KAWASAKI DISEASE VS MIS-C IN COVID-19

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KAWASAKI DISEASE

Idiopathic, self-limited, multisystem disease characterized by vasculitis of small and medium sized vessels, including coronary arteries

Predominantly affects children <5 years of age but rare in <6 months of age

ETIOLOGY

1. Unknown
2. Various case series over the years of localized outbreaks of KD, associated with different bacterial or viral pathogens- parvovirus B19, Propionibacterium, human bocavirus, and others

Immunologic response- systemic, inflammatory condition that particularly affects medium-sized arteries

Blood vessel damage occurs from inflammatory cell infiltration into vascular tissues. The stimulus for this infiltration is unknown (commonly occurs in coronary arteries)

Inflammatory cells infiltrating coronary arteries including neutrophils, CD8 T cells, eosinophils, IgA, and macrophages. (Macrophages are not prominent in other types of vasculitis)

Infectious etiology

- Characterized by febrile exanthem with lymphadenitis and mucositis. Features are similar to contagious diseases such as measles, adenovirus, and scarlet fever.
- Seasonal increase during winter and summer
- Occurs in epidemics and geographic wave like spread of illness
- Boys>Girls
- Siblings of children with KD in Japan and at increased risk, usually occurs within one week of onset

CLINICAL FEATURES

Fever- minimally responsive to antipyretics. Remains above 101.3. Prolonged, unexplained fever >5 days.

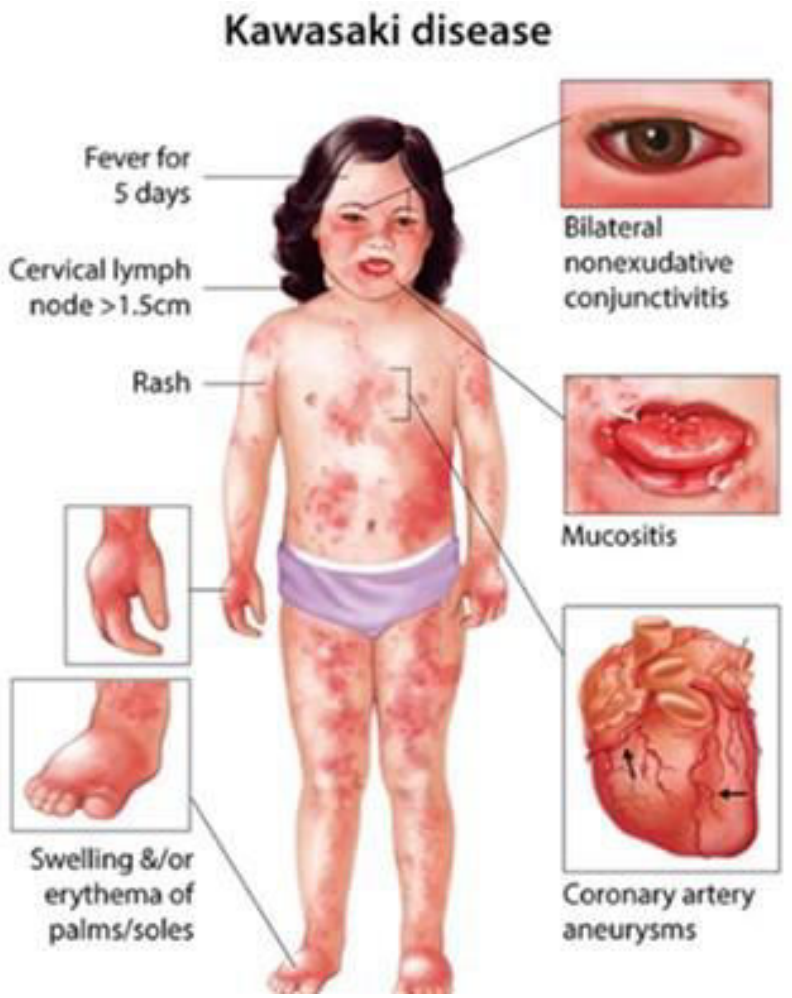
Conjunctivitis- bilateral, nonexudative. Anterior uveitis can be present in 70% of children

Mucositis- cracked, red lips, and "strawberry tongue" are characteristic.

Rash- polymorphous. Rash begins during first few days of illness, typically as perineal erythema and desquamation followed by skin lesions on trunk and extremities.

Extremity changes- last manifestation to appear. Indurated edema on dorsum of hands/feet and diffuse erythema of their palms and soles.

Lymphadenopathy- cervical lymphadenopathy (least consistent manifestation- if present, usually involves anterior)



NEED ATLEAST 4 OF FOLLOWING FEATURES FOR DIAGNOSIS

Signs & Symptoms of Kawasaki Disease

Images courtesy of the Kawasaki Foundation

❑ Other manifestations:

❑ Respiratory

Rhinorrhea, cough, pulmonary infiltrate

❑ GI

Diarrhea, vomiting, abdominal pain, jaundice

❑ Renal

Renal failure, renal artery aneuryms

❑ Musculoskeletal

Myositis, arthralgia, arthritis

❑ Skin

Transverse furrow of fingernails (Beau's line)

❑ Neurology

Irritability, aseptic meningitis, facial paralysis, hearing loss.

- Cardiovascular findings; not a diagnostic criteria but support diagnosis of KD.

1) Myocarditis-manifests as tachycardia
2) Cardiogenic shock- decreased LV function
3) Pericardial effusion (muffled heart sounds)
4) Coronary artery aneurysm- 2nd to 3rd week of illness

CLINICAL PHASES:

- 1) Acute febrile phase; 1-2 weeks from onset. Fever, irritability, toxic-appearing, oral changes, rash, edema/erythema of feet
- 2) Subacute phase: associated with desquamation, persistent arthralgias/arthritis, thrombocytosis, development of coronary artery aneurysm. Last for about 3 weeks.
- 3) Convalescent phase: occurs when clinical signs disappear and continues until ESR becomes normal. Occurs months to years later.

Early	Late
Leukocytosis	Thrombocytosis
Left shift	Elevated CRP
Mild anemia	
Thrombocytosis/Thrombocytopenia	
Elevated ESR/CRP	
Elevated transaminases	
Hypoalbuminemia	
Sterile pyuria	

LABORATORY FINDINGS

DIFFERENTIAL DIAGNOSIS

INFECTIOUS

- Viral: measles, adenovirus, EBV, roseola
- Bacterial: Group A beta-hemolytic strep
- Spirochetal: Lyme disease, leptospirosis
- Parasitic: toxoplasmosis
- Rickettsial: Rocky mountain spotted fever, typhus

IMMUNOLOGIC/ALLERGIC

- Juvenile rheumatoid arthritis
- Atypical acute renal failure
- Hypersensitivity reactions
- Steven-Johnson syndrome

CARDIOVASCULAR MANIFESTATIONS:

EKG CHANGES:

- Arrhythmias
- Prolonged PR intervals and/or QT intervals
- ST-T wave changes
- Low voltage QRS

CHEST X-RAY

- Cardiomegaly
- Pulmonary edema

ECHO:

- Myocarditis
- Pericarditis with effusion
- Valvular insufficiency
- Coronary artery changes- most common including CAA
- Can lead to MI, ischemic heart disease, and sudden death

CORONARY ANEURYSMS

- Commonly seen in children <6 months, older than 8 years
- Males
- Fever >14 days
- Persistent elevated ESR
- Thrombocytosis

Classification

Size:

small <5 mm

medium 5-8 mm

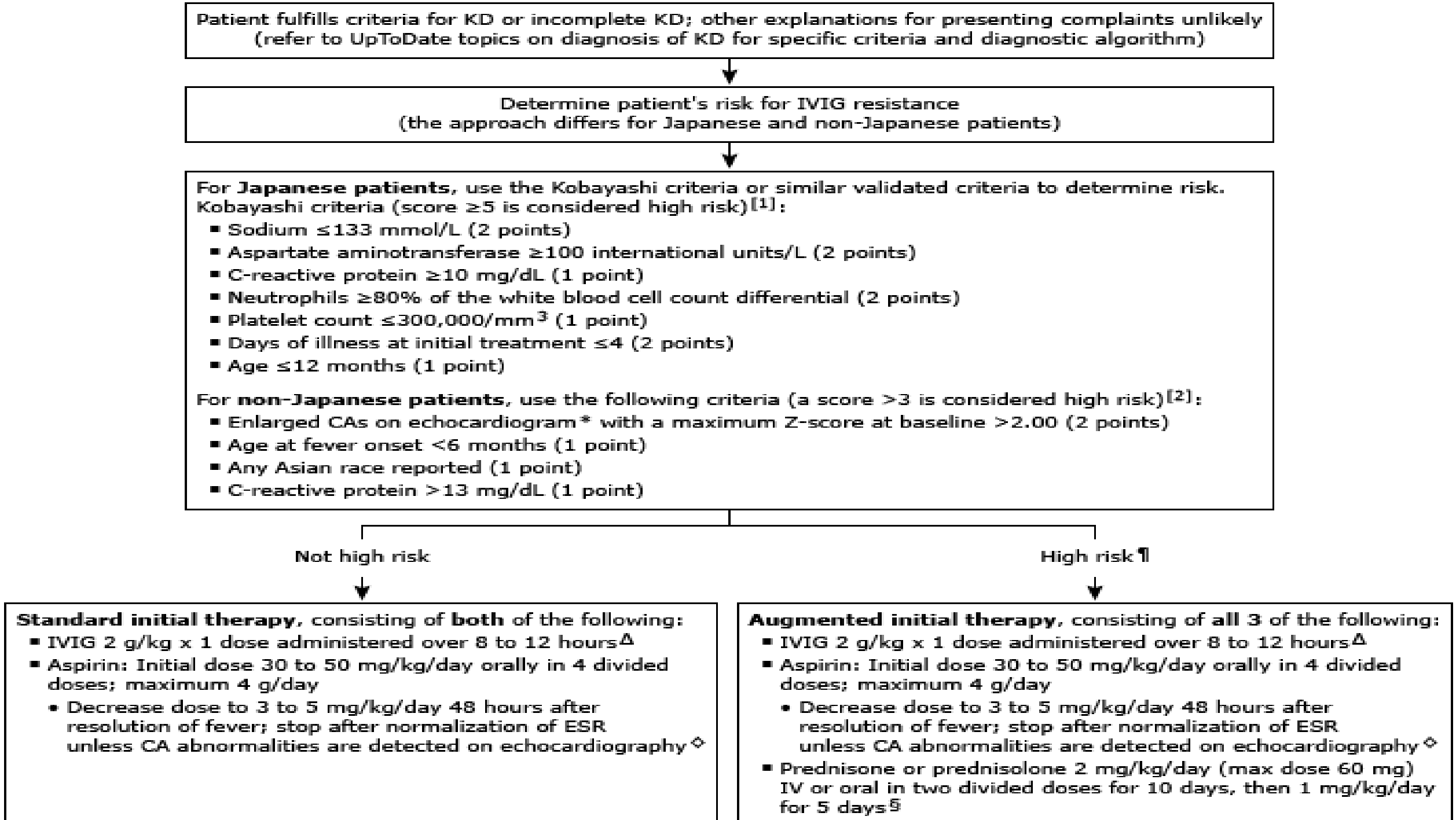
large: >8 mm

Shape:

Saccular

Fusiform


TREATMENT


Patient fulfills criteria for KD or incomplete KD; other explanations for presenting complaints unlikely
(refer to UpToDate topics on diagnosis of KD for specific criteria and diagnostic algorithm)
Determine patient's risk for IVIG resistance
(the approach differs for Japanese and non-Japanese patients)
For Japanese patients, use the Kobayashi criteria or similar validated criteria to determine risk.
Kobayashi criteria (score ≥5 is considered high risk)[1]:
Sodium ≤133 mmol/L (2 points)
Aspartate aminotransferase ≥100 international units/L (2 points)
C-reactive protein ≥10 mg/dL (1 point)
Neutrophils ≥80% of the white blood cell count differential (2 points)
Platelet count ≤300,000/mm3 (1 point)
Days of illness at initial treatment ≤4 (2 points)
Age ≤12 months (1 point)
For non-Japanese patients, use the following criteria (a score >3 is considered high risk)[2]:
Enlarged CAs on echocardiogram* with a maximum Z-score at baseline >2.00 (2 points)
Age at fever onset <6 months (1 point)
Any Asian race reported (1 point)
C-reactive protein >13 mg/dL (1 point)
Not high risk
High risk¶
Standard initial therapy, consisting of both of the following:
IVIG 2 g/kg x 1 dose administered over 8 to 12 hours△
Aspirin: Initial dose 30 to 50 mg/kg/day orally in 4 divided doses; maximum 4 g/day
Decrease dose to 3 to 5 mg/kg/day 48 hours after resolution of fever; stop after normalization of ESR unless CA abnormalities are detected on echocardiography◇
Augmented initial therapy, consisting of all 3 of the following:
IVIG 2 g/kg x 1 dose administered over 8 to 12 hours△
Aspirin: Initial dose 30 to 50 mg/kg/day orally in 4 divided doses; maximum 4 g/day
Decrease dose to 3 to 5 mg/kg/day 48 hours after resolution of fever; stop after normalization of ESR unless CA abnormalities are detected on echocardiography◇
Prednisone or prednisolone 2 mg/kg/day (max dose 60 mg) IV or oral in two divided doses for 10 days, then 1 mg/kg/day for 5 days§

FOLLOW UP

1) Monitor for fever
2) Cardiac evaluations- echocardiography repeated 6-8 weeks after onset of illness
3) Restrict physical activity
4) Vaccinations; avoid live virus vaccines- MMR and varicella for atleast 11 months after treatment with IVIG

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN WITH COVID-19

- Condition where different body parts can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes and GI organs
- The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus (SARS-CoV-2)

EPIDEMIOLOGY

- Rare complication of COVID-19, occurring in <1 percent of children with confirmed SARS-CoV-2
- Most MIS-C cases have occurred in older children and adolescents who were previously healthy
- Black and Hispanic children appear to be disproportionally affected
- First report of MIS-C was a series of eight children seen at a tertiary center in Southeast England
- Most common comorbidities were obesity and asthma
- Median age was 8 to 11 years
- Some studies suggests that MIS-C may represent a post-infectious complication of the virus rather than acute infection

PATHOPHYSIOLOGY

- **Immune dysregulation**

Similar to KD, macrophage activation syndrome and cytokine release syndrome.

Exact mechanism how COVID-19 triggers the abnormal immune response is unknown

Studies suggest patients with severe MIS-C has persistent IgG antibodies to activate monocytes, persistent cytopenia's (T cell lymphopenia) and activation of CD8 + T cells

- **SARS-CoV-2**

Many affected children have negative PCR but positive serology (supports immune dysregulation occur active infection)

- **Myocardial Injury**

Possible causes include injury from systemic inflammation, acute viral myocarditis, hypoxia, or stress cardiomyopathy

PRESENTING SYMPTOMS

Onset of symptoms- usual duration between acute infection and onset of MIS-C is 2-6 weeks

Presenting symptoms include:

- Fever
- Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)
- Rash
- Conjunctivitis
- Mucous membrane involvement (strawberry tongue, swollen lips)
- Neurocognitive symptoms (headache, lethargy, confusion)
- Respiratory symptoms-tachypnea and labored breathing due to shock or pulmonary edema
- Sore throat
- Myalgia
- Swollen hands/feet
- Lymphadenopathy

CLINICAL FINDINGS

- Shock
- Criteria for complete KD met
- Myocardial dysfunction (by echocardiogram or elevated BNP/troponin)
- Arrhythmia
- Acute respiratory failure requiring ventilation
- AKI
- Serositis (small pleural , pericardial, ascitic effusions)
- Hepatitis or hepatomegaly
- Encephalopathy, seizures, coma, or meningoencephalitis

Laboratory findings

- Abnormal blood cell counts
  - Lymphocytopenia
  - Neutrophilia
  - Mild anemia
  - Thrombocytopenia
- Elevated inflammatory markers
  - C-reactive protein
  - Erythrocyte sedimentation rate
  - D-dimer
  - Fibrinogen
  - Ferritin
  - Procalcitonin
  - Interleukin-6
- Elevated cardiac markers
  - Troponin
  - BNP or NT-pro-BNP
- Hypoalbuminemia
- Mildly elevated liver enzymes
- Elevated lactate dehydrogenase
- Hypertriglyceridemia

IMAGING FINDINGS

- ECHOCARDIOGRAM
  - Depressed LV function
  - Coronary artery dilation/aneurysm
  - Other findings include mitral regurgitation and pericardial effusion
- Chest radiograph
  - Normal in many patients
  - Abnormal findings include small pleural effusions, patchy consolidations, atelectasis
- Chest CT
  - Few patients had ground glass opacification
- Abdominal imaging (ultrasound/CT)
  - Nonspecific, including free fluid, ascites, bowel and mesenteric inflammation (terminal ileitis)

DIFFERENTIAL DIAGNOSIS

- Kawasaki disease
- Severe acute COVID-19
- Bacterial sepsis
- TSS
- Appendicitis
- Other viral infections (EBV, CMV, adenovirus, and enteroviruses)
- SLE
- Vasculitis

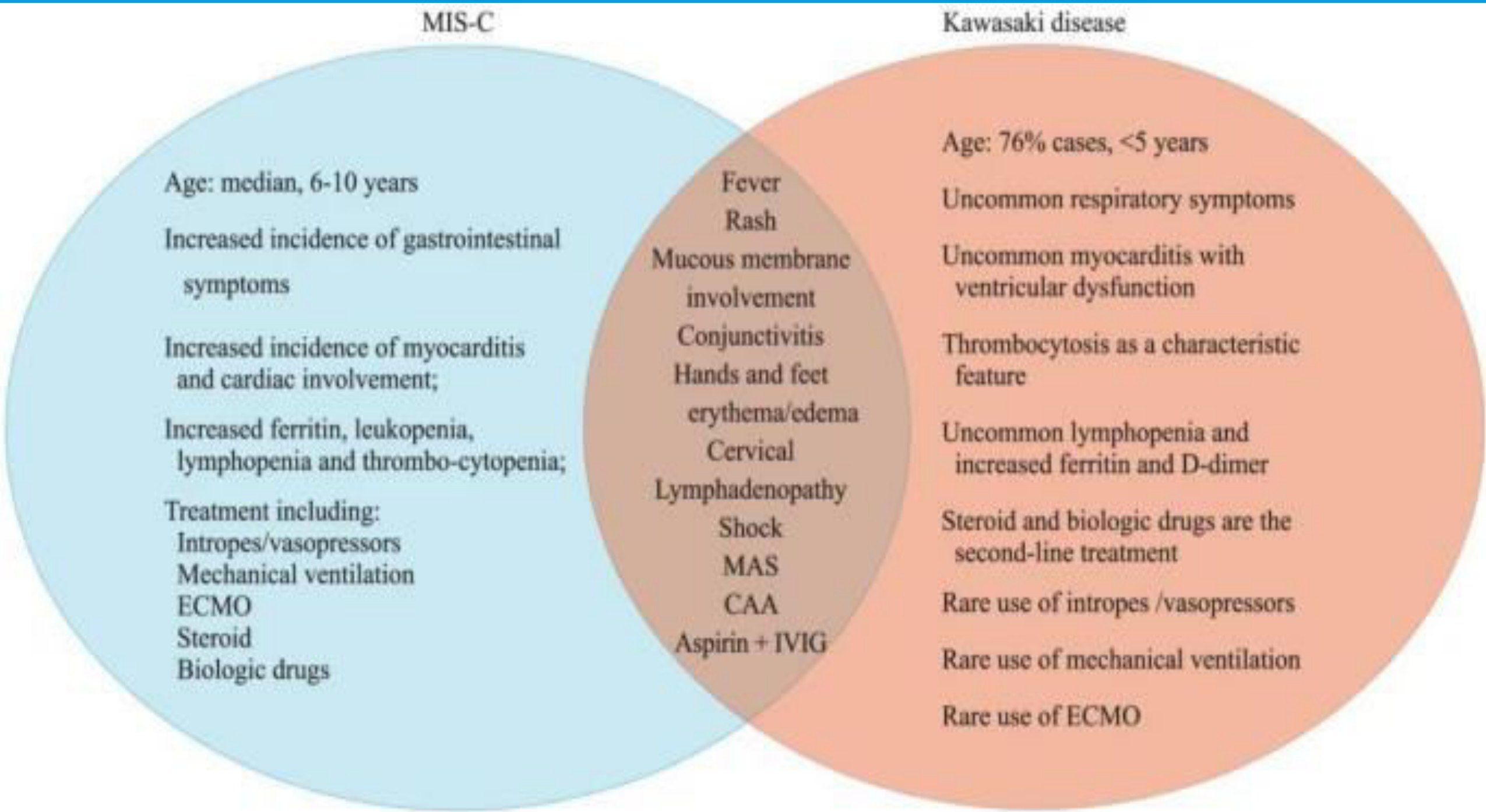
MANAGEMENT

Treatment is based on presentations

1) Shock-Some children may have vasodilatory shock that is refractory to volume expansion. Epinephrine or norepinephrine for fluid-refractory shock. Epinephrine preferred for LV dysfunction.
2) Features of KD-IVIG, aspirin. Signs of coronary artery dilation/aneurysm, glucocorticoids
3) Cardiac dysfunction- monitor BNP. IVIG and glucocorticoids.

Antimicrobial therapy:

- Antibiotics- MIS-C that presents with signs and symptoms of TSS and septic shock. Ceftriaxone plus vancomycin. Alternate therapy include Ceftaroline plus piperacillin-tazobactam.
- Antiviral therapy-Remdesivir


MIS-C
Kawasaki disease
Age: median, 6-10 years
Increased incidence of gastrointestinal symptoms
Increased incidence of myocarditis and cardiac involvement;
Increased ferritin, leukopenia, lymphopenia and thrombo-cytopenia;
Treatment including:
Intropes/vasopressors
Mechanical ventilation
ECMO
Steroid
Biologic drugs
Fever
Rash
Mucous membrane involvement
Conjunctivitis
Hands and feet erythema/edema
Cervical Lymphadenopathy
Shock
MAS
CAA
Aspirin + IVIG
Age: 76% cases, <5 years
Uncommon respiratory symptoms
Uncommon myocarditis with ventricular dysfunction
Thrombocytosis as a characteristic feature
Uncommon lymphopenia and increased ferritin and D-dimer
Steroid and biologic drugs are the second-line treatment
Rare use of intropes /vasopressors
Rare use of mechanical ventilation
Rare use of ECMO