Multisystem inflammatory syndrome in children (MIS-C)

TERMINOLOGY

CLINICAL CLARIFICATION

- MIS-C (multisystem inflammatory syndrome in children) is a clinical syndrome in children and adolescents, originally recognized in temporal association with a high local prevalence of COVID-19. Subsequently, most reported cases have been shown to have laboratory evidence of recent infection with SARS-CoV-2, the virus that causes COVID-19.

- Illness is characterized by persistent fever, laboratory markers of inflammation, and evidence of single or multiorgan dysfunction.

  - May include features suggestive of Kawasaki syndrome (conjunctival and mucosal injection, rash, swelling of hands and feet, coronary artery dilation) or toxic shock syndrome (erythroderma, renal involvement, hypotension).

- Multisystem inflammatory syndrome in children is the designation used by CDC and WHO. It is also known as PIMS-TS (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection) in Europe and pediatric multisystem inflammatory syndrome temporally associated with COVID-19 in the United Kingdom.

CLASSIFICATION

- Several national and international organizations have established case definitions for MIS-C (multisystem inflammatory syndrome in children) that are broadly similar. WHO definition applies to children and adolescents aged 0 to 19 years who meet all of the following clinical criteria:

  - Fever for 3 days or longer
  - 2 or more of the following:
    - Rash or bilateral conjunctivitis (nonpurulent) or mucocutaneous inflammation of mouth, hands, or feet
    - Hypotension or shock
    - Features of myocardial dysfunction, pericarditis, valvulitis, or coronary artery abnormalities, including evidence found through imaging (echography) and laboratory studies (elevated levels of troponin, NT-proBNP [N-terminal–pro hormone brain natriuretic peptide])
    - Coagulopathy (eg, elevated prothrombin time/INR, partial thromboplastin time, D-dimer level)
    - Acute gastrointestinal symptoms (vomiting, diarrhea) or abdominal pain
    - Elevated levels of nonspecific indicators of inflammation (eg, erythrocyte sedimentation rate, C-reactive protein, procalcitonin)
  - No obvious alternate microbial cause of inflammation (bacterial sepsis, staphylococcal or streptococcal toxic shock syndrome)
  - Evidence of COVID-19 (positive reverse transcription polymerase chain reaction test result, detectable antigen, or antibody) or likely exposure to COVID-19

- CDC and Royal College of Paediatrics and Child Health have published case definitions that are slightly broader, emphasize temporal nature of association to COVID-19 (ie, causation not proven), and expand upon resemblance of syndrome to Kawasaki disease.

  - Some children fulfill full or partial criteria for Kawasaki syndrome, but MIS-C diagnosis is applied if they otherwise meet the case definition.

  - Royal College of Paediatrics and Child Health notes that polymerase chain reaction results for SARS-CoV-2 (earlier provisional name was 2019-nCoV) may be positive or negative.

- MIS-C is suspected to exist as a spectrum that includes patients with milder manifestations that do not meet case definitions and who may or may not progress to meet all criteria.

DIAGNOSIS

CLINICAL PRESENTATION

- History

  - Persistent fever, generally lasting 4 days or more, is reported in published cases.
  - Gastrointestinal symptoms including nonbloody diarrhea (which may be profuse), vomiting, and abdominal pain are the most common complaints; the latter may be severe, suggesting acute abdomen.
  - Nonspecific extremity pain and swelling have been reported.
  - Other reported symptoms include odynophagia, vomiting, headache, myalgia, and rash.
  - Respiratory symptoms may be present but are not common and are not predominant.
  - Chest pain is uncommon but may be noted.
  - Altered mental status (confusion, somnolence) and/or syncope may occur.

- Physical examination

  - Patients may appear severely ill with signs of shock.
    - Hypotension plus 2 or more of the following criteria:
      - Tachycardia (heart rate higher than 160 beats per minute in infants or 150 beats per minute in older children) or bradycardia (heart rate lower than 90 beats per minute in infants or 70 beats per minute in older children)

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- Prolonged capillary refill (longer than 2 seconds) or weak pulse (cardiogenic shock); alternatively, pulses may be bounding ("warm" vasodilatory/distributive shock)
- Tachypnea
- Mottled or cool skin, petechiae, or purpura
- Oliguria
- Altered mental status
- Hyperthermia or hypothermia
  - Fever is present by definition \(^1,5,6\) and may be quite high (40 °C or higher \(^7\))
  - Conjunctival injection is often seen, but purulence and exudate are not typically present
  - Oral mucosa may be dry and reddened (eg, fissured lips, strawberry tongue)
  - Meningismus is present in some patients
  - Cervical lymphadenopathy may be palpable
  - Pulmonary findings have not been prominent in published cases
  - Tachycardia and irregular rhythms have been reported
  - Abdominal tenderness and guarding may be noted
  - Erythema of palms and soles, as well as firm edema or induration of the dorsal surfaces, may be present
  - Rash is commonly noted, but reported cases have lacked detailed descriptions
  - Physical findings may not appear simultaneously but may evolve over several days

**CAUSES AND RISK FACTORS**

- **Causes**
  - Cause and mechanism are uncertain; there is a temporal association with COVID-19 both in individual cases (positive RNA test or serology) and in the epidemiologic curve of both conditions: \(^1,5\)
    - Following onset of the pandemic wave in Bergamo, Italy, monthly incidence of Kawasaki disease (or Kawasaki-like disease) increased 30-fold over the preceding 5 years \(^2\)
    - In areas heavily affected by the pandemic, incidence of MIS-C parallels that of COVID-19 after a 4- to 5-week interval, suggesting a postinflammatory mechanism related to COVID-19 \(^10,8,11\)
  - **Risk factors and/or associations**
    - **Age**
      - Case definitions include patients aged 0 to 19 \(^6\) (or younger than 21 \(^12\) years; published cases have ranged from age 4 months to 17 years \(^4\)
    - **Sex**
      - Among published cases that report sex, boys are affected more often than girls \(^13,14\)
    - **Ethnicity/race**
      - Among published cases in which race and ethnicity are reported, the number of patients of African, African-Caribbean, and Hispanic ancestry is disproportionately high based on local demographics \(^14,13,1\)

**DIAGNOSTIC PROCEDURES**

- **Primary diagnostic tools**
  - There is no specific diagnostic test; diagnosis is based on a constellation of clinical, laboratory, and epidemiologic factors \(^5,12\)
    - A subset of patients may fully or partially meet criteria for Kawasaki disease; others may meet criteria for toxic shock syndrome
  - **Suspect the diagnosis when**
    - **history and physical examination reveal characteristic features, knowing that they may evolve over several days**
  - **Obtain laboratory studies** that are typically indicated in the evaluation of severe febrile illness as well as those studies that have been shown to fit the pattern of laboratory abnormalities peculiar to this condition: \(^5,3,4,12,15\)
    - General tests: CBC, chemistry panel (including kidney and liver function, serum amylase, serum lactate, creatine kinase), inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, or procalcitonin), cytokine panel (if available), coagulation studies (prothrombin time/INR, partial thromboplastin time, D-dimer), ferritin, troponin, NT-proBNP, and urinalysis
    - Specific tests: SARS-CoV-2 RNA or antigen test and serology; microbiologic evaluation for alternate infectious causes (blood, throat, urine, stool, and cerebrospinal fluid cultures as clinically indicated; viral nucleic acid amplification test panel for Epstein-Barr virus, enteroviruses, and common respiratory viruses)
  - Results of tests for SARS-CoV-2 antibodies are often positive, even when polymerase chain reaction and antigen test results are negative
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- American College of Rheumatology guidelines suggest that, in children who do not present with clinically severe illness, it is reasonable to adopt a tiered approach to diagnostic testing: 16
  - First-tier testing includes CBC and differential, electrolyte levels, renal function tests, urinalysis, liver function tests, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, procalcitonin), and testing for SARS-CoV-2 and other potential infectious agents
  - In patients in whom results of these initial studies suggest MIS-C, second-tier testing includes cytokine panel, coagulation studies (prothrombin time/INR, partial thromboplastin time, D-dimer), ferritin, troponin, NT-proBNP, chest radiograph, ECG, and echocardiogram
- Obtain ECG and echocardiogram 5, 12
- Assess oxygenation by pulse oximetry or arterial blood gas. Although existing guidance does not specifically recommend chest imaging, a baseline chest radiograph is prudent and many published cases report abnormalities at presentation or during disease course 5, 4
- Abdominal ultrasonography is indicated for patients presenting with severe abdominal pain 5
- Serial monitoring of laboratory markers of inflammation and echocardiography is recommended 3
  - Laboratory
    - CBC
      - Neutrophilia and lymphopenia are typical; anemia and/or thrombocytopenia may be present 5
    - Chemistry
      - Hypoalbuminemia is common; hyponatremia and/or elevated levels of creatinine, BUN, transaminases, and creatine kinase may be seen 5, 17
    - Inflammatory markers
      - C-reactive protein, erythrocyte sedimentation rate, and procalcitonin levels are typically elevated, often markedly 7, 2, 17, 5
    - Coagulation studies
      - Prothrombin time/INR, partial thromboplastin time, and D-dimer levels may be elevated, the latter often quite markedly; fibrinogen levels may be high 2, 5, 17, 2
    - Cardiac markers
      - Troponin and proBNP levels may be elevated, sometimes to very high points 17, 18, 7
    - Others
      - High levels of ferritin are characteristic; IL-6 level (if available) may be elevated 17, 2, 5, 7
      - Mild cerebrospinal fluid pleocytosis has been reported in patients who underwent lumbar puncture for possible meningitis 18, 17
      - Triglyceride levels may be above reference range 5
    - SARS-CoV-2 testing
      - Polymerase chain reaction, antigen, or antibody test result has been positive in nearly all patients; however, negative test results do not exclude disease 19, 7, 18, 1, 17, 2
  - Imaging
    - Chest radiography
      - May reveal unilateral or bilateral infiltrates 2, 17
    - Echocardiogram
      - May reveal general features of myocarditis (left ventricular systolic dysfunction) and/or additional changes characteristic of Kawasaki disease (coronary artery dilation, valvulitis, pericardial effusion) 2, 18
      - Findings (eg, dilation or aneurysms of coronary arteries) may develop during disease course 18, 2
    - Abdominal ultrasonography
      - May reveal hepatosplenomegaly, lymphadenopathy, bowel wall edema, or ascites 5, 1
  - Functional testing
    - ECG
      - Heart block (first, second, or third degree), increased QT interval, ventricular arrhythmias, and ST segment elevation have been reported 18, 19

**DIFFERENTIAL DIAGNOSIS**

- Most common
  - Kawasaki disease
    - A subset of patients who meet diagnostic criteria for MIS-C also meet criteria for Kawasaki disease, partial Kawasaki disease, or Kawasaki disease shock syndrome. Patients in this subset commonly have features that are atypical in Kawasaki disease
      - Kawasaki diagnosis is established by fever lasting 5 or more days and at least 4 of the following criteria: 20
        - Polymorphous rash (excluding bullous or vesicular eruptions)
        - Conjunctival injection
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- Oropharyngeal mucous membrane changes
- Extremity changes
- Lymphadenopathy
- Features common to MIS-C but not typical for classic Kawasaki disease:
  - Abdominal pain is often a predominant feature and severity exceeds that seen in classic Kawasaki disease
  - Thrombocytopenia, anemia, and lymphopenia
  - Elevated levels of ferritin, troponin, proBNP, and D-dimer
- Scarlet fever
  - Severe systemic disease caused by certain strains of group A streptococcus
  - Rash, fever, and lymphadenopathy are present, as in MIS-C
  - Lip, ocular, and extremity changes are not present
  - Positive rapid streptococcal test or culture result is diagnostic
- Toxic shock syndrome
  - Severe systemic disease caused by certain toxin-producing strains of *Staphylococcus aureus* or group A streptococcus
  - Like MIS-C, patients present with fever and rash; hypotension, thrombocytopenia, central nervous system involvement (eg, confusion), and renal failure are common; a subset of patients with MIS-C fulfills clinical criteria for toxic shock syndrome
  - History of retained foreign body (eg, tampon, nasal packing material) may be elicited
  - Edema is generally diffuse and not limited to hands and feet; articular signs are generally absent
  - Case definitions include hypotension and multisystem involvement
- Features of nonstreptococcal toxic shock syndrome:
  - Fever (39 °C or higher)
  - Generalized erythroderma followed by desquamation
  - Hypotension (systolic pressure lower than 90 mm Hg in adults and older adolescents or less than fifth percentile for age in children younger than 16 years)
  - Multiorgan involvement characterized by 3 or more of the following:
    - Gastrointestinal symptoms (vomiting or diarrhea, usually at onset of illness)
    - Muscle involvement (severe myalgias and/or creatine phosphokinase level twice reference range or higher)
    - Mucus membrane changes (hyperemia of conjunctivae, oropharynx, or vagina)
    - Renal impairment (BUN or creatinine level twice upper reference limit or higher or urinary sediment with pyuria in absence of urinary tract infection)
    - Hepatic impairment (transaminase or bilirubin level twice reference range or higher)
    - Coagulopathy (platelet count 100,000/mm³ or less)
    - Central nervous system manifestations (confusion, altered level of consciousness)
  - Cultures are negative (other than *Staphylococcus aureus*, which may or may not be found)
  - No serologic evidence of recent Rocky Mountain spotted fever, leptospirosis, or measles
- Features of streptococcal toxic shock syndrome
  - Hypotension (systolic pressure less than 90 mm Hg in adults and older adolescents or less than fifth percentile for age in children younger than 16 years)
  - Multiorgan involvement characterized by 2 or more of the following:
    - Renal impairment (creatinine level 2 mg/dL or higher for adults or twice upper reference limit or higher for age)
    - Coagulopathy (platelet count 100,000/mm³ or less or presence of disseminated intravascular coagulation)
    - Hepatic impairment (transaminase or bilirubin level twice reference range or higher)
    - Acute respiratory distress syndrome
    - Generalized erythematous rash; may desquamate
    - 1 or more sites of soft tissue necrosis
    - Isolation of group A streptococcus
- Septic shock
  - Life-threatening systemic syndrome caused by microbial infection and dysregulated physiologic response
  - Presentation varies depending on source of infection but includes fever, tachypnea, tachycardia, hypotension, and signs of tissue hypoperfusion
  - Not typical: rash, lip changes, ocular changes, and edema of hands and feet
  - Diagnosis is based on recovery of pathogen by culture or other means
- Rubeola
  - Like MIS-C, characterized by high fever that persists for several days, conjunctival involvement, and diffuse rash
  - Unlike MIS-C, rash typically progresses from head to toe

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- Koplik spots—gray-white punctate spots on buccal mucosa near parotid duct—are pathognomonic for measles, if present
- Diagnosis is confirmed by detection of rubeola IgM in serum

**TREATMENT**

**GOALS**

- Reverse shock
- Reverse organ dysfunction and prevent further injury and complications (eg, coronary artery aneurysms, acute kidney injury)

**DISPOSITION**

- Admission criteria
  - Admission is recommended for children who meet MIS-C criteria, preferably to a hospital with a pediatric ICU
    - Rapid deterioration has been observed, and vasopressor and/or inotrope support has been required in a significant number of patients (73% in 1 large study)
    - It is recognized that there is a population of pediatric patients who have fever and evidence of an inflammatory response but are less severely ill and do not meet the MIS-C case definition; these children may not require admission but need to be closely monitored for progression.
    - Regardless of whether the patient meets MIS-C criteria or is still undergoing evaluation for it, consider admission in the following circumstances:
      - Abnormal vital signs (tachypnea, tachycardia, hypotension)
      - Respiratory distress to any degree
      - Neurologic deficits or altered mental status to any degree
      - Hepatic or renal dysfunction (even if mild)
      - Marked elevation of inflammatory markers
      - Abnormal ECG or serum markers of cardiac injury
  - Criteria for ICU admission
    - Shock (either cardiogenic or vasodilatory/distributive) or borderline/unstable vital signs that suggest impending shock
    - Patient who needs mechanical ventilation
- Recommendations for specialist referral
  - Management by a multidisciplinary team is recommended, including specialists in intensive care, immunology, cardiology, rheumatology, and infectious disease

**TREATMENT OPTIONS**

- Excellent supportive care is essential in all cases; antiinflammatory and immunomodulatory therapies have been used in severely ill patients (particularly those who fulfill criteria for Kawasaki disease)
- Specific guidance for treatment of shock and hypoxemia in MIS-C is lacking but includes oxygen administration (including mechanical ventilation, if necessary), cautious fluid resuscitation (preferably guided by assessment of likely responsiveness), and vasopressor support, using appropriate protocols for shock (ie, cardiogenic versus vasodilatory/distributive)
- Extracorporeal membrane oxygenation has been used in some patients
- American College of Rheumatology guidelines recommend the following approach:
  - Patients in whom MIS-C is suspected and who have life-threatening manifestations may require immunomodulatory treatment for MIS-C before the full diagnostic evaluation can be completed. Some patients with mild symptoms may require only close monitoring without immunomodulatory treatment
  - Primary immunomodulatory therapy is IV immunoglobulin; glucocorticoids are used adjunctively depending on severity of illness or clinical response to IV immunoglobulin
    - High dose IV immunoglobulin (typically 2 g/kg, based on ideal body weight) is recommended for MIS-C patients who are hospitalized or who fulfill Kawasaki disease criteria
    - Assess cardiac function and fluid status before prescribing or administering IV immunoglobulin treatment. Patients with severely impaired myocardium require close monitoring and may need diuretics to avoid volume overload; another recommended strategy is to administer in divided doses (1 g/kg daily over 2 days)
    - Administer low to moderate dose glucocorticoids (eg, methylprednisolone 1-2 mg/kg/day) with IV immunoglobulin as adjunctive therapy to treat patients in shock or who have organ-threatening disease
    - In patients who do not respond to IV immunoglobulin and low to moderate dose glucocorticoids, high dose glucocorticoid pulse therapy (eg, methylprednisolone 10-30 mg/kg/day) may be considered, especially in severe illness requiring high dose or multiple inotropes or vasopressors
    - A second dose of IV immunoglobulin is not recommended owing to potential volume overload and hemolytic anemia seen with large doses of IV immunoglobulin
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- Low to moderate dose corticosteroids (eg, methylprednisolone 1-2 mg/kg/day) also may benefit patients with milder forms of MIS-C whose fever and other symptoms do not resolve after a single dose of IV immunoglobulin.
- Anakinra (greater than 4 mg/kg/day IV or subcutaneous) is an option to treat MIS-C that does not respond adequately to IV immunoglobulin and glucocorticoids, when the clinical presentation suggests associated macrophage activation syndrome, or when there are contraindications to long-term use of glucocorticoids.
- Perform serial laboratory testing and cardiac assessment to assess for response to therapy and to guide tapering of therapy. Tapering of immunomodulating agents may require 2 to 3 weeks or more.

○ Antiplatelet and anticoagulation therapy in MIS-C:
  - Low-dose aspirin (3-5 mg/kg/day; Max: 81 mg/day) is recommended and should be continued until platelet count has returned to normal and echocardiogram 4 or more weeks after diagnosis confirms that coronary arteries are normal. Avoid aspirin therapy in patients with active bleeding, significant bleeding risk, and/or platelet count less than or equal to 80,000/µL.
  - Treat patients who have coronary artery aneurysms and a maximal z-score of 2.5 to 10 with low-dose aspirin. In patients with a z-score 10 or higher use a combination of low-dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1) or warfarin.
  - In patients with documented thrombosis or an ejection fraction less than 35%, provide therapeutic anticoagulation with enoxaparin until at least 2 weeks after discharge from the hospital.
  - Recommended duration of enoxaparin varies depending on the indication:
    - Coronary artery aneurysm with z-score higher than 10: treat indefinitely.
    - Documented thrombosis: treat for 3 or more months pending thrombus resolution.
    - Ongoing moderate to severe left ventricular dysfunction: duration of treatment not specified but included as an indication for “longer outpatient therapeutic dosing”.
  - For MIS-C patients who do not meet these criteria, tailor antiplatelet and anticoagulation management to the patient’s risk for thrombosis.

● American Academy of Pediatrics guidance recommends the following approach:
  - Usual treatment is IV immunoglobulin, 2 g/kg (Max: 100 g); duration of IV immunoglobulin therapy infusion may require modification, depending on cardiac function and fluid status.
  - Glucocorticoids (ranging from 2-30 mg/kg/day of methylprednisolone, depending on severity of illness) and biologics (eg, anakinra, 2-10 mg/kg/day, subcutaneously or IV, divided every 6-12 hours) have been used in patients who do not improve clinically after IV immunoglobulin and in those whose laboratory values do not improve.
  - If there is laboratory or imaging evidence of myocardial injury or findings concerning for coronary artery aneurysms, consult with a pediatric cardiologist before prescribing corticosteroids.
  - Patients treated with corticosteroids or biologics often require a 3-week taper of medication, which can be completed after discharge.
  - Unless contraindications exist (eg, less than 100,000 platelets or active bleeding), give all patients low-dose aspirin for thromboprophylaxis.


○ For children with nonspecific presentations, the study group recommends the following approach:
  - First line therapy is IV immunoglobulin at a dose of 2 g/kg (based on ideal body weight); may administer in a single or divided dose, depending on clinical picture and cardiac function. Can consider a second dose for children who have not responded adequately to the first dose.
  - Second line therapy is IV methylprednisolone (10-30 mg/kg) for children who remain unwell 24 hours after infusion of immunoglobulin, particularly those with persistent fever.
  - Third line therapy, for children who do not respond to IV immunoglobulin and methylprednisolone, is a biologic therapy: tocilizumab, anakinra, or infliximab.
  - All children older than 12 years should wear compression stockings.
  - Administer low-dose aspirin for a minimum of 6 weeks to all patients with PIMS-TS.

● For patients who meet Kawasaki disease criteria, Kawasaki disease guidelines encourage treatment as early as the diagnosis is established and preferably within 10 days of illness onset.

● For patients in whom sepsis caused by other pathogens has not been ruled out, begin empiric antibiotics, which can be de-escalated if indicated based on results of microbiologic studies.

● For children who meet the criteria for toxic shock syndrome, give clindamycin in addition to broad-spectrum antibiotics.

● Because MIS-C appears to be a postinfectious inflammatory response, antiviral therapy generally has not been initiated; nevertheless, use of infection control precautions appropriate for COVID-19 is recommended by some authorities.

● Children who are SARS-CoV-2 positive on reverse transcription polymerase chain reaction or antigen testing might be considered for antiviral therapy; remdesivir is the first choice antiviral therapy for SARS-CoV-2.
Drug therapy
- IV immunoglobulin
  - Immune Globulin (Human) Solution for injection; Infants, Children, and Adolescents: 2 grams/kg (based on ideal body weight; Max: 100 grams) IV. May be given as a single infusion or as divided doses, depending on patient’s clinical status and cardiac function. A second dose may be considered for patients who do not adequately respond to the first dose.
- Methylprednisolone
  - Methylprednisolone Sodium Succinate Solution for injection; Infants, Children, and Adolescents: 2 to 30 mg/kg/day IV for 3 days. Administer at the same time as intravenous immunoglobulin (IVIG) for high-risk children with Kawasaki disease-like phenotype (children younger than 12 months and those with coronary artery changes). Administer as second-line therapy in patients who remain unwell 24 hours after infusion of IVIG, especially if they have ongoing pyrexia.
- Anakinra
  - Anakinra (E. coli) Solution for injection; Children and Adolescents: Available data are limited, and efficacy has not been established. 2 to 10 mg/kg/day via subcutaneous injection or IV divided every 6 to 12 hours has been recommended with a 3-week at-home taper.
- Aspirin
  - Aspirin Oral tablet; Infants, Children, and Adolescents: Available data are limited, and efficacy has not been established. Doses varying from 3 to 5 mg/kg/day PO (low dose) to 30 to 100 mg/kg/day PO (moderate to high dose) have been reported and are being used in combination with IVIG with or without methylprednisolone.

MONITORING
- During acute disease, frequently monitor laboratory studies until values stabilize and improve.
- Serial ECGs (at least every 48 hours) and echocardiograms are appropriate during the acute phase; obtain follow-up echocardiograms 2 and 6 weeks after discharge. Some authorities recommend that children with cardiac involvement during the acute phase have repeat echocardiogram a year after discharge.
- Based on recommendations for Kawasaki disease management and on preliminary observations that MIS-C patients may (like patients with classic Kawasaki disease) develop coronary artery aneurysms late in the disease course or after apparent improvement.
- Coronary artery aneurysms occur in about 20% of patients with MIS-C, even when criteria for Kawasaki disease are not met.
- Consider cardiac MRI 2 to 6 months after acute illness for patients with significant transient or persistent left ventricular dysfunction.

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS
- Development of coronary aneurysms has been documented, and these patients are at risk for thrombosis.

PROGNOSIS
- Published reports indicate recovery in nearly all patients, with resolution of shock and organ function. However, several deaths have been reported, and long-term prognosis of survivors is unknown.

SCREENING AND PREVENTION

PREVENTION
- The only known preventive measures involve efforts to avoid infection with SARS-CoV-2 (ie, diligent distancing, widespread use of facial covering, careful hand and environmental hygiene).

SYNOPSIS

KEY POINTS
- MIS-C (multisystem inflammatory syndrome in children) is a recently described clinical syndrome in children and adolescents aged 0 to 19 years, first recognized in temporal association with a high local prevalence of COVID-19.
- Characterized by persistent fever, laboratory markers of inflammation, and evidence of single or multiorgan dysfunction, including myocarditis. Abdominal pain (often severe) and diarrhea (which may be profuse) are common presenting symptoms. By definition, no microbial cause is evident; most patients have epidemiologic links to or laboratory evidence of COVID-19.
- May include features suggestive of Kawasaki syndrome (conjunctival injection, mucosal membrane changes, rash, lymphadenopathy, swelling of hands and feet, coronary artery aneurysms), or toxic shock syndrome (fever, erythoderma, edema, renal involvement, hypotension).
- Some patients develop shock and require fluid resuscitation and hemodynamic support.
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- There is no specific diagnostic test; diagnosis is based on a constellation of clinical, laboratory, echocardiographic, and epidemiologic factors. Most patients have evidence of evidence of SARS-CoV-2 antibodies, even when polymerase chain reaction or antigen test results are negative.\(^7,17,24,28,2\)
- Patients with mild disease can be managed conservatively. Treat patients who have more severe disease, including those with myocarditis or who meet criteria for Kawasaki disease or toxic shock syndrome, with IV immunoglobulin. Corticosteroids, immune modulators, and aspirin also have a therapeutic role.\(^7,17,24,28,2\)
- Most patients have responded promptly to therapy and have done well. Because MIS-C resembles Kawasaki syndrome and because observation of coronary artery aneurysms is needed in some patients with MIS-C, serial follow-up echocardiography\(^26,24\) is recommended.\(^7,24,17,2\)

**URGENT ACTION**

- Patients in shock require immediate intervention beginning with fluid resuscitation; they may need oxygen supplementation (including mechanical ventilation) and hemodynamic support as well.
- If IV immunoglobulin is indicated, administer promptly. In Kawasaki disease, greatest efficacy in preventing coronary artery aneurysms occurs when IV immunoglobulin is given within 10 days of disease onset.\(^20\)

**PITFALLS**

- Physical findings may not appear simultaneously but may evolve over several days.
- Coronary artery aneurysms may develop late in disease course or after apparent improvement.\(^24\)

**SELECTED REFERENCES**

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