SRI LANKA COLLEGE OF PAEDIATRICIANS

GUIDELINES

Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

July 2021

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1 INTRODUCTION

COVID-19 is usually a mild disease in children. However, in some rare cases, children can be severely affected. In April of 2020, United Kingdom reported a case series of eight children presenting with hyper-inflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome or toxic shock syndrome. Since then, there have been reports of similarly affected children in other parts of the world.

Accordingly, this new disease entity has been called Multisystem Inflammatory Syndrome in Children (MIS-C) as per the Centre for Disease Control (CDC) and World Health Organisation (WHO) and Paediatric Inflammatory Multisystem Syndrome temporally associated with COVID-19 (PIMS-TS) as per the Royal College of Paediatrics and Child Health (RCPCH) case definition.

In Sri Lanka, we are also experiencing an increasing number of cases, some of them needing ICU care.

At present, professionals remain confronted with substantial uncertainties regarding clinical phenotypes, optimal management and long-term outcomes of MIS-C. In the absence of randomized trials, evidence for best treatment is minimal. Recommendations therefore are based primarily on expert opinion. The field is rapidly changing with reports being published on an almost weekly basis hence revision and updates of the recommendations will be required regularly.
It should be emphasized that **MIS-C is a diagnosis of exclusion** thus other cause of systemic inflammation and infections need to be considered and evaluated.

2 EPIDEMIOLOGY

Incidence of MIS-C is about 1 in 5000 in children who were infected with SARS-CoV-2.

Most cases have occurred in older children and adolescents who were previously healthy.

The most common comorbidities were obesity and asthma.

The median age has been 8 to 11 years (range 1 to 21 years).

3 PATHOPHYSIOLOGY

The pathophysiology of MIS-C is not well understood. Many affected children have negative polymerase chain reaction (PCR) testing for SARS-CoV-2 but have positive serology.

It has been suggested that the syndrome results from an abnormal immune response to the virus, with some clinical similarities to Kawasaki disease (KD), macrophage activation

syndrome (MAS), and cytokine release syndrome. However, based on the available studies, MIS-C appears to have an immunophenotype that is distinct from KD and MAS. The exact mechanisms by which SARS-CoV-2 triggers the abnormal immune response are unknown.

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

4 CLINICAL MANIFESTATIONS

Onset of symptoms

The usual duration between acute infection and onset of MIS-C symptoms is two to six weeks. However, rare cases may occur>6 weeks after the acute SARS-CoV-2 infection.

- Fever
- Mucocutaneous symptoms – Rash, Conjunctivitis, red or swollen lips, strawberry tongue
- Myalgia
- Swollen hands/feet
- Cervical Lymphadenopathy

Gastrointestinal symptoms

Abdominal pain, vomiting and diarrhea are **particularly common and prominent**, especially during the initial period of the illness, in some children mimicking **appendicitis**. Some present with clinical evidence of Hepatitis or hepatomegaly.

Cardiovascular symptoms- Cardiac involvement is common.

Hypotension, Myocardial dysfunction, Shock and Arrhythmia (specially bradycardia)

Respiratory symptoms

Tachypnea, labored breathing may be due to shock or cardiogenic pulmonary edema. Cough is uncommon. Severe pulmonary involvement **is not a prominent feature.**

Serositis - Small pleural, pericardial or ascitic effusions.

Acute kidney injury - most cases were mild

Neurocognitive symptoms

Headache, lethargy, confusion, or irritability. More severe neurologic manifestations are rare. (encephalopathy, seizures, coma, stroke, meningoencephalitis, muscle weakness, and brainstem and/or cerebellar signs).

5 LABORATORY FINDINGS

1. FBC
   - Lymphocytopenia
   - Neutrophilia
   - Mild anemia
   - Thrombocytopenia

2. Elevated inflammatory markers:
   - C-reactive protein (CRP)
   - Erythrocyte sedimentation rate (ESR)
   - D-dimer
   - Fibrinogen
   - Ferritin
   - Procalcitonin
   - Interleukin-6 (IL-6)

3. Elevated cardiac markers:
   - Troponin I
   - BNP or N-terminal pro-BNP (NT-pro-BNP)

4. Hypoalbuminemia
5. Mildly elevated liver enzymes
6. Elevated lactate dehydrogenase
7. Hypertriglyceridemia
8. Hyponatremia

Laboratory markers of inflammation appear to correlate with severity of illness.

Echocardiographic findings

- Reduced LV and/or RV function
- Prominent coronary arteries with hyper-echogenic walls, ectasia or aneurysm formation
- Mitral regurgitation
- Pericardial effusion

Chest radiograph -

Most patients have been reported to have normal **chest radiographs**. Abnormal findings included pleural effusions, patchy or focal consolidation, and atelectasis

6 DIAGNOSIS

Based on WHO& CDC Case Definitions

1. Children and adolescents 0–21 years of age

   AND

2. Fever ≥ 3 days

   AND

3. Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

   AND

4. No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

   AND

5. Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19 within the 4 weeks prior to the onset of symptoms.

   PLUS

6. ≥ 2 of the following:

1. Mucocutaneous	Rash, bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
2. Gastrointestinal	Abdominal pain, diarrhea, vomiting, elevated liver enzymes, ileus, gastrointestinal bleeding
3. Cardiac	Shock, hypotension, elevated trop I, elevated NT-pro BNP, abnormal echocardiogram including myo-pericarditis, valve regurgitation and/or coronary artery abnormalities
4. Hematological	Evidence of coagulopathy (PT, aPTT, and elevated D-dimers)
5. Neurological	Seizure, strokes, aseptic meningitis
6. Renal	Acute kidney injury
7. Respiratory	Pneumonia, pediatric acute respiratory distress syndrome (pARDS), pulmonary embolism

- *Consider this syndrome in children with features of typical or atypical Kawasaki disease (KD) or toxic shock syndrome.*

7 DIFFERENTIAL DIAGNOSIS

1. Kawasaki disease (KD)
2. Severe acute COVID-19
3. Bacterial sepsis
4. Dengue
5. Leptospirosis
6. Typhus
7. Toxic shock syndrome
8. Appendicitis
9. Other viral/bacterial infections
10. Hemophagocytic lymphohistiocytosis (HLH) / macrophage activation syndrome (MAS)
11. Systemic lupus erythematosus (SLE)
12. Vasculitis

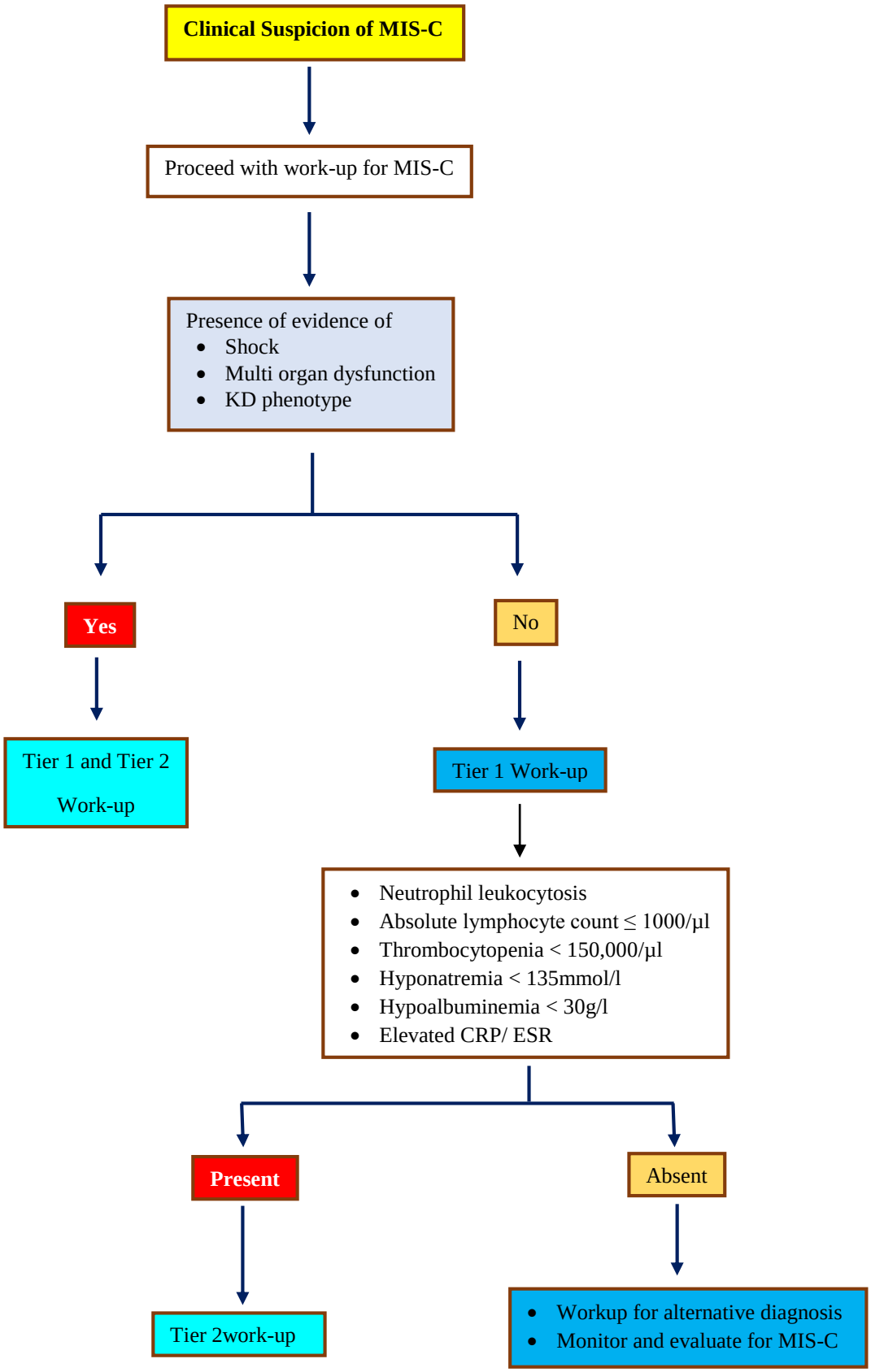
8 SETTING OF CARE

- Attending clinician needs to decide the required level of care depending on the severity of the illness
- Need for isolation should be decided on cycle threshold (CT value) of RT-PCR. Usually, the CT value is inversely proportional to the infectivity
- Should be admitted to a unit where regular monitoring is available.
- Multidisciplinary approach involving cardiologist, hematologist and rheumatologist is recommended

Indications for PICU admission

1. Fluid refractory shock
2. Severe MIS-C

9 Algorithm for MIS-C work-up



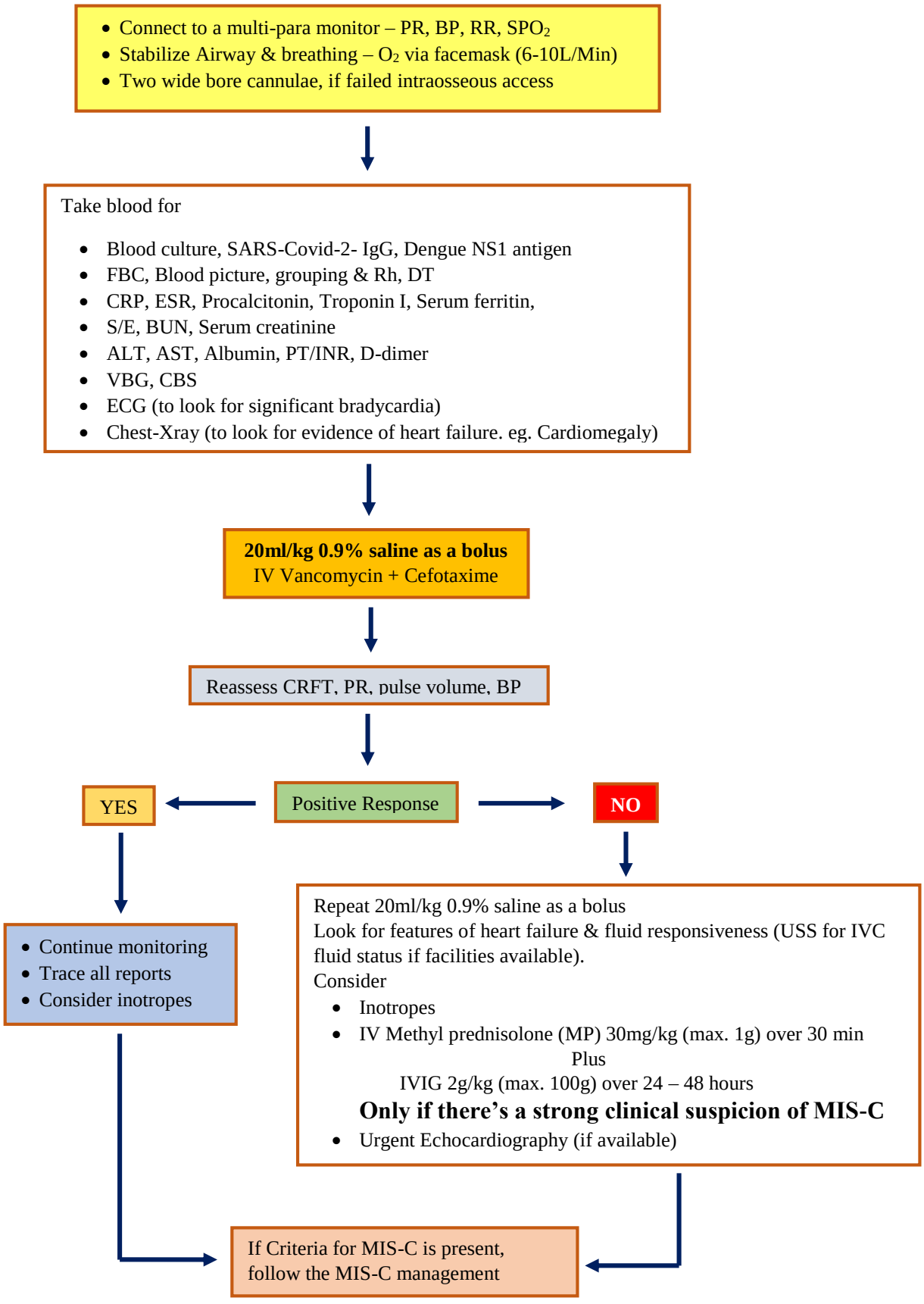
10 Tier 1 and 2 work-up plans for suspected MIS-C

Tier 1 work-up	
Work-up for MIS-C • FBC • ALT, AST, Albumin • BUN, Creatinine, S/E • CRP, ESR • SARS-CoV-2 PCR, SARS-CoV-2 serology	**Work-up for other etiologies** • Blood culture • Urine culture • NS-1 Antigen/ Dengue serology • Chest Xray • Leptospira, Typhus evaluation & USS Abdomen if clinically indicated.

Tier 2 work-up
• Cardiac - ECG, Trop I, Echocardiogram, NT-pro BNP (optional) Blood gas • Coagulopathy – aPTT, PT/ INR, D-dimer, Fibrinogen • LDH, Ferritin, Triglyceride

11 MANAGEMENT

Initial stabilization of children with MIS-C presenting with shock



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Clinical Spectrum of COVID-19 associated MIS-C		
Severe MIS-C	**Kawasaki Disease (KD) Phenotype**	**Febrile Inflammatory state (Mild MIS-C)**
• Markedly elevated inflammatory markers • Severe multisystem involvement. • Cardiac involvement • Shock • Neurologic manifestations • Other manifestations requiring pediatric intensive care unit [PICU] care	• Meet criteria for Complete • or incomplete KD • No shock or severe multisystem involvement	• Persistent Fever and mild symptoms (Headache, Fatigue) • Inflammatory markers may be elevated • No evidence of shock, cardiac dysfunction or KD phenotype

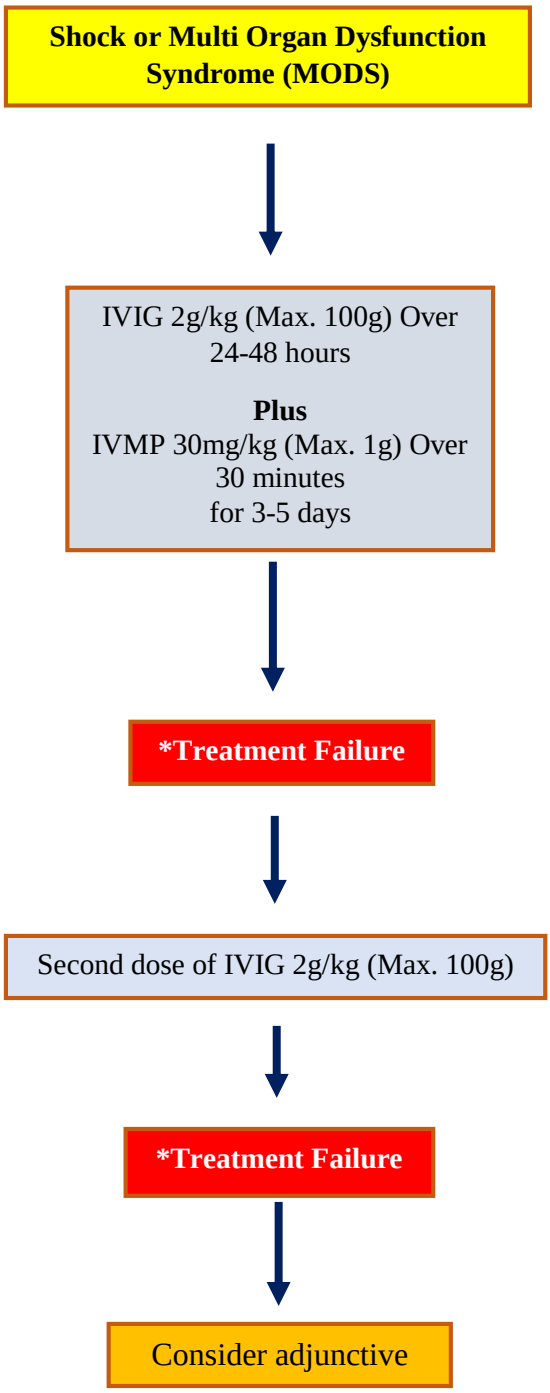
There is considerable phenotypic overlap with MIS-C and KD. It is often very difficult to differentiate each other.

Key distinctions between MIS-C and classic KD include

- MIS-C commonly affects older children and adolescents, whereas classic KD typically affects infants and young children.
- Gastrointestinal symptoms (particularly abdominal pain) are very common in MIS-C, whereas these symptoms are less prominent in classic KD.
- Myocardial dysfunction and shock occur more commonly in MIS-C compared with classic KD where coronary artery changes dominate.
- Inflammatory markers (especially CRP, ferritin, and D-dimer) tend to be more elevated in MIS-C compared with classic KD.

Management of severe MIS-C and KD phenotype is similar.

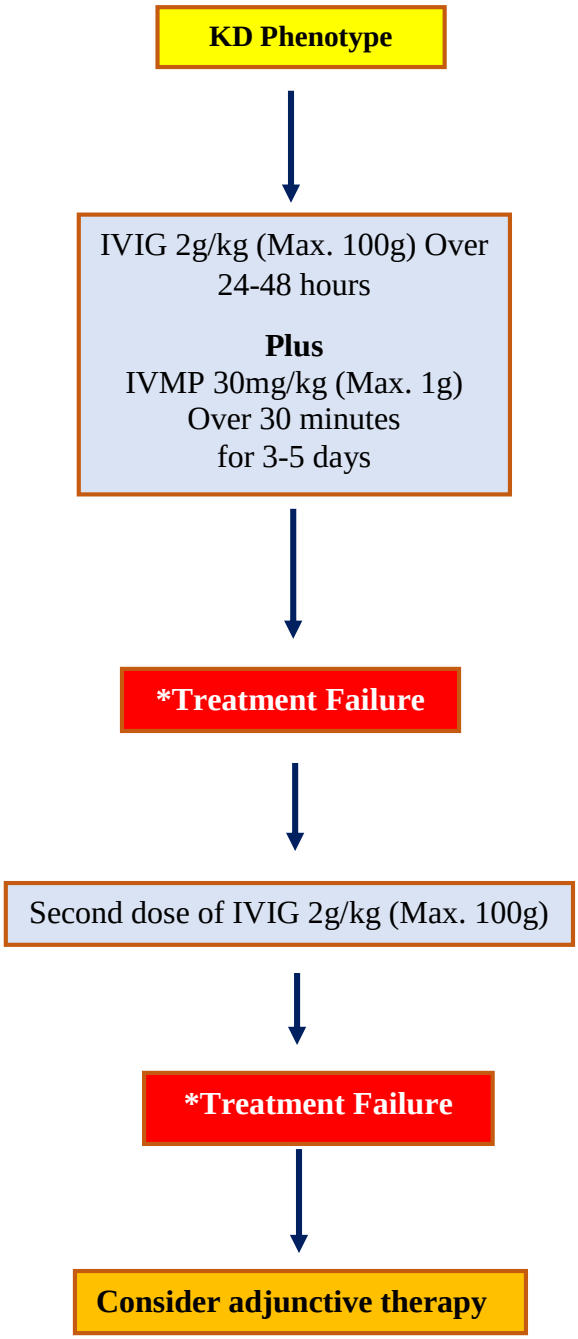
13 Management of severe MIS-C



**Treatment failure*

- *Persistent fever 48-72 hours after IVIG*
- *Persistently high CRP 48-72 hours after IVIG*
- *Recurrence of fever within 7 days of completion of IVIG*

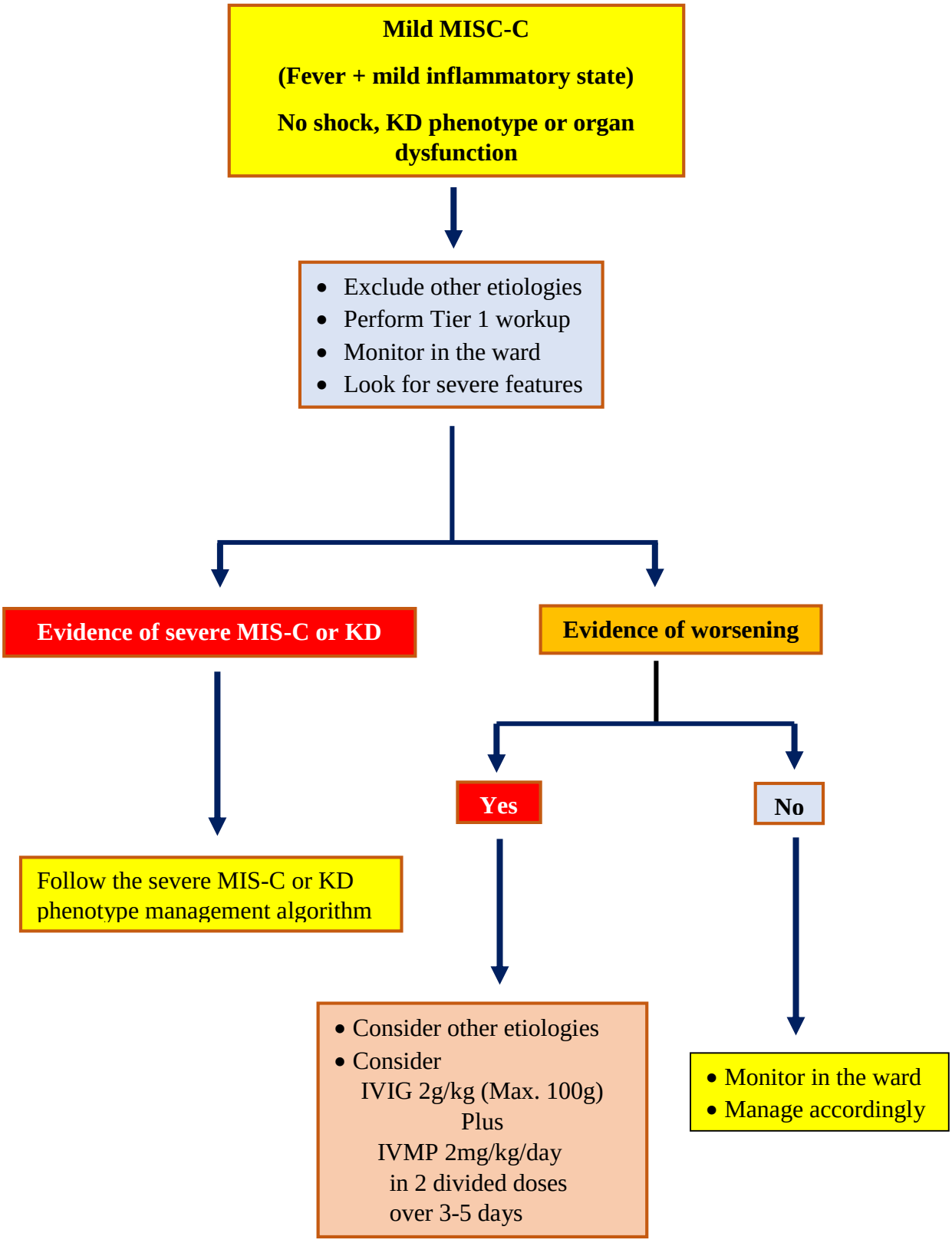
14 Management of KD phenotype



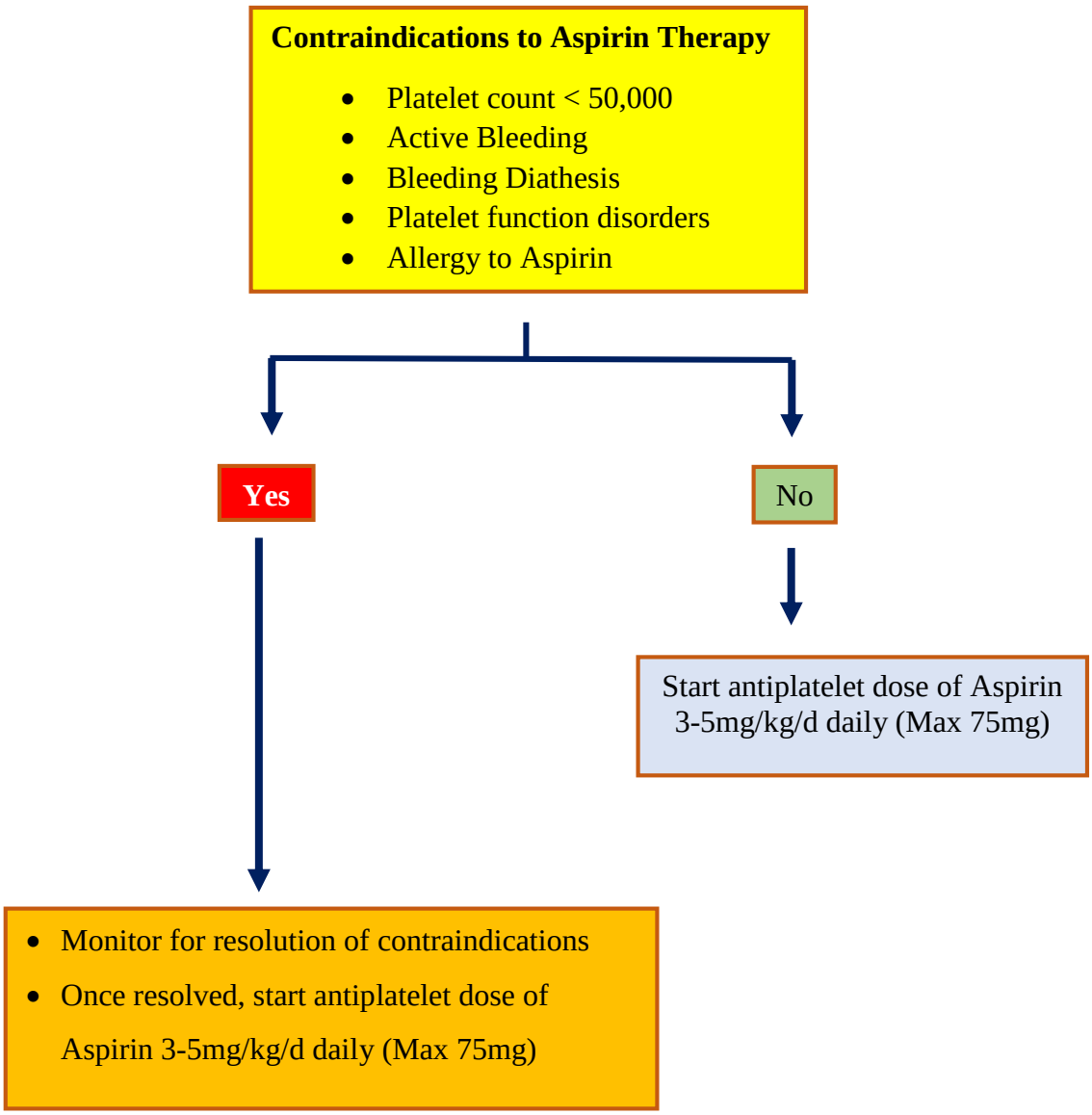
Treatment failure

- *Persistent fever 48-72 hours after IVIG*
- *Persistently high CRP 48-72 hours after IVIG*
- *Recurrence of fever within 7 days of completion of IVIG*

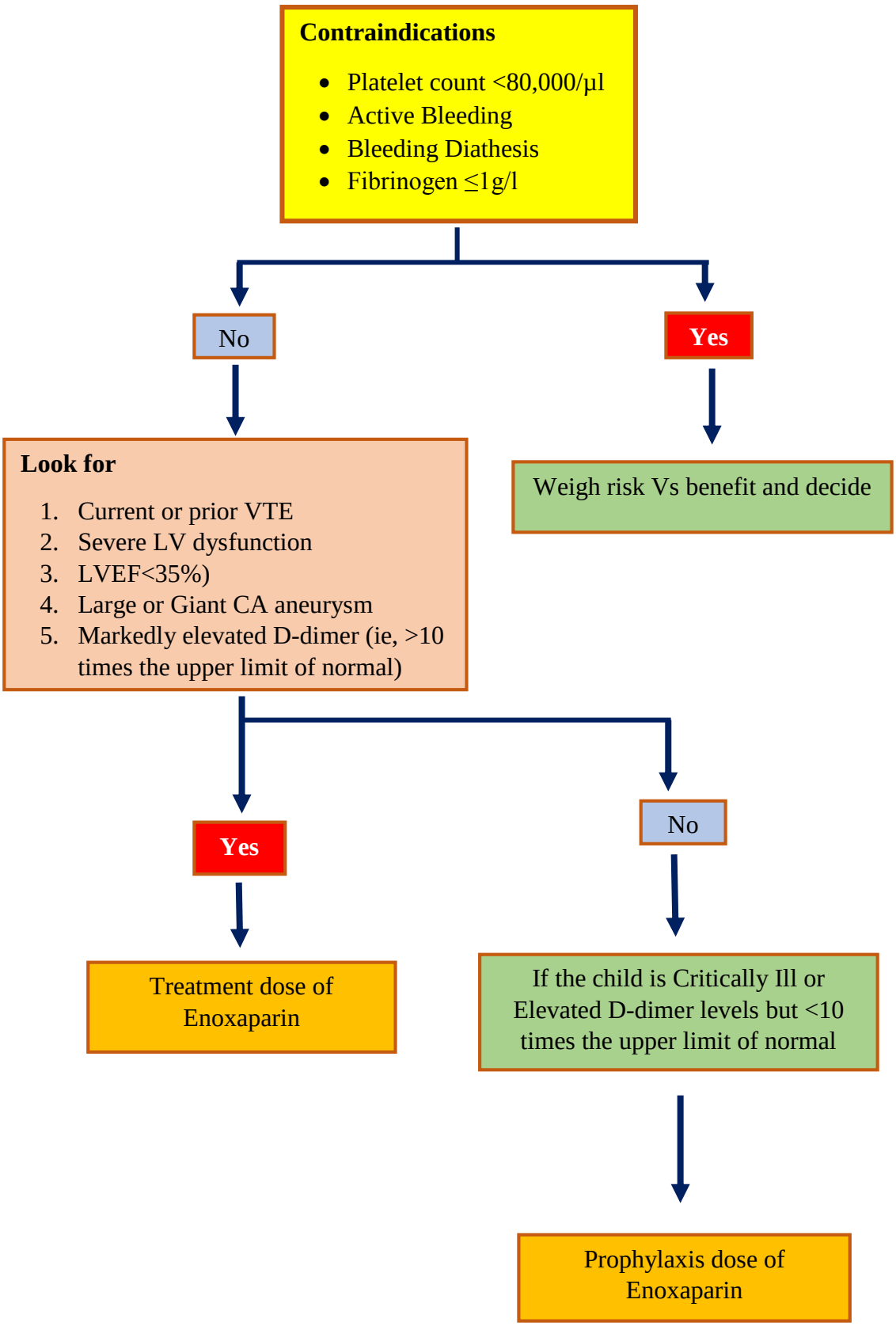
15 Management of mild MIS-C



16 Approach to commencement of Aspirin therapy in MIS-C



17 Approach to commencement of Enoxaparin in MIS-C



16 FOLLOW-UP

The nature and frequency of long-term complications of MIS-C are largely unknown.

- In most children, resolution of systemic inflammation and cardiac dysfunction usually occur by six weeks.
- Many experiences lingering sequelae including muscular weakness, reduced exercise capacity, anxiety, and emotional difficulties.

» At discharge:

- **Steroids** – tail off over 10-14 days, guided by clinical status and inflammatory markers

- **Antiplatelets**- continue anti-platelet dose of aspirin

- **Enoxaparin**
  - Ongoing severe cardiac dysfunction, documented thrombus or suspected macrophage activation syndrome: longer duration or switching over to warfarin as decided by Cardiology, Rheumatology and/or Haematology teams

  - In all other clinical situations, if D-dimer levels have normalized, Enoxaparin could be discontinued when the child is fit for discharge and/or for 10-14 days whichever is earlier

» Exercise restriction (To be decided by the Cardiology team)

- All patients with a diagnosis of MIS-C should avoid strenuous isometric/isotonic physical activities for minimum of 8 weeks

- Patients with MIS-C related cardiac dysfunction during acute stage but has recovered function completely within two weeks should avoid strenuous isometric/isotonic physical activities for minimum of 6 months

- Patients with ongoing cardiac dysfunction and/or coronary artery involvement - as decided by the Cardiology team

» 2 weeks' review (Paediatric and Paediatric Cardiology)

- Clinical assessment
- Bloods – CRP, ESR, FBC, renal function, liver enzymes, electrolytes, Ferratin, D-dimer, RBS
- ECG
- Echocardiography
- Continue antiplatelet dose of Aspirin
- Discuss with Rheumatology team if serum Ferritin remains elevated

» 6 - 8 weeks' review (Paediatric and Paediatric Cardiology)

- Clinical assessment
- ECG
- Echocardiogram
- Aspirin
    - Stop aspirin if cardiac function is normal with normal coronary arteries (Z score <2)
    - Continue aspirin if persistent coronary artery dilatation and/or persistent ventricular dysfunction
- Exercise restriction (refer above)

» 12 months' review (Paediatric and Paediatric Cardiology)

- Clinical assessment
- ECG
- Echocardiogram
- Aspirin
    - Stop aspirin if cardiac function is normal with normal coronary arteries (Z score<2)
    - Continue aspirin if persistent coronary artery dilatation and/or persistent ventricular dysfunction
- Exercise limitation (refer above)

» Follow up beyond one year

Need and timing of follow up beyond one year of complete recovery are to be decided by the Cardiology and/or Rheumatology teams based on residual organ dysfunction.

A_1 *ANNEXURE – 1*

» Testing for SARS-CoV-2

All patients with suspected MIS-C should be tested for SARS-CoV-2, including,

- Serology
- Reverse transcription PCR (RT-PCR) or RAT (Rapid Antigen Test) on a nasopharyngeal swab

RT-PCR and RAT could be either positive or negative.

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

» Testing for other pathogens (as clinically indicated)

- Blood culture
- Urine culture
- Stool culture
- Dengue NS1 Ag
- Leptospirosis Ag (MAT)
- Typhus Ab
- Nasopharyngeal aspirate or throat swab for respiratory viral panel
- Epstein-Barr virus serology and PCR
- Cytomegalovirus serology and PCR
- Enterovirus PCR
- Adenovirus PCR

» Cardiac testing

- ECGs - Nonspecific (eg, Abnormal ST- or T-wave segments), Arrhythmia and Heart block
- Chest Xray
- Troponin I and (BNP/NT-pro-BNP levels – Optional)
- Echocardiographic evaluation for evidence of left ventricular dysfunction and coronary artery involvement (Preferably by a Consultant Cardiologist)

A_2 *ANNEXURE – 2:* FORMULARY

» Aspirin

- For all patients
- Low-dose aspirin 3 to 5 mg/kg daily (Max 75mg/day)
- Duration is 4 - 8 weeks, longer duration may be needed in KD phenotype and some severe MIS-C.
- Has to be continued until platelet count becomes normal or coronary arteries become normal
- Withhold Aspirin if platelet count is below 50,000.

» IV Immunoglobulin

- For all patients with KD phenotype, severe MIS C and worsening MIS-C.
- 2 g/kg (Max 100g) administered in a single infusion over 24 to 48 hours.
- In obese patients, the dose should be based upon ideal body weight.
- Consider 2nd dose in refractory disease
- Patients should have blood drawn for serologic testing for SARS-CoV-2 and other pathogens prior to administration of IVIG.
- IVIG elevates the ESR, so following up ESR is less useful after delivering a 2 g/kg dose of IVIG. Other inflammatory markers (eg, C-reactive protein, ferritin) are more reliable for serial monitoring after IVIG.

» Antibiotics

- For all patients
  - Patients with COVID-19 are at risk of secondary bacterial or viral co-infections (e.g., pneumonia).
  - Patients presenting with severe multisystem involvement and shock should receive prompt empiric broad-spectrum antibiotic therapy within 1 hour of initial recognition of shock, pending culture results.

- Suggested antibiotics
  - Cefotaxime plus Vancomycin
  - Flucloxacillin or Teicoplanin 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/ Toxic Shock Syndrome).

» Glucocorticoids

- **Mild MIS-C (Consider IV MP)**

  Dose - IV methylprednisolone 2 mg/kg/day in two divided doses for 3-5 days

- **Severe MIS-C and KD phenotype**

  - Pulse therapy
  - Dose- IV methylprednisolone (MP) 30 mg/kg/dose, (maximum of 1 g) for 3-5 days
  - Once the patient has improved clinically can be transitioned to 2mg/kg/day oral prednisolone (Maximum of 60mg/day), then tapered off over two weeks.

» Enoxaparin

- **Rationale**
  - Patients with MIS-C are at risk of experiencing thrombotic complications due to hypercoagulability associated with COVID-19.
  - MIS-C itself is a major risk factor for venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolus.
  - In addition, patients with severe LV dysfunction are at risk for apical LV thrombus and those with coronary artery aneurysms are at risk for myocardial infarction.

- **Indications**
  - Current or prior VTE
  - Severe LV dysfunction
  - Large or giant CA aneurysms
  - Markedly elevated D-dimer
    - > 10 times of normal level --- Treatment dose
    - < 10 times of normal level --- Prophylactic dose

- **Contraindications**
  - Platelet count <80,000/µl
  - Active Bleeding
  - Bleeding Diathesis
  - Fibrinogen ≤1g/l

When platelet count is <80,000/µl, the risk and benefit should be considered when deciding on administration.

- **Dose**
  - Treatment doses in
    - Current or prior VTE
    - Severe LV dysfunction
    - Large or giant CA aneurysms
    - Severe MIS-C
    - Patients with less severe MIS-C if the D-dimer level is markedly elevated (>10 times the upper limit of normal)

  - Prophylactic dose in
    - Patients with less severe MIS-C if the D-dimer level is <10 times the upper limit of normal
    - Patients with risk factors for thrombosis (eg. Nephrotic syndrome)

- **Duration**
  - Ongoing severe cardiac dysfunction, documented thrombus or suspected macrophage activation syndrome: longer duration or switching over to warfarin as decided by Cardiology and Haematology teams

  - In all other clinical situations, if D-dimer levels have normalized, Enoxaparin could be discontinued when the child is fit for discharge and/or for 10-14 days whichever is earlier
  - D-dimer levels should be repeated every 10 days.
  - Discontinue enoxaparin once D-dimer level has normalized
  - If D-dimer level between normal and 10 times upper limit of normal, convert to prophylactic dose.

Liver functions need to be monitored during enoxaparin therapy as hepatotoxicity has been reported.

	Age dependent dose of Enoxaparin	
	<2 months	**≥2 months**
Treatment Dose	1.5mg/kg/dose b.d	1mg/kg/dose b.d
Prophylactic Dose	0.75mg/kg/dose b.d	0.5mg/kg/dose b.d

- Consider compression stockings in children >12 years of age.

» Inotropes

- Epinephrine is preferred over Norepinephrine when there is evidence of left ventricular dysfunction.
- Milrinone or Dobutamine can be used for severe left ventricular dysfunction with stable blood pressure.
- These could be commenced via a peripheral line inserted through a large vein.

Drug	Dose	Dilution	Rate & Strength
Adrenaline 1:1000 1ml=1mg	0.01-1.0µ/kg/min	0.03mg/kg in 50ml of Dextrose/ Saline	1ml/h=0.01µ/kg/min
Dobutamine	5-20µ/kg/min	15mg/kg in 50ml of Dextrose/ Saline	1ml/h=5µ/kg/min
Nor-adrenaline	0.01-0.5µ/kg/min	0.03mg/kg in 50ml of Dextrose/ Saline	1ml/h=0.01µ/kg/min
Milrinone	0.33-0.99µ/kg/min	1mg/kg in 50ml of Saline	1ml/h=0.33µ/kg/min

» Adjunctive therapies

Use of adjunctive therapies are uncertain.
Consultation with rheumatology specialist is advised.

- IL-6 inhibitors [eg, **Tocilizumab** 4-8mg/kg per dose]
- TNF inhibitors [Infliximab]

»» Refractory MIS-C

- 2nd dose of IVIG
- Consider adjunctive therapy

** Multi-Disciplinary Guidelines Development Committee

This updated guideline on management of MIS-C was developed by the following multi-disciplinary committee.

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********** End of the guidelines **********