In a large United Kingdom study, admission to critical care was independently associated with hospitalized children who self-reported as being of Black ethnicity.[15] 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.[21] 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 are 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.[22] The most common signs and symptoms of COVID-19 in hospitalized children are fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms.[15,23] 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.[24,25] For more information, see Therapeutic Management of Hospitalized Children With COVID-19 and Introduction to Critical Care Management of Children With COVID-19.

Risk Factors for Severe COVID-19

Observational studies and meta-analyses have found that children with certain comorbidities are at increased risk of severe COVID-19. These comorbidities include cardiac disease, neurologic disorders, prematurity (in young infants), diabetes, obesity (particularly severe obesity), chronic lung disease, feeding tube dependence, and immunocompromised status.[26-29] Demographic factors, such as age (<1 year and 10–14 years)[30] and non-White race/ethnicity,[15,19-21] have also been associated with severe disease. However, many studies did not assess the relative severity of underlying medical conditions in children with severe COVID-19.

Many published studies reported an increased relative risk of severe disease in children with comorbidities,[20,26-30] but the overall risk of severe COVID-19 among children remains low. Protocolized admissions for certain populations (e.g., febrile young infants) may confound the association between comorbidities and severe COVID-19. However, nearly half of the children aged 8 months to <5 years who were hospitalized for COVID-19 from September 20, 2022, to May 31, 2023, were previously healthy.[31] Most children who have been hospitalized for severe COVID-19 have not been fully vaccinated, as many were not eligible for COVID-19 vaccination because of their age when the studies were conducted.[5] The CDC has additional information on the underlying conditions that are risk factors for severe COVID-19.

The risk of severe disease is an important factor to consider when making treatment decisions for children with COVID-19. The children most likely to benefit from antiviral treatment are those who are nonhospitalized, have mild to moderate COVID-19, and are at the highest risk of severe COVID-19 (e.g., those with severe comorbidities). For a description of children who are considered at high risk of severe COVID-19 and for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for their treatment, see Therapeutic Management of Nonhospitalized Children With COVID-19.

Age

Among all children, infants and adolescents have the highest risk of COVID-19–related hospitalization, 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.[32] Children aged 5 to 11 years had the lowest hospitalization rates. From July to August 2021, when the Delta variant was the dominant variant, 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.[26] From March 2020 to mid-June 2021, 26.5% of 3,116 U.S. children hospitalized for COVID-19 were admitted to an ICU.[32] In 2023, children aged <6 months had the highest weekly COVID-19–related pediatric hospitalization rates.[5]

A meta-analysis of individual patient data showed that among hospitalized children with COVID-19, patients aged <1 year and those aged 10 to 14 years had the highest risks of ICU admission and death.[30] In another meta-analysis, neonates had an increased risk of severe COVID-19 when compared with other pediatric age groups, but infants aged 1 to 3 months did not.[27] When the original Omicron variant was the dominant circulating variant, children and adolescents had higher hospitalization rates than they did when the Delta variant was dominant, and children aged <5 years had the highest rates.[7,33] However, the proportion of hospitalized children who required ICU admission was significantly lower when the original Omicron variant was dominant.

Comorbidities

Several chronic conditions are prevalent in hospitalized children with COVID-19. When the Delta variant was the dominant variant in the United States, 68% of hospitalized children had ≥1 underlying medical conditions, such as obesity (32%), asthma or reactive airway disease (16%), or feeding tube dependence (8%).[26] Obesity was present in approximately a third of hospitalized children aged 5 to 11 years, 60% of whom had severe obesity (i.e., 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.

Meta-analyses and observational studies identified risk factors for ICU admission, mechanical ventilation, or death among hospitalized children with COVID-19.[27-29] 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 children with more severe chronic diseases (e.g., active cancer treated within the previous 3 months or asthma with hospitalization within the previous 12 months) had a higher risk of critical COVID-19 or death than those with less severe conditions. 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 comorbidities, and the risk increased substantially as the number of comorbidities increased.[30]

COVID-19 Vaccination

Staying up to date with COVID-19 vaccinations remains the most effective way to prevent severe COVID-19. See the CDC webpages Stay Up to Date With COVID-19 Vaccines and Use of COVID-19 Vaccines in the United States for more information on COVID-19 vaccination schedules. Estimates of

vaccine effectiveness vary by age group and time period. From July 2022 to September 2023 (when Omicron subvariants were dominant in the United States), 86% of vaccine-eligible U.S. children aged 6 months to <5 years who were hospitalized or sought care for acute respiratory illness in emergency departments had not received any COVID-19 vaccines.[35] Two or more doses of COVID-19 vaccine were 40% effective in preventing emergency department visits or hospitalization due to COVID-19 in children aged <5 years compared with unvaccinated children. In a study of U.S. children aged 8 months to <5 years who were hospitalized for COVID-19 from September 20, 2022, to May 31, 2023, only 4.5% had completed a primary COVID-19 vaccine series.[31]

The estimates for vaccine effectiveness against severe COVID-19 in adolescents aged 12 to 18 years exceeded 90% while Delta was the dominant variant in the United States.[36,37] When Omicron was the dominant variant, vaccine effectiveness against hospitalization for noncritical COVID-19 was 20% in adolescents; vaccine effectiveness against critical illness was 79% in these patients.[37] In children aged 5 to 11 years, vaccine effectiveness against hospitalization was more variable, with an estimated effectiveness of 68% after Omicron became the dominant variant in the United States.

A meta-analysis of COVID-19 vaccination in adolescents aged 12 to 17 years reported a vaccine effectiveness of 88% against severe disease and 35% against nonsevere COVID-19.[38] An Italian study estimated that vaccine effectiveness was 38% in children aged 5 to 11 years during the Omicron period.[39] A Canadian study reported that the effectiveness of 2 doses of COVID-19 vaccine against symptomatic COVID-19 in children aged 5 to 11 years varied widely.[40] Vaccine effectiveness decreased over time after the last dose and decreased against Omicron subvariants that were antigenically distinct from the vaccine. See Prevention of SARS-CoV-2 Infection for more information about COVID-19 vaccines.

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, the number of deaths associated with COVID-19 has 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.[41,42]

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.[30] In the same study, an individual patient data meta-analysis found that the risk of death related to COVID-19 was greater for children with 1 chronic condition than for those with no comorbidities, and the risk increased substantially as the number of comorbidities increased.

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

Systematic reviews and meta-analyses have reported that confirmed vertical transmission of SARS-CoV-2 appears to be rare, but severe maternal COVID-19 has been associated with SARS-CoV-2 infection in babies.[43] In 2 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.[44] A systematic review and meta-analysis of prospective observational studies from high-income countries estimated that the frequency of SARS-CoV-2 infection in infants born to people with SARS-CoV-2 infection was 2.3%.[45]

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 variant.[46,47] 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.[48] Evidence of placental SARS-CoV-2 infection was reported in 5 stillbirths and for a live-born neonate in Sweden.[49]

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 the infected birth parent.[50] Two systematic reviews reported that newborn infants rooming-in with an infected birth parent did not have an increased risk of SARS-CoV-2 transmission when compared with newborns who were isolated from the birth parent.[45,51]

Detection of SARS-CoV-2 RNA in the breast milk of individuals with confirmed cases of COVID-19 is very uncommon.[52] Currently, there is no evidence of SARS-CoV-2 transmission through breast milk.[53] Breast milk from people with SARS-CoV-2 infection can contain antibodies to SARS-CoV-2.[54-56] For information regarding the safety of feeding infants breast milk from individuals who are receiving treatment for COVID-19, see Pregnancy, Lactation, and COVID-19 Therapeutics.

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 inflammatory multisystem syndrome—temporally associated with SARS-CoV-2 (PIMS-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 features similar to Kawasaki disease were identified as having current or recent infection with SARS-CoV-2.[57,58] Subsequently, children with MIS-C were identified in the United States and in many other locations outside of Europe.[59] 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.[60,61] The peak, population-based incidence of MIS-C lags about 4 weeks behind the peak of acute pediatric COVID-19–related hospitalizations.

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.[62] 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 comorbidities other than obesity.[62] 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.[42]

Several studies have suggested that COVID-19 vaccination protects against the development of MIS-C.[63-65] Following the emergence of the Omicron variant, the incidence of MIS-C and the clinical severity of MIS-C have declined.[66-70] This decline may be a result of several factors. For example, more children have now received COVID-19 vaccines and have had infection with SARS-CoV-2, which may provide some protection against MIS-C.

Clinical Manifestations of Multisystem Inflammatory Syndrome in Children

The CDC and the Council of State and Territorial Epidemiologists (CSTE) issued an updated case definition for MIS-C on January 1, 2023.[71] The 2023 CSTE/CDC Surveillance Case Definition for MIS-C is an individual aged <21 years who:

- Presents with fever,[a] laboratory evidence of inflammation,[b] and illness with a clinical severity that

requires hospitalization or results in death, with new-onset clinical manifestations in ≥2 categories (i.e., cardiac, shock, hematologic, gastrointestinal, dermatologic)[c]; *and* does not have a more likely alternative diagnosis; *and*

- Has a positive viral test result from a molecular test that detects SARS-CoV-2 RNA or a SARS-CoV-2 antigen test up to 60 days prior to or during hospitalization or in a postmortem specimen; *or*
- Has a positive viral test result from a test that detects SARS-CoV-2–specific antibodies associated with current illness; *or*
- Has a close contact with a confirmed or probable case of COVID-19 in the 60 days prior to hospitalization; *or*

- Has a death certificate that lists MIS-C as an underlying cause of death or a significant condition contributing to death.

[a] Subjective or documented fever ≥38.0°C.
[b] C-reactive protein level ≥3.0 mg/dL (30 mg/L).
[c] See Table A for a list of categories for these organ manifestations.

Table A. Clinical Manifestation Criteria for the 2023 CSTE/CDC MIS-C Surveillance Case Definition

Clinical Manifestation	Criteria
Cardiac Involvement	• Left ventricular ejection fraction <55% • Coronary artery dilatation, aneurysm, or ectasia • Troponin levels elevated above laboratory normal range or indicated as elevated in a clinical note
Shock	• Clinician diagnosis, as documented in clinical note
Hematologic Involvement	• Thrombocytopenia (i.e., platelet count <150,000 cells/μL) • Lymphopenia (i.e., absolute lymphocyte count <1,000 cells/μL)
Gastrointestinal Involvement	• Abdominal pain • Vomiting • Diarrhea
Dermatologic/Mucocutaneous Involvement	• Rash • Inflammation of the oral mucosa • Conjunctivitis or conjunctival injection • Extremity findings (e.g., erythema, edema)

Key: CDC = Centers for Disease Control and Prevention; CSTE = Council of State and Territorial Epidemiologists; MIS-C = multisystem inflammatory syndrome in children

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, particularly with the declining incidence of MIS-C, but the presence of persistent fever, multisystem manifestations, and laboratory abnormalities could help early recognition.[72] 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; however, data collected while Omicron was the dominant variant in the United States suggest that the cases of MIS-C reported during this period were less severe than those reported when other variants were dominant.[66,73,74] Most patients with MIS-C have markers of cardiac injury or dysfunction, including

elevated levels of troponin and brain natriuretic protein.[62] 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. During the period when Omicron was the dominant variant in the United States, the clinical phenotype of MIS-C appeared to be more consistent with classic Kawasaki disease.[66,73] 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 a unique, distinct antibody response; excessive activation of elements of the innate immune system; or aberrant T cell responses, including a superantigen effect.[75] Several studies reported that an expansion of T cells that express the T cell receptor beta variable 11-2 (TRBV11-2) gene was detected in many children with MIS-C.[76-79] This expansion of T cells was not seen in children who had conditions similar to MIS-C, including Kawasaki disease and bacterial toxic shock syndrome, which supports the hypothesis that a superantigen effect may be involved in MIS-C. Another study demonstrated that 1% of patients with MIS-C had inborn errors of immunity.[80] Other studies have demonstrated that MIS-C and typical Kawasaki disease have differences in epidemiology, cytopenias, cytokine expression, and elevation of inflammatory markers.[81,82] Immunologic profiling has shown that MIS-C and COVID-19 in children have differences in cytokine expression (e.g., tumor necrosis factor–alpha, interleukin-10, and interferon gamma).[78,83,84]

For the Panel's recommendations on the treatment of MIS-C, see Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A.

Post-COVID Conditions

The persistent symptoms after COVID-19 that have been described in children are similar to those seen in adults. The terminology for these collective symptoms is evolving and includes long COVID, post–COVID-19 condition, and post-acute sequelae of SARS-CoV-2 infection (PASC). The data on the incidence of post-COVID conditions in children are limited and somewhat conflicting, but the overall incidence appears to be lower in children than in adults (see Clinical Spectrum of SARS-CoV-2 Infection).[85-92]

Case definitions for post-COVID conditions vary between studies, which makes determining the true incidence of these conditions challenging. The incidence of post-COVID symptoms in children appears to increase with age. The most common symptoms reported include persistent fatigue, headache, shortness of breath, sleep disturbances, gastrointestinal symptoms, and an altered sense of smell.[93] Cardiopulmonary injury, neurocognitive impairment, and new-onset diabetes may occur. However, some studies did not include control groups of children who did not have SARS-CoV-2 infection, which makes assessing the relative risk of these symptoms a challenge.

Details on the pathogenesis, clinical presentation, and treatment for post-COVID conditions in children are beyond the scope of these Guidelines. The CDC provides additional information about the incidence, presentation, and management strategies for post-COVID conditions in children as well as adults. Additional research is needed to define the incidence, pathophysiology, spectrum, and severity of post-COVID conditions in children and to identify the optimal strategies for the prevention, diagnosis, and treatment of these conditions.

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