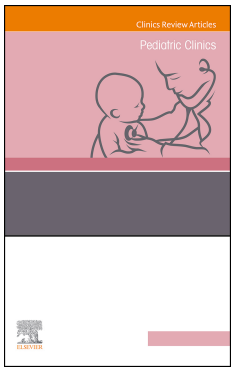
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



COVID-19 in Children

Meena Kalyanaraman, MD, Michael R. Anderson, MD MBA

PII: S0031-3955(22)00013-X

DOI: https://doi.org/10.1016/j.pcl.2022.01.013

Reference: PCL 1919

To appear in: *PEDIATRIC CLINICS OF NORTH AMERICA*

Please cite this article as: Kalyanaraman M, Anderson MR, COVID-19 in Children, *PEDIATRIC CLINICS OF NORTH AMERICA* (2022), doi: https://doi.org/10.1016/j.pcl.2022.01.013.

TITLE PAGE

TITLE: COVID-19 in Children

Author: Meena Kalyanaraman MD

Affiliations:

Associate Director, Pediatric Critical Care Medicine, Children's Hospital of New Jersey at Newark Beth Israel Medical Center, Newark, NJ

Contact:

C-5, 201 Lyons Ave, Newark, NJ 07112

Phone: 7326937964 Email: Meena.Kalyanaraman@rwjbh.org

Corresponding author: Meena Kalyanaraman, MD

Author: Michael R Anderson MD MBA

Affiliations:

Senior Advisor, Children's National Hospital

Adjunct Professor of Leadership and Clinical Research

George Washington University School of Medicine and Health Sciences

Contact:

1331 Maryland Ave SW, Washington DC 20021

Disclosure: The authors have no conflict to report.

KEYWORDS: SARS-CoV-2, COVID-19, ARDS, MIS-C, Pediatric COVID, Risk Factors, Epidemiology.

KEY POINTS:

-While children are less affected than adults with coronavirus disease 2019 (COVID-19), over 5 million children in the United States have been infected and the overall public health implications of the pandemic on children are severe.

-Certain high-risk conditions make children more prone to severe disease.

- Children are admitted to the pediatric intensive care unit (PICU) for severe acute COVID-19 which is SARS-CoV-2 infection associated with one or more organ system involvement or multisystem inflammatory syndrome in children (MIS-C).

- Pediatric critical care physicians should be cognizant of complications from hyperinflammation in SARS-CoV-2 infections, management of COVID-19 associated acute respiratory failure, and special precautions to be taken during aerosol generating procedures.

- Presentations of MIS-C can be like other diseases and might be especially hard to differentiate from Kawasaki disease.

- Diagnosis and treatment of MIS-C using available guidelines can result in favorable outcomes in critically ill children.

SYNOPSIS

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic caused by the SARS-CoV-2 virus. While less susceptible to SARS-CoV-2 than adults, over five million children have been infected in the United States. Several important risk factors for more severe disease progression include obesity, pulmonary disease, gastrointestinal disorders, and neurological co-morbidities. Children with COVID-19 are admitted to the PICU because of severe acute COVID-19 illness or COVID-19 associated MIS-C. The primary reasons for admission for severe acute COVID-19 are respiratory problems such as pneumonia and acute respiratory distress syndrome (ARDS). Patients with MIS-C require PICU admission because of cardiac, cardiorespiratory, and gastrointestinal complications. MIS-C can be especially difficult to differentiate from Kawasaki disease. Hyperinflammation seen in SARS-CoV-2 infections plays a major role in pathogenesis and complications seen in severe acute COVID-19. Precautions to be taken during aerosol generating procedures, management strategies of COVID-19 acute respiratory failure, recognition and management of hypercoagulable states, and diagnosis and treatment of MIS-C have demanded unprecedented, rapid and unique adaptations in the PICU. The delta surge of 2021 was responsible for an increased disease burden in children and points to the key role of vaccinating children against this sometimes-deadly disease. Other long term public health impacts of the pandemic (mental health crisis, strain on the medical home and school disruption) will be felt for a long time.

INTRODUCTION

The COVID-19 pandemic has wreaked havoc across the world, with an estimated 242,688,319 human infections and 4,932,928 deaths worldwide as of November of 2021.[1] Children were first thought to be "immune" from infection, but the truth is a much more sobering tale of infections, hospitalizations, deaths, and long-term (long-haul) symptoms. In this section, we will outline what is known about the epidemiology of COVID-19 infection in children to date. In addition, we will discuss severe COVID-19 disease in children and address the public health toll the pandemic has exerted on children and issues that we must address with "lessons learned" to help prepare for the next pandemic.

Epidemiology and Early Pandemic Reports:

Unlike many pediatric illnesses where knowledge of epidemiology, clinical course, and outcomes are gathered over a long time, the COVID-19 pandemic saw a shift to fast-track publication of case reports, meta-analysis, and essential updates from both the private sector and government (i.e., CDC/MMWR, etc.). At a time of a public health emergency, one must balance rapid publication of domestic and international experience with academic and scientific rigor.

The first reports of pediatric COVID-19 illness emerged from the Shanghai Children's Medical Center in China in March 2020 with data from 2,135 children with COVID-19 reported to the Chinese Center for Disease Control and Prevention.[2] The median age of children with COVID-19 was seven years, and 56% were male. Although 51% of the patients had "mild symptoms," 38% had moderate symptoms (pneumonia and wheezing), and 6% had severe or critical clinical findings such as hypoxia and respiratory failure**.** Lu et. al. published a cohort analysis of 171 COVID-19 positive children from Wuhan Children's Hospital in

April 2020.[3] Seventy had fever, twelve had pneumonia, three required mechanical ventilation, and one died. While these early reports showed that children had a less severe clinical course than adults, a small but concerning percentage of children progressed to respiratory failure.

The University of Texas-San Antonio and Texas Children's Hospital published meta-analysis/case summary of children with COVID-19[4], with 131 studies from 26 countries and 7,780 children from January to May 2020 (Fig.1). The median age was 8.9 years, and 75.6% were exposed to an adult with COVID-19. Need for ICU care was 3.3%, and length of hospital stay was 11.6 days. Approximately 35% had underlying medical conditions, with immunodeficiency being the most common at 30.5%. (Fig.2)

Children and Susceptibility to SARS-CoV-2:

Viner et. al. performed a meta-analysis on 13,926 published articles and summarized 32 studies with data from 41,460 children[5]. Compared with data from 14 studies on adults with COVID-19, children had lower susceptibility to SARS-CoV-2 with a pooled OR of 0.56 (95% CI, 0.37 to 0.85). Data regarding transmission of COVID-19 by children were inconclusive. Gaythorpe et.al. reviewed 128 studies to examine COVID-19 susceptibility and transmissibility in children and showed the odds ratio of an asymptomatic child having an infection was 21.1% (95% CI; 14.0-28.1%), and the proportion of children with severe disease was 3.8% (95% CI; 1.5-6.0%)[6]. The authors were not able to determine a child's ability to spread COVID-19.

UNITED STATES EXPERIENCE

An analysis of 12,306 children from the United States infected with COVID-19 from April to October 2020 examined symptoms and clinical course.[7] Symptoms included respiratory

(16%), gastrointestinal (13.9%), rash (8.1%) and neurological (4.8%)**.** Eighteen percent had nonspecific findings such as fever and malaise. Five percent required hospitalization, of whom 17.6% needed mechanical ventilation. Male and female children are equally affected, and risk of hospitalization is greater among non-Hispanic black and Hispanic children compared to non-Hispanic whites. Among hospitalized children, the rate of intensive care unit admissions is similar to adults.[8]

PROGRESSION AND SEVERITY OF DISEASE

Graff et. al. reported on which children are at most significant risk for severe complications from COVID-19 infection.[9] At the time, there were up to 1.3 million children infected with COVID-19 in the US. This group examined the clinical course of children with the diagnosis of COVID-19 at their institutions from March to July 2020, where 454 children tested positive for SARS-CoV-2. The most frequent risk factor for COVID-19 exposure was a family member testing positive for SARS-CoV-2. Participation in social gatherings of 10 or more was a significant risk factor as well. Forty-five percent of the children with COVID-19 were identified with at least one co-morbid condition: pulmonary (16%), GI (11%), and neurologic (11%). Among the comorbid conditions, asthma, diabetes and obesity were predictors of severe COVID-19 in children. Eighty-five were hospitalized, of whom sixty-six were symptomatic. (The remaining nineteen patients were admitted for other reasons and never had COVID symptoms). Of the sixty-six symptomatic patients, 55% required respiratory support, and 17% required critical care (Fig.3). The need for hospitalization was associated with younger age (0-3 months) and the presence of co-morbidities. Requirement for respiratory support was associated with Hispanic ethnicity, age 0-3 months, obesity, and

asthma. The need for critical care was associated with obstructive sleep apnea and elevated CRP at the time of admission.

Investigators from the Centers for Disease Control (CDC) examined disease severity in children admitted with COVID-19 from March to October 2020 utilizing the Premier Health Care Database and identified 20,714 children with COVID-19, 2,430 of whom were hospitalized.[10] Severe COVID-19 disease was associated with males younger than 1 year, and the presence of co-morbidity. There was no association between race/ethnicity and severe COVID-19.

THE DELTA VARIANT SURGE AND CHILDREN

The American Academy of Pediatrics (AAP) and the Children's Hospital Association (CHA) began publishing pediatric data weekly starting in the Fall of 2020, indicating increasing numbers of children (<17 y) with COVID-19 and hospitalization rates, especially during the Delta surge of 2021.[11]

As of October 2021, 5,899,148 children were reported to have COVID-19, representing 16.2% of US cases with an overall rate of 7,838 cases per 100,000 children.

Compared to adults, the hospitalization rate for children with COVID-19 remained low until a spike in September 2021. Pediatric hospitalization rates varied between 1.3-3.2 per 100,000 children for ages 0-4 years and 0.8 to 1.4 for children 5-17 years.

Per CDC data:

"During a subsequent 6-week period after the Delta variant became predominant, COVID infection rates rose each week to 1.4 during the week ending August 14, 2021, which was 4.7 times the rate during the week ending June 26, 2021 and approached the peak hospitalization rate of 1.5 observed during the week ending January 9, 2021. Weekly rates

increased among all age groups; the sharpest increase occurred among children aged 0–4 years, for whom the rate during the week ending August 14, 2021 (1.9) was nearly ten times that during the week ending June 26, 2021 (0.2).”

While overall hospitalization rates remained lower in children compared to adults, 20-26.4% of hospitalized children required ICU care, and 9-12% of children required mechanical ventilation. The mortality rate from COVID-19 is relatively low (for states reporting, 0-0.26% of total COVID deaths were children.)

EFFECT OF COMMUNITY VACCINATION ON PEDIATRIC COVID-19

Unfortunately, due to areas in the US with low vaccination rates in adults, the Delta variant emerged in 2021 as the predominant strain of COVID-19 causing infection in children. In addition, because children less than 12 years were ineligible to receive any of the emergency use approval (EUA) vaccines in early 2021, and the refusal to wear masks and adhere to social distancing recommendations, the number of children with COVID-19 infections increased, and were 1.5-3 times more likely to require emergency care for COVID-19.[12]

Clinics Care Points

- Despite lower overall hospitalization rates for COVID-19 in children, the rate of intensive care unit admissions among hospitalized children is similar to adults.
- Intensivists should be aware of underlying conditions which can put children at risk for severe COVID-19.
- Hospitalization rates for children have increased since the start of the pandemic especially during the Delta surge of 2021.

- Efficacy studies for vaccines in children and vaccination recommendations for children are underway.

Tags for SEO: COVID-19, CDC, Delta variant

PATHOGENESIS

Transmission of SARS-CoV-2 is primarily through airborne droplets and to a lesser extent from contaminated surfaces and rarely through body fluids. The virus can transmit over long distances especially when indoors. Incubation period is 3-6 days. The entry into host cells is mediated by its spike glycoprotein (S-glycoprotein) binding to ACE2 cellular receptor in the upper respiratory tract to begin primary replication.[13] Patients can be asymptomatic carriers or have mild symptoms at this stage. Viral load is elevated in the first week followed by a progressive decline in seven to ten days with increase in IgM and IgG antibodies against viral antigens. The persistence of high viral load leads to migration of virus in the airway with entry into alveolar epithelial cells where it replicates, causing localized inflammation and pneumonia. Cell apoptosis occurs, with increased capillary permeability and release of proinflammatory proteins. Cytokine storm can ensue with release of inflammatory markers such as interleukins (IL) - IL-2/6/7/10, granulocyte colony stimulating factor (GCSF), interferon gamma-induced protein 10 (IP-10), macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), and tumor necrosis factor-α (TNF-α) which can cause acute respiratory distress syndrome (ARDS), septic shock and multi-organ dysfunction.[14]

COVID-19 IN CRITICALLY ILL CHILDREN

Children with COVID-19 are admitted to the PICU because of severe acute COVID-19 illness which is SARS-CoV-2 infection with one or more organ system involvement or COVID-19 associated MIS-C.

SEVERE ACUTE COVID -19

Children with severe acute COVID-19 are admitted to the PICU for respiratory problems such as pneumonia and ARDS. Cardiovascular, gastrointestinal, neurologic, hematologic, and acute kidney injury (AKI) complications can result from severe acute COVID-19. Risk factors for severe acute COVID-19 are the presence of one or more underlying conditions such as obesity, chronic pulmonary disease, neurological disease, cardiovascular disease, medical complexity and technology dependence, sickle cell disease, or immunosuppresion.[15-19] Underlying chronic respiratory diseases such as asthma and cystic fibrosis were not significantly exacerbated by SARS-CoV-2.[19] Younger age, obesity, hypoxia on admission, elevated white blood cell count, and bilateral infiltrates on chest radiograph, are predictors of severe respiratory disease.[20]

DIAGNOSIS:

Laboratory tests:

Detection of SARS-CoV-2 nucleic acid using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) is considered the gold-standard for the diagnosis of COVID-19.[21] The virus can be detected in the upper airway (nasopharynx swab) or lower airway secretions (tracheal aspirates, bronchoalveolar lavage), blood, urine, and stool. Leukocytosis or leukopenia, lymphocytosis or lymphopenia, and elevations of C-reactive protein (CRP), serum ferritin, lactate dehydrogenase (LDH), D-dimers, procalcitonin, erythrocyte sedimentation rate (ESR),

serum aminotransferases, and creatine kinase-myocardial bands (CK-MB) have been observed.[22,23] Elevations of CRP, procalcitonin, pro-B type natriuretic peptide (BNP) and platelet count are more common in children requiring PICU admission compared to other hospitalized patients.[24] Organ dysfunction was associated with elevated CRP, elevated white blood cell (WBC) count, and thrombocytopenia.[25]

Hyperinflammation associated with elevated LDH, D-dimer, IL-6, CRP, ferritin and decreased lymphocyte count, platelet count, and albumin level were associated with worse outcomes in adult patients with COVID-19.[26]

Imaging studies:

Chest radiography is routinely performed in most children hospitalized for acute respiratory failure from COVID-19. While chest radiographs do not have high sensitivity and specificity for the diagnosis of COVID-19, it is useful to monitor disease progression. Bilateral distribution with presence of peripheral or subpleural ground glass opacifications and consolidation are common findings in COVID-19 pneumonia or ARDS (Fig.4). Typical features of viral respiratory infections in children such as increased perihilar markings and hyperinflation were not reported in children with COVID-19.[27,28]

Computerized tomography (CT) scans are considered the 'gold-standard' for imaging with COVID-19 respiratory disease.[29] CT scans are highly sensitive and specific and can detect infection before the appearance of clinical signs.[29,30] Three phases of evolution have been observed in children with COVID-19 disease. These include the "halo" sign defined as nodules or masses surrounded by ground glass opacifications seen in the early phase of the disease, widespread ground-glass opacifications in the progressive phase and consolidative opacities in the developed phase. Peribronchial thickening and inflammation along the bronchovascular

bundle are observed more frequently in children than adults.[31] Fine mesh reticulations and "crazy paving" sign have been reported. Pleural effusion and lymphadenopathy are rare.[31] When compared to adults, children were found to have less positive CT findings, lower number of pulmonary lobes involved, and lower overall semiquantitative lung score which measures the extent of lung involvement.[31] Because of these findings and concerns for radiation exposure, transport of unstable patients to CT suites, and infection control issues, chest CT is not recommended as the initial diagnostic test in children suspected of having COVID-19. However, it may be considered to answer specific clinical questions such as presence of pulmonary embolism, assessment of those not responding to treatment and to track evolution of fibrotic disease. Lung ultrasound is a useful imaging modality as semiquantitative scores in lung ultrasound have been shown to be consistent with those in lung CT scans in adults who are critically ill with COVID-19, and should be considered in children.[30,32]

Recommendations for diagnostic tests in Severe Acute COVID-19:

Laboratory tests: SARS-CoV-2 RT-PCR, COVID-19 IgG, complete blood count (CBC), complete metabolic panel (CMP), LDH, CRP, procalcitonin, ESR, prothrombin time (PT), partial thromboplastin time (PTT), troponin, BNP. Ferritin, and cytokine panel when available will provide additional information about the hyperinflammatory state.

Cardiac evaluation: Baseline electrocardiogram (ECG) should be obtained in all patients, and those with abnormal troponin should undergo echocardiography.

Imaging studies: chest radiograph in all patients, CT scan if pulmonary embolism is suspected.

Clinics Care Points

- Severe acute COVID-19 which is SARS-CoV-2 infection with one or more organ system involvement requires PICU admission.

- Pediatric intensivists should be familiar with MIS-C and its complications.
- The gold-standard for diagnosis of COVID-19 is detection of SARS-CoV-2 nucleic acid using RT-PCR.
- Hyperinflammation plays a major role in pathogenesis of SARS-CoV-2 and complications of severe acute COVID-19.
- Intensivists should be familiar with chest radiograph changes in severe acute COVID-19 and Chest CT should be considered only in those patients in whom pulmonary embolism is a concern.

SEVERE ACUTE COVID-19 COMPLICATIONS:

Acute Respiratory Failure

Clinical Features: SARS-CoV-2 pneumonia can cause acute respiratory failure and progress to ARDS. Diagnostic criteria for COVID-19 ARDS are the same as for pediatric ARDS (PARDS) from other causes. Patients typically have worsening respiratory symptoms one week after disease onset, new opacities on chest imaging that are not due to cardiac failure or volume overload, partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio $\leq$ 300 mm Hg or oxygen saturation by pulse oximetry/FiO_2 $\leq$ 264 during non-invasive ventilation, oxygenation index (OI) $\geq$ 4 or oxygen saturation index (OSI) $\geq$ 5 during invasive mechanical ventilation. Mild, moderate, and severe PARDS is defined as OI/OSI of 4-8/5-7.5, 8-16/7.5-12.3, and >16/>12.3 respectively.[33]

Pathologic changes in these patients are like PARDS from other causes with initial diffuse alveolar damage and fibrosis with disease progression. Differences have been noted in adults between ARDS from COVID-19 as compared to ARDS from other causes including phenotypic subtypes such as 'Type L', characterized by low elastance with preserved compliance and 'Type

H', characterized by high elastance with low compliance, and increased association with thrombosis.[34] Studies in children have not shown significant differences in compliance between PARDS from COVID-19 and other causes.

Management:

I: General principles of management:

Management of COVID-19 associated acute respiratory failure is outlined in figure 5. The principles of management and end goals of respiratory therapy are the same as for other causes of acute respiratory failure in children.[33,35,36] Patients who have SpO2 < 90% will need supplemental oxygen, non-invasive ventilation or intubation and mechanical ventilation based on severity. Intubation protocols with special precautions for patients with COVID-19 should be developed based on resources available.[37,38] Ventilator strategies as outlined in figure 5 will help in the management of COVID-19 PARDS and ARDSNet protocols for PEEP/FiO_2 may be followed. In a retrospective study in children prior to the COVID-19 pandemic, use of lower PEEP relative to FiO_2 than what is recommended by the ARDSNet model resulted in higher mortality.[38-40] In addition to recommendations in figure 5, intravascular volume expansion should be avoided in patients without hypotension. Adequate mean arterial pressure should be maintained, and inotropic support provided as needed, and nutritional support must be adequate.[38,41] Patients who have refractory hypoxemia may need treatment such as inhaled nitric oxide, high-frequency oscillatory ventilation, or extracorporeal membrane oxygenation (ECMO) as recommended in the management of PARDS from other causes.

II: COVID-19 specific management:

1. Rapid spread of infection from SARS-CoV-2 can occur during various aerosol generating procedures (AGP). Appropriate personal protection equipment (PPE) should be used by all staff

and visitors. Special precautions should be taken to minimize spread during AGP such as coughing and sneezing, use of non-invasive ventilation including HFNC, bag-mask ventilation, intubation, tracheal suction, planned or accidental extubation, chest physiotherapy, cardiopulmonary resuscitation, and use of nebulized medications outside of a closed circuit.[38]

2. Antiviral therapy: Remdesivir is an antiviral medication that is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is approved by the Food and Drug Administration (FDA) for treatment of patients ≥ 12 years old hospitalized with COVID-19, who weigh ≥ 40 kg, and is FDA authorized via EUA for use in hospitalized patients < 12 years of age or weigh between 3.5 to <40kg.[42,43] In neonates <3.5 kg, use should be directed by recommendations from infectious disease consultants upon weighing the risks versus benefits. Intravenous remdesivir is most beneficial if used early in the course of illness (<10 days) and has been shown to reduce symptom duration in adults but does not appear to reduce mortality. There are few studies in children, but remdesivir appears to be well tolerated.[44,45] Lyophilized powder formulation should be used in children <40 kg as it contains half the amount of sulfobutylether-β-cyclodextrin sodium salt, an excipient in remdesivir which is cleared through the kidneys and can accumulate in patients with decreased renal function**.** Children weighing ≥3.5 kg and <40kg should receive a loading dose of 5 mg/kg on day one followed by 2.5 mg/kg/dose once daily. For those ≥40 kg, a loading dose of 200 mg is recommended on day one followed by 100 mg daily. Duration of therapy is five days or until hospital discharge, whichever is earlier, and ten days for those who require mechanical ventilation or ECMO. Laboratory monitoring during remdesivir therapy should include CBC, CMP, PT/INR at baseline, day five of therapy, and more often if there is concern for toxicity. Common adverse reactions to remdesivir include reversible transaminase elevations and

hypersensitivity reactions. Bradycardia and hypotension have been reported in adults but may have been related to concomitant use of other medications.[46] Contraindications to its use are hypersensitivity to remdesivir or any component of the formulation. Remdesivir is not recommended in children older than 28 days with estimated glomerular filtration rate <30 mL/min, and in full-term neonates with serum creatinine level 1 mg/dL or greater and should be used with caution in those with baseline alanine transaminase (ALT) levels more than 5 times the upper limit of normal. Transaminases might be elevated due to COVID-19 and if remdesivir is used it should be discontinued if ALT levels increase to more than 10 times the upper limit of normal or if ALT elevation is accompanied by signs or symptoms of liver inflammation. Dose adjustments will be needed for those on ECMO or renal replacement therapy (RRT) because of interactions between remdesivir and the circuits which can cause significant changes in pharmacokinetics of the drug.

3. Anti-inflammatory therapy: Dexamethasone is recommended for hospitalized children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or ECMO.[47] The dexamethasone dosing regimen for children is 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to ten days. Steroids should be used with caution as there are reports of increased mortality and decreased viral clearance with certain viral infections and development of neuropathy and myopathy in critically ill patients. However, dexamethasone significantly reduces mortality in adult patients with COVID-19 who require mechanical ventilation and is recommended for treatment of children with severe acute COVID-19 disease.[48-50] Patients with exacerbation of asthma with COVID-19 should receive methylprednisolone and those with adrenal insufficiency and catecholamine resistant refractory shock should receive hydrocortisone in doses recommended for such conditions.

4. Immunomodulator therapy: IL-1 receptor antagonist like anakinra should be considered in children for whom corticosteroids is contraindicated, are refractory to corticosteroids or have severe acute COVID-19 causing ARDS, shock, or signs of significant hyperinflammation.[50] Dosing guidelines as mentioned in the MIS-C treatment section may be followed.

3. Other specific treatments such as monoclonal antibodies, convalescent plasma, and IL-6 inhibitors are not recommended in critically ill children.[50]

Sepsis And Septic Shock

Manifestations are like those resulting from other infections and recommendations of the ‘‘2020 Surviving Sepsis Campaign’ should be followed.[51]

Acute Kidney Injury (AKI)

Presentation and management are the same as for any critically ill patient developing AKI. The hypercoagulable state in COVID-19 can cause clotting of filters used in RRT and can be prevented with the addition of prefilter heparin and/or citrate.[52]

Neurological Complications

Meningitis, encephalitis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, myositis, acute necrotizing hemorrhagic encephalopathy**,** seizures, and cerebrovascular disease from hypercoagulable state have all been reported in severe acute COVID-19.[53] Diagnosis and management are the same as when these complications arise from other causes.

Hypercoagulable State

COVID-19 induces a prothrombotic state from hyper-activation of the inflammatory and hemostatic pathways.[54] Thrombotic complications in adults with COVID-19 is well recognized but are rare in children with COVID-19 and when it occurs, is usually in the lungs.[55] Serum D-dimer levels are used to assess for hypercoagulation and a daily screen of D-dimer, PT, and

platelet count is recommended.[38] When not contraindicated, pharmacologic thromboprophylaxis combined with mechanical thromboprophylaxis with sequential compression devices are recommended. Anticoagulant thromboprophylaxis with low molecular weight heparin is recommended in patients who have elevated D-dimer levels or clinical risk factors for venous thromboembolism. Children who are at high risk for venous thromboembolism include those who are critically ill, with a history of thromboembolism, or those who have increased inflammatory markers (CRP>150 mg/l, D-dimer >1500 ng/ml, IL-6 >100pg/ml, ferritin >500 ng/ml), and should be treated with subcutaneous low molecular weight heparin (< 2months: 1.5mg/kg/dose every 12 hours; ≥ 2 months: 1mg/kg/dose every 12 hours) to achieve Anti-Xa factor levels of 0.5-1 IU/mL.[56] Children who are clinically unstable or have severe renal impairment should receive continuous intravenous infusion of unfractionated heparin as anticoagulant thromboprophylaxis using pediatric heparin nomogram to guide therapy.[57,58]

Myocarditis

Patients with MIS-C commonly have myocarditis, and occasionally, in severe acute COVID-19. Presentation and management are the same as that for myocarditis from other infections.

Clinics Care Points

- Pathophysiology and diagnosis of PARDS from COVID-19 is the same as PARDS from other causes.
- Intensivists must be familiar with additional precautions to be taken during intubation and aerosol generating procedures.
- Intensivists should know ventilator strategies, and therapies used specifically in COVID -19 acute respiratory failure including antiviral, anti-inflammatory, and immunomodulator therapies.

● Multiorgan dysfunction and failure from severe acute COVID-19 should be recognized and treated.

● COVID-19 induces a prothrombotic state and thrombotic complications in severe acute COVID-19 should be diagnosed and treated and thromboprophylaxis instituted in children at high risk for venous thromboembolism.

● A multi-disciplinary approach should be instituted to minimize spread of the virus within critical care units while still providing excellent patient care.

COVID-19 ASSOCIATED MIS-C

The diagnosis of MIS-C is usually made weeks after a child is infected with SARS-CoV-2 and almost all patients are positive for SARS-CoV-2 either by RT-PCR, SARS-CoV-2 antibody testing or both, while the rest have a history of contact with someone with COVID-19.[59-61] The CDC, World Health Organization (WHO) and Royal College of Paediatrics and Child Health (RCPCH) provided a definition of MIS-C from SARS-CoV-2 infection.[62-64] All three definitions have many similarities but the CDC definition is the most widely used in North America.

DEFINITION:

CDC definition of MIS-C:

- An individual <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); and
- No alternative plausible diagnoses; and

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms.

*Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.

**Including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin.

The CDC suggests that some individuals may fulfill full or partial criteria for Kawasaki disease (KD) but should be reported if they meet the case definition for MIS-C and to consider MIS-C in any child who dies with evidence of SARS-CoV-2 infection.

CLINICAL FEATURES:

Patients with MIS-C usually present with persistent fever, cardiorespiratory and gastrointestinal symptoms, mucocutaneous lesions, and in severe cases, hypotension, and shock. Cardiac, cardiorespiratory, and gastrointestinal complications are the most common reasons for PICU admission. Belay and colleagues reported illness involving at least four organ systems in almost 90% of cases in a cohort of 1,733 patients.[60] Children with MIS-C have required intensive care more than severe acute COVID-19 and intensivists should be cognizant of the similarities and differences between MIS-C and severe acute COVID-19.[60,61,65] Children with MIS-C are often male and previously healthy, while severe acute COVID-19 is more common in children with existing risk factors with no gender predilection. Large studies from US and UK have shown that MIS-C and severe acute COVID-19 are both more common in African American, Hispanic, and Asian children compared with white children. Mortality in hospitalized children is <2%.[60,61,66,67] Differences have been observed between the occurrence of MIS-C and severe acute COVID-19

among various age groups. Severe acute COVID -19 rates are higher in children 0-5 years and 13-20 years of age while MIS-C is higher in the 6–12-year age group.[61] MIS-C has been associated with more severe outcomes in children older than 5 years while severe acute COVID-19 is associated with worse outcomes in children < 1 year of age.[68,69] Higher values of D-dimer, CRP, ferritin, lower platelet and absolute lymphocyte count have been shown to be predictive of severe MIS-C. Higher neutrophil to lymphocyte ratio, higher CRP, and lower platelet count have been observed in MIS-C compared to COVID-19.[61] Mucocutaneous signs and symptoms on presentation are seen in almost two-thirds of patients with MIS-C, but only in 10% of patients with COVID-19.[61]

Abdominal pain and vomiting can occur in sixty percent of patients with MIS-C and of such severity as to be mistaken for acute appendicitis.[60] The possibility of MIS-C coexisting with acute appendicitis should be considered.[70,71] Patients with severe acute COVID-19 can present with gastrointestinal symptoms but usually not as severe as that seen in patients with MIS-C. Feldstein and colleagues reported gastrointestinal symptoms on presentation in ninety percent of patients with MIS-C compared to fifty eight per cent of patients with severe acute COVID-19.[61] Abdominal imaging in patients with MIS-C have demonstrated inflammation including mesenteric adenopathy, mesenteric edema, ascites, bowel wall thickening and gallbladder wall thickening (Fig.6).

Cardiorespiratory involvement, and the need for vasoactive agents were observed in fifty six percent, sixty seven percent, and forty five percent respectively in patients with MIS-C compared to nine, twelve, and nine percent respectively in patients with severe acute COVID-19 in a case series of 1,116 patients studied by Feldstein et al.[61] Belay and colleagues reported hypotension (51%), shock (37%), cardiac dysfunction (31%), and myocarditis (17%) in the largest cohort of

patients with MIS-C reported thus far.[60] Mucocutaneous lesions and conjunctival injection and laboratory markers of BNP and IL-6 were associated with coronary artery abnormalities.[61,68] The incidence of coronary artery dilation and aneurysms (CAA) in MIS-C is four to twenty four percent.[60,61,72-74] In patients with KD, the risk of coronary artery thrombosis is directly related to size of CAA and increases exponentially above a z-score of 10.[75,76] Depressed left ventricular function (LV) has been noted in a third of patients.[60,61] Similar to patients with other causes of poor cardiac function, children with MIS-C or severe acute COVID-19 with LV dysfunction are at risk for intracardiac thrombosis.[77] Knowledge of duration of persistence of abnormalities in inflammatory markers, troponin, D-dimer, LV dysfunction, and CAA is limited because of lack of consistent follow-up protocols and patient compliance. In the small number of children seen in follow-up so far, most of the abnormalities return to normal.[61,78]

Respiratory complications in MIS-C can be like those seen in severe acute COVID-19 with some differences. Lower respiratory infection was reported in seventeen percent of patients with MIS-C compared to thirty six percent of patients with severe acute COVID-19. Severe respiratory disease without cardiovascular involvement was observed in twenty four percent of MIS-C compared to seventy one percent of patients with severe acute COVID-19 in the study by Feldstein et al.[61] However patients with MIS-C had a greater need for noninvasive and invasive ventilation (36% and 18%) compared to those with severe acute COVID-19 (33% and 15%). This may be related to higher prevalence of cardiorespiratory complications in patients with MIS-C. Radiographic abnormalities in MIS-C with cardiorespiratory complications include pleural effusions, bilateral pulmonary consolidation with lower zone predominance (Fig.7,8). Pleural effusions are rarely reported in patients with severe acute COVID-19.[79] Depressed myocardial function, shock, need for aggressive intravascular volume expansion, severe systemic

inflammation, and hypoalbuminemia are seen more often in patients with MIS-C compared to those with severe acute COVID-19, likely contributing to third spacing and pleural effusion in patients with MIS-C.

DIAGNOSIS:

The diagnostic pathway for MIS-C recommended by the American College of Rheumatology is a clinically useful tool.[50] The tier 1 and tier 2 evaluations shown in figure 9 are a comprehensive list of tests for evaluation of MIS-C. Recommendations for laboratory studies for patients in the ICU include daily CBC, basic metabolic panel, and D-dimer, troponin every six hours, and BNP every forty-eight hours and adjusted in frequency based on clinical condition. Recommendations for monitoring of cardiac complications in MIS-C in addition to those listed in tier 2 include the following: 1. EKG every forty-eight hours in hospitalized patients or more frequently for those with conduction abnormalities and again at follow-up. 2. Echocardiogram repeated one to two weeks and four to six weeks after initial presentation. Patients with LV dysfunction and coronary artery aneurysm require more frequent echocardiography. 3. Cardiac MRI two to six months after the acute illness to assess for myocardial fibrosis and scarring.

Patients who do not meet all the criteria for diagnosis of MIS-C should be evaluated for diseases with similar presentations, such as KD, toxic shock syndrome or hemophagocytic lymphohistiocytosis.

MANAGEMENT:

Treatment should be directed at supportive care of multi-organ dysfunction and mitigation of the underlying inflammatory process. The treatment of MIS-C as recommended by the American College of Rheumatology is outlined in figure 10.[50]

Additional treatment guidelines:

1. Initial treatment with IVIG and glucocorticoids is associated with lower risk of left ventricular dysfunction, shock, and decreased need for adjunctive therapy than with IVIG alone.[80]
2. Anakinra 1-2mg/kg/d should be considered in patients in whom corticosteroids are contraindicated.
3. High dose anakinra, > 4mg/kg/d is recommended for those refractory to treatment with IVIG with or without steroids. In some cases, anakinra as high as 10 mg/kg/day (max 100 mg/ dose) through subcutaneous or intravenous routes divided every six to twelve hours may be needed. If the patient does not show improvement with this regimen, the diagnosis of MIS-C should be reconsidered.
4. If used, immunomodulation therapy should be tapered over 2-3 weeks or longer to avoid rebound inflammation.
5. Antiplatelet and antithrombotic therapy with low dose aspirin (3-5mg/kg/d up to 81mg/d) is recommended in all patients with MIS-C if they do not have uncontrolled bleeding or risk for bleeding. Aspirin therapy should be continued until normalization of platelet count and normal coronary arteries are confirmed at $\geq$ 4 weeks after diagnosis.
6. Anticoagulation with enoxaparin to achieve anti-factor Xa level of 0.5-1 or warfarin with INR level of 2 to 3 is recommended in patients with coronary artery Z-score greater than 10 and in those with moderate or severe LV dysfunction with ejection fraction <35%.
7. Empiric antibiotics should be used in all patients with severe MIS-C until cultures are negative for forty-eight hours or as directed by infectious disease consultants. Ceftriaxone may be used alone or in combination with metronidazole for possible appendicitis or vancomycin/clindamycin for those with possible toxic shock syndrome.

8. Stress ulcer prophylaxis is recommended in patients receiving aspirin and or steroids.
9. Consultation with infectious disease, immunology and cardiology subspecialists is recommended for all patients. Hematologists and endocrinologists may also be needed to guide anticoagulation and steroid management.

MIS-C AND KAWASAKI DISEASE (KD)

MIS-C may be especially difficult to differentiate from KD despite well-established diagnostic criteria.[62,81] The following are differences between MIS-C and KD:

1. MIS-C is common among black and Hispanic children while incidence of KD is highest in children of Asian descent.

2. MIS-C is reported in children from three months to twenty years with those older than five years more severely affected while KD is usually seen in children less than five years of age.

3. Patients with MIS-C frequently need PICU admission while patients with KD rarely do.

4. Increased serum ferritin, leukopenia, lymphopenia, and thrombocytopenia are common in MIS-C. Thrombocytosis is a characteristic feature of KD.

5. Myocarditis, LV cardiac dysfunction, shock, the need for intravascular fluid expansion, and vasopressor/inotropic support is more common in MIS-C.

6. Coronary artery dilatations and aneurysms are reported in four to twenty four percent of children with MIS-C. The progression and long-term sequelae are not known at this time. In the pre–IVIG era, CAA occurred in twenty-to-twenty five percent of children with KD.[82] With IVIG therapy, persistent CAAs are much less but still noted in four percent to six percent of patients, with approximately one percent who develop giant CAA despite treatment.[83,84]

7. Respiratory and cardiorespiratory complications requiring non-invasive or invasive ventilation are more common in children with MIS-C.

8. Gastrointestinal, and neurological complications and coagulopathy are more common in MIS-C.

9. IVIG and moderate-high dose aspirin are established recommended treatment for KD.[85] In addition to IVIG and aspirin, steroids and biological drugs are frequently used in patients with MIS-C.[50]

10. Most children with KD have a good prognosis while the long-term clinical outcomes of MIS-C are not clear.

Clinics Care Points

- Intensivists should be familiar with the CDC definition of MIS-C and various clinical presentations of MIS-C.
- Intensivists should know the differences in clinical manifestations of severe acute COVID-19 and MIS-C.
- Algorithms for diagnosis and management of MIS-C should be followed.
- Intensivists should be aware of the cardiorespiratory, cardiac, and gastrointestinal complications of MIS-C, their presentation, and management.
- Intensivists should be familiar with the differential diagnosis for MIS-C and especially its differentiation from Kawasaki disease.

UNIQUE PICU CARE ISSUES RELATED TO THE PANDEMIC

The SARS-CoV-2 pandemic has demanded unprecedented and rapid adaptation of all personnel involved in the care of critically ill children. Surges of this pandemic which caused acute

shortage of ICU beds worldwide resulted in many PICU teams providing care for adults with COVID-19 in addition to children with severe acute COVID-19.[86,87] Hospitals must develop protocols for implementation in their critical care units based on their needs and resources with emphasis on minimizing the spread of virus while still providing excellent patient care.

The following recommendations can help PICUs during the current pandemic and future infection outbreaks:[88]

1. Monitoring: Monitoring patients from outside the room while having a direct line of sight might require installation of windows or glass doors.

2. Nursing care: Moving intravenous pumps outside of patient rooms while paying attention to the possibilities of inadvertent dislodgement of catheters, increased risk of central line-associated bloodstream infection and inability of nurses to hear pump alarms when they are inside the patient rooms with PPE. Reduction, or grouping of blood sampling as much as possible.

3. Respiratory care: Coordination of team members to minimize entry into rooms, address measures to decrease aerosol generation, set appropriate ventilator alarm limits, change ventilator circuits or filters as needed rather than by protocol, and use of metered dose inhalers instead of nebulizers when possible. Consider vibrating mesh nebulizer rather than in-line gas-driven nebulizer when nebulized medication must be given. Prone positioning teams and protocols should be in place to safely place patients in the prone position while addressing possible dislodgement of tubes and catheters and development of pressure ulcers.

4. Pharmacy: Critical care pharmacists can help with development of specific management guidelines as treatments evolve during the pandemic and help with measures to reduce the number of times a nurse must enter patient rooms for medication administration.

5. Structure related: Zones and protocols should be developed for donning and doffing PPE. A protocol should be developed for room cleaning and disinfection with approved disinfectants while ensuring safety of environmental service workers.

6. Patient communication**:** Social workers, child-life specialists, patient representatives, and pastoral care providers can be enlisted along with use of audio or video communication to help facilitate communication with family members during pandemic-induced restricted visiting.

7. Mental health issues of all team members should be addressed. Posttraumatic stress (PTS) has been noted to be high among pediatric critical care physicians in association with various COVID-19 patient care experiences. These observations along with association of PTS with thoughts of quitting the profession because of the pandemic could have implications for the workforce in the future.[89]

PUBLIC HEALTH CONCERNS FOR CHILDREN

1. Mental Health: The mental health crisis facing children was substantial even prior to the pandemic. The significant pressures on families, schools, and communities resulting from the pandemic have made the situation worse. Children's hospitals are feeling the considerable burden of this crisis every day. Emergency Rooms are filled to capacity, and staff is at the breaking point. According to the Kaiser Family Foundation, there have been marked increases in suicidal ideations, anxiety disorders, OCD diagnosis, and substance abuse in children.[90] Significant efforts and resources are needed to address the mental health crisis in children.

2. The fragility of the medical home and health system: Children are best served in a coordinated, fully staffed medical home. Care is coordinated, and the most medically fragile children receive timely and coordinated care. The pandemic, however, has had a negative impact

on America's pediatric practices. In a recent survey by the American Academy of Pediatrics, two-thirds of practices have experienced a significant decrease in visits.[91] This has both public health impact (delays in vaccines, late diagnosis) and a negative fiscal impact on the long-term survival of the medical home.

Tags for SEO: severe acute COVID-19, MIS-C, hyperinflammation, Kawasaki disease

ACKNOWLEDGEMENT

The authors thank Dr. Tej Phatak, MD, MBA, Chief of Pediatric Radiology at Children's Hospital of New Jersey at Newark Beth Israel Medical Center for providing us with radiology images used in this review article.

REFERENCES

1. Centers for Disease Control and Prevention (2021): Laboratory-Confirmed COVID-19-Associated Hospitalizations. https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html#virusTypeDiv
2. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China**.** Pediatrics 2020 Vol. 145 Issue 6. doi: 10.1542/peds.2020-0702
3. Lu X, Zhang L, Du H, et al. N Engl J Med 2020 Vol. 382 Issue 17 Pages 1663-1665. doi: 10.1056/NEJMc2005073
4. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine 2020 Vol. 24 Pages 100433. doi: 10.1016/j.eclinm.2020.100433
5. Viner RM, Ward JL, Hudson LD, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Arch Dis Child 2020. doi: 10.1136/archdischild-2020-320972
6. Gaythorpe KAM, Bhatia S, Mangal T, et al. Children's role in the COVID-19 pandemic: a systematic review of early surveillance data on susceptibility, severity, and transmissibility. Sci Rep 2021 Vol. 11 Issue 1 Pages 13903. doi: 10.1038/s41598-021-92500-9
7. Parcha V, Booker KS, Kalra R, et al. A retrospective cohort study of 12,306 pediatric COVID-19 patients in the United States. Sci Rep 2021 Vol. 11 Issue 1 Pages 10231. doi: 10.1038/s41598-021-89553-1

8. Delahoy MJ, Ujamaa D, Whitaker M, et al. Hospitalizations associated with COVID-10 among children and adolescents-COVID-NET, 14 states, March 1, 2020-August 14, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1255-60
9. Graff K, Smith C, Silveira L, et al. Risk Factors for Severe COVID-19 in Children. Pediatr Infect Dis J 2021 Vol. 40 Issue 4 Pages e137-e145. 10.1097/INF.0000000000003043
10. Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. JAMA Netw Open 2021 Vol. 4 Issue 4 Pages e215298. doi: 10.1001/jamanetworkopen.2021.5298
11. Children's Hospital Association and the American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report
12. Siegel DA, Reses HE, Cool AJ, et al. Trends in COVID-19 Cases, Emergency Department Visits, and Hospital Admissions Among Children and Adolescents Aged 0-17 Years - United States, August 2020-August 2021. MMWR Morb Mortal Wkly Rep 2021 Vol. 70 Issue 36 Pages 1249-1254. doi: 10.15585/mmwr.mm7036e1
13. Cevik M, Kuppalli K, Kindrachuk J, et l. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ 2020;371:m3862.
14. Mangalmurti N, Hunter CA. Cytokine Storms: understanding COVID-19. Immunity 2020;53(1):19–25.
15. Bixler D, Miller AD, Mattison CP, et al. SARS-CoV-2-associated deaths among persons aged <21 years – United States, February 12-July 31, 2020. MMWR Morb Mortal Wkly report 2020; 69:1324.

16. Gonzalez-Dambrauskas S, Vasquez-Hoyos P, Camporesi A, et al. Pediatric Critical Care and COVID-19. Pediatrics. 2020;146(3):e20201766. doi: 10.1542/peds.2020-1766.

17. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr 2020:174(9):868-73.

18. Kalyanaraman M, McQueen D, Morparia K, et al. ARDS in an ex-premature infant with bronchopulmonary dysplasia and COVID-19. Pediatric Pulmonology 2020;55(10):2506–7

19. Moeller A, Thanikkel L, Duijts L, et al. COVID-19 in children with underlying chronic respiratory diseases: survey results from 174 centres. ERJ Open Res. 2020;6(4):00409-2020. doi: 10.1183/23120541.00409-2020.

20. Fernandes DM, Oliveira CR, Guerguis S, et al. Severe acute respiratory syndrome Coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr 2021;230:23-31.

21. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill.* 2020;25:2000045. doi: 10.2807/1560-7917.ES.2020.25.3.2000045.

22. Chen Z, Fu J, Shu O, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr. 2020;16(3):240-246. doi: 10.1007/s12519-020-00345-5.

23. Lu X, Zhang L, Hui D, et al. SARS-CoV-2 infection in children. N Engl J Med. N Engl J Med 2020; 382:1663-5.

24. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. J Pediatr 2020; 223:14-9.e2.

25. Fisler G, Izard SM, Shah S, et al: Ann Intensive Care: Characteristics and risk factors associated with critical illness in pediatric COVID-19. Ann Intensive Care. 2020;10(1):171. doi: 10.1186/s13613-020-00790-5.

26. Hariyanto TI, Japar KV, Kwenandar F, et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. Am J Emerg Med. 2021;41:110–9. doi: 10.1016/j.ajem.2020.12.076.

27. Foust AM, Phillips GS, Chu WC, et al. International expert consensus statement on chest imaging in pediatric COVID-19 patient management: imaging findings, imaging study reporting, and imaging study recommendations radiology: Cardiothoracic Imaging 2020;2(2):e200214.

28. Nino G, Zember J, Sanchez-Jacob R, et al. Pediatric lung imaging features of COIVD-19: a systematic review and meta-analysis. Pediatr Pulmonol. 2021;56(1):252-263. doi: 10.1002/ppul.25070.

29. Chung M, Bernheim A, Mei X. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV) *Radiology.*2020;295:202–7.

30. Kumar J, Meena J, Yadav A, Yadav J. Radiological Findings of COVID-19 in Children: A Systematic Review and Meta-Analysis. J Trop Pediatr. 2021;67(3):fmaa045. doi: 10.1093/tropej/fmaa045.

31. Chen A, Huang J, Liao Y, et al. Differences in clinical and imaging presentation of pediatric patients with COVID-19 in comparison with adults. Radiol Cardiothorac Imaging 2020;2(2):e200117.

32. Denina M, Scolfaro C, Silvestro E, Pruccoli G, Mignone F, Zoppo M, Ramenghi U, Garazzino S. Lung ultrasound in children with COVID-19. Pediatrics. 2020;146(1):e20201157. doi: 10.1542/peds.2020-1157.

33. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5):428-39. doi: 10.1097/PCC.0000000000000350.

34. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: Different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-1102.

35. Kneyber MCJ, de Luca D, Calderini E, et al.; Section Respiratory Failure of the European Society for Paediatric and Neonatal Intensive Care. Recommendations for mechanical ventilation of critically ill children from the paediatric mechanical ventilation consensus conference (PEMVECC). Intensive Care Med. 2017;43:1764–80.

36. Rimensberger PC, Cheifetz IM. Pediatric Acute Lung Injury Consensus Conference Group: Ventilatory support in children with pediatric acute respiratory syndrome: proceedings from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med 2015; 16:S51-S60.

37. Matava CT, Kovatsis PG, Lee JK, et al. Pediatric airway management in COVID-19 patients: Consensus guidelines from the society for pediatric anesthesia's Pediatric Difficult Intubation Collaborative and the Canadian Pediatric Anesthesia Society. Anesth Analg. 2020;131(1): 61-73.doi: 10.1213/ANE.0000000000004872.

38. Rimensberger PC, Kneyber MCJ, Deep A, et al. Caring for critically ill children with suspected or proven coronavirus disease 2019 infection: recommendations by the scientific sections' collaborative of the European Society of Pediatric and Neonatal Intensive Care. Pediatr Crit Care Med. 2021;22(1):56-67.
39. Brower RG, Matthay MA, Morris A, et al. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–08.
40. Khemani RG, Parvathaneni K, Yehya N, et al. Positive end-expiratory pressure lower than the ARDS network protocol is associated with higher pediatric acute respiratory distress syndrome mortality. Am J Respir Crit Care Med. 2018;198(1):77-89. doi: 10.1164/rccm.201707-1404OC. PMID: 29373802; PMCID: PMC6034123.
41. Kache S., Chisti MJ, Gumbo F, et al. COVID-19 PICU guidelines: for high- and limited-resource settings. Pediatr Res. 2020 Nov;88(5):705-716. doi: 10.1038/s41390-020-1053-9.
42. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf
43. https://www.fda.gov/media/137564/download
44. Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate use of remdesivir in children with severe acute COVID-19. Pediatrics. 2021;147(5):e2020047803.
45. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. J Pediatric Infect Dis Soc. 2021;10(1):34-48. doi: 10.1093/jpids/piaa115. PMID: 32918548; PMCID: PMC7543452.

46. Jacinto JP, Patel M, Goh J, et al. Remdesivir-induced symptomatic bradycardia in the treatment of COVID-19 disease. Heart Rhythm Case Rep. 2021 Aug; 7(8): 514–517.

47. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/. Accessed October 20, 2021.

48. Horby P, Lim WS, Emberson J, et al. Dexamathasone in hospitalized patients with COVID-19. N Engl J Med 2021;384(8):693-704.

49. Sterne JA, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA. 2020;324(13):1330–1341. doi:10.1001/jama.2020.17023.

50. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 2. Arthritis Rheumatol. 2021;73(4):e13-e29. doi: 10.1002/art.41616. Epub 2021 Feb 15. PMID: 33277976. Arthritis Rheumatol. 2021;73(4):e13-e29.doi: 10.1002/art.41616.

51. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med. 2020;21(2):e52-e106.

52. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179–c184.

53. Siracusa, L., Cascio, A., Giordano, S. *et al.* Neurological complications in pediatric patients with SARS-CoV-2 infection: a systematic review of the literature. Ital J Pediatr 2021;47:123. https://doi.org/10.1186/s13052-021-01066-9.

54. Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19.Lancet Haematol. 2020;7(6):e438-e440.doi: 10.1016/S2352-3026(20)30145-9.

55. Zaffanello M, Piacentini G, Nosetti L, et al. Thrombotic risk in children with COVID-19 infection: A systematic review of the literature. Thromb Res. 2021;205: 92–8. doi: 10.1016/j.thromres.2021.07.011.

56. Loi M, Branchford B, Kim J, et al. COVID-19 anticoagulation recommendations in children. Pediatr Blood Cancer. 2020;67(9):e28485. doi: 10.1002/pbc.28485. Epub 2020 Jun 18. PMID: 32558124; PMCID: PMC7323104.

57. Goldenberg NA, Sochet A, Albisetti M, et al. Consensus- based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID- 19- related illness. J Thromb Haemost 2020;18(11):3099-3105. doi: 10.1111/jth.15073.

58. Monagle P, Chan A, Goldenberg N, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis 9th edition: American College of Chest Physicians evidence based clinical practice guidelines. Chest 2012;141(2 Suppl):e737S-e801S.doi: 10.1378/chest.11-2308.

59. Hospitalizations associated with COVID-19 among children and adolescents — COVID-NET, 14 states, March 1, 2020–August 14, 2021. *Weekly* / September 10, 2021 / 70(36);1255- 1260 https://www.cdc.gov/mmwr/volumes/70/wr/mm7036e2.htm.

60. Belay ED, Abrams J, Oster ME et al. Trends in geographic and temporal distribution of US children with Multisystem Inflammatory Syndrome during the COVID-19 pandemic. JAMA Pediatr. 2021;175(8):837-45. Doi:10.1001/jamapediatrics.2021.0630.

61. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 2021;323(11):1074-87. DOI:10.1001/jama2021.2091.

62. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html.

63. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. June 2020. URL: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims.

64. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. May 2020. URL: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.

65. Fernandes DM, Oliveira CR, Guerguis S, et al. Severe acute respiratory syndrome Coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr 2021;230:23-31. Doi: https://doi.org/10.1016/j.jpeds.2020.11.016.

66. Saatci D, Ranger TA, Garriga C, et al. Association between race and COVID-19 outcomes among 2.6 million children in England. JAMA Pediatr. *2*021;175(9):928–938. doi:10.1001/jamapediatrics.2021.1685.

67. Payne AB, Gilani Z, Godfred-Cato S, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Network Open. 2021;4(6):e2116420.doi:10.1001/jamanetworkopen.2021.16421.

68. Abrams JY, Oster ME, Godfred-Cato SE. et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021;5(5):323-31. doi: 10.1016/S2352-4642(21)00050-X. Epub 2021 Mar 10. PMID: 33711293; PMCID: PMC7943393.

69. Bellino S, Punzo O, Rota MC, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics. 2020;146(4):e2020009399.

70. Anderson JE, Campbell JA, Durowoju L, et al. COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) presenting as appendicitis with shock. J Pediatr Surg Case Rep. 2021;71: 101913. doi: 10.1016/j.epsc.2021.101913

71. Meyer JS, Robinson G, Moonah S, et al. Acute appendicitis in four children with SARS-CoV-2 infection. J Pediatr Surg Case Rep. 2021;64:101734. Doi:10.1016/j.epsc.2020.101734

72. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347– 58.

73. Kavurt AV, Bağrul D, Gül AEK, et al. Echocardiographic findings and correlation with laboratory values in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. Pediatr Cardiol. 2021 Sep 26:1–13. doi: 10.1007/s00246-021-02738-3. Epub ahead of print. PMID: 34564734; PMCID: PMC8475320.

74. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19

infection in Europe. Circulation 2021;143(1):21-32. https://doi.org/10.1161/CIRCULATIONAHA.120.050065

75. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association [review]. Circulation 2017;135(17): e927– 99.
76. Tsuda E, Tsujii N, Hayama Y. Stenotic lesions and the maximum diameter of coronary artery aneurysms in Kawasaki disease. J Pediatr 2018;194:165–70.
77. Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. Circulation 2013;128(24):2622–703.
78. Davies P, du Pré P, Lillie J, Kanthimathinathan HK. One-year outcomes of critical care patients post-COVID-19 multisystem inflammatory syndrome in children. JAMA Pediatr. 2021Aug 30:e212993. doi: 10.1001/jamapediatrics.2021.2993. Epub ahead of print. PMID: 34459875; PMCID: PMC8406209.
79. Rostad BS, Shah JH, Rostad CA, et al. Chest radiograph features of multisystem inflammatory syndrome in children (MIS-C) compared to pediatric COVID-19. *Pediatr Radiol*. 2021;51(2):231-238. doi:10.1007/s00247-020-04921-9.
80. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children - Initial Therapy and Outcomes. N Engl J Med. 2021;385(1):23-34. doi: 10.1056/NEJMoa2102605. Epub 2021 Jun 16. PMID: 34133855; PMCID: PMC8220972.
81. Zhang QY, Xu BW, Du JB. Similarities and differences between multiple inflammatory syndrome in children associated with COVID-19 and Kawasaki disease: clinical presentations, diagnosis, and treatment. World J Pediatr. 2021;17(4):335-340. doi:

10.1007/s12519-021-00435-y. Epub 2021 May 20. PMID: 34013488; PMCID: PMC8134825.

82. Kato H, Sugimura T, Akagi T, et al. Long- term consequences of Kawasaki disease. A 10- to 21- year follow- up study of 594 patients**.** Circulation 1996;94(6):1379–85.
83. Newburger JW. Treatment of Kawasaki disease. Lancet 1996;347(9009):1128.
84. Ogata S, Tremoulet AH, Sato Y, et al. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. Int J Cardiol. 2013;168(4):3825–8.
85. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med. 1986;315(6):341-7.
86. Yager PH, Whalen KA, Cummings BM. Repurposing a pediatric ICU for adults. N Engl J Med. 2020;382(22):e80.
87. Wasserman E, Toal M, Nellis M, et al. Rapid transition of a PICU space and staff to adult coronavirus disease 2019 ICU care. Pediatr Crit Care Med 2021;22(1):50-55.
88. Halpern NA, Kaplan LJ, Rausen M, et al. Configuring ICUs in the COVID-19 era. Updated June 15, 2020. https://www.sccm.org/COVID19RapidResources/Resources/Configuring-ICUs-in-the-COVID-19-Era-A-Collection.
89. Kalyanaraman M, Sankar A, Timpo E, et al. Posttraumatic stress among pediatric critical care physicians in the United States in association with coronavirus disease 2019 patient care experiences. Accepted for publication in Journal of Intensive Care Medicine.
90. Kaiser Family Foundation. www.kff.org/coronavirus-covid-19/issue-brief/mental-health-and-substance-use-considerations-among-children-during-the-covid-19-pandemic/

91. American Academy of Pediatrics: PLACES Survey. https://publications.aap.org/aapnews/news/14172/Survey-Pediatricians-reeling-from-pandemic-s?searchresult=1 November 2020.

Fig. 4. Chest radiograph of infant with bronchopulmonary dysplasia who developed COVID-19 ARDS showing bilateral ground glass opacities.

Fig. 5. Management of acute respiratory failure in severe COVID-19.

Abbreviations: SpO_2, oxygen saturation by pulse oximetry; NIV, non-invasive ventilation; HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; FiO_2, fraction of inspired oxygen; PPE, personal protective equipment; PAPR, powered air purifying respirator; LMA, laryngeal mask airway; HEPA, high-efficiency particulate air filter; RSI, rapid sequence intubation; ETT, endotracheal tube; POCUS, point-of-care ultrasound; PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome; Pplat, plateau pressure; PaO_2, arterial partial pressure of oxygen; OI, oxygenation index; OSI, oxygenation saturation index.

Fig. 6. Abdominal CT of 11-year-old black male with MIS-C who presented with fever, mucocutaneous symptoms, severe abdominal pain, vomiting, and CoV-2 Ab Ig G +. Bowel wall thickening of ascending colon (black arrow) with several enlarged lymph nodes (white arrow).

Fig.7. Chest radiographs of a 5-year-old Hispanic male with MIS-C who presented with fever, cardiorespiratory, mucocutaneous, and abdominal symptoms; hypoalbuminemia; positive for SARS-CoV-2 RT-PCR and CoV-2 Ig G antibody.

(A) On presentation when he had moderately decreased left ventricular systolic function and required BiPAP.
(B) Three days after presentation with normal biventricular systolic function and resolution of respiratory symptoms, hypoalbuminemia, and fever.

Fig. 8. Chest CT of an 18-year-old black male with MIS-C who presented with fever, shock with LV dysfunction requiring inotropic/vasoactive medication, pneumonia, mucocutaneous symptoms, hypoalbuminemia, CoV-2 Ab Ig G +, requiring BiPAP with pleural effusion (black arrow) and bilateral lower lobe consolidation (white arrow).

Fig. 9. (with permission from Henderson LA, et al. Arthritis & Rheumatology, Volume: 73, Issue: 4, Pages: e13-e29, First published: 05 December 2020, DOI: (10.1002/art.41616).

Diagnostic pathway for multisystem inflammatory syndrome in children (MIS- C). Moderate-to- high consensus was reached by the Task Force in the development of this diagnostic pathway for MIS- C associated with severe acute respiratory syndrome coronavirus 2 (SARS–CoV- 2).

[1]An epidemiologic link to SARS–CoV- 2 infection is defined as a child with any of the following criteria: positive for SARS–CoV- 2 by polymerase chain reaction (PCR), positive for SARS–CoV- 2 by serology, preceding illness resembling coronavirus disease 2019 (COVID-19), or close contact with an individual with confirmed or suspected COVID- 19 in the past 4 weeks. [2]Suggestive clinical features include rash (polymorphic, maculopapular, or petechial, but not vesicular), gastrointestinal symptoms (diarrhea, abdominal pain, or vomiting), oral mucosal changes (red and/or cracked lips, strawberry tongue, or erythema of the oropharyngeal mucosa), conjunctivitis (bilateral conjunctival infection without exudate), and neurologic symptoms (altered mental status, encephalopathy, focal neurologic deficits, meningismus, or papilledema). [3]The complete metabolic panel (CMP) includes measurement of sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, creatinine, glucose, calcium, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin. [4]Procalcitonin, cytokine panel, and blood smear test results should be sent, if available. [5]Serologic test results should be sent if not sent in tier 1 evaluation, and if possible, SARS–CoV- 2 IgG, IgM, and IgA test results should be sent.

Abbreviations: CRP, C- reactive protein; ESR, erythrocyte sedimentation rate; ALC, absolute lymphocyte count; CBC, complete blood cell count; BNP, B- type natriuretic peptide; PT, prothrombin time; PTT, partial thromboplastin time; LDH, lactate dehydrogenase; u/a, urinalysis; EKG, electrocardiogram.

Fig. 10. (with permission from Henderson LA et al. Arthritis & Rheumatology, Volume: 73, Issue: 4, Pages: e13-e29, First published: 05 December 2020, DOI:10.1002/art.41616).

Algorithm for initial immunomodulatory treatment of multisystem inflammatory syndrome in children (MIS- C). Moderate- to- high consensus was reached by the Task Force in the development of this treatment algorithm for MIS- C associated with severe acute respiratory syndrome coronavirus 2.

[1]Intravenous immunoglobulin (IVIG) dosing is 2 gm/kg based on ideal body weight. Cardiac function and fluid status should be assessed before IVIG is given. In some patients with cardiac dysfunction, IVIG may be given in divided doses (1 gm/kg daily over 2 days). [2]Methylprednisolone or another steroid at equivalent dosing may be used. [3]Refractory disease is defined as persistent fevers and/or ongoing and significant end- organ involvement. [4]Low- to- moderate–dose glucocorticoids (methylprednisolone 1–2 mg/kg/day) may be considered for first- line therapy in some MIS- C patients with concerning features (ill appearance, highly elevated B- type natriuretic peptide levels, unexplained tachycardia) who have not yet developed shock or organ- threatening disease. [5]If the patient was given low- to- moderate–dose glucocorticoids as first- line therapy, methylprednisolone IV dosing should be 10–30 mg/kg/day for intensification treatment.

Fig. 1. Characteristics of children with COVID-19.

Hoang, A., Chorath, K., Moreira, A., Evans, M., Burmeister-Morton, F., Burmeister, F., Naqvi, R., Petershack, M., & Moreira, A. (2020). COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine*, *24*, 100433. https://doi.org/10.1016/j.eclinm.2020.100433

Table 2
Patient characteristics, exposure status, and hospital stay.

	# Studies	# Patients	N (%)
Male gender	113	4640	2582 (55.6)
Mean age (years)	116	4517	8.9 ± 0.5
Exposure from family member	94	1360	1028 (75.6)
Travel to/lived-in high-risk area	84	962	689 (71.6)
NP/throat SARS-CoV-2 detection	89	787	681 (86.5)
Positive fecal viral shedding	31	321	67 (20.9)
Positive urine viral shedding	22	54	2 (3.7)
Length of hospital stay (days)	68	652	11.6 ± 0.3
Intensive care unit admission	88	3564	116 (3.3)

Continuous data presented as Mean ± SD. NP-nasopharyngeal.

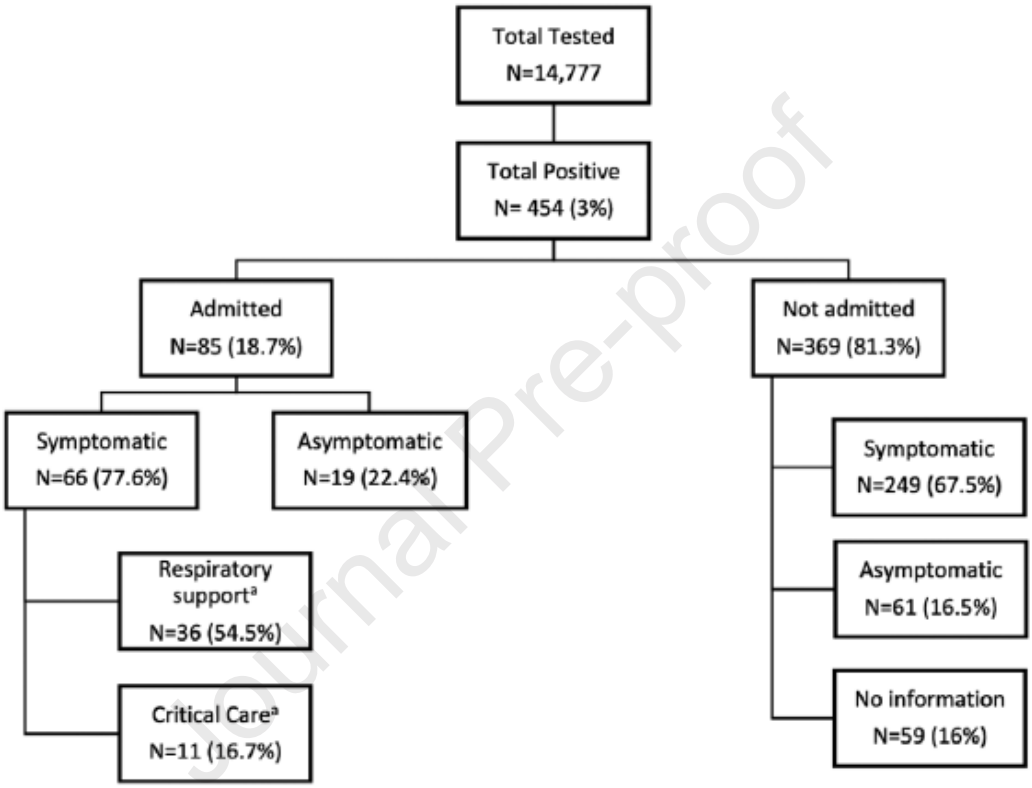
Fig. 2. Characteristics of children with COVID-19.

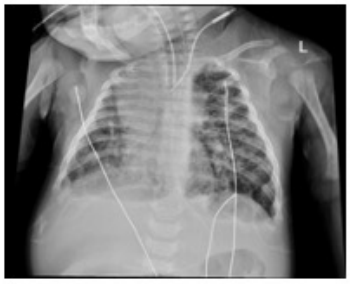
Table 3
Underlying medical conditions and co-infection.

	# Studies	# Patients	N (%)
Underlying conditions	**20**	**655**	**233 (35.6)**
Immunosuppression			71 (30.5)
Respiratory			49 (21.0)
Cardiovascular			32 (13.7)
Medically complex/congenital malformations			25 (10.7)
Not reported			17 (7.3)
Hematologic			8 (3.8)
Neurologic			8 (3.4)
Obesity			8 (3.4)
Prematurity			5 (3.4)
Endocrine/metabolic			5 (2.1)
Renal			4 (1.7)
Gastrointestinal			1 (0.5)
Co-infections	**35**	**1183**	**72 (5.6)**
Bacterial			
Mycoplasma pneumoniae			42 (58.3)
Enterobacter sepsis			2 (2.8)
Streptococcus pneumoniae			1 (1.4)
Viral			
Influenza virus A/B			8 (11.1)
Respiratory syncytial virus			7 (9.7)
Cytomegalovirus			3 (4.2)
Epstein-Barr virus			3 (4.2)
Adenovirus			2 (2.8)
Human metapneumovirus			2 (2.8)
Human parainfluenza virus			2 (2.8)

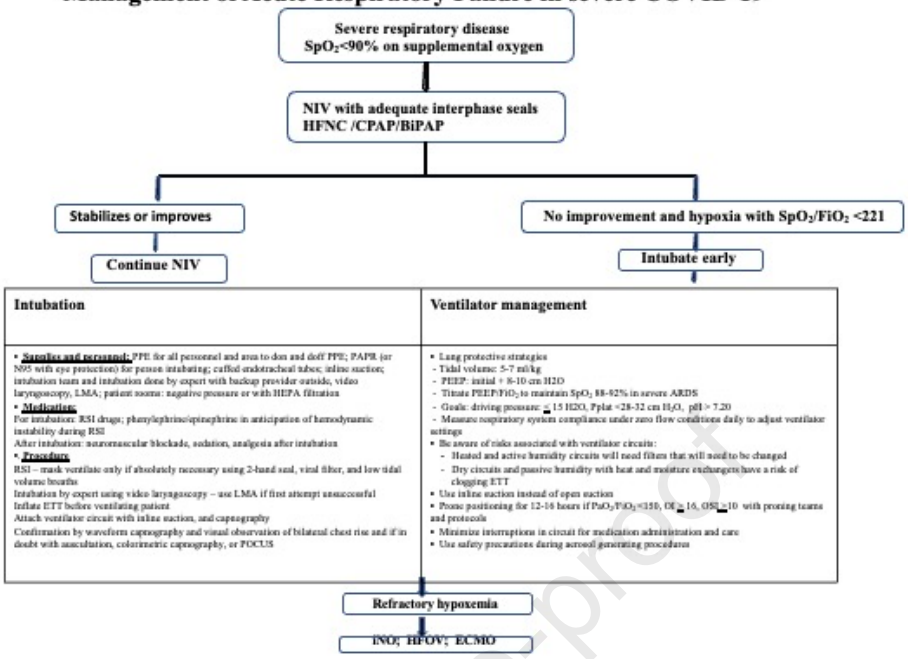
Fig. 3. Summary of children with positive COVID-19 test (Denver, Colorado).

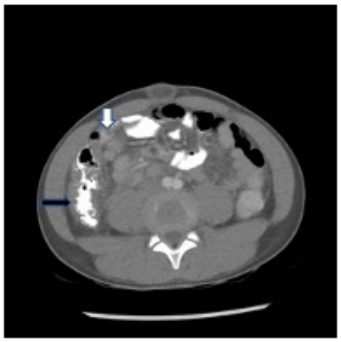
Graff, K., Smith, C., Silveira, L., Jung, S., Curran-Hays, S., Jarjour, J., Carpenter, L., Pickard, K., Mattiucci, M., Fresia, J., McFarland, E. J., Dominguez, S. R., & Abuogi, L. (2021). Risk Factors for Severe COVID-19 in Children. *Pediatr Infect Dis J, 40*(4), e137-e145. https://doi.org/10.1097/INF.0000000000003043

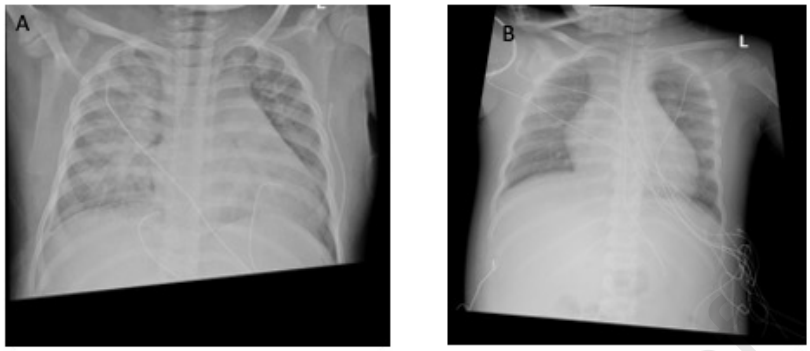


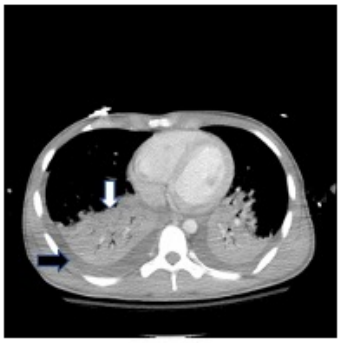


Management of Acute Respiratory Failure in severe COVID-19

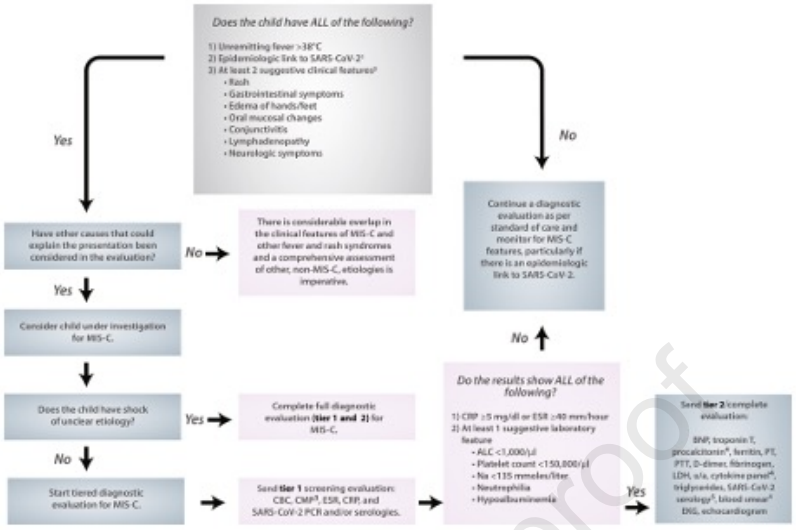








Diagnostic Pathway for Multisystem Inflammatory Syndrome In Children



Initial Immunomodulatory Treatment of Multisystem Inflammatory Syndrome In Children