**TERMINOLOGY**

**CLINICAL CLARIFICATION**

- MIS-C (multisystem inflammatory syndrome in children) is a recently described clinical syndrome in children and adolescents, originally recognized in temporal association with a high local prevalence of COVID-19 (coronavirus disease 2019). Subsequently, most reported cases have been shown to have laboratory evidence of recent infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the virus that causes COVID-19.\(^1\)\(^2\)\(^3\)\(^4\)\n
- Illness is characterized by persistent fever, laboratory markers of inflammation, and evidence of single or multiorgan dysfunction.\(^5\)\(^6\)\(^7\)
  - 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 (paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection) in Europe and paediatric multisystem inflammatory syndrome temporally associated with COVID-19 in the United Kingdom.\(^7\)\(^5\)
  - In October 2020, an analogous syndrome was reported in adults and is called MIS-A (multisystem inflammatory syndrome in adults).\(^8\)
  - Several comprehensive clinical reviews of published individual reports and series have been compiled and provide extensive clinical and demographic data on this emerging disease.\(^6\)\(^3\)

**CLASSIFICATION**

- Several national and international organizations have established case definitions that are broadly similar. WHO definition applies to children and adolescents aged 0 to 19 years who meet all of the following clinical criteria:\(^10\)
  - 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\(^2\) and Royal College of Paediatrics and Child Health\(^5\) 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 diagnosis of MIS-C is applied if they otherwise meet the case definition.\(^2\)\(^5\)
  - 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.\(^5\)

- 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.\(^1\)

**DIAGNOSIS**

**CLINICAL PRESENTATION**

- History
  - Persistent fever, generally lasting 4 days or more, is reported in published cases.\(^11\)
  - 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.\(^11\)\(^12\)
  - Nonspecific extremity pain and swelling have been reported.\(^5\)
  - Other reported symptoms include odynophagia, vomiting, headache, myalgia, and rash.\(^5\)
  - Respiratory symptoms may be present but are not common and are not predominant.\(^5\)
  - Chest pain is uncommon but may be noted
  - Altered mental status (confusion, somnolence) and/or syncope may occur.\(^5\)
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- Physical examination
  - Patients may appear severely ill with signs of shock
    - Hypotension plus 2 or more of the following criteria:\(^\text{13}\)
      - 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)
      - Prolonged capillary refill (longer than 2 seconds) or warm vasodilation and bounding pulses
      - Tachypnea
      - Mottled skin, petechiae, or purpura
      - Oliguria
      - Altered mental status
  - Fever is present by definition\(^\text{10, 5, 2}\) and may be quite high (40 °C or higher\(^\text{11}\))
  - 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:\(^\text{2, 5}\)
    - Following onset of the pandemic wave in Bergamo, Italy, monthly incidence of Kawasaki disease (or Kawasaki-like disease) increased 30-fold over preceding 5 years\(^4\)
    - In areas heavily affected by the pandemic, incidence of this condition parallels that of COVID-19 after a 4- to 5-week interval, suggesting a postinflammatory mechanism related to COVID-19\(^\text{14, 12, 15}\)
  - Risk factors and/or associations
    - Age
      - Case definitions include patients aged 0 to 19\(^\text{10}\) (or 21\(^\text{16}\)) years; published cases have ranged from age 4 months to 17 years\(^7\)
    - Sex
      - Among published cases that report sex, boys are affected more often than girls\(^3, 9\)
    - 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\(^3, 2, 17, 9\)

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
  - There is no specific diagnostic test; diagnosis is based on a constellation of clinical, laboratory, and epidemiologic factors\(^\text{18, 5}\)
    - 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:\(^18, 1, 7, 5, 19\)
    - 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 or antigen test results are negative
  - Obtain ECG and echocardiogram\(^\text{18, 5}\)
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- 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.\(^1,5\)
- Abdominal ultrasonography is indicated for patients presenting with severe abdominal pain.\(^5\)
- Serial monitoring of laboratory markers of inflammation and echocardiography is recommended.\(^1\)

**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.\(^20,5\)
- Inflammatory markers
  - C-reactive protein, erythrocyte sedimentation rate, and procalcitonin levels are typically elevated, often markedly.\(^5,11,20,4\)
- 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.\(^4,5,20,4\)
- Cardiac markers
  - Troponin and proBNP levels may be elevated, sometimes to very high points.\(^11,21,20\)
- Others
  - High levels of ferritin are characteristic; IL-6 level (if available) may be elevated.\(^4,20,11,5\)
  - Mild cerebrospinal fluid pleocytosis has been reported in patients who underwent lumbar puncture for possible meningitis.\(^22,20\)
  - 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.\(^4,21,11,2,20,22\)

**Imaging**
- Chest radiography
  - May reveal unilateral or bilateral infiltrates.\(^20,4\)
- 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).\(^4,21\)
  - Findings (eg, dilation or aneurysms of coronary arteries) may develop during disease course.\(^21,4\)
- Abdominal ultrasonography
  - May reveal hepatosplenomegaly, lymphadenopathy, bowel wall edema, or ascites.\(^5,2\)

**Functional testing**
- ECG
  - Heart block (first, second, or third degree), increased QT interval, ventricular arrhythmias, and ST segment elevation have been reported.\(^22,21\)

**DIFFERENTIAL DIAGNOSIS**
- **Most common**
  - Kawasaki disease
    - A subset of patients who meet diagnostic criteria for MIS-C also meet the 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:\(^23\)
      - Polymorphous rash (excluding bullous or vesicular eruptions)
      - Conjunctival injection
      - Oropharyngeal mucous membrane changes
      - Extremity changes
      - Lymphadenopathy
    - Features common to MIS-C but not typical for classic Kawasaki disease:\(^2,4\)
      - 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
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- 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
    - Rash, lip changes, ocular changes, and edema of hands and feet are not typical
    - 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
    - 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
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- 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
  - For patients who meet Kawasaki disease criteria, consider treating with IV immunoglobulin and aspirin; Kawasaki disease guidelines encourage treatment as early as the diagnosis is established and preferably within 10 days of illness onset.
  - Most patients respond promptly to a single dose of IV immunoglobulin, but as in Kawasaki disease, resistance occurs in some patients. A second dose of IV immunoglobulin, with or without methylprednisolone, is often effective in patients with aneurysms and z scores of 10 or higher, documented thrombosis, or ejection fraction less than 35% are given therapeutic anticoagulation in addition to aspirin.
  - For patients who meet criteria for toxic shock, consider using IV immunoglobulin.
  - IV immunoglobulin has also been used successfully in children who do not meet criteria for Kawasaki disease or toxic shock but who do have severe manifestations of MIS-C, including myocarditis, shock, persistent fever, and elevated inflammatory markers or other clinical indicators of severe illness. Consider such therapy for critically ill patients even before the evaluation is complete.
  - Glucocorticoids are commonly used in conjunction with IV immunoglobulin or as follow-up to it if response is less than desired.
  - Other treatments that have been associated with apparently successful outcomes include infliximab, anakinra, and tocilizumab, but data are scant and noncomparative.
  - American College of Rheumatology suggests considering using anakinra for patients who do not respond to IV immunoglobulin and glucocorticoids.
  - 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.
  - 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.
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Drug therapy
- IV immunoglobulin
  - Immune Globulin (Human) Solution for injection; Infants, Children, and Adolescents: Available data are limited, and efficacy has not been established. 1,000 to 2,000 mg/kg IV as a single dose in combination with aspirin and/or methylprednisolone has been reported and is being used in some institutional protocols. Depending on the severity of illness, additional doses have been administered.
- 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.
- Methylprednisolone
  - Methylprednisolone Sodium Succinate Solution for injection; Infants, Children, and Adolescents: Available data are limited, and efficacy has not been established. 2 to 30 mg/kg/day IV has been reported, depending on the severity of illness, and is being used in combination with IVIG with or without aspirin. A 3-week at-home taper has been recommended.

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, and follow-up echocardiograms should be obtained 2 and 6 weeks 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.
- 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 such 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, first recognized in temporal association with a high local prevalence of COVID-19. Subsequently, most reported cases have had laboratory evidence of recent infection with SARS-CoV-2, the virus that causes 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.
- 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).
- Some patients develop severe shock and require fluid resuscitation and hemodynamic support.
- There is no specific diagnostic test; diagnosis is based on a constellation of clinical, laboratory, echocardiographic, and epidemiologic factors. Most patients have laboratory evidence of SARS-CoV-2 (polymerase chain reaction, antigen, or antibody).
- 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 and immune modulators also have been used.
- Most patients have responded promptly to therapy and have done well. Owing to resemblance to Kawasaki syndrome and observation of coronary artery aneurysms in some patients with MIS-C, serial follow-up echocardiography is recommended.
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URGENT ACTION

- Patients with 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.13

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.26

SELECTED REFERENCES


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