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COVID-19 IN CHILDREN

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Abstract
Although COVID-19 has impacted many children, severe disease is rare and most recover with supportive care. Manifestations are diverse and often nonrespiratory. Adolescents/children with medical comorbidities are at risk for severe respiratory compromise. The most serious manifestation in previously healthy children is a delayed multisystem inflammatory syndrome with cardiac compromise in severe cases. Anti–SARS-CoV-2 monoclonal antibodies are available for adolescents at risk of progression and not hospitalized. Therapeutic options for severe respiratory disease with hypoxia include remdesivir and glucocorticoids. Therapies for multisystem inflammatory syndrome in children include intravenous immunoglobulin and glucocorticoids. Refractory cases may benefit from additional immunomodulators.

Keywords: COVID-19, SARS-CoV-2, MIS-C, Children, Pediatrics

Introduction

The historic advent of COVID-19 has not spared children. Since March 2020, close to 7 million children have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the United States,[1] infected in the household and rarely other communal settings.[2, 3] Current evidence is mixed on the differential susceptibility of children versus adults to be infected once exposed,[4] but more conclusive on the effectiveness of standard infection control strategies (masking, social distancing).[5] Hypotheses to why rates of infection and severe disease are lower in pediatrics include age-specific differences in the expression of the binding receptors for SARS-COV-2 (angiotensin-converting enzyme 2 and TMPRSS2)[6, 7] or pre-existing immunity to seasonal coronaviruses.[8] Variability in the immune response once infected compared with adults seems likely.[9] Infected children demonstrate stronger innate immune responses compared with adults with a higher expression of genes associated with interferon signaling and the NLRP3 inflammasome.[7] The striking racial and socioeconomic disparities in clinical disease and severe outcomes, well-described in adults, have been noted in multiple pediatric studies and non-White children are overrepresented in many case series.

Clinical spectrum and manifestations of pediatric COVID-19

The clinical spectrum of pediatric COVID-19 is diverse, arguably more than in adults. The majority of children are asymptomatic or mildly symptomatic. Rates of asymptomatic disease are estimated to be around 30% overall[14] and could be as high as

50% in children.[15] Asymptomatic seroconversion in hospitalized children has been noted.[16]

Among symptomatic patients, distinct syndromes occur at varying time points, with severe disease occurring either early or late in an individual child. Adolescents and medically complex children present early with predominantly respiratory manifestations.[12, 17] Infants often have fever without additional manifestations.[18, 19] A subset of mostly previously healthy children presents 4 to 6 weeks after an initial mild or inapparent infection with a delayed immune response characterized by higher fever, rising inflammatory markers, with what is now termed multisystem inflammatory syndrome in children (MIS-C).[20, 21] The community peak of MIS-C has been noted to be 2 to 5 weeks after the peak of acute COVID-19 in a particular locality.[22] The case definition for MIS-C is broad[23] and includes the presence of fever and laboratory evidence of inflammation, along with evidence of severe multisystem involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic). Two groups feature prominently in MIS-C presentations: (i) older children with shock and cardiac dysfunction, gastrointestinal symptoms and highly abnormal laboratory parameters (lymphopenia and elevated markers of cardiac injury) and (ii) younger children with features of Kawasaki disease (KD) with rash and mucocutaneous findings and a higher risk of coronary artery aneurysms.[24] Although MIS-C symptoms overlap with KD, cytopenia in the former is an important distinction.[25] This hyperinflammatory response has been variously attributed to a superantigen-mediated process,[24] activation of specific T-cell subsets,[26] and/or higher antibody levels.[18]

The overall rates of hospitalization for pediatric COVID-19 are low (approximately 2%), but among those hospitalized, rates of intensive care admission are comparable with those of adults and higher for MIS-C.[19] The median duration of hospitalization is typically close to 1 week.[30] Data from the Centers for Disease Control and Prevention on patients with COVID-19 aged 0 to 24 years from March to December 2020 showed 2.5% requiring hospitalization and 0.8% requiring admission to an intensive care unit.[21] The rarity of severe disease in pediatrics continues to be born out with current estimates suggesting that only 0.1% to 2.0% of all child COVID-19 cases result in hospitalizations and that mortality is extraordinarily rare, but can be up to 1% of hospitalizations.[1, 22] The circulation of the more transmissible delta variant has significantly increased COVID-19–associated pediatric hospitalization rates, but the proportions of those hospitalized with severe disease has remained similar in the United States.[23]

Respiratory Manifestations

Respiratory manifestations typically include upper respiratory or influenza-like symptoms, with fever variably present.[13] Pathognomonic symptoms such as anosmia and loss of taste are seen in older children.[12] Infants may present with apnea.[14]

A higher fever curve and the presence of multisystem findings suggests overlap with MIS-C where respiratory findings are rarely predominant.[15] Around 30% of patients hospitalized in critical care units show evidence of acute respiratory distress syndrome with higher inflammatory markers, pronounced radiographic findings and pathology that shows type 2 pneumocyte atypia, pulmonary microthrombosis, and exudative diffuse alveolar damage. Viral bronchiolitis or asthma exacerbations are not typical presentations and rates of both initially plummeted during early waves of COVID-19.[17, 18] The presence of either of these conditions should raise suspicion for viral coinfections.

Gastrointestinal and Hepatic Manifestations

The prevalence of gastrointestinal symptoms as the index presentation for pediatric COVID-19 has varied across case series.[17] However, gastrointestinal manifestations occur in the majority of cases of MIS-C,[24] and persistent antigenemia from a gastrointestinal source has been linked to pathogenesis.[19] Symptoms range from nausea, vomiting, and diarrhea to more severe phenotypes that may mimic acute appendicitis or intussusception.[12, 20] In severe cases, radiographic findings can resemble those of inflammatory bowel disease.[21]

Cardiac Manifestations

The cardiac manifestations of SARS-Cov2 are predominantly seen in severe cases of MIS-C with accompanying evidence of myocardial inflammation, necrosis, and direct viral invasion.[22] In case series of MIS-C, a reduced left ventricular ejection fraction is present in more than one-half of the patients, and the overwhelming majority of children with cardiac manifestations had elevated cardiac troponins.[20, 13] In a large case series of 1733 patients, cardiac dysfunction was reported in 484 patients (31.0%), pericardial effusion in 365 (23.4%), myocarditis in 300 (17.3%), and coronary artery dilatation or aneurysms in 258 (16.5%).[23]

Neurologic Manifestations

Neurologic symptoms occur in 20% of children with COVID-19 and more commonly in those with pre-existing neurologic disorders.[14] Infants may present with nonlocalizing neurologic symptoms (eg, new seizures, apneic episodes). Adolescents can have severe headaches, sometimes overlapping with pseudotumor cerebri syndrome.[15] Classic postinfectious sequelae, for example, peripheral neuropathy, demyelination, transverse myelitis, and Guillain–Barre syndrome, all can follow recent SARS-CoV-2 infection, sometimes without additional systemic manifestations.[16, 17] Other severe manifestations such as encephalopathy, stroke, demyelination, and cerebral edema are rare.[24] Interestingly, neuropathology does not suggest viral infection of the central nervous system and SARS-CoV-2 is rarely detected in the cerebrospinal fluid.[18]

Identify Competing Diagnoses

Because the absolute risk for hospitalizations owing to acute COVID-19 is low in children, a careful assessment for competing causes should be considered in severely ill children. Both common (eg, bacterial enteritis)[23] and uncommon (eg, primary immunodeficiency syndromes)[24] diagnoses have been misidentified as MIS-C, so a comprehensive diagnostic approach with subspecialist input is encouraged for children with diverse symptoms and SARS-CoV-2 positivity. Coinfections have been described in acute COVID-19 and MIS-C including both bacterial (eg, *Staphylococcus aureus*, group A Streptococcus) and viral (eg, Epstein–Bar virus, parvovirus, herpes viruses, and other respiratory viruses) pathogens.[25]

Additional Laboratory Testing to Risk Stratify and Classify Disease

The role of outpatient laboratory testing to triage admission is undefined but higher trends in inflammatory markers (eg, C-reactive protein [CRP]) may predict disease trajectory.[16] For hospitalized children with acute severe COVID-19 or MIS-C, initial investigations usually include complete blood counts, comprehensive metabolic panel, inflammatory markers (CRP, procalcitonin, ferritin) and coagulation parameters. For patients with features of MIS-C, markers for cardiac injury (B-type natriuretic peptide, troponin) are included in initial testing. Cardiac investigations (electrocardiogram and echocardiogram) should be obtained in patients suspected to have MIS-C and are usually repeated during the hospital stay based on institutional protocols.[17]

Accurate risk prediction scores are not available, although it seems clear that severe COVID-19 correlates with an overall derangement of most of these parameters, which are more severe in MIS-C.[18] Elevated CRP is a prognostic marker for critical care admission in pediatric acute COVID-19,[19] whereas CRP, lymphopenia, and B-type natriuretic peptide elevations are the strongest predictors for intensive care admission in MIS-C.[17, 18] Genetic screening for immune system defects, usually as a part of research efforts, may be considered, particularly for younger children with no associated comorbidities who present with severe acute COVID-19. Defects in interferon signaling and the presence of interferon antibodies have been described. Immune phenotyping can also help to distinguish between MIS-C and acute COVID-19, with the activation of $CD8^+$ cells and specific cytokine elevations observed in MIS-C.

Therapeutic options for COVID-19

Neutralizing antibodies target conserved epitopes on the SARS-CoV-2 spike protein located on the receptor-binding domain. Currently available products include bamlanivimab/estevimab, casirivimab/imdevimab, and sotrovimab. Administered as a single dose infusion or subcutaneously(casirivimab/imdevimab), these products have been shown to decrease COVID-19–related hospitalizations and mortality in placebo-controlled trials in adults.

The magnitude of this reduction is sizable (approximately 70% relative reduction) when administered within a short window (72 hours) from diagnosis[16] and also correlates with biological endpoints like decreases in viral load.[7] Adverse events seem mostly limited to rare infusion reactions in adults (approximately 1%). The US Food and Drug Administration has issued an emergency use authorization for these agents in patients 12 years and over, weighing 40 kg or more, who are not hospitalized for COVID-19 and are at high risk for disease progression. Risk factors relevant to adolescents mentioned in these emergency use authorizations include obesity, immunosuppressive disease, chronic cardiac or pulmonary disease, neurodevelopmental delay, technology dependence, sickle cell disease, chronic renal disease, and diabetes.[17] The lower absolute risk, lack of accurate risk factor stratification, and the logistics of administration complicate pediatric use. Most hospitals have chosen a more targeted approach using local data to select subgroups at highest use within the current US Food and Drug Administration criteria.[19] A significant drawback with the use of these products is the evolution of viral variants (eg, those with L452R or E484K substitutions in the spike protein) with decreased susceptibility and clinicians should monitor the local distribution of variants before use.[20]

Multiple large randomized controlled trials have failed to demonstrate an effect of azithromycin either alone or in combination with hydroxychloroquine to improve outcomes in hospitalized patients or outpatients with COVID-19.[17] Ivermectin and nitazoxanide are also agents with other pediatric indications that have been proposed for use in COVID-19, but have not yet shown any benefit.[24]

Supportive Care

Optimum ventilatory strategies for children with COVID-19 have not been defined, but trials of noninvasive support followed by lung-protective strategies that minimize acute respiratory distress syndrome are advised.[25] Consensus guidelines advise systemic anticoagulation with low-dose low-molecular-weight heparin for children hospitalized for COVID-19–related illness (including MIS-C) in the presence of markedly elevated D-dimer levels or other risk factors for hospital associated venous thromboembolism.[19] The rate of secondary infections in adults have been estimated to be 24%,[20] but is likely lower in children and antibiotic use should be minimized in the absence of known bacterial coinfection.

Long-term outcomes

The majority of children recover from COVID-19 without complications. Neonates born to pregnant mothers with COVID-19 have been reported to have small increases in adverse outcomes like respiratory complications, but perinatal transmission is rare.[21] Follow-up for children with MIS-C done at 6 months shows limited residual organ-specific sequalae.[22]

Potential long-term effects, collectively known as postacute sequelae of SARS-CoV-2 infection, after an initial mild infection, is described in adults but accurate measures of the incidence of and therapeutic options for this entity in children are undefined and are the focus of ongoing work led by the National Institutes of Health.[23]

Summary

COVID-19 has not spared children, and the manifestations of pediatric COVID-19 are diverse, ranging from mild upper respiratory tract infection to acute respiratory failure and MIS-C. Supportive care remains the mainstay of treatment for acute infection with the addition of antiviral and immunomodulatory therapy for the rare cases of severe infection.

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