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Erciyes Clinical Guideline for Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) is an inflammatory response to prior SARS-CoV-2 infection. Clinical features of MIS-C could resemble those seen in other diseases, including Kawasaki Disease, Hemophagocytic Lymphohistiocytosis, and cardiovascular shock. The pathogenesis is unclear; however, it is thought to develop 4 to 6 weeks after infection. This guideline aims to provide a framework for physicians to use to evaluate patients and manage those diagnosed with MIS-C.

Keywords: Pediatric, COVID-19, MIS-C, guideline

Introduction and Purpose

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) causes acute and post-acute illness in the pediatric population. One of the post-acute illnesses is Multisystem Inflammatory Syndrome in Children (MIS-C). MIS-C most consistently presents with prolonged fever and GI complaints (abdominal pain, vomiting, and diarrhea). Additional features include rash, extremity swelling, conjunctivitis, and lymphadenopathy similar to Kawasaki Disease. The most concerning feature of MIS-C is progression to cardiovascular abnormalities (myocarditis, coronary aneurysms, ventricular dysfunction) and potentially shock. Children with MIS-C rarely exhibit respiratory complaints, and death is rare.

This guideline was developed by a multi-specialty team of Erciyes University Department of Pediatrics clinicians to assist with evaluating and treating pediatric patients (< 18 years old) who present to Erciyes University with confirmed or suspected MIS-C secondary to infection with SARS-CoV-2.

This guideline is not for the management of acute SARS-CoV-2 infection. This guideline does not address isolation precautions, transport, airway, and treatment of suspected active SARS-CoV-2 infection.

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This guideline is intended as a general guide, should be applied, and interpreted with caution, and is likely to change over time. As this guideline was developed for Erciyes University patients, any use of this document by other clinicians or facilities should be based on the individual clinical circumstances of their patients and the resources available to the patient's treating clinicians.

BOX 1 POSSIBLE SYMPTOMS AND FINDINGS FOR MIS-C

(In the evaluation of the cases in terms of MIS-C, the following must be questioned)

- Presence of findings consistent with ACTIVE COVID-19 in the patient and/or in the close contacts
- A history of illness compatible with COVID-19 in the patient and/or close contacts in the last six weeks

- Systemic inflammation findings:
  - Fever
  - Myalgia
  - Bone pain in extremities
  - Tachycardia
  - Hypotension
  - Hypoperfusion or hyperperfusion
  - Lymphadenopathy
- Respiratory:
  - Chest pain
  - Respiratory distress
- Neurologic:
  - Headache
  - Altered mental status/confusion
  - Meningismus
  - Convulsion
  - Focal neurological deficit
- Gastrointestinal:
  - Nausea / vomiting
  - Diarrhea
  - Abdominal pain
- Skin and mucosal changes:
  - Rash (polymorphous exanthem, erythroderma, erythematous macules, and/or papules)
  - Swollen hands and feet
  - Bilateral non-purulent conjunctivitis
  - Mucous membrane changes (erythematous mucous membranes, strawberry tongue)
  - Peeling of skin

BOX 2 INITIAL WORK-UP FOR SUSPECTED MIS-C (LABORATORY AND RADIOLOGICAL)

- SARS-CoV-2 PCR: Nasal oropharyngeal combined swab sample (if suspected of an active disease, a total of 3 consecutive samples should be sent daily from patients)
- COVID-19 Rapid Antibody Test: The test should be seen before IVIG treatment. If this is not possible, the sample should be kept for testing before IVIG. Antibody testing is not obligatory in children with positive PCR positivity in the past.
- SARS-CoV-2 Rapid Antigen Test (if available)

- Complete blood count with differential, basic renal and liver function panel, blood gas with lactate, lactate dehydrogenase
- Acute phase reactants: C-reactive protein, erythrocyte sedimentation rate, ferritin, procalcitonin
- Coagulation tests: Prothrombin time, active partial thromboplastin time, fibrinogen, D-dimer
- Cardiac enzymes: CK, CK-MB, troponin, BNP
- Urinalysis with microscopy
- Blood culture, respiratory viral PCR panel, rapid influenza, and RSV tests
- If concern for viral co-infection; Cytomegalovirus, Epstein-Barr virus, Parvovirus, Adenovirus PCRs

- Chest X-Ray→If there is an abnormality, consider thorax CT
- If there is an abdominal finding→Abdominal X-ray and/or abdominal USG
- Electrocardiogram (ECG)
- Transthoracic echocardiogram focused on ventricular function and coronary arteries
- An echocardiogram should be performed urgently if there is a suspicion of cardiac involvement. Otherwise, it can be done in the first 6 hours.

Abbreviations: BNP, brain natriuretic peptide; CT, computed tomography; COVID-19, Coronavirus Disease 2019; CK, creatinine kinase; CK-MB, creatine kinase-MB; IVIG, intravenous immune globulin; MIS-C, Multisystem Inflammatory Syndrome in Children; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; USG, ultrasonography

BOX 3 CASE-BASED ADDITIONAL EVALUATIONS

- Cases evaluated for MIS-C should be followed up separately from other cases
- In all evaluation processes, hospital isolation rules for COVID-19 cases should be obtained
- Head Imaging - consider if focal neurologic deficit, altered mental status, seizure, or severe headache with or without meningeal signs. The first choice should be cranial MRI, and the second is CT
- Imaging should be performed with contrast if renal functions are normal. If a thorax CT scan is planned for COVID-19, a non-contrast scan should be done. In these cases, the radiology department should be informed before.
- Cerebrospinal fluid (CSF) studies - if there is a neurological finding and lumbar puncture indicated;
  - Opening pressure
  - Cell count
  - Glucose, protein, sodium, and chloride
  - Culture (aerobic blood culture bottle)
  - Infectious meningitis/encephalitis PCR panel
- Any rash should be photographed and documented
- In the presence of diarrhea, rotavirus, and adenovirus rapid antigen tests, gastrointestinal pathogen PCR panel
- Triglycerides after 12 hours of fasting in suspected hemophagocytosis
- Serology and blood culture for brucellosis in the presence of fever and/or joint complaints lasting for ≥7 days
- Thoracic USG should be requested if pleural fluid is suspected
- While making the differential diagnosis of cases with known primary or secondary immunodeficiency, appropriate antibiotic treatments should be started within the indications without any delay. Cefepime or piperacillin-tazobactam intravenous can be started in the first step in patients with febrile neutropenia whose focus of fever is unclear. A glycopeptide or antifungal drug may be added to the initial treatment regimen according to the additional characteristics of the cases

Abbreviations: CT, computed tomography; COVID-19, Coronavirus Disease 2019; MRI, magnetic resonance imaging; MIS-C, multisystem Inflammatory Syndrome in Children; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; USG, ultrasonography

BOX 4 DIFFERENTIAL DIAGNOSIS OF MIS-C

- Kawasaki Disease
- Brucellosis
- Bacterial infection / sepsis / septic shock
- Staphylococcal and streptococcal toxin-related diseases
- Vasculitis
- Viral infections (CMV, EBV, adenoviruses)
- Myocarditis (Non-SARS-CoV-2 viral agents)
- Drug hypersensitivity reactions
- Systemic juvenile idiopathic arthritis
- Other autoinflammatory diseases can cause macrophage activation syndrome
- Hematological malignancies

BOX 5 *CASE DEFINITIONS*

Criteria	CDC	WHO	ERCİYES
Fever	• Documented > 38.0°C and lasting ≥ 24 hr, or; • Declared fever lasting ≥24 hrs	• ≥ 3 day lasting fever	• Documented or declared fever lasting ≥24 hrs
Inflammation	≥1 abnormal marker of inflammation; • CRP ↑ • Sedimentation ↑ • Procalcitonin ↑ • Fibrinogen ↑ • D-dimer ↑ • Ferritin ↑ • LDH ↑ • IL-6 ↑ • Neutrophilia, lymphopenia • Hypoalbuminemia	≥1 abnormal marker of inflammation; • CRP ↑ • Sedimentation ↑ • Procalcitonin ↑	≥1 abnormal marker of inflammation; • CRP ↑ • Sedimentation ↑ • Procalcitonin ↑ • Fibrinogen ↑ • D-dimer ↑ • Ferritin ↑ • Lymphopenia
Multi-system involvement	► **Hospitalization AND** ≥ 2 systems involvement; • Cardiovascular: Hypotension or shock, elevated troponin and BNP, arrhythmia, abnormal ECHO finding • Respiratory: Pneumonia, ARDS, emboli • Renal: Acute kidney injury • Neurologic: Seizures, encephalitis, aseptic meningitis • Hematologic: Coagulopathy • GIS: Nausea/vomiting, diarrhea, abdominal pain, ileus, bleeding, elevated liver enzymes • Skin/mucosa: Erythema, mucositis, rash	► **≥ 2 systems** involvement; • Rash, bilateral nonpurulent conjunctivitis, mucocutaneous inflammation • Hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (elevated troponin or BNP values) • Coagulopathy • Acute GIS symptoms (diarrhea, vomiting, or abdominal pain)	► **≥ 2 systems** involvement; • Skin: Mucositis, conjunctivitis, erythroderma, polymorphic rash • Cardiovascular: Hypotension, shock, troponin ↑, BNP ↑, arrhythmia, abnormal ECHO findings (pericarditis, valvulitis, decreased EF, coronary abnormalities) • Respiratory: Pneumonia, ARDS • Renal: Acute renal injury, renal insufficiency • Gastrointestinal: Diarrhea, vomiting/ nausea, abdominal pain, elevated liver enzymes • Neurologic: Seizures, neurological deficit, meningitis • Hematologic: Coagulopathy
Evidence of COVID-19	• PCR; • Antigen test; • Serology positive; or • Likely contact with patients with COVID-19	• PCR; • Antigen test; • Serology positive; or • Likely contact with patients with COVID-19 in the last 4 weeks	• PCR; • Antigen test; • Serology positive; or • Likely contact with patients with COVID-19 in the last 4-8 weeks
Exclusion	No alternative plausible diagnoses	No other apparent microbial cause of inflammation	No alternative plausible diagnoses
DIAGNOSIS	Fever + inflammation + multisystem involvement + hospitalization + evidence of COVID-19 + no alternative plausible diagnoses	Fever + inflammation + multisystem involvement + evidence of COVID-19 + No other apparent microbial cause of inflammation	Fever + inflammation + multisystem involvement + evidence of COVID-19 + no alternative plausible diagnoses

Abbreviations: ARDS, acute respiratory distress syndrome; BNP, brain natriuretic peptide; CRP, C-reactive protein; COVID-19, Coronavirus Disease 2019; ECHO, echocardiogram; EF, ejection fraction; GIS, gastrointestinal system; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

BOX 6 CLASSIFICATION OF CLINICAL SEVERITY*

	MILD	MODERATE	SEVERE
Vital signs (instead of fever)	Normal	Abnormal	Abnormal
Vasoactive requirement** (Vasoactive-inotropic score)	None	≤ 10	> 10
Respiratory support	None	Oxygen	• High-flow O2 support (> 1 lt/kg) **OR** • Non-invasive or invasive ventilatory support
Organ injury	• None	• Mild/limited	• Moderate or severe
Cardiac involvement***	• None **OR** • Mild valvular insufficiency without elevated a cardiac marker (troponin and/or BNP)	• No clinical finding • No hypotension or arrhythmia **AND** • At least one criteria; • Troponin ≥ 2x upper normal limit • Mild abnormalities in ECHO • Elevated BNP	• At least one clinical finding; • Hypotension, arrhythmia, tachycardia, poor perfusion **OR** • Abnormalities in ECHO • Moderate to severe ventricular dysfunction
Mental status (Evaluated in the absence of fever)	Normal	Normal	Altered

*There is no generally accepted classification of disease severity yet. Clinical severity can be determined based on the criteria given here or additional findings and clinical course. Since not all systems may be equally involved in cases, clinical grading should be made according to the system most affected.

** Vasoactive-Inotropic Score (VIS) Calculation;

VIS= dopamine dose (µg/kg/min) +
dobutamine dose (µg/kg/min) +
100 x epinephrine dose (µg/kg/min) +
10 x milrinone dose (µg/kg/min) +
10,000 x vasopressin dose (U/kg/min) +
100 x norepinephrine dose (µg/kg/min)

*** While assessing the severity of cardiac involvement, ECHO findings and laboratory (BNP or pro-BNP and troponin) results should be evaluated together. BNP and pro-BNP are acute phase reactants, and unless other ECHO, laboratory, or clinical findings are accompanied, the elevation of these markers should not be considered as cardiac involvement alone.

Abbreviations: BNP, brain natriuretic peptide; ECHO, echocardiogram; pro-BNP, pro-brain natriuretic peptide.

BOX 7 MANAGEMENT BY CLINICAL SEVERITY

(For doses and administration, refer to Box 8)

	MILD	MODERATE	SEVERE
Intravenous immune globulin	+	+	+
Steroid	2 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Anticoagulation[a] (LMWH)	+/-[a]	+	+
GIS prophylaxis with proton pump inhibitor	+	+	+
Immunomodulation[b,c,d] (Anakinra or tocilizumab)[e]	-	Refractory illness (consider high-dose steroid)	+
Antiagregan[f] Aspirin© (ASA)	If there is coronary dilatation and/or thrombocytosis	If there is coronary dilatation and/or thrombocytosis	If there is coronary dilatation and/or thrombocytosis
If Kawasaki Disease criteria meet	ASA[f]	ASA[f]	ASA[f]
Antibiotics[g]	If needed	If needed	If needed

[a]Unless there is a contraindication, **prophylactic** LMWH should be started in cases with a diagnosis of MIS-C. If aspirin is started in the treatment of mild cases and there is no additional risk factor in the case, prophylactic LMWH should be added to the treatment according to the disease course. In the following conditions, LMWH should be given in the **treatment dose**;
- The documented presence of thrombosis or a history of thrombosis (hematology consultation), moderate or severe ventricular dysfunction (EF<35%), coronary artery aneurysm Z score >10, rhythm abnormalities, D-dimer >3000 µg/L, and progressive increase, presence of a central venous catheter, inotropic infusion.

[b]In the presence of hemophagocytosis, the addition of immunomodulators to treatment should be considered.

[c]High-dose steroid therapy can be used before immunomodulator therapy.

[d]An online application should be made to the Ministry of Health for off-label use approval.

[e]The short half-life, availability, and side-effect profile are the advantages of anakinra over tocilizumab.

[f]In the presence of Kawasaki disease features (complete or incomplete) or coronary artery dilatation, it is recommended to add aspirin to the treatment. In cases where the platelet count is >400.000 /mm3, aspirin can be added to the treatment. However, caution should be exercised in the simultaneous use of LMWH and aspirin. There is no generally accepted recommendation regarding the use of LMWH and ASA in treating MIS-C, yet, it should be decided on a case-by-case basis. Aspirin should be avoided in cases with bleeding risk. Platelet value should be kept at >80.000 /mm3 during aspirin therapy. **See box 8 for aspirin dosage.**

[g]If there is a risk of sepsis, septic shock, or a concomitant bacterial infection, antibiotics are started considering the age of the patient and the underlying disease, if any.

Abbreviations: ASA, acetylsalicylic acid; ECHO, echocardiogram; EF, ejection fraction; GIS, gastrointestinal system; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin.

BOX 8 DOSES OF DRUGS USED IN MIS-C TREATMENT, ADMINISTRATION WAYS, AND POINTS TO BE CONSIDERED

Intravenous immune globulin (IVIG)	1 - 2 gr/kg, IV infusion in 12 hours Maximum dose: 100 gr (It should be given according to the ideal weight in obese) In refractory cases, a second dose of IVIG can be given if other treatments are contraindicated	Adverse events; • Infusion reactions • Anaphylaxis • Elevated liver enzymes • Aseptic meningitis • Hemolysis
Steroid (methylprednisolone)	Starting (low dose): 2 mg/kg/day IV, once per day, max: 60 mg/day Moderate cases; 10 mg/kg/day IV once per day, For 1 – 3 days, max: 1 gr/day High dose: 30 mg/kg/day IV, once per day, For 2 – 3 days, max: 1 gr/day	• In obese patients, it should be given according to the ideal weight • It can be given orally when the clinic improves • **The maintenance dose of steroid is 2 mg/kg/day** • Steroid taper for 2 to 4 weeks with gradually reducing the dose.
Low molecular-weight heparin (LMWH) Enoxaparin	• Prophylaxis (low-risk patients) SC, **dose per 12 hours**	

CrCl	<37 week GA	37 wk GA - <3 month	3 month – <1 yr	1 - <6 yr	6 - <18 yr
≥ 30 mL/min	0.7 mg/kg	0.83 mg/kg	0.78 mg/kg	0.6 mg/kg	0.53 mg/kg
< 30 mL/min	0.5 mg/kg	0.58 mg/kg	0.55 mg/kg	0.42 mg/kg	0.37 mg/kg

• Therapeutic (high-risk patients refer to *Box 7* and the note a)
1 mg/kg/dose SC, per 12 hours (consider hematology consultation if thrombosis exists)

Dose adjustment is required in renal insufficiency!!!!	Contraindications	Active major bleeding, heparin-induced thrombocytopenia, or plt <25000 /mm3
	Relative contraindications	Plt <50000 /mm3, fibrinogen <75 mg/dL, ≥2 sec above the upper limit of PT, ≥4 sec above the upper limit of APTT
Aspirin In obese patients, it should be given according to the ideal weight It is contraindicated if Plt ≤ 80000 /mm3 **It should be used with caution in renal failure!!!!**	• Kawasaki Disease like; • Plt ≥ 450000/mm3;	3 – 5 mg/kg/day PO, once per day, max: 325 mg/day
	• If Kawasaki criteria are met and not taking steroids **OR** • If there is coronary artery involvement and fever continues	80 – 100 mg/kg/day PO, 4 doses in a day, Max: 4 gr/day
	In these cases, 48 hours after the afebrile period	Continue with 3 – 5 mg/kg/day PO
	• If Kawasaki Disease criteria are fully met + taking steroids in the treatment	3 – 5 mg/kg/day PO, once per day, max: 81 mg/day
GIS prophylaxis	Pantoprazole 1 mg/kg/day IV	
Anakinra	4 – 10 mg/kg/day, 4 dose per a day, SC or IV Max. **100 mg/dose** (400 mg/day) IV infusion should last at least 1 hour (100 mg/100 ml in 0.9% saline solution) The opened syringe should be used within 24 hours	

Abbreviations: APTT, active partial thromboplastin time; GA, gestational age; GIS, gastrointestinal system; IV, intravenous; Plt, platelet; PO, per oral; PT,Prothrombin time; SC, subcutaneous.

BOX 9 LABORATORY AND RADIOLOGICAL FOLLOW-UP DURING THE HOSPITALIZATION

Lab parameters to be checked daily until the fever is under control	Complete blood count Ferritin D-dimer	CRP Troponin Sodium	Procalcitonin BNP Albumin
ECG	Every 48 hours (every 24 hours if cardiac involvement is present)		
ECHO	Cardiac involvement (+) and clinical findings (+) → Everyday Cardiac involvement (-) and clinical findings (+) → 2 per week Cardiac involvement (-) and clinical findings improve → Decision on case-based Coronary artery involvement (+) → Every 2-3 days until findings are stable, then weekly until discharge		
Radiological studies	If needed in the follow-up		

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiogram; ECHO, echocardiogram.

BOX 10 INTENSIVE CARE ADMISSION CRITERIA

Need for vasoactive infusion	Unresponsiveness to fluid resuscitation (shock)
The need for positive pressure ventilation	Clinically manifested cardiac failure
The need for hemodynamic monitoring	Severe electrolyte imbalance
Severe organ failure (kidney, liver, etc.)	Altered mental status (confusion, stupor, etc.)

BOX 11 DISCHARGE CRITERIA (ALL CRITERIA MUST BE MET)

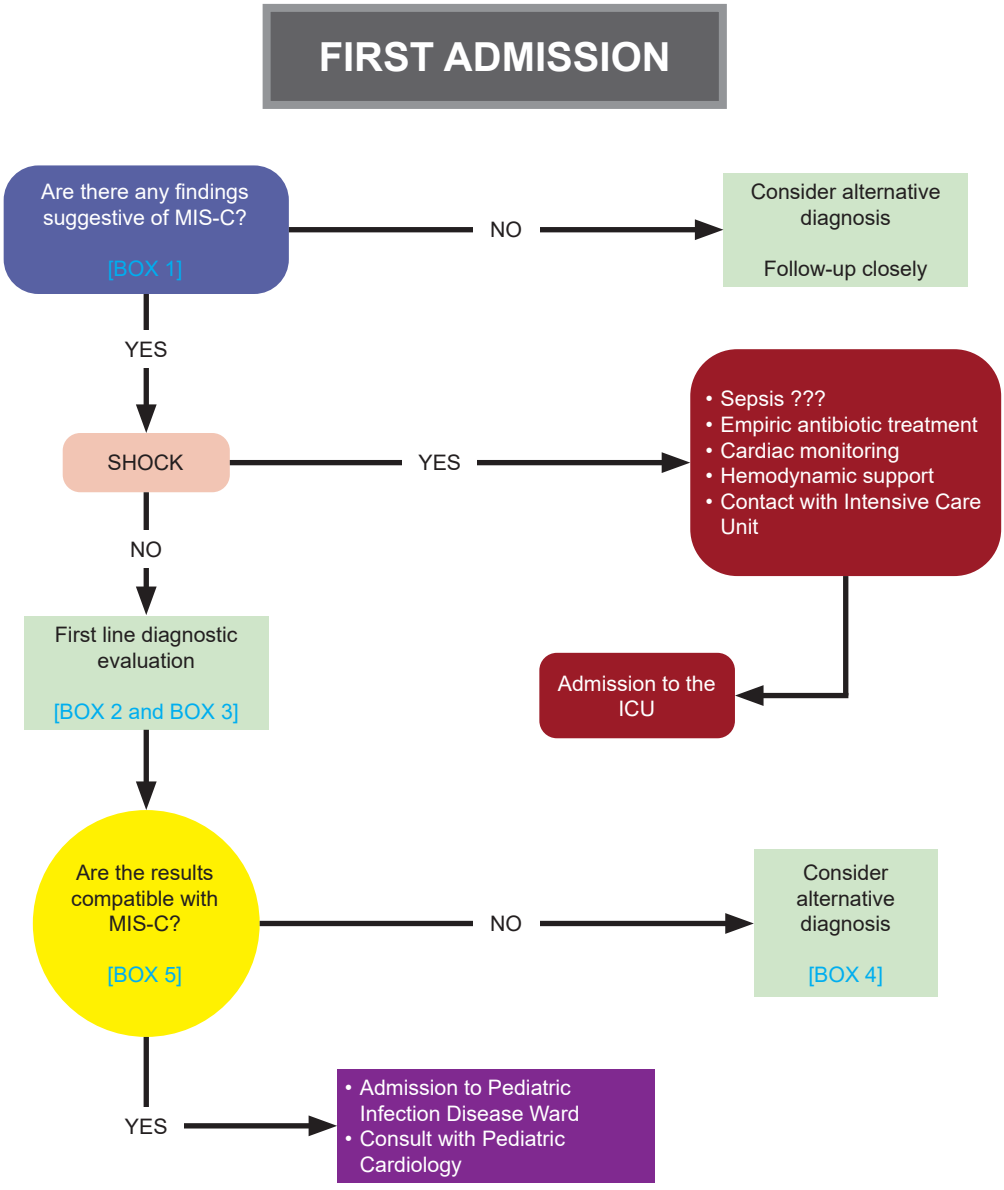
- Good general condition, stable vital signs, fever-free for at least 72 hours
- Acute phase reactants (CRP, procalcitonin, BNP, D-dimer) tend to decrease significantly (3 samples taken at least 24 hours apart in the last 96 hours should show a decreasing trend)
- Good oral intake, enteral feeding, no nausea - vomiting, can take oral medication (steroid and/or aspirin)
- There is no tendency to decrease in platelet values , and platelet value is within normal limits.
- ECG normal in the last 48 hours
- Recent ECHO findings are normal or stable
- Not receiving oxygen support (for at least 48 hours)
- Compatible family with a follow-up plan

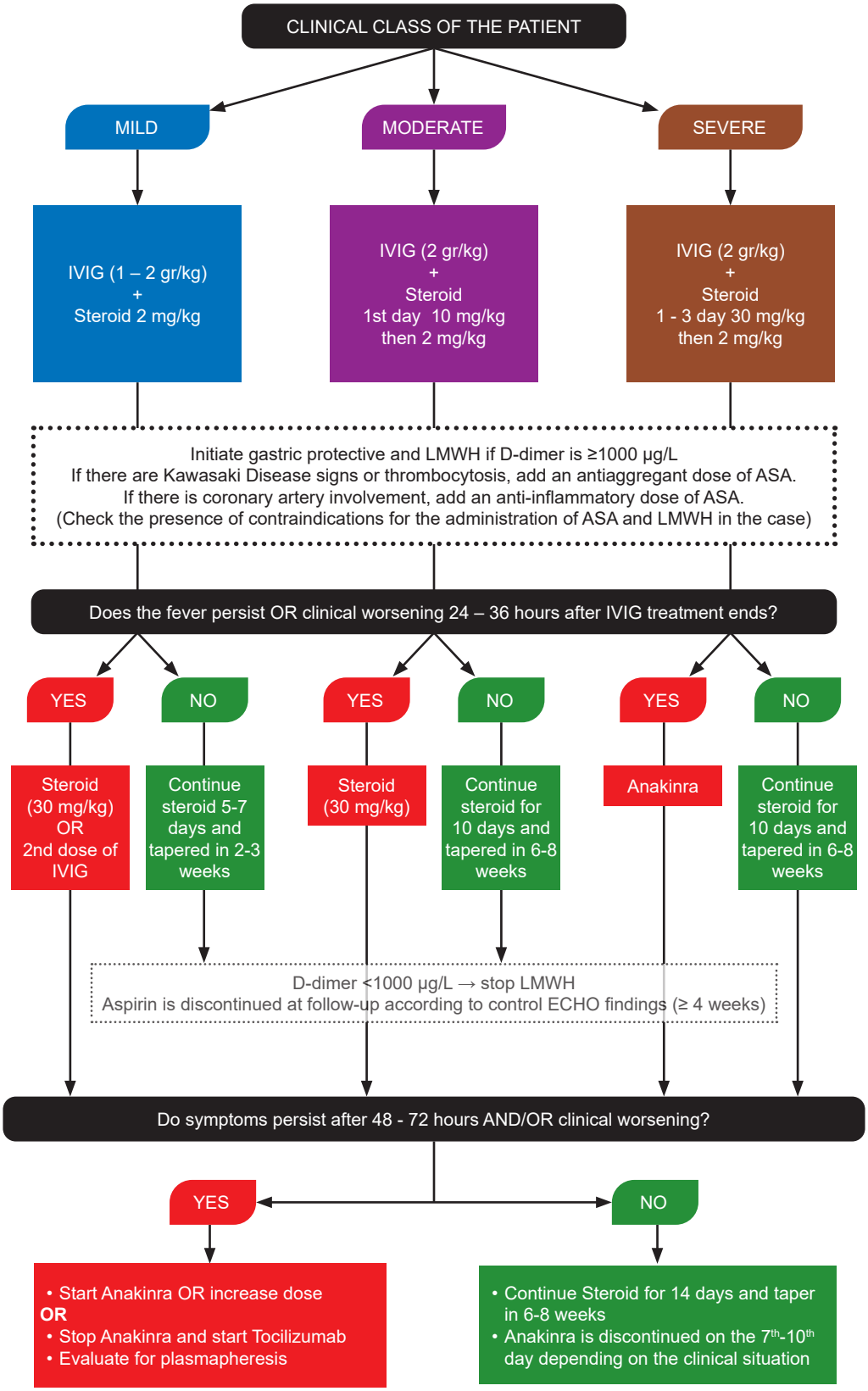
Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiogram; ECHO, echocardiogram.

BOX 12 POST-DISCHARGE FOLLOW-UP

Low-dose Aspirin (moderate-severe cases) should be completed in a total of at least 4 weeks
The duration of LMWH use should be determined according to thrombosis risk factors, In non-risk groups, LMWH can be discontinued when D-dimer falls below <1000, and acute phase reactants decrease
In cases with EF <35%, LMWH for 2 more weeks after discharge (cardiology and hematology opinion should be obtained)
ECG and ECHO → To be planned by Cardiology Department, depending on cardiac involvement and clinical findings
Steroid treatment should be tapered gradually in 2 weeks in mild cases and in 4-6 weeks in moderate and severe cases, depending on the clinical course

Abbreviations: ECG, electrocardiogram; ECHO, echocardiogram; EF, ejection fraction; LMWH, low molecular weight heparin.




CLINICAL CLASS OF THE PATIENT
MILD
MODERATE
SEVERE
IVIG (1 – 2 gr/kg) + Steroid 2 mg/kg
IVIG (2 gr/kg) + Steroid 1st day 10 mg/kg then 2 mg/kg
IVIG (2 gr/kg) + Steroid 1 - 3 day 30 mg/kg then 2 mg/kg
Initiate gastric protective and LMWH if D-dimer is ≥1000 µg/L
If there are Kawasaki Disease signs or thrombocytosis, add an antiaggregant dose of ASA.
If there is coronary artery involvement, add an anti-inflammatory dose of ASA.
(Check the presence of contraindications for the administration of ASA and LMWH in the case)
Does the fever persist OR clinical worsening 24 – 36 hours after IVIG treatment ends?
YES
NO
YES
NO
YES
NO
Steroid (30 mg/kg) OR 2nd dose of IVIG
Continue steroid 5-7 days and tapered in 2-3 weeks
Steroid (30 mg/kg)
Continue steroid for 10 days and tapered in 6-8 weeks
Anakinra
Continue steroid for 10 days and tapered in 6-8 weeks
D-dimer <1000 µg/L → stop LMWH
Aspirin is discontinued at follow-up according to control ECHO findings (≥ 4 weeks)
Do symptoms persist after 48 - 72 hours AND/OR clinical worsening?
YES
NO
• Start Anakinra OR increase dose
OR
• Stop Anakinra and start Tocilizumab
• Evaluate for plasmapheresis
• Continue Steroid for 14 days and taper in 6-8 weeks
• Anakinra is discontinued on the 7th-10th day depending on the clinical situation

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