**Authors:** Adrienne G Randolph, MD, MSc, Mary Beth F Son, MD
**Section Editors:** David R Fulton, MD, Sheldon L Kaplan, MD
**Deputy Editors:** Carrie Armsby, MD, MPH, Elizabeth TePas, MD, MS

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

**Literature review current through:** Apr 2020. | **This topic last updated:** May 20, 2020.

## INTRODUCTION

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019 [1]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV. The WHO declared COVID-19 a pandemic on March 11, 2020 [2].

In children, COVID-19 is usually mild. However, in rare cases, children can be severely affected, and clinical manifestations may differ from adults. In late April of 2020, reports emerged from the United Kingdom of a presentation in children similar to incomplete Kawasaki disease (KD) or toxic shock syndrome [3,4]. Since then, there have been increasing reports of similarly affected children in other parts of the world [5-8]. The syndrome has been termed multisystem inflammatory syndrome in children (MIS-C; also referred to as pediatric multisystem inflammatory syndrome [PMIS], pediatric inflammatory multisystem syndrome [PIMS], pediatric hyperinflammatory syndrome, or pediatric hyperinflammatory shock).

This topic will outline what is known about the epidemiology, clinical presentation, diagnosis, and management of MIS-C. Other aspects of COVID-19 in children and adults are discussed separately:

- (See "Coronavirus disease 2019 (COVID-19): Considerations in children".)

- (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention".)
- (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings".)
- (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults".)
- (See "Coronavirus disease 2019 (COVID-19): Hypercoagulability".)
- (See "Coronavirus disease 2019 (COVID-19): Outpatient management in adults".)

Understanding of COVID-19 and MIS-C is evolving. Interim guidance has been issued by the WHO and by the United States Centers for Disease Control and Prevention (CDC) [5,9,10]. Links to these and other related society guidelines are found elsewhere. (See 'Society guideline links' below.)

## EPIDEMIOLOGY

While the incidence of MIS-C is unknown, it appears to be a rare complication of COVID-19 in children.

The initial reports of MIS-C emerged from the United Kingdom in late April, 2020 [3,4]. Since then, there have been reports of similarly affected children in other parts of the world, including Europe, Canada, and the United States (the majority of cases in the United States have been in New York) [5-8].

The first report of MIS-C was a series of eight children seen at a tertiary center South East England [3]. All eight children were previously healthy. Six of the children were of Afro-Caribbean descent, and five of the children were boys. The mean age of was 8.9 years (range 6 to 14 years). Based on the subsequent early published and unpublished reporting, there is a suggestion that school-aged children and teenagers may be at higher risk for MIS-C compared with infants and young children [6]. This pattern differs from classic Kawasaki disease (KD), which typically affects infants and young children. (See "Kawasaki disease: Epidemiology and etiology", section on 'Epidemiology'.)

It is unclear if the risk varies by race, though black children account for a disproportionally high number of cases and Asian children account for only a small number of cases in the initial reports. The initial data suggest that the frequency of MIS-C by race/ethnicity differs from that of classic KD, in which the highest incidence is seen in East Asia and in children of Asian descent. (See "Kawasaki disease: Epidemiology and etiology", section on 'Epidemiology' and "Kawasaki disease: Epidemiology and etiology", section on 'Geographic variation'.)

Based on the patterns seen in the United Kingdom and Italy, there seems to be a lag of several weeks between the peak of COVID-19 cases within communities to the peak of MIS-C cases [6,11].

For example, in London, the peak of COVID-19 cases occurred in the first to second weeks of April, while the peak of MIS-C cases occurred in the first to second week of May [11]. This suggests that MIS-C may be a postinfectious complication temporally associated with the virus.

## PATHOPHYSIOLOGY

The pathophysiology of MIS-C is not well understood. It has been suggested that the syndrome results from an abnormal immune response to the virus, with some similarities to Kawasaki disease (KD), macrophage activation syndrome, and cytokine release syndrome. The mechanisms by which SARS-CoV-2 triggers the abnormal immune response are unknown. A postinfectious process is suggested, based on the timing of the rise of these cases relative to the peak of COVID-19 cases in communities, as discussed above (See 'Epidemiology' above.). This is also supported by the finding that many affected children have negative testing for SARS-CoV-2 on polymerase chain reaction (PCR) swabs but have positive serology. However, some children do have positive PCR testing and appear to have an acute infection. This is an area of active investigation. The pathophysiology of KD, macrophage activation syndrome, and cytokine release syndrome are discussed separately. (See "Kawasaki disease: Epidemiology and etiology", section on 'Immunologic response' and "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Pathophysiology' and "Cytokine release syndrome (CRS)", section on 'Pathophysiology'.)

## CLINICAL MANIFESTATIONS

**Presentation** — In the available case reports, clinical presentations were similar, including [3,7]:

- Persistent fevers (38 to 40°C)
- Rash
- Conjunctivitis
- Peripheral edema
- Generalized extremity pain
- Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)

Many patients presented with three to five days of fever, then went on to develop warm shock. Patients presenting with fewer days of fever have been reported. Shock is often refractory to volume resuscitation, requiring vasopressors and, in some cases, mechanical hemodynamic support.

Respiratory disease was **not** a prominent feature in most cases, though most children required mechanical ventilation for cardiovascular stabilization.

Some patients had evidence of serositis, with small pleural, pericardial, and ascitic effusions.

**Laboratory findings** — Laboratory abnormalities noted in the available case series include [3,6,12]:

- Elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, procalcitonin)
- Neutrophilia
- Lymphocytopenia
- Thrombocytopenia
- Elevated D-dimer
- Hyperfibrinogenemia
- Elevated ferritin
- Elevated interleukin-6 (IL-6) levels
- Elevated troponin
- Elevated brain natriuretic peptide
- Mildly elevated liver enzymes
- Hypertriglyceridemia

## CASE DEFINITION

The criteria used for case definition vary slightly between different health agencies [5,8,12]:

- **Centers for Disease Control and Prevention (CDC) case definition** – According to the case definition put forth by the United States CDC, MIS-C is defined by meeting **all** of the following criteria (table 1) [5]:
    - Age <21 years
    - A presentation consistent with MIS-C, including **all** of the following:
        - Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
        - Laboratory evidence of inflammation (eg, elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin-6 [IL-6] level; neutrophilia; lymphocytopenia; and/or hypoalbuminemia)
        - Severe illness requiring hospitalization

- ≥2 organ systems involved (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, and/or neurologic)

- No alternative plausible diagnoses
- Recent or current SARS-CoV-2 infection or exposure, defined as **any** of the following:
  - Positive SARS-CoV-2 polymerase chain reaction (PCR)
  - Positive serology for SARS-CoV-2
  - Positive antigen test
  - COVID-19 exposure within the four weeks prior to the onset of symptoms

Patients who meet these criteria and who also fulfill full or partial criteria for Kawasaki disease (KD) should be considered to have MIS-C and should be reported. In addition, MIS-C should be considered in any pediatric death with evidence of SARS-CoV-2 infection.

- **World Health Organization (WHO) case definition** – The case definition put forth by the WHO is as follows [8]:
  - Age 0 to 19 years old, **and**
  - Fever for ≥3 days, **and**
  - Elevated markers of inflammation (eg, erythrocyte sedimentation rate, C-reactive protein, or procalcitonin), **and**
  - No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal shock syndromes, **and**
  - Evidence of SARS-CoV-2 infection (positive reverse transcription PCR [RT-PCR], antigen test, or serology) or contact with an individual with COVID-19, **and**
  - Clinical signs of multisystem involvement (at least two of the following):
    - Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
    - Hypotension or shock
    - Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/brain natriuretic peptide)
    - Evidence of coagulopathy (prolonged prothrombin time or partial thromboplastin time; elevated D-dimer)

- Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

While these definitions are similar, there are some key differences. The CDC's definition takes into account the child's severity of illness (ie, the child must have severe symptoms requiring hospitalization to meet criteria for case definition), whereas the WHO's case definition does not. Based on the available case reports, most children have severe manifestations (most require intensive care), and it seems appropriate to include this criterion in the case definition. On the other hand, an advantage of the WHO definition is that it provides more detail regarding clinical signs of multisystem involvement. These definitions are likely to change as more information becomes available.

## EVALUATION

**Laboratory testing** — The initial laboratory evaluation of a child with suspected MIS-C includes:

- Complete blood cell count with differential
- C-reactive protein and erythrocyte sedimentation rate (optional: procalcitonin)
- Ferritin level
- 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, antithrombin-3)
- Troponin
- Brain natriuretic peptide
- Creatine kinase-MB
- Blood culture
- Cytokine panel (if available)

Inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, procalcitonin, ferritin) are measured at the time of admission and then serially to monitor progression.

**Testing for SARS-CoV-2** — All patients with suspected MIS-C should be tested for SARS-CoV-2, including both serology and reverse transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab. As previously discussed, many affected children have negative PCR testing (see 'Pathophysiology' above). In these patients, antibody testing can provide supportive information. Testing for SARS-CoV-2 is discussed in greater detail separately. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Microbiologic diagnosis'.)

**Testing for other pathogens** — Testing for other viral and bacterial pathogens includes [12]:

- 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.

Additional testing for other pathogens may be warranted, depending on the geographic location and exposure history. This may include:

- Murine typhus
- Leptospirosis serology

**Cardiac testing** — In addition to troponin and brain natriuretic peptide levels, the cardiac evaluation of a patient with suspected MIS-C includes a 12-lead electrocardiogram (ECG) and echocardiography. Echocardiography is also recommended for children with documented SARS-CoV-2 who do not meet all criteria for MIS-C but who have either shock or features consistent with incomplete or complete Kawasaki disease (KD).

Children and adolescents with mild COVID-19 without signs of systemic inflammation are unlikely to have coronary artery (CA) changes or myocarditis. In such children, echocardiography is generally not necessary but may be considered if there are specific clinical concerns.

In children with MIS-C, baseline ECGs may be nonspecific, though arrhythmia and heart block have been described [3,13]. Findings on initial echocardiography may include CA dilation, left ventricular (LV) systolic dysfunction, and pericardial effusion. The CA abnormalities can progress to aneurysm, including giant coronary aneurysms [3].

- **Echocardiographic evaluation** – The echocardiographic evaluation includes the following:
    - 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
- Evaluate for 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)

The CA assessment is the same as in KD, as discussed separately. (See "Cardiovascular sequelae of Kawasaki disease: Clinical features and evaluation", section on 'Echocardiography'.)

- **Timing of follow-up echocardiography** – At our center, echocardiography is performed at the time of diagnosis, with follow-up examinations at the following intervals:

  - In patients who initially have normal function and normal CA dimensions, follow-up echocardiogram is performed one to two weeks post-diagnosis to recheck CA size.

  - In patients who have CA dilation/aneurysm on initial echocardiogram, echocardiography is repeated every two to three days until CA size is stable and then approximately once a week.

  - For patients with systolic dysfunction/myocarditis and normal CAs on initial echocardiogram, the echocardiogram is repeated as clinically indicated, including repeat imaging of the CAs with each study.

  - For patients who had evidence of CA involvement or systolic dysfunction/myocarditis in the acute phase, cardiac magnetic resonance imaging can be considered at approximately one to three months after the acute illness to assess ventricular function and evaluate for edema, diffuse fibrosis, and scar by myocardial delayed enhancement.

## MANAGEMENT

**Multidisciplinary care** — By definition, MIS-C is a multisystem disease, and care for affected children requires coordination of many different specialties. This may include:

- Pediatric infectious disease specialists
- Pediatric rheumatologists
- Pediatric cardiologists
- Pediatric intensivists
- Pediatric hematologists

### Antimicrobial therapy

**Antibiotic therapy** — MIS-C can present with signs and symptoms that mimic those of septic shock and toxic shock syndrome. Thus, patients presenting with severe multisystem involvement, particularly those with shock, should receive prompt empiric broad-spectrum antibiotic therapy pending culture results. An appropriate empiric regimen consists of ceftriaxone plus vancomycin. Ceftaroline plus piperacillin-tazobactam is an alternative regimen, particularly for children with acute kidney injury. Clindamycin is added if there are features consistent with toxin-mediated illness (eg, erythroderma). Antibiotics should be discontinued once bacterial infection has been excluded if the child's clinical status has stabilized. (See "Septic shock in children: Rapid recognition and initial resuscitation (first hour)", section on 'Empiric regimens' and "Staphylococcal toxic shock syndrome", section on 'Empiric therapy'.)

**Antiviral therapy** — The role of SARS-CoV-2 antiviral therapies (eg, remdesivir, specific SARS-CoV-2-immune hydroxychloroquine) in the management of MIS-C is uncertain. Many patients are polymerase chain reaction (PCR)-negative for SARS-CoV-2, and MIS-C may represent a postinfectious complication rather than active infection (see 'Pathophysiology' above). However, some children do have positive PCR testing and may have an acute infection. Thus, antiviral therapy may have potential to impact the disease process in some, but not all, patients. Use of antiviral agents is generally limited to children with severe MIS-C manifestations. We advise consultation with an infectious disease specialist to guide decision-making. Choice of SARS-CoV-2 antiviral agent, dosing, side effects, and monitoring are discussed separately. (See "Coronavirus disease 2019 (COVID-19): Considerations in children", section on 'Antiviral therapy for select patients'.)

**Additional therapy based on presentation** — Additional therapy depends on the clinical presentation. These presentations can overlap, and it may be appropriate to provide interventions from more than one category. For example, patients presenting with Kawasaki disease (KD) with associated warm shock should receive treatment for KD (ie intravenous immune globulin [IVIG] and aspirin) and appropriate hemodynamic support (ie, volume expansion and epinephrine).

**Shock** — Children presenting with shock should be resuscitated according to standard protocols (algorithm 1). In the available case series, most children with MIS-C presented with warm shock that was refractory to volume expansion. Epinephrine is the preferred vasoactive agent for the management of warm shock in children. In children presenting with significant ventricular dysfunction, milrinone may be helpful. Management of shock in pediatric patients is discussed in greater detail separately. (See "Initial management of shock in children".)

**Signs and symptoms of Kawasaki disease** — Patients who meet criteria for incomplete or complete KD (table 2) should receive standard therapies for KD, including IVIG, aspirin, and, if there are persistent signs of inflammation or coronary artery (CA) dilation, glucocorticoids. Treatment of KD is summarized in the figure (algorithm 2) and is discussed in greater detail separately. (See "Kawasaki disease: Initial treatment and prognosis" and "Incomplete (atypical) Kawasaki disease".)

**Myocardial dysfunction** — During the acute inflammatory phase of illness, children with myocardial dysfunction may present with arrhythmias and hemodynamic compromise. Serial echocardiographic assessment of cardiac function and monitoring of brain natriuretic peptide and troponin levels can help guide therapy. Management focuses on supportive care to maintain hemodynamic stability and ensure adequate systemic perfusion. IVIG is often used in severe cases when the clinical picture is consistent with myocarditis, though conclusive evidence of benefit is lacking. Continuous cardiac monitoring is essential so that arrhythmias are promptly detected and treated. Patients with significant ventricular dysfunction are treated with intravenous diuretics and inotropic agents, such as milrinone, dopamine, and dobutamine. In cases of fulminant disease, mechanical hemodynamic support may be necessary in the form of extracorporeal membrane oxygenation (ECMO) or a ventricular assist device. Management of myocarditis is discussed separately. (See "Treatment and prognosis of myocarditis in children".)

**Thrombotic complications** — Patients with MIS-C are at risk of experiencing thrombotic complications. For example, patients with KD who have large or giant CA aneurysms are at risk for myocardial infarction. In addition, patients may be at risk for venous thromboembolism (VTE), including pulmonary embolus, due to hypercoagulability associated with COVID-19. (See "Coronavirus disease 2019 (COVID-19): Hypercoagulability".)

- **Patients with KD** – All patients with complete or incomplete KD should receive antithrombotic therapy, which, at a minimum, includes low-dose aspirin. Additional antiplatelet and/or anticoagulant therapy may be warranted in select patients, depending on the degree of CA dilation, as summarized in the figure (algorithm 3) and discussed separately. (See "Cardiovascular sequelae of Kawasaki disease: Management and prognosis", section on 'Prevention of coronary thrombosis'.)

- **Patients with left ventricular (LV) dysfunction** – Systemic anticoagulation may be appropriate for patients with moderate to severe LV dysfunction, as discussed separately. (See "Treatment and prognosis of myocarditis in children", section on 'Anticoagulation'.)

- **Other patients** – In patients without KD or significant LV dysfunction, the decision to initiate therapy for prevention of VTE is individualized. The diagnosis of COVID-19-related MIS-C itself should be considered a major risk factor for VTE. VTE prophylaxis is generally appropriate for

older children and adolescents hospitalized with moderate to severe MIS-C, provided that bleeding risk is low. In infants and young children, the decision is made on a case-by-case basis, weighing other VTE risk factors and the patient's bleeding risk. When VTE prophylaxis is used, low molecular weight heparin is generally the preferred agent. Nonpharmacologic strategies for VTE prophylaxis (eg, intermittent pneumatic compression devices [size permitting] and early mobilization) are encouraged, but MIS-C-related coagulopathy may merit a higher level of intervention. The approach to VTE prophylaxis in hospitalized children is discussed in greater detail separately. (See "Venous thrombosis and thromboembolism in children: Treatment, prevention, and outcome", section on 'Venous thromboembolism prophylaxis'.)

**Adjunctive immune-modifying therapies** — The benefits and risks of adjunctive therapies (glucocorticoids, interleukin-1 [IL-1] inhibitors [eg, anakinra, canakinumab], IL-6 inhibitors [eg, tocilizumab], convalescent plasma from recovered COVID-19 patients) are uncertain. Consultation with pediatric infectious disease and rheumatology specialists is advised. We make decisions about the use of adjunctive therapies on a case-by-case basis, according to disease severity.

As discussed above, glucocorticoids are appropriate for patients with features of KD who have persistent fever after IVIG or signs of CA dilation (see 'Signs and symptoms of Kawasaki disease' above). In addition, glucocorticoids can be considered for patients with cytokine release syndrome (also called cytokine storm, which is manifested by persistent fever, markedly elevated inflammatory markers [eg, C-reactive protein, D-dimer, ferritin) and elevated proinflammatory cytokines, including IL-6). Anakinra, canakinumab, and tocilizumab are alternative options for treatment of cytokine release syndrome in patients who cannot receive glucocorticoids and those who are refractory to glucocorticoids. Such decisions should be made under the direction of a pediatric rheumatologist and should occur in the context of a clinical trial whenever possible. (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults", section on 'IL-6 pathway inhibitors' and "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults", section on 'Others'.)

## OUTCOME

The prognosis of MIS-C is uncertain, given that it is a new clinical entity and our understanding of the disease is still evolving. Though MIS-C has many similarities to Kawasaki disease (KD) and toxic shock syndrome, it is clear that the disease course in MIS-C can be more severe, with most children requiring intensive care interventions. Most children survive, but there have been several deaths reported [3,5,7]. Of the approximately 230 cases of suspected MIS-C reported by mid-May of 2020, there were at least five deaths [7].

## CASE REPORTING

Health care providers who have cared or are caring for patients younger than 21 years of age meeting MIS-C criteria (table 1) should report suspected cases to their local, state, or territorial health department. Additional information can be found on the Centers for Disease Control and Prevention (CDC) website and the World Health Organization (WHO) website.

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately:

- (See "Society guideline links: Coronavirus disease 2019 (COVID-19) – International and government guidelines for general care".)
- (See "Society guideline links: Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care".)
- (See "Society guideline links: Coronavirus disease 2019 (COVID-19) – Resources for patients".)
- (See "Society guideline links: Kawasaki disease".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10$^{th}$ to 12$^{th}$ grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient education" and the keyword[s] of interest.)

- Basics topics:
  - (See "Patient education: Coronavirus disease 2019 (COVID-19) and children (The Basics)".)

- (See "Patient education: Coronavirus disease 2019 (COVID-19) overview (The Basics)".)
- (See "Patient education: Kawasaki disease (The Basics)".)

## SUMMARY AND RECOMMENDATIONS

- Coronavirus disease 2019 (COVID-19) in children is usually mild. However, in rare cases, children can be severely affected, and clinical manifestations may differ from adults. In late April of 2020, reports emerged from the United Kingdom of a presentation in children similar to atypical Kawasaki disease (KD) or toxic shock syndrome. Since then, there have been increasing reports of similarly affected children in other parts of the world. The syndrome has been termed multisystem inflammatory syndrome in children (MIS-C). (See 'Introduction' above.)

- The clinical presentation of MIS-C may include persistent fevers, rash, conjunctivitis, peripheral edema, generalized extremity pain, and gastrointestinal symptoms. Patients typically present with three to five days of fever, followed by development of shock. (See 'Presentation' above.)

- Laboratory abnormalities may include (see 'Laboratory findings' above):

  - Elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate)
  - Neutrophilia
  - Leukopenia
  - Lymphocytopenia
  - Thrombocytopenia
  - Elevated D-dimer
  - Hyperfibrinogenemia
  - Elevated ferritin
  - Elevated interleukin-6 (IL-6) levels
  - Elevated troponin
  - Elevated brain natriuretic peptide
  - Creatine kinase-MB
  - Mildly elevated liver enzymes
  - Hypertriglyceridemia

- Case definitions for MIS-C are summarized in the table (table 1). (See 'Case definition' above.)

- The initial evaluation of a child with suspected MIS-C includes (see 'Evaluation' above):

  - Laboratory testing:

  - Complete blood cell count with differential
  - C-reactive protein and erythrocyte sedimentation rate (optional: procalcitonin)
  - Ferritin level
  - Liver function tests and lactate dehydrogenase
  - Serum electrolytes and renal function tests
  - Coagulation studies (activated partial thromboplastin time, international normalized ratio/prothrombin time, D-dimer, fibrinogen, antithrombin-3)
  - Troponin
  - Brain natriuretic peptide
  - Blood culture
  - Cytokine panel (if available)

- Testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (see "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Microbiologic diagnosis')

- Testing for other viral and bacterial pathogens (see 'Testing for other pathogens' above)

- Cardiac evaluation including 12-lead electrocardiogram (ECG) and echocardiography (see 'Cardiac testing' above)

- Management of MIS-C includes the following (see 'Management' above):

  - Multidisciplinary care – By definition, MIS-C is a multisystem disease, and care for affected children requires coordination of many different specialties. Infectious disease and rheumatology specialists should be consulted early. Pediatric cardiologists should be consulted in patients with myocardial dysfunction or signs of KD. (See 'Multidisciplinary care' above.)

  - Children presenting with shock should be resuscitated according to standard protocols (algorithm 1). (See "Initial management of shock in children".)

  - Empiric antibiotic therapy is appropriate for patients presenting with severe multisystem involvement and particularly those with shock. (See 'Antibiotic therapy' above.)

  - Use of antiviral therapies (eg, remdesivir, hydroxychloroquine) is generally limited to children with severe MIS-C manifestations and should be guided by an infectious disease specialist, preferably in the context of a clinical trial. (See 'Antiviral therapy' above.)

  - Patients who meet criteria for incomplete or complete KD (table 2) should receive standard therapies for KD, including intravenous immune globulin (IVIG), aspirin, and, in high-risk

patients, glucocorticoids (algorithm 2). (See "Kawasaki disease: Initial treatment and prognosis" and "Incomplete (atypical) Kawasaki disease".)

- Management of myocarditis focuses on supportive care to maintain hemodynamic stability and ensure adequate systemic perfusion. IVIG is often used, though conclusive evidence of benefit is lacking. Continuous cardiac monitoring is essential so that arrhythmias are promptly detected and treated. (See "Treatment and prognosis of myocarditis in children".)

- Patients with MIS-C are at risk of experiencing thrombotic complications, and antithrombotic therapy is warranted in many cases (eg, low-dose aspirin in patients with KD, systemic anticoagulation in patients with moderate to severe ventricular dysfunction). (See 'Thrombotic complications' above.)

- The benefits and risks of adjunctive therapies (glucocorticoids, IL-1 inhibitors [eg, anakinra, canakinumab], IL-6 inhibitors [eg, tocilizumab], convalescent plasma from recovered COVID-19 patients) are uncertain. Consultation with pediatric infectious disease and rheumatology specialists is advised. (See 'Adjunctive immune-modifying therapies' above.)

- Children with cardiac dysfunction or coronary artery (CA) abnormalities should have follow-up with cardiology after discharge, with serial echocardiography to assess for CA aneurysms. (See 'Cardiac testing' above.)

- Health care providers who have cared or are caring for patients younger than 21 years of age meeting MIS-C criteria (table 1) should report suspected cases to their local, state, or territorial health department. Additional information can be found on the Centers for Disease Control and Prevention (CDC) website and the World Health Organization (WHO) website. (See 'Case reporting' above.)

- The prognosis of MIS-C is uncertain, given that it is a new clinical entity and our understanding of the disease is still evolving. Most children survive, though deaths have been reported. (See 'Outcome' above.)

## REFERENCES

1. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed on February 12, 2020).

2. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 -- 11 March 2020. Available at: https://www.who.int/dg/speeches/detail/wh

o-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (Accessed on May 01, 2020).

3. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020.

4. Paediatric Intensive Care Society (PICS) Statement: Increased number of reported cases of novel presentation of multi system inflammatory disease. Available at https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf (Accessed on May 15, 2020).

5. Health Alert Network (HAN): Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp (Accessed on May 15, 2020).

6. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet 2020; epub.

7. European Centre for Disease Prevention and Control Rapid Risk Assessment: Paediatric inflammatory multisystem syndrome and SARS CoV 2 infection in children. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf (Accessed on May 17, 2020).

8. World Health Organization Scientif Brief: Multisystem inflammatory syndrome in children and adolescents with COVID-19. Available at: World Health Organization Scientif Brief: Multisystem inflammatory syndrome in children and adolescents with COVID-19 (Accessed on May 17, 2020).

9. Centers for Disease Control and Prevention. 2019 Novel coronavirus, Wuhan, China. Information for Healthcare Professionals. https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html (Accessed on February 14, 2020).

10. World Health Organization. Novel Coronavirus (2019-nCoV) technical guidance. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance (Accessed on February 14, 2020).

11. Mahase E. Covid-19: Cases of inflammatory syndrome in children surge after urgent alert. BMJ 2020; 369:1990.

12. Royal College of Paediatrics and Child Health Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf (Accessed on May 17, 2020).

13. Liu PP, Blet A, Smyth D, Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. Circulation 2020.

Topic 128190 Version 2.0