# Coronavirus disease 2019 (COVID-19): Clinical manifestations and diagnosis /management in children

SOMAYE JAFRASTE

PEDIATRIC INTENSIVIST

**Age distribution** —

Children of all ages can get COVID-19 .

The incidence increases with increasing age .

- **Preschool (age 0 through 4 years) – 17.4 percent**
- Elementary school (age 5 through 10 years) – 25.7 percent
- Middle school (age 11 through 13 years) – 18.6 percent
- High school (age 14 through 17 years) – 38.3 percent

**How do children get COVID-19?** —
In case series early in the pandemic, most cases in children resulted from household exposure, usually with an adult .

**Do children transmit SARS-CoV-2 to others?** —
Children of all ages can transmit SARS-CoV-2 to others, but the rate of transmission by young children is uncertain.Older children and adolescents transmit SARS-CoV-2 effectively in household and community settings .
Infected children appear to shed SARS-CoV-2 virus with nasopharyngeal viral loads comparable to or higher than those in adults .

**Transmission by asymptomatic children** – transmission from children with confirmed asymptomatic SARS-CoV-2 to household contacts has been reported . In addition, there are reports of familial clusters that included asymptomatic children and possible transmission from asymptomatic children to adults outside their family . These reports suggest that asymptomatic children may play a role in transmission . Asymptomatic transmission by adults is well documented.

Among >69,700 laboratory-confirmed cases of COVID-19 in children <20 years reported to the CDC by May 30, 2020, the hospitalization rate ranged from 2.5 to 4.1 percent. Among children who were hospitalized with COVID-19 from 14 states by late July 2020, approximately 33 percent required intensive care and 6 percent required invasive mechanical ventilation .

# CLINICAL MANIFESTATIONS

## Clinical findings

**In children of all ages** — The symptoms of COVID-19 are similar in children and adults, but the frequency of symptoms varies .

COVID-19 appears to be milder in children than in adults, but severe cases have been reported . In a systematic review of 61 observational studies of persons of all ages, at least one-third of SARS-CoV-2infections are asymptomatic .

In a systematic review of observational studies including 7480 children with laboratory-confirmed COVID-19, the weighted mean age was 7.6 years .

Although the clinical findings in children with COVID-19 are diverse, fever or chills and cough are the most common reported symptoms .

Among children age 0 through 9 years, the frequency of symptoms was as follows:

- Fever, cough, or shortness of breath – 63 percent
  - Fever – 46 percent
  - Cough – 37 percent
  - Shortness of breath – 7 percent
- Myalgia – 10 percent
- Rhinorrhea – 7 percent
- Sore throat – 13 percent
- Headache – 15 percent
- Nausea/vomiting – 10 percent
- Abdominal pain – 7 percent
- Diarrhea – 14 percent
- Loss of smell or taste – 1 percent

Among children age 10 through 19 years, the frequency of symptoms was as follows:

- Fever, cough, or shortness of breath – 60 percent
  - Fever – 35 percent
  - Cough – 41 percent
  - Shortness of breath – 16 percent
- Myalgia – 30 percent
- Rhinorrhea – 8 percent
- Sore throat – 29 percent
- Headache – 42 percent
- Nausea/vomiting – 10 percent
- Abdominal pain – 8 percent
- Diarrhea – 14 percent
- Loss of smell or taste – 10 percent

fatigue, ocular symptoms (eg, conjunctival discharge), and heart failure or arrhythmias (particularly in children with preexisting heart disease) have been reported in smaller case series .

Gastrointestinal symptoms may occur without respiratory symptoms. Diarrhea, vomiting, and abdominal pain are the most common gastrointestinal symptoms reported in children . Acute cholestasis and pancreatitis have been reported in children and adolescents . Gastrointestinal bleeding has been reported in adults but has not been reported in children .
Cutaneous findings have been reported infrequently and are not well characterized; they include maculopapular, urticarial, and vesicular eruptions; transient livedo reticularis; and acral peeling . Reddish-purple nodules on the distal digits (sometimes called "COVID toes") similar in appearance to pernio (chilblains) are described predominantly in children and young adults, although an association with COVID-19 has not been clearly established .

Among symptomatic children, altered smell or taste, nausea or vomiting, and headache were more strongly associated with SARS-CoV-2 than other symptoms. Cough, rhinorrhea, nasal congestion, sore throat, and fever were common in children with and without SARS-CoV-2.

**In infants <12 months of age** —
clinical findings include feeding difficulty and fever without an obvious source .
although cough may be less prominent.
SARS-CoV--associated bronchiolitis has also been reported in infants
.

**Laboratory findings** — Laboratory findings are variable.

- The complete blood count was normal in most children; 17 percent had low white blood cell count and 13 percent had either neutropenia or lymphocytopenia; severe neutropenia has been described .
- Approximately one-third had elevated C-reactive protein (CRP; defined as >5 mg/L in most studies) or procalcitonin (defined as >0.5 ng/mL)

Elevated inflammatory markers and lymphocytopenia may indicate multisystem inflammatory syndrome in children (MIS-C) .

- Creatine kinase was elevated in 15 percent
- Serum aminotransferases were elevated in 12 percent

elevated lactate dehydrogenase (LDH) was another common laboratory abnormality .

Kidney dysfunction may occur in severely ill children.

Most cases of AKI occurred in children admitted to the ICU and those with MIS-C. None of the children with AKI required kidney biopsy or continuous kidney replacement therapy.

**Imaging findings** — Imaging findings are variable and may be present before symptoms . Ground glass opacities (37 percent) and consolidation or pneumonic infiltrates (22 percent) were most common. Findings typical of other viral respiratory infections ( hyperinflation, peribronchial markings) were not reported. In a study of eight Italian children hospitalized with documented COVID-19, findings on lung ultrasonography included subpleural consolidations and individual or confluent B lines .

**Severe disease in children**

**Frequency of severe disease in children —**

most children appear to have asymptomatic, mild, or moderate disease and recover within one to two weeks of disease onset . Although the impact of emerging variants of SARS-CoV-2 on disease severity remains uncertain, no evidence of more severe disease was detected among children admitted .

Why COVID-19 appears to be less common and less severe in children than in adults is unclear. One possibility is that children have a less intense immune response to the virus than adults; cytokine release syndrome is thought to be important in the pathogenesis of severe COVID-19 infections . Other possibilities include viral interference in the respiratory tract of young children, which may lead to a lower SARS-CoV-2 viral load; different expression of the angiotensin converting enzyme 2 receptor (the receptor for SARS-CoV-2) in the respiratory tracts of children and adults; pre-existing cross-reactive antibody; protective off-target effects of live vaccines; and relatively healthier blood vessels in children .

**Risk factors for severe disease** — :

- Obesity (body mass index [BMI] >95$^{th}$ percentile for age and sex
- Medical complexity
- Severe genetic disorders
- Severe neurologic disorders
- Inherited metabolic disorders
- Sickle cell disease
- Congenital heart disease
- Diabetes
- Chronic kidney disease
- Asthma and other chronic pulmonary diseases
- Immunosuppression due to malignancy or immune-weakening medications

Down syndrome has also been proposed to predispose to severe disease . Age <1 year also has been associated with increased risk for severe disease

The CDC's COVID-NET provides information about underlying medical conditions .the most common of which were obesity (38 percent of children ≥2 years), chronic pulmonary disease (18 percent), and prematurity (15 percent of children <2 years)
.
In a systematic review of 587 children the most common underlying conditions were chronic pulmonary disease, including asthma (45 percent), congenital heart disease (23 percent), immune suppression (12 percent), and hematologic or oncologic conditions (6 percent).

**Potential markers of severe disease** —
In observational studies, elevated inflammatory markers (CRP, procalcitonin, interleukin 6, ferritin, D-dimer) at admission or during hospitalization, hypoxia at admission, and gastrointestinal symptoms at admission have been associated with severe disease in children.

In adult patients, lymphocytopenia (specifically CD4+ and CD8+ T lymphocytes and elevated liver enzymes, LDH, and inflammatory markers (CRP, ferritin) have been associated with increased severity or worse outcomes.

**Multisystem inflammatory syndrome in children** —
MIS-C is a rare but serious condition associated with COVID-19 that has been reported in children from Europe and North America. The clinical features of MIS-C may be similar to those of Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome .
They include persistent fever, hypotension, gastrointestinal symptoms, rash, myocarditis, and laboratory findings associated with increased inflammation; respiratory symptoms may be lacking .

## APPROACH TO DIAGNOSIS

the Royal College of Paediatrics and Child Health suggests avoidance of examination of the oropharynx unless it is essential .

**What are the criteria for testing for COVID-19 in children?** —
Laboratory testing is necessary to confirm the diagnosis of COVID-19 because no single symptom or combination of symptoms reliably differentiates SARS-CoV-2 from other community-acquired viruses and coinfection is common.

For children who are evaluated for symptoms consistent with COVID-19 ( fever, persistent cough, shortness of breath, vomiting, diarrhea, altered sense of smell or taste) in the emergency department, urgent care, or outpatient setting, we perform testing for SARS-CoV-2 if the child has any of the following:

- An underlying condition that may increase the risk for severe disease
- Known in-person exposure to a laboratory-confirmed case of COVID-19 within the previous 14 days
- Presentation with severe illness (new requirement for supplemental oxygen or increased requirement from baseline, new or increased need for ventilation [invasive or noninvasive or clinical manifestations of multisystem inflammatory syndrome in children(MIS) .

**Preoperative patients** —
perform testing for SARS-CoV-2 24 to 48 hours before elective surgical procedures.

Detection of other respiratory pathogens ( influenza, respiratory syncytial virus, *Mycoplasma pneumoniae*) in nasopharyngeal specimens does **not** exclude COVID. In a systematic review of COVID-19 in 1183 children from 26 countries, coinfection was detected in 5.6 percent. *M. pneumoniae* was most common (58 percent of coinfections), followed by influenza (11 percent) and respiratory syncytial virus (9.7 percent) .

**Laboratory testing during influenza season** — During influenza season, children who are tested for SARS-CoV-2 generally should also be tested for influenza . The clinical features of SARS-CoV-2 and influenza overlap , and coinfection with these pathogens may occur.

**Imaging studies** — **Chest imaging is not routinely necessary for the diagnosis of COVID-19 in children** . It should be obtained as indicated to evaluate clinical findings suggestive of lower respiratory involvement, risk factors for disease progression, potential complications, or worsening respiratory status.

# Coronavirus disease 2019 (COVID-19): Management in children

## **ASSESSMENT OF SEVERITY**:

- Mild or moderate disease – No new or increased supplemental oxygen requirement
- Severe disease – New requirement for supplemental oxygen or increased requirement from baseline without new or increased need for ventilatory support (noninvasive or invasive)
- Critical disease – New or increased need for noninvasive or invasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory.

**MANAGEMENT OF HOSPITALIZED CHILDREN**Children with COVID-19 and severe or critical lower respiratory tract disease generally require hospital admission. Children with nonsevere COVID-19 may require hospital admission if they are at risk for severe disease due to underlying conditions (eg, immune compromise) or are febrile infants younger than 30 days.

**Supportive care for all patients** —
Supportive care is the mainstay of therapy for patients with severe or critical COVID-19 . Most children with COVID-19 improve with supportive care, even those with severe disease .

Routine supportive care measures include:

- Provision of respiratory support, including supplemental oxygen and ventilatory support (noninvasive or invasive); **respiratory status may change suddenly after approximately one week of symptoms** .
- Provision of fluid and electrolyte support.
- Provision of empiric antibiotics as indicated for community-acquired or health care-associated pneumonia; continuation of empiric antibiotics should be determined by cultures and other microbial tests and clinical condition. Bacterial coinfections appear to be infrequent .

- Monitoring for cytokine release syndrome by monitoring blood pressure for hypotension, oxygen saturation for worsening hypoxemia, and biomarkers. We obtain baseline C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase (LDH), and interleukin-6 (IL-6).

- Provision of thromboprophylaxis – Interventions to reduce the risk of venous thromboembolism (VTE) may be warranted for children hospitalized with COVID-19 .

For hospitalized children without multisystem inflammatory syndrome in children (MIS-C), we make decisions about pharmacologic VTE prophylaxis on a case-by-case basis, considering other VTE risk factors and the child's risk of bleeding. Nonpharmacologic strategies for VTE prophylaxis ( intermittent pneumatic compression devices [size permitting] and early mobilization) are encourage.

| |
|---|
| **Most common risk factors in pediatric patients** |
| Central venous catheter |
| Congenital heart disease |
| Immobilization |
| Obesity |
| Oral contraceptives |
| Malignancy (eg, leukemia) |
| Prematurity |
| Surgery, especially orthopedic |
| Systemic infection |
| Trauma |
| **Other risk factors** |
| Antiphospholipid syndrome |
| Certain cancer therapies (eg, asparaginase) |
| Heart failure |
| Inflammatory bowel disease |
| Inherited thrombophilia:<br>▪ Factor V Leiden mutation<br>▪ Prothrombin G20210A mutation<br>▪ Protein S deficiency<br>▪ Protein C deficiency<br>▪ Antithrombin deficiency |
| Nephrotic syndrome |
| Pregnancy |
| Severe liver disease |

**SARS-CoV-2 antiviral therapy for select patients** —
Given the lack of data from controlled trials supporting the efficacy of antiviral agents for the treatment of COVID-19 in children.
**antiviral therapy should be considered on a case-by-case basis and preferably occur in the context of a clinical trial**.

- **Potential indications** – Decisions to use antiviral therapy should be individualized according to disease severity, clinical trajectory, existing evidence of effectiveness, and underlying conditions that may increase the risk for progression.

Despite the unproven benefits, we suggest antiviral therapy for children with documented severe or critical COVID-19. Antiviral therapy also may be warranted for children with mild or moderate disease and an underlying condition that increases or may increase the risk of severe disease ( medical complexity, congenital heart disease, among others).

- **Choice of agent/regimen**
  - **Remdesivir** – we suggest remdesivir rather than other antiviral agents, in agreement with the multicenter panel . Although data regarding the benefits of remdesivir for children with COVID-19 are lacking, it is preferred to other antiviral agents because data from randomized trials and case series in adult patients suggest that it reduces time to recovery (particularly in patients who are not critically ill) and appears to be well tolerated .

    When the supply of remdesivir is limited, it should be prioritized for patients with severe rather than critical disease (as defined above); the benefits for those with critical disease are uncertain .

    The optimal role of remdesivir in patients with COVID-19 remains uncertain, and some experts (including the World Health Organization [WHO]) suggest not using it in hospitalized patients . In the United States, remdesivir has been approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19 requiring hospitalization in adults and children ≥12 years of age who weigh ≥40 kg it remains available for other hospitalized children with suspected or laboratory-confirmed COVID-19 who weigh ≥3.5 kg through emergency use authorization

Remdesivir is dosed according to weight as follows:

- ≥3.5 to <40 kg: 5 mg/kg intravenous (IV) loading dose on day 1, followed by 2.5 mg/kg IV every 24 hours
- ≥40 kg: 200 mg IV loading dose on day 1, followed by 100 mg IV every 24 hours

The usual duration of therapy is up to 5 days for children with severe disease; for children with critical disease who are not improving after 5 days, the duration may be extended to up to 10 days .

Remdesivir should not be administered with hydroxychloroquine or chloroquine, because coadministration may decrease remdesivir's antiviral activity . Remdesivir is a prodrug of a nucleotide analog that inhibits RNA-dependent RNA polymerase and has activity against coronaviruses .
Reported adverse effects of remdesivir include nausea, vomiting, and transaminase elevations.

•**Remdesivir in combination with baricitinib** – Although the FDA has issued an emergency use authorization for baricitinib to be used in combination with remdesivir in patients ≥2 years of age who are hospitalized with COVID-19 and require oxygen or ventilatory support .

Baricitinib is a Janus kinase inhibitor used for the treatment of rheumatoid arthritis. In addition to its immunomodulatory effects, it is thought to have antiviral effects through interference with viral entry. In studies in patients ≥18 years of age, adding baricitinib to remdesivir appeared to modestly improve the time to recovery without increased rates of infection, VTE, or other adverse events .

•**Hydroxychloroquine and chloroquine** –

We recommend **not using** hydroxychloroquine or chloroquine for the treatment of COVID-19 in children, except in the context of a clinical trial. The efficacy of hydroxychloroquine in the treatment of COVID-19 is uncertain and it is associated with severe adverse reactions . **It is ideally used only in hospitalized patients in the context of a clinical trial** .

Hydroxychloroquine should be avoided in children with underlying QTc abnormalities and those who require other medications with potential for serious drug interactions with hydroxychloroquine.
Hydroxychloroquine is thought to alter endosomal and lysosomal pH, inhibiting viral replication and propagation, although the exact mechanism of antiviral activity remains uncertain .

•**Lopinavir-ritonavir** – We do not recommend routine use of lopinavir-ritonavir given the absence of efficacy and unfavorable pharmacodynamics

**Individualized adjunctive therapy**

**Glucocorticoids** — trials in children are ongoing and the benefits and risks are uncertain. Pending results of these trials, administration of glucocorticoids ideally should occur in the context of a clinical trial.

For select children with severe or critical COVID-19 who cannot participate in a clinical trial (ie, those who require mechanical ventilation or those who require supplemental oxygen and have risk factors for disease progression), low-dose glucocorticoids may be warranted ; the duration of therapy is up to 10 days or until discharge, whichever is shorter. Low-dose glucocorticoid regimens include one of the following :

- Dexamethasone 0.15 mg/kg orally, IV, or nasogastrically (NG) once daily (maximum dose 6 mg)
- Prednisolone 1 mg/kg orally or NG once daily (maximum dose 40 mg)
- Methylprednisolone 0.8 mg/kg IV once daily (maximum dose 32 mg)
- Hydrocortisone
  - For neonates (<1 month of age): 0.5 mg/kg IV every 12 hours for 7 days followed by 0.5 mg/kg IV once daily for 3 days
  - For children ≥1 month: 1.3 mg/kg IV every 8 hours (maximum dose 50 mg; maximum total daily dose 150 mg)

Preliminary evidence from the Randomized Evaluation of COVID-19 therapy (RECOVERY) trial suggested that low-dose glucocorticoids were beneficial in the management of adults with severe COVID-19

We do not routinely use other immune modulators (IL-6 inhibitors [eg, tocilizumab], interferon-beta 1b, convalescent plasma from recovered COVID-19 patients) in the treatment of children with COVID-19, except in the context of a clinical trial . The benefits and risks are uncertain .

Although there are no available data on the use of vitamin A for the treatment of COVID-19.Vitamin A deficiency may be associated with impairment of humoral and cell-mediated immunity, and even mild vitamin A deficiency may lead to increased morbidity from measles and other viral respiratory infections .

## Outpatient monoclonal antibody therapy

Bamlanivimab, bamlanivimab-etesevimab, and casirivimab-imdevimab are authorized for use in **nonhospitalized** patients age ≥12 years weighing ≥40 kg who have mild to moderate illness (ie, no new or increased supplemental oxygen requirement) and have certain risk factors for severe disease or hospitalization . Risk factors for children age 12 through 17 years include **any** of the following:

- Body mass index ≥85$^{th}$ percentile
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (eg, cerebral palsy)
- Medical-related technological dependence (eg, tracheostomy, gastrostomy, or positive pressure ventilation unrelated to COVID-19)
- Chronic respiratory disease that requires daily medication for control (eg, asthma, reactive airway disease)

Bamlanivimab, bamlanivimab-etesevimab, and casirivimab-imdevimab should be administered as soon as possible after positive SARS-CoV-2 test and within 10 days of symptom onset

- **Monitoring for clinical deterioration** – Caregivers of children who are managed at home should be counseled about symptoms of clinical deterioration, which may occur suddenly after approximately one week of symptoms and should prompt urgent re-evaluation

**Manifestations of clinical deterioration include**

- Severe respiratory distress, difficulty breathing (for infants: grunting, central cyanosis, inability to breastfeed)
- Chest pain or pressure
- Blue lips or face
- Findings associated with shock (eg, cold, clammy, mottled skin; new confusion; difficulty arousing; substantially reduced urine output)
- Inability to drink or keep down any liquids

**When can home isolation be discontinued?** — The optimal duration of home isolation is uncertain. How long a person remains infectious is uncertain. The duration of viral shedding is variable; there appears to be a wide range, which may depend on severity of illness. Among 110 children at Wuhan Children's Hospital, the median duration of viral shedding was 15 days from onset of illness (interquartile range 11 to 20 days); the duration was longer for symptomatic than asymptomatic children (17 versus 11 days)

**Adequate vitamin D intake**

the role of vitamin D in the treatment and prevention of COVID-19 is uncertain, and doses exceeding the upper level intake are **not** recommended

**Avoidance of unproven interventions** — Hydroxychloroquine, ivermectin, and other investigational agents should be used only in the context of a clinical trial; misuse of nonpharmaceutical forms of the investigational agents (eg, chloroquine phosphate, which is used in home aquariums; ivermectin intended for animals) may lead to severe toxicity, including death .

**Hygiene and social distancing** — Prevention of transmission focuses on hygiene and social distancing.

**Use of cloth face coverings or disposable masks** — The CDC and AAP recommend that individuals ≥2 years of age wear a cloth face covering (eg, homemade masks or bandanas) or disposable (nonmedical) mask when they are in public settings where social distancing may be difficult to achieve (eg, grocery stores, clinician offices), especially in areas with substantial community transmission

**Pre- and postexposure prophylaxis** — We recommend that pre- and postexposure prophylaxis for COVID-19 in children not be attempted outside of a clinical trial.
Clinical trials evaluating the efficacy of various agents (eg, monoclonal antibodies developed to neutralize SARS-CoV-2, convalescent plasma) in preventing SARS-CoV-2 infections are being conducted, though none has proven effective in children. In a completed trial, hydroxychloroquine was not effective for postexposure prophylaxis .

# Coronavirus disease 2019 (COVID-19):

## Multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis

## Epidemiology

the incidence of MIS-C is uncertain, it appears to be a rare complication of COVID-19 in children. In one report, the estimated incidence of laboratory-confirmed SARS-CoV-2 infection in individuals <21 years old was 322 per 100,000 and the incidence of MIS-C was 2 per 100,000 .

# Pathophysiology

- **Immune dysregulation** – It has been suggested that the syndrome results from an abnormal immune response to the virus, with some clinical similarities to Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome.

**Mechanisms of myocardial injury** – The mechanisms of myocardial injury in MIS-C are not well characterized. Possible causes include injury from systemic inflammation, acute viral myocarditis, hypoxia, stress cardiomyopathy, and, rarely, ischemia caused by coronary artery (CA) involvement .

**Presenting symptoms** — :

- Persistent fevers (median duration four to six days) – 100 percent
- Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) – 60 to 100 percent
- Rash – 45 to 76 percent
- Conjunctivitis – 30 to 81 percent
- Mucous membrane involvement – 27 to 76 percent
- Neurocognitive symptoms (headache, lethargy, confusion) – 29 to 58 percent
- Respiratory symptoms – 21 to 65 percent
- Sore throat – 10 to 16 percent
- Myalgia – 8 to 17 percent
- Swollen hands/feet – 9 to 16 percent
- Lymphadenopathy – 6 to 16 percent

Respiratory symptoms (tachypnea, labored breathing), when present, are most often due to severe shock. Cough is uncommon. Though some children require supplemental oxygen or positive pressure ventilation for cardiovascular stabilization, severe pulmonary involvement (eg, acute respiratory distress syndrome) is **not** a prominent feature.

Neurocognitive symptoms are common and may include headache, lethargy, confusion, or irritability. A minority of patients present with more severe neurologic manifestations, including encephalopathy, seizures, coma, meningoencephalitis, muscle weakness, and brainstem and/or cerebellar signs .

Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) are particularly common and prominent, with the presentation in some children mimicking appendicitis . Some children have been noted to have terminal ileitis on abdominal imaging and/or colitis on colonoscopy.

**Clinical findings** — :

- Shock – 32 to 76 percent
- Criteria met for complete Kawasaki disease (KD) – 22 to 64 percent
- Myocardial dysfunction (by echocardiogram and/or elevated troponin or brain natriuretic peptide [BNP]) – 51 to 90 percent
- Arrhythmia – 12 percent
- Acute respiratory failure requiring noninvasive or invasive ventilation – 28 to 52 percent
- Acute kidney injury (most cases were mild) – 8 to 52 percent
- Serositis (small pleural, pericardial, and ascitic effusions) – 24 to 57 percent
- Hepatitis or hepatomegaly – 5 to 21 percent
- Encephalopathy, seizures, coma, or meningoencephalitis – 6 to 7 percent

**Laboratory findings** —

- Lymphocytopenia – 80 to 95 percent
- Neutrophilia – 68 to 90 percent
- Mild anemia – 70 percent
- Thrombocytopenia – 31 to 80 percent

- Elevated inflammatory markers, including:
  - C-reactive protein (CRP) – 90 to 100 percent
  - Erythrocyte sedimentation rate – 75 to 80 percent
  - D-dimer – 67 to 100 percent
  - Fibrinogen – 80 to 100 percent
  - Ferritin – 55 to 76 percent
  - Procalcitonin – 80 to 95 percent
  - Interleukin-6 (IL-6) – 80 to 100 percent
- Elevated cardiac markers:
  - Troponin – 50 to 90 percent
  - BNP or N-terminal pro-BNP (NT-pro-BNP) – 73 to 90 percent
- Hypoalbuminemia – 48 to 95 percent
- Mildly elevated liver enzymes – 62 to 70 percent
- Elevated lactate dehydrogenase – 10 to 60 percent
- Hypertriglyceridemia – 70 percent

**Echocardiography** — Echocardiographic findings may include :

- Depressed LV function
- Coronary artery (CA) abnormalities, including dilation or aneurysm
- Mitral valve regurgitation
- Pericardial effusion

- **Chest radiograph** – Many patients had normal chest radiographs. Abnormal findings included pleural effusions, patchy consolidations, focal consolidation, and atelectasis.
- **Computed tomography (CT) of chest** – Chest CT (when obtained) generally had findings similar to those on chest radiograph. A few patients had nodular ground-glass opacification.
- **Abdominal imaging** – Findings on abdominal ultrasound or CT included free fluid, ascites, and bowel and mesenteric inflammation including terminal ileitis, mesenteric adenopathy/adenitis, and pericholecystic edema

# EVALUATION

Patients with suspected MIS-C should have laboratory studies performed to look for evidence of inflammation and to assess cardiac, renal, and hepatic function . Testing should also include polymerase chain reaction (PCR) and serology for SARS-CoV-2.

**Laboratory testing** —

- **Moderate to severe** –
  - Complete blood count (CBC) with differential
  - C-reactive protein (CRP) and erythrocyte sedimentation rate (optional: procalcitonin)
  - Ferritin
  - Liver function tests and lactate dehydrogenase
  - Serum electrolytes and renal function tests
  - Urinalysis
  - Coagulation studies (prothrombin time/international normalized ratio, activated partial thromboplastin time, D-dimer, fibrinogen)
  - Troponin
  - Brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP)
  - Cytokine panel (if available)

- **Mild symptoms** – For patients presenting with fever for ≥3 days and who are well-appearing (ie, normal vital signs and reassuring physical examination) with only mild symptoms suggestive of MIS-C, we suggest a more limited evaluation initially. We typically start with the following:
    - CBC with differential
    - CRP
    - Serum electrolytes and renal function tests

  If these results are abnormal, additional testing is performed (listed above).

  The clinician should also assess for other common causes of fever (eg, streptococcal pharyngitis, mononucleosis).

**Testing for SARS-CoV-2** — All patients with suspected MIS-C should be tested for SARS-CoV-2, including both serology and reverse transcription PCR (RT-PCR) on a nasopharyngeal swab .

As previously discussed, approximately 60 percent of patients have positive serology with negative PCR, and approximately 30 to 35 percent are positive on both tests.

A minority of patients (approximately 5 to 10 percent) have negative results on both tests. In these cases, the diagnosis of MIS-C requires an epidemiologic link to SARS-CoV-2 (eg, exposure to an individual with known COVID-19 within the four weeks prior to the onset of symptoms).

**Testing for other pathogens** — Testing for other viral and bacterial pathogens includes :

- Blood culture
- Urine culture
- Throat culture
- Stool culture
- Nasopharyngeal aspirate or throat swab for respiratory viral panel
- Epstein-Barr virus serology and PCR
- Cytomegalovirus serology and PCR
- Enterovirus PCR
- Adenovirus PCR

Detection of other respiratory pathogens (eg, rhinovirus, influenza, respiratory syncytial virus) in nasopharyngeal specimens does not exclude COVID-19.

- **Echocardiographic evaluation** –

  - Quantitative assessment of LV size and systolic function (LV end-diastolic volume, ejection fraction)
  - Qualitative assessment of right ventricular systolic function
  - CA abnormalities (dilation or aneurysm)
  - Assessment of valvar function
  - Evaluation for the presence and size of pericardial effusion
  - Evaluation for intracardiac thrombosis and/or pulmonary artery thrombosis, particularly apical thrombus in severe LV dysfunction
  - Strain imaging and LV diastolic function (optional)

## CDC and WHO case definitions of MIS-C —

Both definitions require fever (though they differ with respect to duration), elevated inflammatory markers, at least two signs of multisystem involvement, evidence of SARS-CoV-2 infection or exposure, and exclusion of other potential causes.

- **MIS-C without overlap with acute COVID-19 or Kawasaki disease (KD)** – Patients in this group were more likely to have shock, cardiac dysfunction, and markedly elevated C-reactive protein (CRP) and ferritin.

- **MIS-C overlapping with severe acute COVID-19** –Many children in this group presented with respiratory involvement, including cough, shortness of breath, pneumonia, and acute respiratory distress syndrome. Most of these children had positive SARS-CoV-2 PCR without seropositivity. patients in this category tend to be older than those with KD-like features and they more commonly have comorbidities.

- **MIS-C overlapping with KD** –They more commonly had rash and mucocutaneous involvement and less commonly had shock or myocardial dysfunction. Approximately two-thirds of patients in this group had positive SARS-CoV-2 serology with negative PCR, and one-third were positive on both tests.

Importantly, the incidence of coronary artery (CA) abnormalities was similar in all three subgroups (21, 16, and 18 percent, respectively), highlighting the importance of routine echocardiography in all children with MIS-C, regardless of apparent subphenotype.

## Differentiating MIS-C and Kawasaki disease —

Key distinctions between MIS-C and KD include:

- MIS-C commonly affects older children and adolescents, whereas classic KD typically affects infants and young children.
- In MIS-C, black and Hispanic children appear to be disproportionally affected and Asian children account for only a small number of cases. By contrast, classic KD has a higher incidence in East Asia and in children of Asian descent.
- Gastrointestinal symptoms (particularly abdominal pain) are very common in MIS-C, whereas these symptoms are less prominent in classic KD.
- Myocardial dysfunction and shock occur more commonly in MIS-C compared with classic KD
- Inflammatory markers (especially CRP, ferritin, and D-dimer) tend to be more elevated in MIS-C compared with classic KD and KDSS .
- In addition, absolute lymphocyte and platelet counts tend to be lower in MIS-C compared with KD .

- It is unclear if the risk of CA involvement in MIS-C is comparable with the risk in classic KD.

## DIFFERENTIAL DIAGNOSIS

- **Bacterial sepsis** –cardiac involvement, particularly coronary artery (CA) involvement, is uncommon in bacterial sepsis. Ultimately, microbiologic tests (ie, SARS-CoV-2 testing, bacterial cultures) are necessary to make the distinction

- **Kawasaki disease (KD)** –
- **Toxic shock syndrome** –
- **Appendicitis** – many children with MIS-C present with fever associated with abdominal pain and vomiting
- **Other viral infections** – Other viral pathogens that may manifest with multisystem involvement and/or myocarditis include Epstein-Barr virus, cytomegalovirus, adenovirus, and enteroviruses. These viruses rarely cause severe multisystem disease in immunocompetent children.
- **Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)** – Most children with HLH/MAS are acutely ill with multiorgan involvement, cytopenias, liver function abnormalities, and neurologic symptoms. Cardiac and gastrointestinal involvement are less common, and neurologic symptoms are more prominent.

- **Systemic lupus erythematosus (SLE)** – SLE can present with fulminant multisystem illness. Such patients generally have considerable kidney and central nervous system involvement, which are not common features of MIS-C. in SLE , most report feeling fatigued and unwell for a period of time prior to the onset of severe symptoms

- **Vasculitis** – Vasculitides other than KD can present with fevers, rash, and elevated inflammatory markers.

## Diagnostic criteria for Kawasaki disease

| |
|---|
| The diagnosis of KD requires the presence of fever lasting at least 5 days* without any other explanation combined with at least 4 of the 5 following criteria. A significant proportion of children with KD have a concurrent infection; therefore, ascribing the fever to such an infection or to KD requires clinical judgment. |
| Bilateral bulbar conjunctival injection |
| Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue |
| Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase) |
| Polymorphous rash |
| Cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter) |

KD: Kawasaki disease.


A
B
C
D


Signs & Symptoms of Kawasaki Disease

# Our suggested approach to the evaluation of patients with suspected COVID-19-associated multisystem inflammatory syndrome in children (MIS-C)

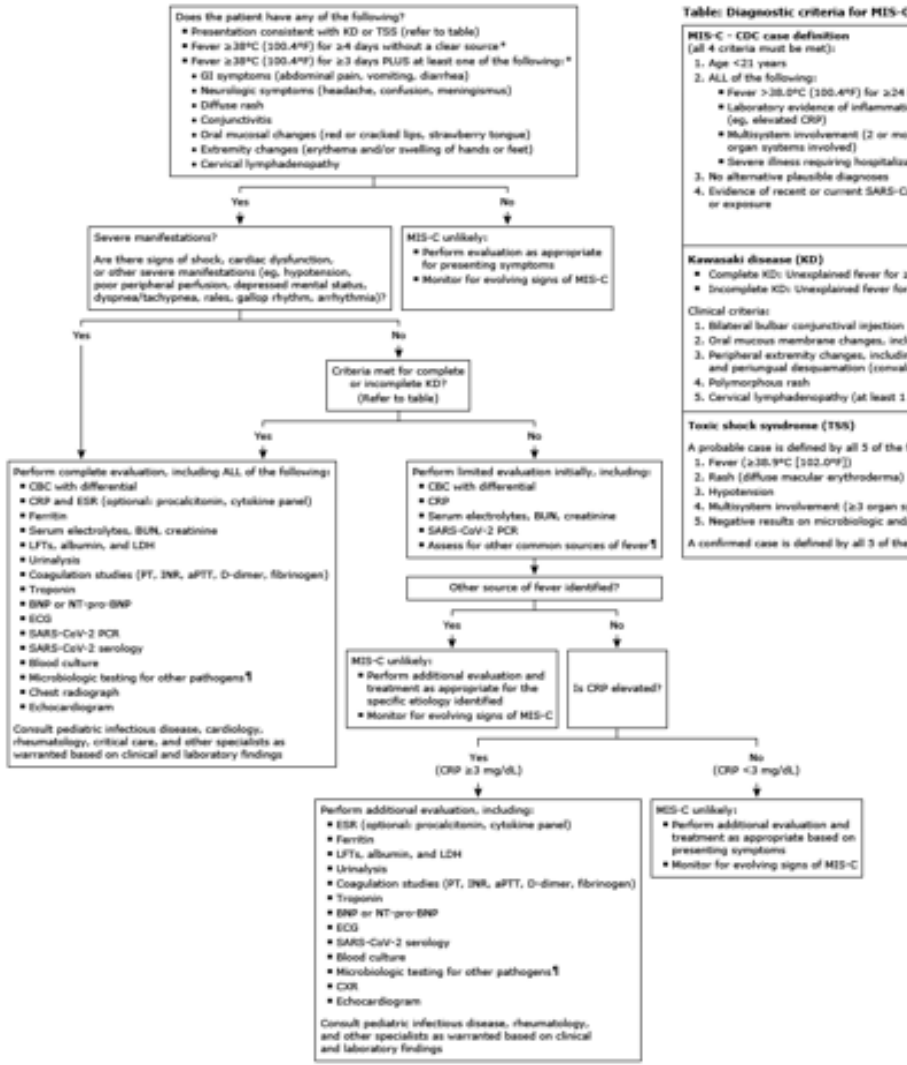



**Table: Diagnostic criteria for MIS-C, KD, and TSS**

| **MIS-C – CDC case definition** (all 4 criteria must be met): | **MIS-C – WHO case definition** (all 6 criteria must be met): |
|---|---|
| 1. Age <21 years<br>2. ALL of the following:<br>• Fever >38.0°C (100.4°F) for ≥24 hours<br>• Laboratory evidence of inflammation (eg, elevated CRP)<br>• Multisystem involvement (2 or more organ systems involved)<br>• Severe illness requiring hospitalization<br>3. No alternative plausible diagnoses<br>4. Evidence of recent or current SARS-CoV-2 infection or exposure | 1. Age <20 years<br>2. Fever for ≥3 days<br>3. Signs of multisystem involvement (at least 2):<br>• Rash, conjunctivitis, mucositis, swollen hands or feet<br>• Hypotension or shock<br>• Coagulopathy<br>• Acute GI symptoms (diarrhea, vomiting, abdominal pain)<br>4. Elevated markers of inflammation (eg, CRP)<br>5. No other obvious cause of inflammation<br>6. Evidence of recent or current SARS-CoV-2 infection or exposure |

**Kawasaki disease (KD)**

- Complete KD: Unexplained fever for ≥4 days PLUS at least 4 of the 5 clinical criteria below
- Incomplete KD: Unexplained fever for ≥5 days PLUS 2 to 3 of the 5 clinical criteria below

Clinical criteria:

1. Bilateral bulbar conjunctival injection
2. Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
3. Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase)
4. Polymorphous rash
5. Cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter)

**Toxic shock syndrome (TSS)**

A probable case is defined by all 5 of the following criteria:

1. Fever (≥38.9°C [102.0°F])
2. Rash (diffuse macular erythroderma)
3. Hypotension
4. Multisystem involvement (≥3 organ systems involved)
5. Negative results on microbiologic and/or serologic testing for other causative organisms

A confirmed case is defined by all 5 of the above criteria PLUS desquamation 1 to 2 weeks after onset of rash.

# Our suggested approach to the evaluation of patients with suspected COVID-19-associated multisystem inflammatory syndrome in children (MIS-C)

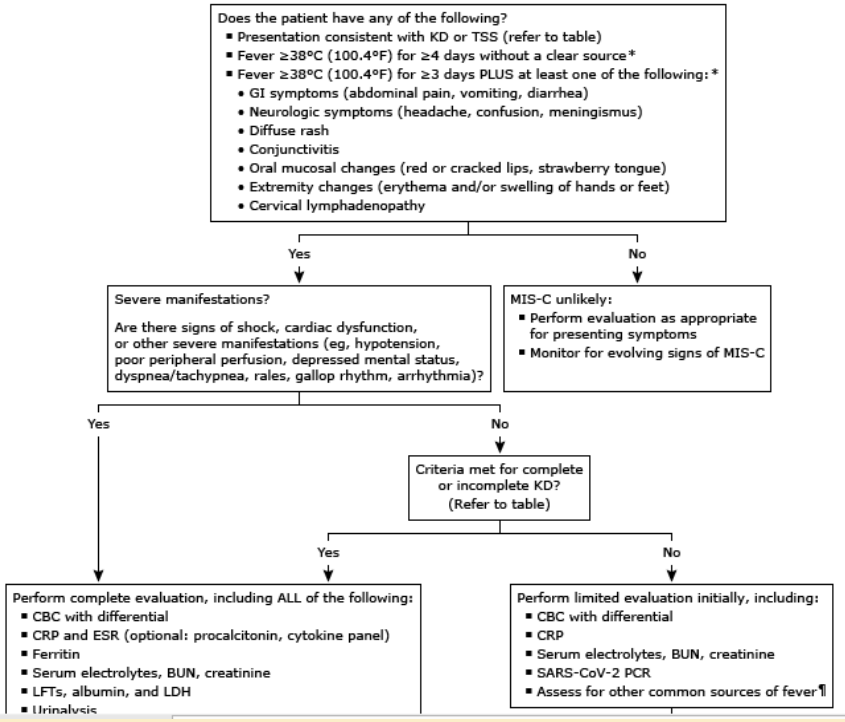



**Table: Diagnostic criteria for MIS-C, KD, and TSS**

| **MIS-C - CDC case definition** (all 4 criteria must be met): | **MIS-C - WHO case definition** (all 6 criteria must be met): |
|---|---|
| 1. Age <21 years<br>2. ALL of the following:<br>▪ Fever >38.0°C (100.4°F) for ≥24 hours<br>▪ Laboratory evidence of inflammation (eg, elevated CRP)<br>▪ Multisystem involvement (2 or more organ systems involved)<br>▪ Severe illness requiring hospitalization<br>3. No alternative plausible diagnoses<br>4. Evidence of recent or current SARS-CoV-2 infection or exposure | 1. Age <20 years<br>2. Fever for ≥3 days<br>3. Signs of multisystem involvement (at least 2):<br>▪ Rash, conjunctivitis, mucositis, swollen hands or feet<br>▪ Hypotension or shock<br>▪ Coagulopathy<br>▪ Acute GI symptoms (diarrhea, vomiting, abdominal pain)<br>4. Elevated markers of inflammation (eg, CRP)<br>5. No other obvious cause of inflammation<br>6. Evidence of recent or current SARS-CoV-2 infection or exposure |

**Kawasaki disease (KD)**

▪ Complete KD: Unexplained fever for ≥4 days PLUS at least 4 of the 5 clinical criteria below
▪ Incomplete KD: Unexplained fever for ≥5 days PLUS 2 to 3 of the 5 clinical criteria below

Clinical criteria:

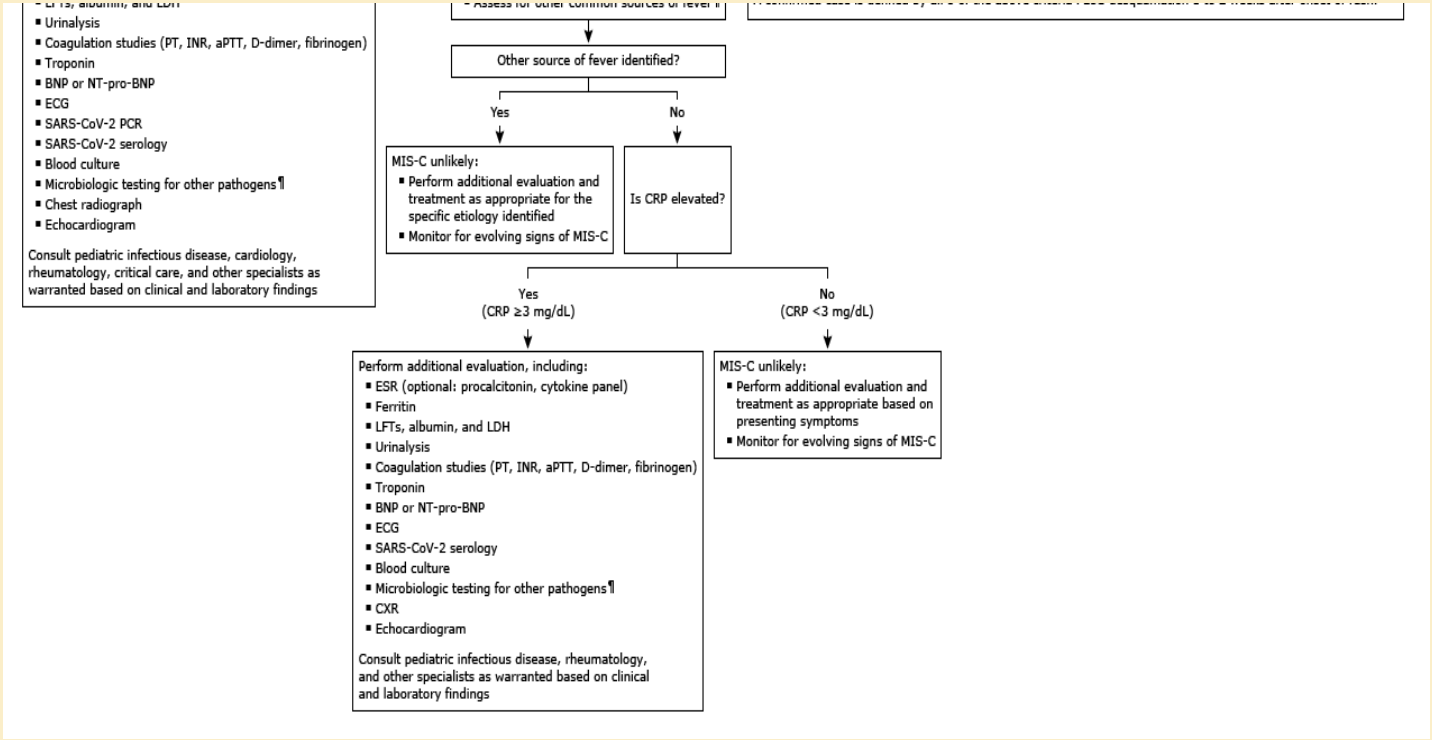
1. Bilateral bulbar conjunctival injection
2. Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
3. Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase)
4. Polymorphous rash
5. Cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter)

**Toxic shock syndrome (TSS)**

A probable case is defined by all 5 of the following criteria:

1. Fever (≥38.9°C [102.0°F])
2. Rash (diffuse macular erythroderma)
3. Hypotension
4. Multisystem involvement (≥3 organ systems involved)
5. Negative results on microbiologic and/or serologic testing for other causative organisms

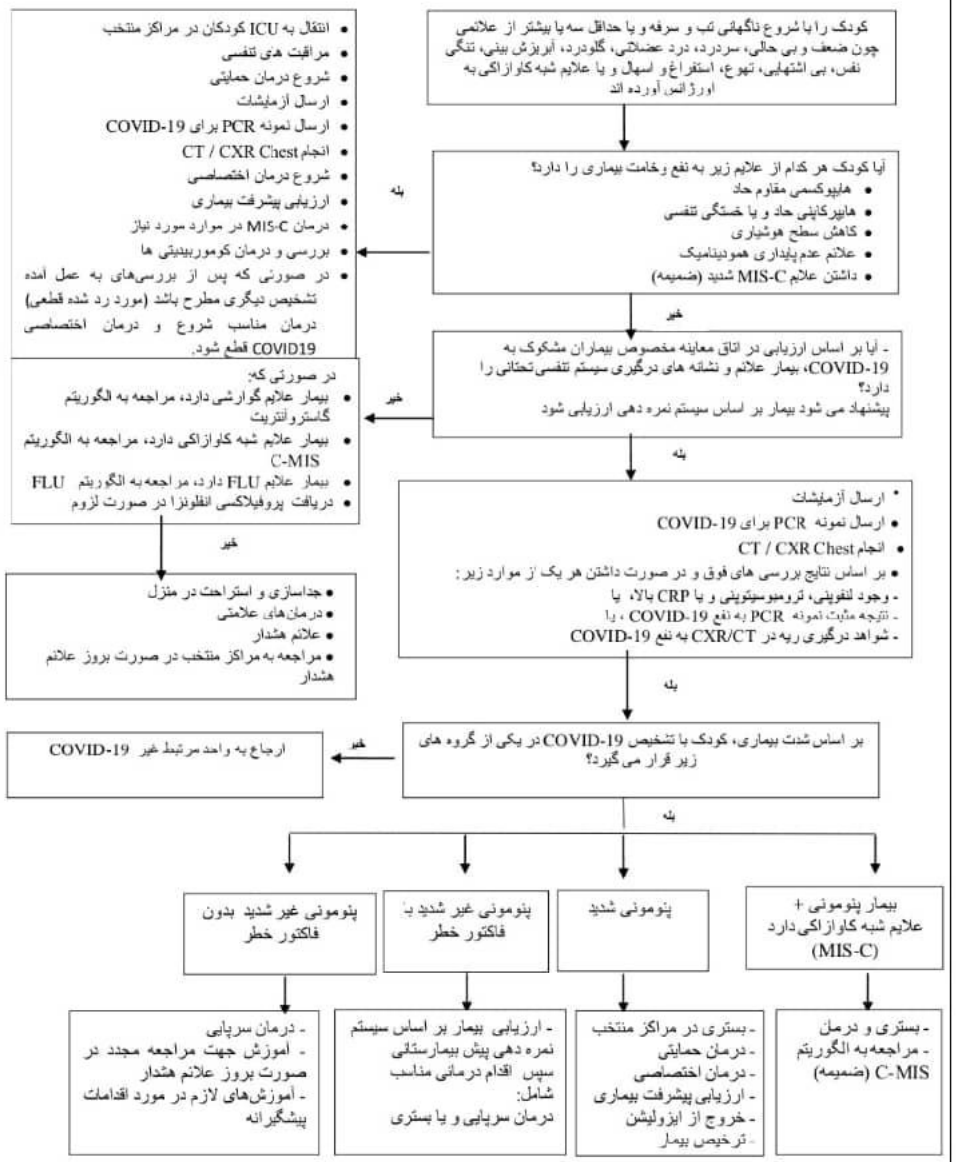
A confirmed case is defined by all 5 of the above criteria PLUS desquamation 1 to 2 weeks after onset of rash.

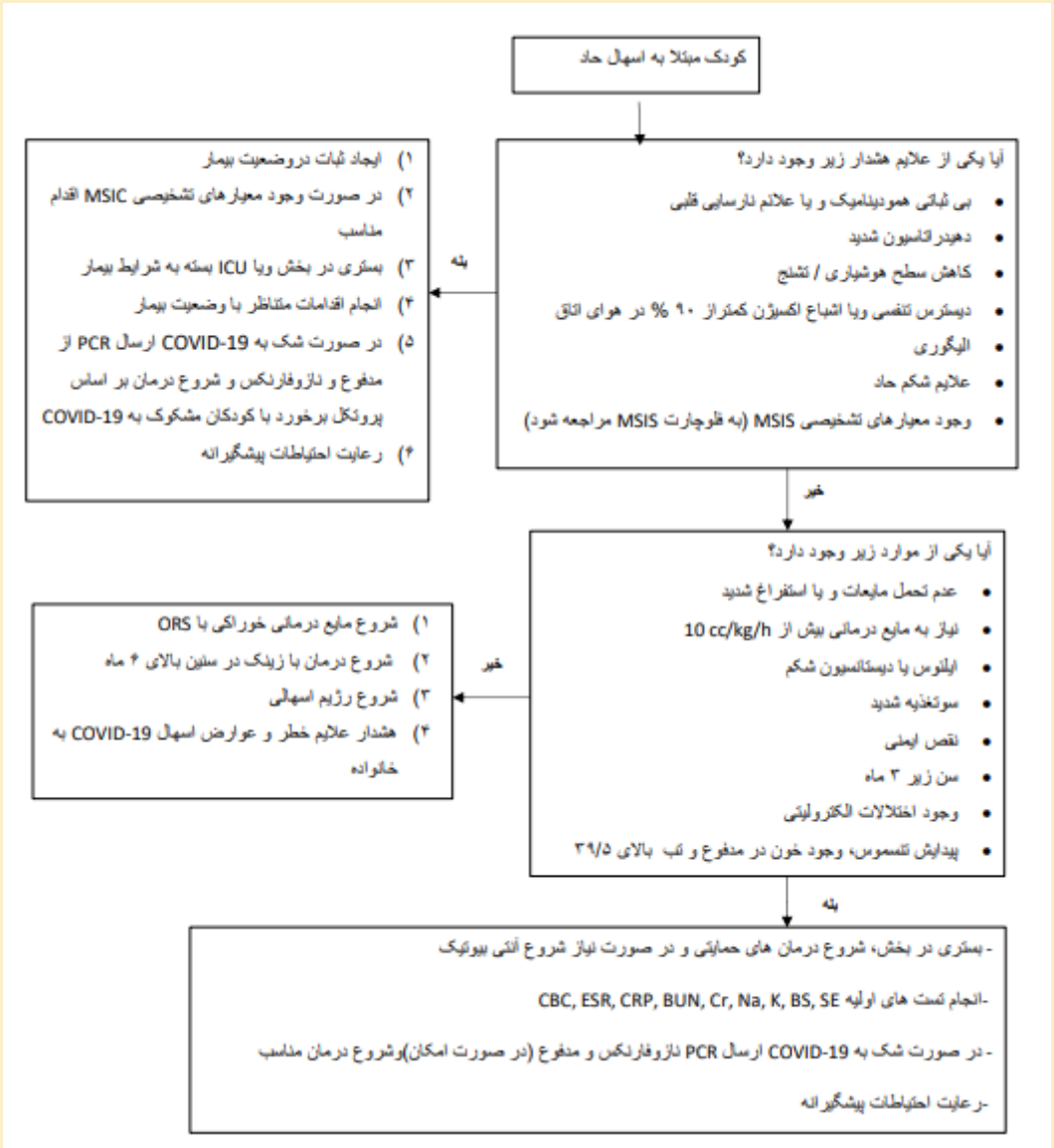

Urinalysis
Coagulation studies (PT, INR, aPTT, D-dimer, fibrinogen)
Troponin
BNP or NT-pro-BNP
ECG
SARS-CoV-2 PCR
SARS-CoV-2 serology
Blood culture
Microbiologic testing for other pathogens¶
Chest radiograph
Echocardiogram
Consult pediatric infectious disease, cardiology, rheumatology, critical care, and other specialists as warranted based on clinical and laboratory findings
Other source of fever identified?
Yes
No
MIS-C unlikely:
Perform additional evaluation and treatment as appropriate for the specific etiology identified
Monitor for evolving signs of MIS-C
Is CRP elevated?
Yes
(CRP ≥3 mg/dL)
No
(CRP <3 mg/dL)
Perform additional evaluation, including:
ESR (optional: procalcitonin, cytokine panel)
Ferritin
LFTs, albumin, and LDH
Urinalysis
Coagulation studies (PT, INR, aPTT, D-dimer, fibrinogen)
Troponin
BNP or NT-pro-BNP
ECG
SARS-CoV-2 serology
Blood culture
Microbiologic testing for other pathogens¶
CXR
Echocardiogram
Consult pediatric infectious disease, rheumatology, and other specialists as warranted based on clinical and laboratory findings
MIS-C unlikely:
Perform additional evaluation and treatment as appropriate based on presenting symptoms
Monitor for evolving signs of MIS-C

## Clinical spectrum of COVID-19 and COVID-19-associated multisystem inflammatory syndromes in children

| Acute COVID-19 | | COVID-19-associated MIS-C | | |
|---|---|---|---|---|
| **Mild** | **Severe** | **Febrile inflammatory state** | **KD-like illness** | **Severe MIS-C** |
| In most children, COVID-19 causes no or only mild symptoms. | A small minority of children present with severe acute COVID-19 manifestations, including respiratory failure, ARDS, neurologic symptoms, coagulopathy, and shock. This occurs most commonly in children with underlying medical conditions. Some children with severe acute COVD-19 may develop signs of cytokine storm. | Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers may be elevated, but signs of severe multisystem involvement are lacking. | Some children meet criteria for complete or incomplete KD and do not develop shock and severe multisystem involvement. | Children with severe MIS-C have markedly elevated inflammatory markers and severe multisystem involvement. Cardiac involvement and shock are common. |

## فلوچارت مدیریت غربالگری، اقدامات تشخیصی و درمان کودکان با علائم به نفع COVID19




کودک مبتلا به اسهال حاد
آیا یکی از علایم هشدار زیر وجود دارد؟
بی ثباتی همودینامیک و یا علائم نارسایی قلبی
دهیدراتاسیون شدید
کاهش سطح هوشیاری / تشنج
دیسترس تنفسی ویا اشباع اکسیژن کمتراز ۹۰ % در هوای اتاق
الیگوری
علایم شکم حاد
وجود معیارهای تشخیصی MSIS (به فلوچارت MSIS مراجعه شود)
بله
۱) ایجاد ثبات دروضعیت بیمار
۲) در صورت وجود معیارهای تشخیصی MSIC اقدام مناسب
۳) بستری در بخش ویا ICU بسته به شرایط بیمار
۴) انجام اقدامات متناظر با وضعیت بیمار
۵) در صورت شک به COVID-19 ارسال PCR از مدفوع و نازوفارنکس و شروع درمان بر اساس پروتکل برخورد با کودکان مشکوک به COVID-19
۶) رعایت احتیاطات پیشگیرانه
خیر
آیا یکی از موارد زیر وجود دارد؟
عدم تحمل مایعات و یا استفراغ شدید
نیاز به مایع درمانی بیش از 10 cc/kg/h
ایلئوس یا دیستانسیون شکم
سوءتغذیه شدید
نقص ایمنی
سن زیر ۳ ماه
وجود اختلالات الکترولیتی
پیدایش تنفسوس، وجود خون در مدفوع و تب بالای ۳۹/۵
خیر
۱) شروع مایع درمانی خوراکی با ORS
۲) شروع درمان با زینک در سنین بالای ۶ ماه
۳) شروع رژیم اسهالی
۴) هشدار علایم خطر و عوارض اسهال COVID-19 به خانواده
بله
- بستری در بخش، شروع درمان های حمایتی و در صورت نیاز شروع آنتی بیوتیک
-انجام تست های اولیه CBC, ESR, CRP, BUN, Cr, Na, K, BS, SE
- در صورت شک به COVID-19 ارسال PCR نازوفارنکس و مدفوع (در صورت امکان)وشروع درمان مناسب
-رعایت احتیاطات پیشگیرانه

## ضمیمه ۶-برخورد با شبه کاوازاکی و سندرم التهاب چند سیستمی در کودکان مبتلا به کووید-۱۹ (MIS-C)

(تدوین: دکتر عبدالله کریمی، دکتر زهرا پورمقدسی، دکتر رکسانا منصورفتاحی، دکترکتایون طایری، دکتر محمدرضا صبری، دکتر رضا شیاری، دکتر حمید رحیمی، دکتر وحید ضیایی، دکتر علی اکبر زینالو، دکتر سید رضا رئیس کرمی، دکتر حمید اسحاقی، دکتر احسان آقایی، دکترصدیقه طباطبایی، دکترشهناز آرمین، دکتر راحله عصاری، دکترسیدعلیرضافقیم زاد، دکترجوادی پروانه)

- **بیمار با تب بالا و یا مساوی ۳۸ درجه برای بیش از ۴ روز یا ۲ تا ۵ علامت بیماری کاوازاکی مراجعه می کند:**

بثورات جلدی ( پلی مورفیک و یا ماکولوپاپولار)
اریتم و ادم دست و یا
اریتم و ترک خوردگی لب ها زبان توت فرنگی و اریتم مخاط دهان و حلق
لنفادنوپاتی گردن یکطرفه با اندازه بیش از ۱/۵ سانتیمتر
کنژنکتویت دو طرفه غیر چرکی
و CRP>=30 ، ESR>=40
در ضمن بیمار یافته غیر طبیعی به نفع بیماری دیگری غیر از KD نداشته باشد و تشخیص های افتراقی رد شده باشد.
**در آن صورت:**

- **اکوکاردیوگرافی برای بیمار انجام شود.**
- **در صورت مطرح شدن کاوازاکی آتیپیک یا کلاسیک درمان استاندارد با IVIG و آسپیرین شروع شود.**
- **در صورت داشتن سابقه مبتلا بودن به کووید-۱۹ یا تماس با بیمار بهبود یافته طی دو هفته اخیر از نظر ابتلا به کووید -۱۹ بررسی شود و اقدامات درمانی و پیشگیرانه مطابق با ویرایش دوم دستورالعمل کشوری کووید در اطفال (۱۰ اردیبهشت ۱۳۹۹) به عمل آید.**

بیمار سیر بیماری کاوازاکی را طی و تب با اولین دز IVIG قطع می شود و طبق پروتکل درمان کاوازاکی پس ازتبدیل دز ضد التهاب آسپرین به ضد ترومبوز ۷۲-۴۸ ساعت بدون تب بوده و از نظر قلبی با ثبات است.

بله

ترخیص با توصیه های لازم
شامل هشدار علایم خطر

خیر

- در صورت وجود یکی و یا بیشتر از علایم ناسازگار با کاوازاکی:
- شوک یا فشار خون پایین
- نارسایی قلبی و یا کاردیت
- شواهد دال بر شکم حاد، گاسترو آنتریت حاد
- آسیت غیرر قابل توجیه
- هپاتیت با و یا بدون زردی
- اسپلنومگالی
- بثورات جلدی پاپولار، وزیکولار و یا پتشی و پورپورا
- شواهد بالینی به نفع کوآگولوپاتی
- شواهد به نفع انسفالیت (مثل کاهش سطح هوشیاری – تشنج و درگیری اعصاب کرانیال و ...)

تشخیص افتراقی‌های مثل، سپتی سمی ، TSS ناشی از استرپ گروه A و یا استافیلوکوک، KD-Shock syndrome تب های هموراژیک ( به خصوص CCHF ) و سندرم التهابی چند سیستمی ناشی از کرونا ویروس (MIS-C) و MAS مد نظر باشد و ازمایشات مرتبط طبق کتب مرجع بعمل آید.

**اگرمعیارهای زیر وجودداشته باشدبیماربه عنوان MISCدرنظرگرفته شود:**

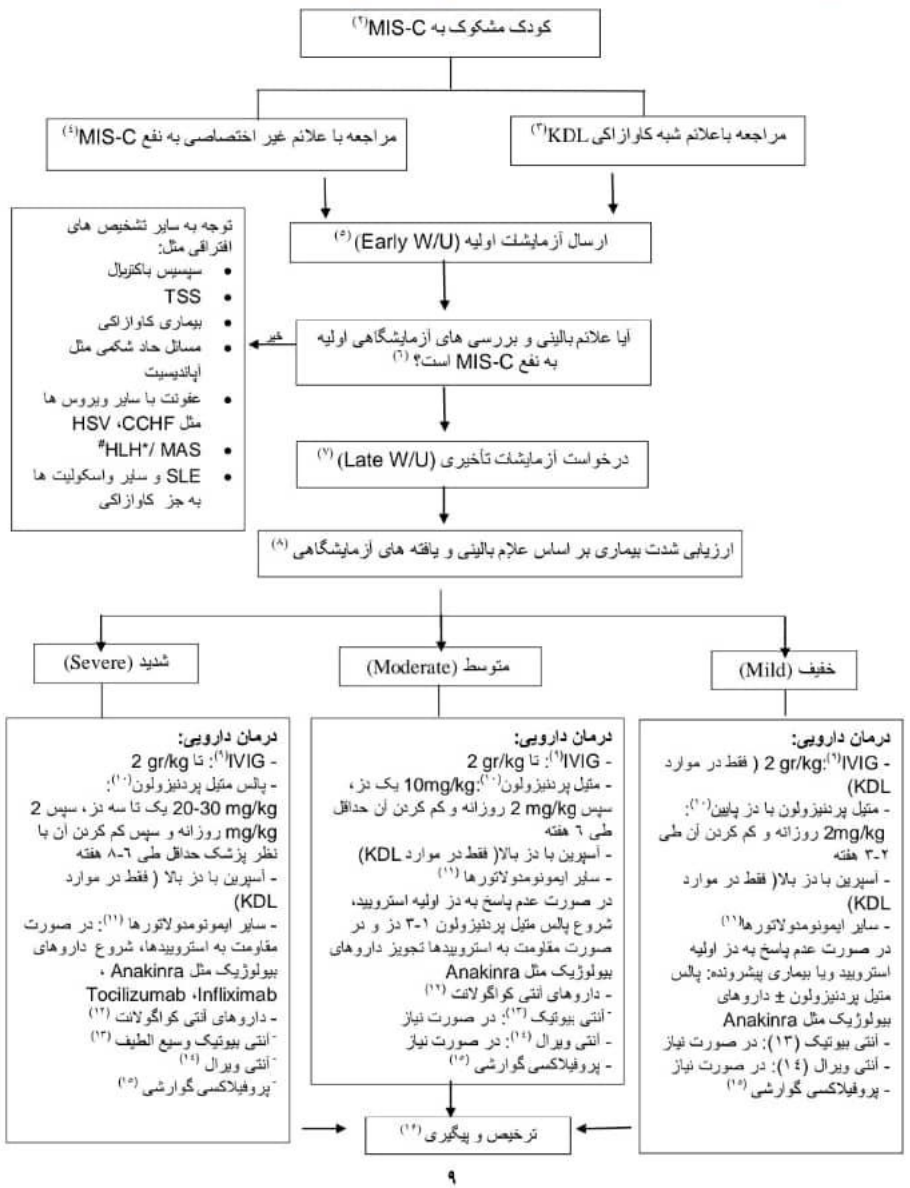
A. سن ۱۹-۰ سال
B. تظاهرات بالینی شامل تمام موارد زیر :
۱.تب ثابت شده بالای ۳۸ درجه برای بیش از ۲۴ ساعت
۲. درگیری دو ارگان یا بیشتر شامل : کاردیو واسکولار (مثل شوک، افزایش troponin، BNP، اکوی غیر طبیعی و

شماره ۱ )

**جدول شماره ۱- ارزیابی شدت بیماری در کودکان با تشخیص MIS-C**

| شدت بیماری / میزان درگیری | خفیف (Mild) | متوسط (Moderate) | شدید (Severe) |
|---|---|---|---|
| نیاز به دریافت اکسیژن/ حمایت تنفسی | ندارد | نیازمند اکسیژن با کانولا یا ماسک | نیازمند اکسیژن با فلوی بالا (HFO[1]) و یا ونتیلاتور |
| نیاز به داروهای وازواکتیو | ندارد | دارد | دارد |
| صدمه به ارگان ها | مختصر | درگیری مختصر و یا محدود ارگان یا درگیری عروق کرونری | درگیری متوسط تا شدید در ارگان ها مثل اختلال عملکرد ونتریکولار، آنوریسم عروق کرونری |
| بیماری پیشرونده | خیر | بلی | بلی |

## فلوچارت نحوه برخورد با کودک مشکوک به سندرم التهابی چند سیستمی (C-MIS ) مرتبط با COVID-19



سپاس