

Diagnosis and Acute Management of COVID-19 and Multisystem Inflammatory Syndrome in Children

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Abstract: Most children with coronavirus disease 2019 (COVID-19) infection are asymptomatic or have mild disease. About 5% of infected children will develop severe or critical disease. Rapid identification and treatment are essential for children who are critically ill with signs and symptoms of respiratory failure, septic shock, and multisystem inflammatory syndrome in children. This article is intended for pediatricians, pediatric emergency physicians, and individuals involved in the emergency care of children. It reviews the current epidemiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children, summarizes key aspects of clinical assessment including identification of high-risk patients and manifestations of severe disease, and provides an overview of COVID-19 management in the emergency department based on clinical severity.

Key Words: COVID-19, multisystem inflammatory syndrome in children, MIS-C, sepsis, critical illness

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TARGET AUDIENCE

This article is for pediatric emergency physicians, emergency physicians, pediatricians, family physicians, and other health care providers caring for acutely ill children in emergency departments and urgent care settings.

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LEARNING OBJECTIVES

After completion of this article, the reader should be better able to:

1. Describe the common, uncommon, and severe presentations of COVID-19 infection in children.
2. Identify children with COVID-19 at higher risk for severe disease.
3. Propose management strategies in the emergency department according to illness severity.

INTRODUCTION, BACKGROUND, AND EPIDEMIOLOGY OF SARS-CoV-2 IN CHILDREN

As of June 2021, more than 177 million cases of coronavirus disease 2019 (COVID-19), the infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been confirmed worldwide, with over 3.8 million deaths.¹ The prevalence of symptomatic COVID-19 infection is lower in children compared with adults.² Data from several large-cohort studies suggest that children account for approximately 2.0% of total COVID-19 infections³ or more than 3.5 million known COVID-19 infections globally. Although most of the children infected with SARS-CoV-2 have asymptomatic or mild disease, approximately 5% to 7% will present with or develop severe or critical manifestations of COVID-19, including myocardial dysfunction, shock, acute respiratory distress syndrome (ARDS), altered mental status, multiple organ dysfunction syndrome, or multisystem inflammatory syndrome in children (MIS-C).⁴⁻⁶

CLINICAL ASSESSMENT AND DIAGNOSIS

Initial Evaluation and Triage

Infection prevention and control measures should be in place at the first point of in-person contact (eg, screening and/or triage). This includes personal protective equipment for all providers and staff and evaluating children presenting with signs and symptoms of COVID-19 in separate clinical spaces. Outpatient clinics, emergency departments, and hospitals should consider developing a clear, clinical pathway to help with patient flow and isolation of patients with suspected COVID-19 infection.

A child with confirmed or suspected COVID-19 infection should be triaged on arrival to determine disease severity, need for immediate stabilization and treatment, and appropriate disposition. Previously healthy children and adolescents with mild symptoms may be candidates for virtual triage and evaluation.⁷ Children who should be evaluated immediately, however, include infants less than 3 months old with fever and older infants and children with more than 3 days of fever, respiratory distress, or any sign of organ dysfunction such as decreased urine output.⁸ Patients who are immunocompromised or have a chronic disease

such as lung disease or congenital heart disease, or obesity (body mass index, >40) are at higher risk of severe disease.⁸

Asymptomatic, Mild, and Moderate COVID-19

Asymptomatic COVID-19 infection and mild or nonspecific symptoms are more common in children compared with adults.⁹ Even children with asymptomatic or mild infection can transmit the virus, however.¹⁰ By some estimates, 25% to 73% of children who test positive for SARS-CoV-2 by polymerase chain reaction are asymptomatic.^{10,11} In a study from 28 children's hospitals across the United States, SARS-CoV-2 polymerase chain reaction positivity rates in asymptomatic children presenting for medical or surgical care varied from 0% to 2.2% (pooled prevalence of 0.65%) and were significantly associated with infection rates in the general population at the time of testing.¹²

Common symptoms in children include fever, dry cough, fatigue, and nasal congestion.¹³ Gastrointestinal symptoms, such as vomiting and diarrhea, are also common in children, far more so than in adults.¹³ Younger children and infants can present with a wide range of nonspecific signs and symptoms including fever, decreased feeding, or lethargy in the absence of respiratory symptoms; therefore, a high index of suspicion for COVID-19 infection is needed.¹⁴

Severe and Critical COVID-19

Although rare, children with COVID-19 infection can present with severe manifestations: respiratory failure and ARDS; sepsis and septic shock; acute kidney injury and renal failure; myocarditis, heart failure, and cardiac arrest; acute liver failure with cholestasis; severe neurological manifestations such as seizures and stroke; and MIS-C.^{15–17} It is critical to recognize the ominous signs of impending respiratory failure and/or shock and immediately initiate appropriate support and therapy.

Multisystem inflammatory syndrome in children is a rare manifestation of SARS-CoV-2 that has been described in children and young adults and is likely related to immune dysregulation and subsequent cytokine storm.^{4,6,18,19} Multisystem inflammatory syndrome in children often presents as a postviral manifestation 2 to 3 weeks after SARS-CoV-2 infection or after a peak of infections in the community.^{19,20} Many children with MIS-C do not exhibit respiratory symptoms and may have had a previous, asymptomatic COVID-19 infection.²⁰ Common symptoms of MIS-C include fever; gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and nonbloody diarrhea, sometimes 1 to 2 weeks before presentation; dermatologic manifestations such as rash and malar erythema that often develop 2 to 3 days after onset of fever and last for approximately 5 days; mucocutaneous features such as conjunctival injection, periorbital edema and/or distal extremity edema, and strawberry tongue; and cardiovascular involvement including coronary artery aneurysms, myocardial dysfunction, pericarditis, valvulitis, or coronary dysfunction.^{6,18,19,21,22}

SARS-CoV-2 Testing and Diagnostics

Testing for COVID-19 infection typically involves a nucleic acid amplification test such as a reverse transcriptase polymerase chain reaction, an antigen rapid diagnostic test, or an antibody (immunoglobulin M or immunoglobulin G)/serology test. Nucleic acid amplification tests are considered to be the gold standard and are more sensitive than antigen testing. Antibody tests can be used to support the diagnosis of COVID-19 in patients with late symptoms (≥8 days after symptom onset) or to help assess whether sequelae (eg, MIS-C) are due to a past infection; however, they cannot be used to rule out or diagnose acute infection active disease. Indications for testing vary by local epidemiology and hospital protocol.

Common laboratory findings in children with COVID-19 infection include leukocytosis, lymphopenia, coagulopathy, and

elevated inflammatory markers (lactate dehydrogenase, C-reactive protein [CRP], erythrocyte sedimentation rate, ferritin, and interleukin-6), D-dimer, and troponin.²³ Lymphopenia, elevated white blood cell count, elevated platelet count, elevated creatine kinase (CK) MB, elevated brain natriuretic peptide, higher levels of CRP, and higher levels of procalcitonin at admission are associated with increased disease severity.^{11,24,25} Please refer to Figure 1 for an approach to laboratory testing in acute COVID-19 infection.

Common radiologic findings include peribronchial and bronchial wall thickening as well as basilar and peripheral ground-glass opacities, which can be found in both symptomatic and asymptomatic children.¹³ Normal chest x-rays, however, do not rule out COVID-19 infection.²⁶ Low-risk patients with mild COVID-19 infection do not routinely need chest imaging. Consider obtaining a chest x-ray if there is a high clinical concern for lobar pneumonia, heart failure, or tuberculosis; in patients with hypoxia requiring supplemental oxygen, increased work of breathing, or new or sudden decompensation; high clinical suspicion for COVID-19 despite negative testing (possible false-negative test); or to check line and/or endotracheal tube placement. Lung ultrasound may also be a reasonable method to detect lung abnormalities in children.²⁷ Routine imaging by computed tomography is not recommended and may be normal in up to 50% of children with mild COVID-19 infection.²⁸

HIGH-RISK GROUPS

Among infected children, adolescents more than 15 years of age are more likely to require hospitalization and intensive care.²⁹ Some studies show that neonates are also more likely to be hospitalized and have severe infection; however, most cases are mild to moderate.^{3,29} Life-threatening respiratory disease in neonates is rare.³⁰ Adolescents and children with comorbidities, such as congenital heart disease, diabetes, severe obesity (body mass index, >40), chronic respiratory disease, and immunocompromising conditions, are at higher risk for developing severe COVID-19 disease requiring hospitalization and may need different criteria for admission and/or closer follow-up upon discharge.^{3,9,24,29,31–34}

DIFFERENTIAL DIAGNOSIS

The differential for COVID-19 infection is broad for symptomatic infants and children. Other diseases that mimic COVID-19 infection or that can occur concurrently include tuberculosis, bacterial or viral pneumonia, congestive heart failure, urinary tract infections, bacteremia, and gastrointestinal illnesses.¹⁴ Other respiratory viral infections, such as influenza, adenovirus, respiratory syncytial virus, parainfluenza, and metapneumovirus, and atypical pneumonias (mycoplasma and chlamydia pneumoniae) can also present similarly to COVID-19.

Multisystem inflammatory syndrome in children may be confused with toxic shock syndrome (TSS), Kawasaki disease (KD), severe sepsis, or macrophage activation syndromes, all of which can occur in a post-acute illness setting and involve fever, rash, erythema, edema, conjunctivitis, and oral mucosal changes (eg, “strawberry tongue”). However, the average age of children with MIS-C is 7 to 9 years, whereas for KD, it is 2 years^{21,35,36}; MIS-C has more diffuse cardiovascular involvement than KD^{19,35,36}; and children with MIS-C tend to have a greater elevation in inflammatory markers (CRP, interleukin-6, and fibrinogen) compared with those with TSS or KD.^{35,36}

MANAGEMENT AND DISPOSITION

Supportive care is the mainstay of therapy for children with COVID-19 infection and should be provided to all pediatric patients.^{37,38} In general, home medications should be continued, although immunosuppressants should be considered on a case-by-

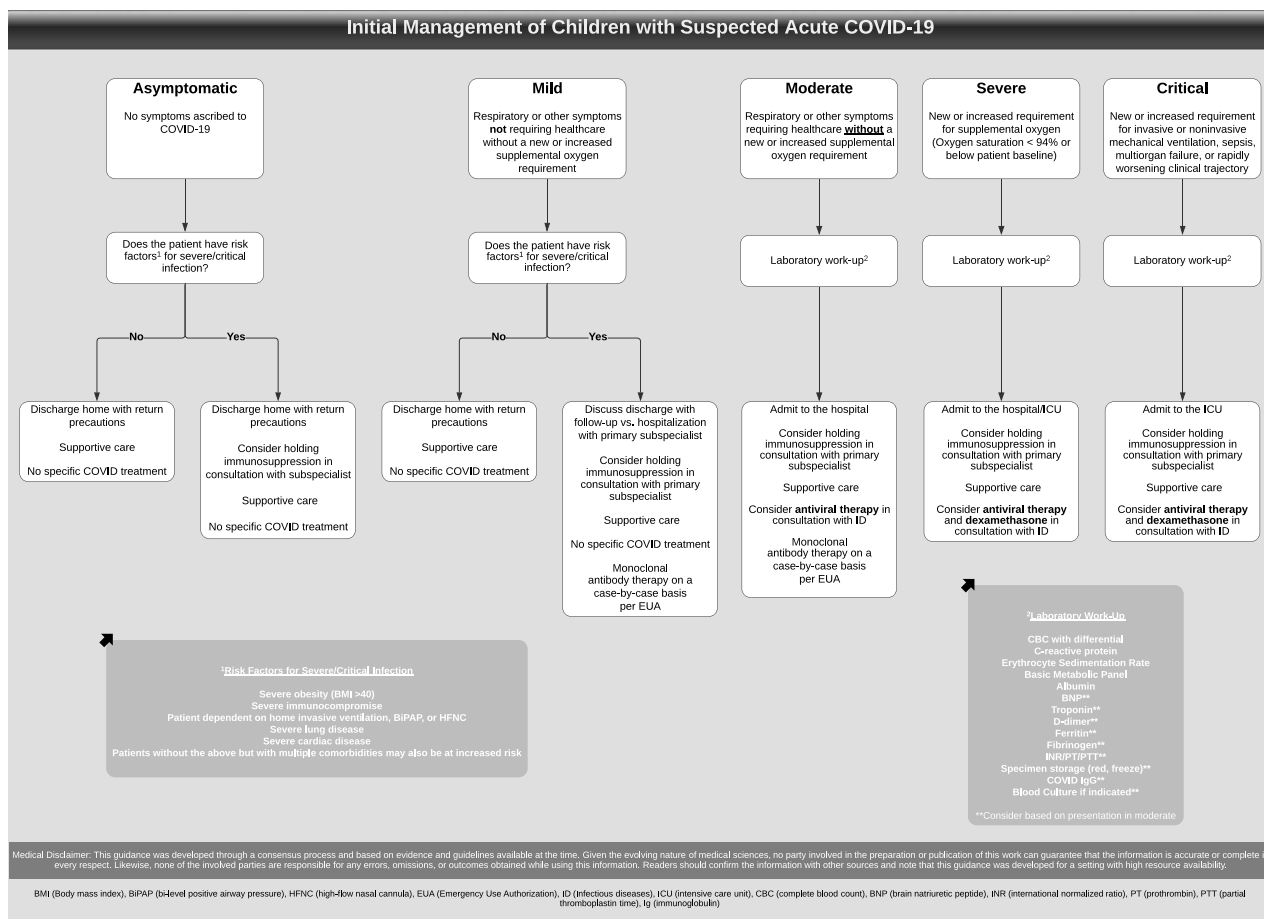


FIGURE 1. Initial management of children with suspected acute COVID-19. Adapted and printed with permission from the UCSF Benioff Children's Hospital Pediatric COVID/MIS-C Guidelines developed by the Pediatric COVID/MISC Working Group (Version 1, last updated: April 1, 2021).

case basis in discussion with the child's primary medical doctor or prescribing subspecialty physician. Figure 1 outlines the initial management of children with suspected acute COVID-19 infection for asymptomatic to critical disease.

Mild and Moderate COVID-19

Mild infection in children is characterized by a generally well-appearing child with respiratory or other mild symptoms without significant tachypnea, hypoxia (oxygen saturation <94%), or a new or increased oxygen requirement. Most patients with mild disease and no significant risk factors do not require laboratory testing, diagnostic imaging, specific monitoring, or COVID-19 therapies; rather, they can be managed at home with symptomatic treatment and home isolation. Some children with comorbidities may be candidates for outpatient monoclonal antibody therapy on a case-by-case basis. Certain comorbid conditions (eg, type 1 diabetes, adrenal insufficiency) may need adjustment in their medications for these conditions and closer monitoring.

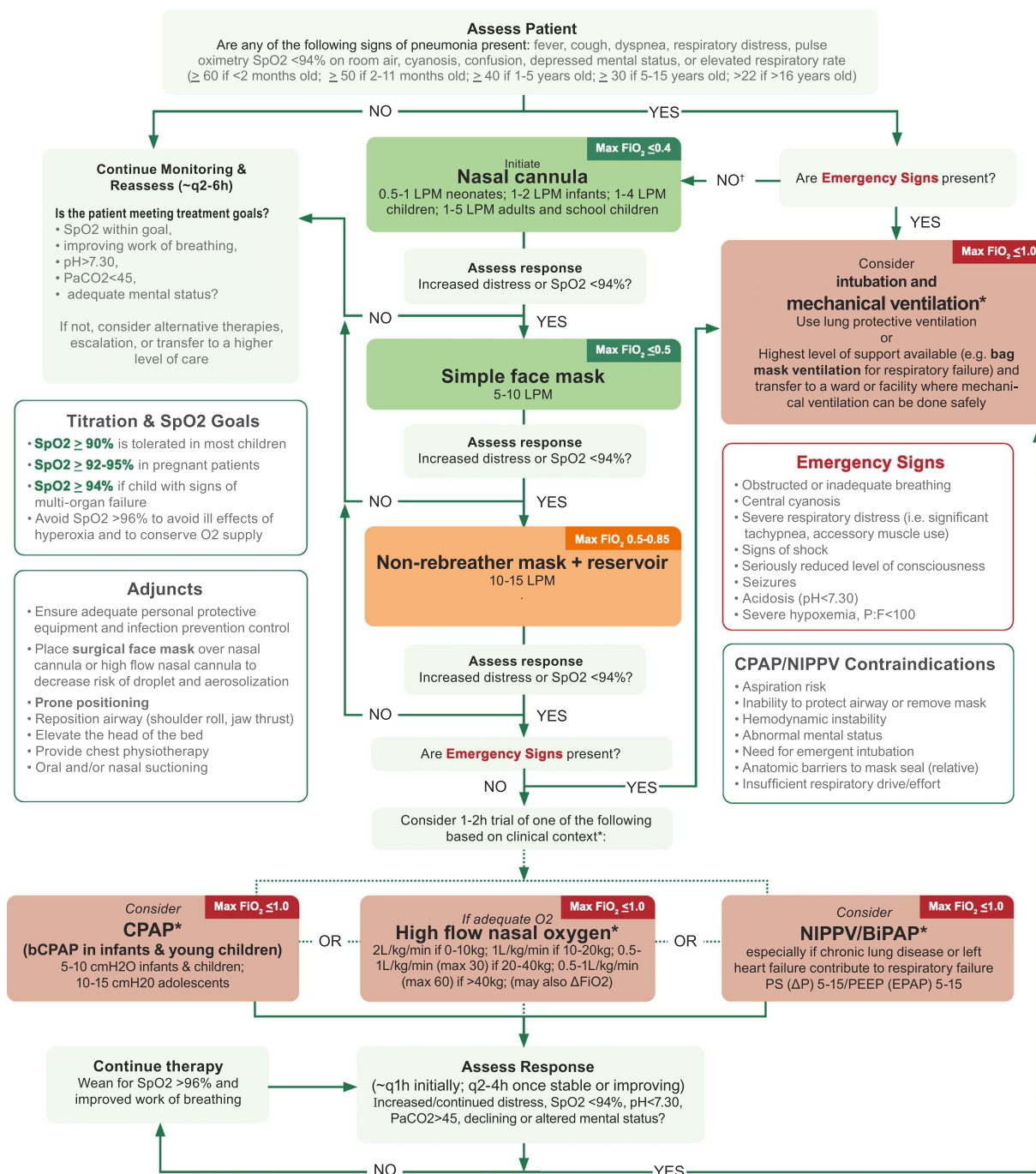
COVID-19 disease severity can progress rapidly; parents and caregivers should be counseled to seek medical care if their child experiences new or progressing symptoms.³⁹ Infants more than 28 days old and young children with more than 3 days of fever should follow-up with their primary medical doctor to assess for bacterial suprainfection and monitor hydration and respiratory status.

Moderate infection is characterized by respiratory or other symptoms, like dehydration, requiring health care, but without a new or increased oxygen requirement. Symptom management and supportive care are the foundations of treatment, whereas routine diagnostic imaging and COVID-19–specific therapies are not recommended, although some hospitalized children early in their course may be candidates for monoclonal antibody therapy. Admission to the general inpatient ward with possible infectious disease consultation is recommended. As mentioned above, children with COVID-19 infection can decompensate quickly; so, monitoring is recommended.

Severe COVID-19

Severe infection in children is characterized by new or increased oxygen requirement (oxygen saturation, <94% or below the patient's baseline) requiring hospital admission for oxygen therapy, supportive care, COVID-19–specific treatment, and/or monitoring. Hospital admission and possible initiation of Remdesivir and dexamethasone (off-label use) therapy in consultation with appropriate pediatric subspecialty teams (eg, infectious disease) are recommended. Although there is little evidence to support the use or benefit of Remdesivir in children with COVID-19 infection, it is approved in the United States by the Food and Drug Administration and used to treat both adults and children older than 12 years and more than 40 kg with COVID-19 due to pharmacological rationale. It is not labeled for use in younger or smaller children,

Managing Pediatric Respiratory Distress, Hypoxia and Failure Algorithm



*Initial O₂ delivery device should be selected to match the severity of hypoxemic respiratory failure (mild, moderate or severe) based on clinical assessment.

* Selection of optimal delivery device should be based on local clinician's judgment and risk-benefit assessment tailored to the individual patient, global and local outcomes data, as well as local resources including O₂ supply, skill of personnel, availability of consumables, monitoring and therapeutic adjuncts, among other factors.

LPM (liters per minute), EPAP (expiratory positive airway pressure), PS (pressure support), SpO₂ (oxygen saturation), PaCO₂ (arterial partial pressure of carbon dioxide), P:F (ratio between arterial partial pressure of oxygen and the fraction of inspired oxygen - FIO₂), CPAP (continuous positive airway pressure), bCPAP (bubble CPAP), NIPPV (non-invasive positive pressure ventilation), BiPAP (bi-level positive airway pressure); Δ - change



FIGURE 2. Managing pediatric respiratory distress, hypoxia, and failure algorithm. Adapted and printed with permission from Open Critical Care available at: <https://opencriticalcare.org/resources/>.

although many institutions choose to administer it. Guidelines for the use of Remdesivir have mixed recommendations, and evidence continues to evolve.

Goals of supplemental oxygen therapy include resolution of hypoxia and manageable work of breathing (Fig. 2). If the child worsens, develops respiratory failure, or progresses to ARDS, the child should be intubated and mechanically ventilated.⁴⁰ If the child does not show signs of dehydration and/or is not in shock, a conservative approach to intravenous fluid administration should be used as aggressive fluid resuscitation may worsen oxygenation and pulmonary compliance.⁴⁰

Critical COVID-19

Respiratory Failure

Critical COVID-19 in children is characterized by a new or increased invasive or noninvasive mechanical ventilation requirement (respiratory failure/ARDS), sepsis, shock, multiorgan failure, or rapidly worsening clinical trajectory. Admission to the pediatric intensive care unit; possible initiation of Remdesivir, corticosteroid therapy, and/or prophylactic anticoagulation therapy; and consultation with appropriate pediatric subspecialty teams (eg, infectious disease, hematology) are recommended (Fig. 1). Interventions such as high flow oxygen are being used, although there have not yet been large trials in children with COVID-19. A child with respiratory distress and hypoxia should be closely

monitored for signs of clinical deterioration as children can rapidly progress to respiratory failure and shock (Fig. 2). Children who develop pediatric ARDS should be managed with lung-protective ventilation per current guidelines.^{41,42} Because of the risk of aerosolization with many of the interventions for respiratory failure, such as high flow oxygen, noninvasive positive pressure, and frequent suctioning, special attention to infection prevention and control protocols is needed along with placing patients in a single, negative pressure room whenever possible.

Shock

Sepsis and septic shock are rare but potentially life-threatening manifestations of COVID-19 in children and must be promptly recognized and treated.⁴³ Immediate goals when managing pediatric septic shock are to maintain perfusion to the organs and to treat the underlying infection. For improved survival, initiate empiric, broad-spectrum antimicrobial therapy and fluid bolus resuscitation with balanced or buffered crystalloids within 1 hour of recognition and titrate fluid resuscitation to clinical markers of increased perfusion.^{40,44} Fluid resuscitation may lead to volume overload and capillary leak, which may exacerbate respiratory failure, so frequent reassessment for signs of fluid responsiveness and fluid overload during resuscitation is imperative.^{40,44} If signs of fluid overload are present or signs of shock persist after 2 fluid boluses, initiate vasoactive therapy for hemodynamic support.

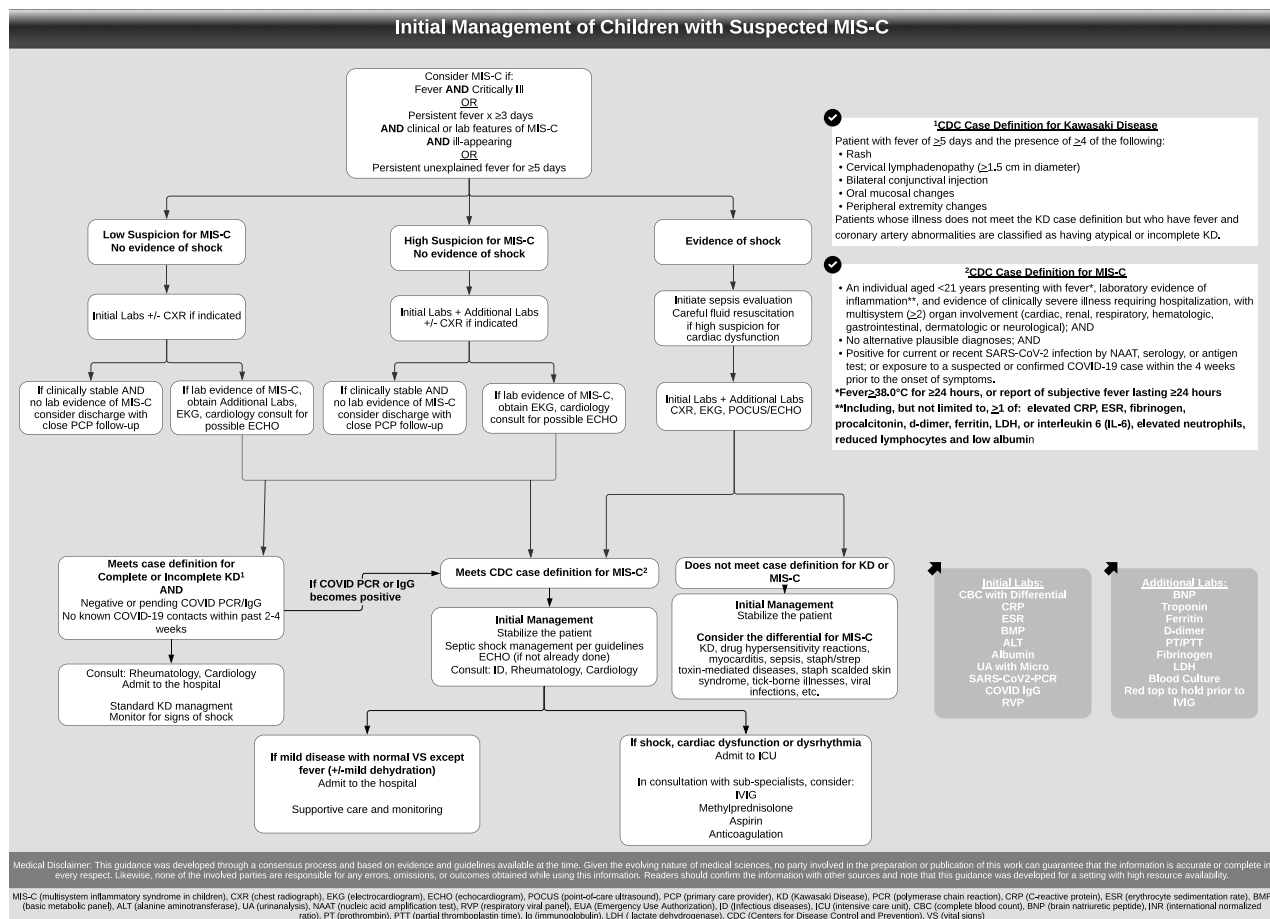


FIGURE 3. Initial management of children with suspected MIS-C. Adapted and printed with permission from the UCSF Benioff Children's Hospital Pediatric COVID/MIS-C Guidelines developed by the Pediatric COVID/MIS-C Working Group (Version 1, last updated: April 1, 2021).

Monitor blood pressure frequently and titrate vasoactive medications to the minimum dose necessary to maintain perfusion and prevent side effects. Inodilators should not be used routinely and are typically not used for septic shock in the absence of cardiac dysfunction.^{40,44}

Children with sepsis frequently show signs of decreased cardiac output, which can be due to hypovolemia or direct myocardial dysfunction.^{45,46} Acute myocardial dysfunction due to myocardial injury is especially prevalent in children with MIS-C as indicated by higher levels of troponin and brain natriuretic peptide compared with children with non-COVID-19-related sepsis.^{6,21} Early and thorough cardiac evaluation including electrocardiogram, echocardiography (ECHO), and biomarkers (troponin, CK and CK MB, lactate, and mixed venous oxygen saturation) on all children who present in shock to rule out cardiac involvement or cause is important.^{40,44} In children with suspected MIS-C, early cardiology consultation and specific attention to the coronary arteries on ECHO to rule out aneurysms is recommended. In cases where cardiac dysfunction is suspected or known, reserve fluid resuscitation for patients demonstrating decreased preload, ideally assessed by ECHO, and small volume boluses (5–10 mL/kg) over 30 to 60 minutes should be used with frequent reassessment. In consultation with pediatric cardiology subspecialists, discuss whether inodilators should be initiated and optimize ventilation/gas exchange by providing oxygen therapy with a goal of SpO₂ greater than 94%. If noninvasive or invasive ventilation are indicated, be aware of the cardiopulmonary interactions and prepare for the possibility of cardiac arrest on intubation.^{40,44} Currently, there is insufficient evidence to recommend for or against corticosteroids to treat refractory shock in children with COVID-19; however, corticosteroids may be indicated for the treatment of acute COVID-19 infection. Routine red blood cell transfusions are generally not recommended in hemodynamically stable children with a blood hemoglobin concentration of 7 g/dL or greater.^{40,44}

Cardiac Arrest

The American Heart Association, in collaboration with the American Academy of Pediatrics and the American College of Emergency Physicians, published interim guidance for management of pediatric cardiac arrest with suspected/confirmed COVID-19. Pediatric advanced life support algorithms should be followed with several important additions: use appropriate personal protective equipment; limit personnel to the minimum number necessary; use a bag-mask device with a filter and tight seal; if intubating, have the person with the highest likelihood of success intubate, use video-assisted laryngoscopy, and use a cuffed endotracheal tube; and, finally, minimize closed-circuit disconnection in intubated patients.⁴⁷

Multisystem Inflammatory Syndrome in Children

Like acute COVID-19, MIS-C can present along a spectrum of severity ranging from mild symptoms to shock. The initial management approach for children with suspected MIS-C should focus on stabilization, improving end-organ perfusion, and early cardiac evaluation given the high incidence of myocardial involvement (Fig. 3). Treatments for MIS-C target different aspects of the pathophysiology and include antiplatelet therapy like aspirin (off-label use), immunomodulating therapies like intravenous immunoglobulin or anakinra (off-label use), and anti-inflammatory medications like methylprednisolone (off-label use). If MIS-C is suspected, early consultation or referral to a center with pediatric subspecialist care including critical care, rheumatology, hematology/oncology, cardiology, infectious diseases, and immunology is recommended. For patients with signs of shock, coronary artery dilation, arrhythmia, or cardiac dysfunction, even in the absence of KD- and/or MIS-C–

like features, consider urgent transfer to a pediatric intensive care unit and urgent consultation of the above subspecialists.⁴⁸

PUBLISHED OUTCOMES

Hospitalization rates, need for intensive care unit (ICU)–level care, and mortality tend to be lower in children than adults but are highly variable depending on testing patterns, case definitions, and resources. According to data from the US Department of Health, as of September 2020, children represented 1.7% of total SARS-CoV-2 hospitalizations and 0.07% of total deaths.⁴⁹ These rates may vary by age and geographic location. One large retrospective cohort study that included people less than 25 years of age in the United States found that 7% of SARS-CoV-2–infected children required hospitalization, and of those hospitalized, 28% required ICU-level care and 9% required mechanical ventilation. Case fatality rate was 0.2%.⁵⁰ Children with MIS-C tend to require ICU-level care more often (74% vs 44%) and have a slightly higher probability of mortality compared with those with acute COVID-19 (1.9% vs 1.4%).²¹ Among children with MIS-C and decreased left ventricular systolic function, more than 90% had normalized function within 30 days.²¹

SUMMARY

Although COVID-19 disease severity is lower in children compared with adults, symptoms in children can be atypical and vary widely. COVID-19 infection should be considered when a child presents with respiratory, gastrointestinal, or neurological complaints, especially when community infection rates are high. Children can still experience severe and critical disease including shock, ARDS, sepsis, and MIS-C. Early recognition and management of respiratory failure, septic shock, and myocardial dysfunction are essential. Although MIS-C has overlapping features with other diseases such as KD and TSS, it is characterized by a greater elevation of inflammatory markers and diffuse cardiac involvement. Supportive care is the mainstay of therapy for children with COVID-19 infection and MIS-C, and additional therapies such as Remdesivir, corticosteroids, prophylactic anticoagulation, aspirin, and immunomodulating therapies should be considered in severe and critical disease in consultation with appropriate pediatric specialty team(s). Although death is rare in children with COVID-19 infection, children with severe and critical infection or MIS-C should be closely monitored as they can rapidly deteriorate and progress to respiratory failure and shock.

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