COVID-19 in Children

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KEYWORDS

- COVID-19 • SARS-CoV-2 • MIS-C • Children • Pediatrics

KEY POINTS

- COVID-19 is less severe in children than in adults and usually only requires supportive therapy.
- The 2 main phenotypes of severe disease are acute respiratory failure in children with co-morbidities and a delayed hyperinflammatory response called multisystem inflammatory syndrome in children with cardiac dysfunction.
- Multisystem inflammatory syndrome in children mostly occurs in previously healthy children.
- Remdesivir and steroids are options for worsening acute respiratory disease and hypoxia.
- Intravenous immune globulin and steroids are first-line agents for multisystem inflammatory syndrome in children.

INTRODUCTION AND EPIDEMIOLOGY

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 corona-virus 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 socio-economic disparities in clinical disease and severe outcomes, well-described in

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adults, have been noted in multiple pediatric studies and non-White children are over-represented in many case series.[10–13]

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,[26] activation of specific T-cell subsets,[27] and/or higher antibody levels.[28]

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.[29] 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.[31] 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.[32]

Respiratory Manifestations

Respiratory manifestations typically include upper respiratory or influenza-like symptoms, with fever variably present.[33] Pathognomonic symptoms such as anosmia and loss of taste are seen in older children.[12] Infants may present with apnea.[34] A higher fever curve and the presence of multisystem findings suggests overlap with MIS-C where respiratory findings are rarely predominant.[24] Around 30% of patients hospitalized in critical care units show evidence of acute respiratory distress syndrome with higher inflammatory markers, pronounced radiographic findings,[35] and pathology that shows type 2 pneumocyte atypia, pulmonary microthrombosis, and exudative

diffuse alveolar damage.[36] Viral bronchiolitis or asthma exacerbations are not typical presentations and rates of both initially plummeted during early waves of COVID-19.[37,38] 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.[39] Symptoms range from nausea, vomiting, and diarrhea to more severe phenotypes that may mimic acute appendicitis or intussusception.[12,40] In severe cases, radiographic findings can resemble those of inflammatory bowel disease.[41]

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.[42] 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.[20,43] 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%).[43]

Neurologic Manifestations

Neurologic symptoms occur in 20% of children with COVID-19 and more commonly in those with pre-existing neurologic disorders.[44] Infants may present with nonlocalizing neurologic symptoms (eg, new seizures, apneic episodes). Adolescents can have severe headaches, sometimes overlapping with pseudotumor cerebri syndrome.[45] 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.[46,47] Other severe manifestations such as encephalopathy, stroke, demyelination, and cerebral edema are rare.[44] Interestingly, neuropathology does not suggest viral infection of the central nervous system and SARS-CoV-2 is rarely detected in the cerebrospinal fluid.[48]

Dermatologic Manifestations

Transient rash, usually maculopapular in nature, can occur in both acute and late COVID-19.[12,17] SARS-CoV-2 infection can trigger cutaneous vasculitis, causing benign entities like perniosis (COVID toes) to acral gangrene. Petechiae can occur as part of thrombocytopenia-associated syndromes like Henoch–Schoenlein purpura.[49] Mucocutaneous manifestations seen in MIS-C are similar to that in KD, including polymorphous rash and involvement of the oral mucosa.[50]

Other Systemic Manifestations

Clinical thrombotic events are rare in children in comparison with adults with COVID-19; they are more common in older children with MIS-C and in those with pre-existing risk factors for thrombosis (eg, cancer, presence of a central line). These manifestations can include deep vein thrombosis, pulmonary embolism, and strokes.[51] Diabetic ketoacidosis has been reported as a presentation for children hospitalized with MIS-C,[52] as well as a complication in those children with known diabetes.[53] Acute renal

failure is noted in up to one-quarter of children hospitalized in the intensive care unit with MIS-C, but usually resolves by discharge.[54]

EVALUATION AND APPROACH

The initial approach to a pediatric patient with suspected COVID-19 should aim to (i) confirm the diagnosis, (ii) identify competing causes, (iii) define the risk of disease progression in an individual child using clinical and/or laboratory risk factors, (iv) choose antiviral and immunomodulatory therapy as applicable, and (v) provide excellent supportive care.

Confirm SARS-Cov2 Infection

Testing for SARS-CoV-2 is ideally done using nucleic acid amplification and antigen tests should be interpreted accounting for pretest probability. Antigen testing has a reduced sensitivity, but usually correlates with nucleic acid amplification results when the viral load and infectiousness are highest and thus can be a useful adjunct. The possibility of false negatives should be considered taking into account the local average positivity rate over the past 7 to 10 days.[55]

Although nasopharyngeal swabs specimens are the gold standard, studies show equivalent performance using midturbinate, anterior nasal, saliva, or a combined anterior nasal/oropharyngeal swabs in symptomatic adults.[56] Prolonged shedding and viral evolution are described particularly in immunocompromised children.[57] SARS-CoV-2 polymerase chain reaction testing is mostly negative in MIS-C[20] and serology testing should be done to confirm exposure.[58]

Increased viral loads have been associated with severity of disease in adults,[59] but data in pediatrics are conflicting.[60,61] Viral loads seem to be similar between adults and children.[7] The routine use of cycle thresholds from polymerase chain reaction tests is not currently part of clinical care, and caution must be exercised when comparing across assays and in light of the potential variability attributable to different sampling practices.[62]

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)[63] and uncommon (eg, primary immunodeficiency syndromes)[64] 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.[65]

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.[66] 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.[67]

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.[68] Elevated CRP is a prognostic marker for critical care admission in pediatric acute COVID-19,[69] whereas CRP, lymphopenia, and B-type natriuretic peptide elevations are the strongest predictors for intensive care admission in MIS-C.[17,68] 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.[70] Immune phenotyping can also help to distinguish between MIS-C and acute COVID-19, with the activation of CD8$^+$ cells[27] and specific cytokine elevations observed in MIS-C.[71]

THERAPEUTIC OPTIONS: RISK STRATIFICATION

The majority of children with acute COVID-19 recover completely with supportive care alone.[1] Comparative data on efficacy for therapeutic agents are mostly derived from studies in adults, so any observed relative risk reduction must be interpreted in light of the lower absolute risk and the larger number needed to treat in pediatrics.[72] Ongoing updated guidance is available from the Pediatric Infectious Diseases Society,[73] National Institutes of Health,[74] and the Infectious Disease Society of America.[75]

Most pediatric patients hospitalized with acute COVID-19 patients have comorbidities.[10,12] Obesity is an independent risk factor for severe disease in adults and most likely in adolescents.[17,35,76] Medical complexity, an amalgam of conditions including neurodevelopmental delay, genetic syndromes, and respiratory technology dependence, is prevalent in most severe COVID-19 case series,[30] but individual risk ratios are not available. The role of immunocompromise is nuanced. Unexpectedly lower rates of morbidity and mortality have been reported in immunocompromised patients, including those with hematologic malignancies, hematopoietic stem cell transplantation, and solid organ transplantation, but these do contribute to disease severity.[77–79] Adults with primary immune deficiency (eg, specific antibody deficiency) have had severe outcomes,[80] but data are scarce in pediatrics.[81] Children and adolescents with COVID-19 and sickle cell disease often present with typical vasoocclusive crisis, but severe outcomes are rarely described.[82] Asthma has been noted to be prevalent in hospitalized children,[76,83] but whether it is an independent risk factor for COVID-19 is unclear.[84] Diabetes mellitus and chronic renal failure despite initial reports[85] have not been shown conclusively to be independent risk factors for severe disease in children.

THERAPEUTIC OPTIONS FOR COVID-19
Outpatient Care: Monoclonal Antibodies

Neutralizing antibodies target conserved epitopes on the SARS-CoV-2 spike protein located on the receptor-binding domain.[86] 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.[87,88] The magnitude of this reduction is sizable (approximately 70% relative reduction) when administered within a short window (72 hours) from diagnosis[86] and also correlates with biological endpoints like decreases in viral load.[74] 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.[87] 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.[89] 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.[90]

Inpatient Care: Antivirals—Remdesivir

Remdesivir, an RNA polymerase inhibitor, was previously studied for pediatric use in Ebola.[91] Data for efficacy in COVID-19 are drawn from an randomized controlled trial of 1062 adults where remdesivir decreased time to recovery compared with placebo (10 days vs 15 days; relative risk reduction, 1.29; 95% confidence interval, 1.12–1.49; $P < .001$), but showed no statistically significant difference in mortality by day 29. The benefit was greatest in patients randomized during the first 10 days after symptom onset and those requiring supplemental oxygen but not higher respiratory support (eg, mechanical ventilation) at enrollment (relative risk, 1.45; 95% confidence interval, 1.18–1.79).[92] Currently remdesivir is standard of care for adults who require supplemental oxygen in the United States, but other studies have demonstrated no impact on mortality and it is not currently recommended by the World Health Organization.[93,94] Remdesivir can be considered in children with new or worsening oxygen requirements in addition to supportive care alone, although data regarding efficacy and safety in children are lacking.[73] Equivalency has been demonstrated between 5- and 10-day courses in adults.[95] A pediatric-specific pharmacokinetic study is ongoing, but results are not available yet. Adverse events are rare and include elevated transaminases, transient gastrointestinal symptoms, and elevation of prothrombin levels.[96]

Agents with Presumed But Not Proven Antiviral Activity and Existing Pediatric Indications

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.[97] 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.[74]

Glucocorticoid Therapy for Acute COVID-19

Evidence for glucocorticoid use comes from a large trial of 2104 adults who were randomized to receive dexamethasone 6 mg once per day for 10 days compared with 4321 patients randomized to usual care. Dexamethasone reduced deaths in ventilated patients (rate ratio, 0.65; 95% confidence interval, 0.48–0.88; $P = .0003$) and in patients receiving supplemental oxygen only (rate ratio, 0.80; 95% confidence interval, 0.67–0.96; $P = .0021$), but there was no benefit among those patients who did not require respiratory support.[98] A meta-analysis of the use of steroids for the treatment of acute COVID-19 showed a significant decrease in all-cause mortality (rate ratio, 0.65, 95% confidence interval, 0.50–0.82).[99] Corticosteroid are the primary

immunomodulatory therapy in hypoxic children with severe acute COVID-19 requiring noninvasive positive pressure or mechanical ventilation.[67] Dexamethasone is commonly used at a dose of 0.15 mg/kg/dose (maximum of 6 mg) orally or intravenously every 24 hours for 10 days; alternate agents include hydrocortisone or methylprednisone.[98] Caution should be exercised in the setting of uncontrolled concurrent infections, hyperglycemia, delirium, or underlying psychiatric illness.

Glucocorticoid Therapy for Multisystem Inflammatory Syndrome in Children

For MIS-C, glucocorticoids are part of first-line therapy in a majority of centers, although others choose to reserve steroids for severe disease or as intensification therapy in patients with refractory disease.[100] Retrospective comparisons of intravenous immunoglobulin (IVIG) alone (first-line therapy for MIS-C) with IVIG with steroids have shown faster resolution of fever, improvement in cardiac function, and less of a requirement for sequential immunomodulators,[101,102] but outcome this has not been replicated consistently and the impact on long-term outcomes not fully known. The dosing of steroids is conditional on the severity of disease with typical dosing of IV methylprednisolone 1 to 2 mg/kg/d and the highest dosing (eg, methylprednisolone 10–30 mg/kg/d) usually reserved for children presenting with shock.[67]

Intravenous Immune Globulin for Multisystem Inflammatory Syndrome in Children

The use of IVIG as a first-line therapy for MIS-C evolved from its known efficacy in preventing coronary artery aneurysms in KD, the overlapping presentations of MIS-C with KD, and its potential effectiveness in non–SARS CoV-2 myocarditis.[67] The administration of IVIG is the primary treatment modality for MIS-C and is usually administered at a dose of 2 g/kg similar to use in KD.[67,103] Second doses of IVIG, although typically used for unresponsive KD, are not usually recommended for MIS-C.[67]

Second-line Immunomodulatory Therapy

Other immunomodulators can be considered in refractory cases or in the rare instance of contraindications to using steroids. Tocilizumab, an IL-6 inhibitor used to treat cytokine storm, has shown decreased mortality when added to steroids, for adults with rapidly increasing respiratory support and evidence of systemic inflammation.[104] In adults, baricitinib, an oral agent that inhibits Janus kinases 1 and 2, seems to have an impact on time to recovery when used along with remdesivir and can be considered in the rare instances of contraindications to steroid use or as an addition to standard of care.[105,106] Anakinra has not conclusively shown a benefit for adults with COVID-19 pneumonia,[107] but is the most accepted immunomodulatory therapy in MIS-C that is refractory to both IVIG and steroids.[67,103] Based on previous experience with KD, tumor necrosis factor-α blockade with infliximab can be considered as a potential therapeutic agent for those with a MIS-C phenotype that most closely resembles refractory KD.[103]

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.[108] 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.[109] The rate of secondary infections in adults have been estimated to be

24%,[110] 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.[111] Follow-up for children with MIS-C done at 6 months shows limited residual organ-specific sequalae.[112] 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.[113]

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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