



MIS-C

COVID-19 SYNDROME

NEW DEVELOPMENTS

MIS-C
COVID-19 SYNDROME

FIRST CASE OF MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN IN RIVERSIDE COUNTY

10:00 PM

CORONAVIRUS SUPERVISORS TODAY UNANIMOUSLY APPROVED FORMATIO

NEWS CHANNEL 3

4:00 PM 107'

Coronavirus disease 2019 (COVID-19): Multisystem inflammatory syndrome in children (**MIS-C**)



Dr. Dorreh

In children, COVID-19 is usually mild.

in rare cases, children can be severely affected.

April of 2020, reports from the United Kingdom documented a presentation in children similar to incomplete Kawasaki disease (KD) or toxic shock syndrome.

in children (**MIS-C**; also referred to as pediatric multisystem inflammatory syndrome [**PMIS**], pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [**PIMS-TS**], pediatric hyperinflammatory syndrome, or pediatric hyperinflammatory shock)



EPIDEMIOLOGY

incidence of MIS-C is uncertain, it appears to be a rare

. In one report, the estimated incidence of laboratory-confirmed SARS-CoV-2 infection in individuals <21 years old was **322 per 100,000**

the incidence of MIS-C was **2 per 100,000**



EPIDEMIOLOGY

Most MIS-C cases have occurred in **previously healthy >70 percent**

Black and Hispanic

. The median age was **8 to 11 years** (range 1 to 20 years)

. a lag of several weeks between the peak of COVID-19 cases and the rise of MIS-C cases

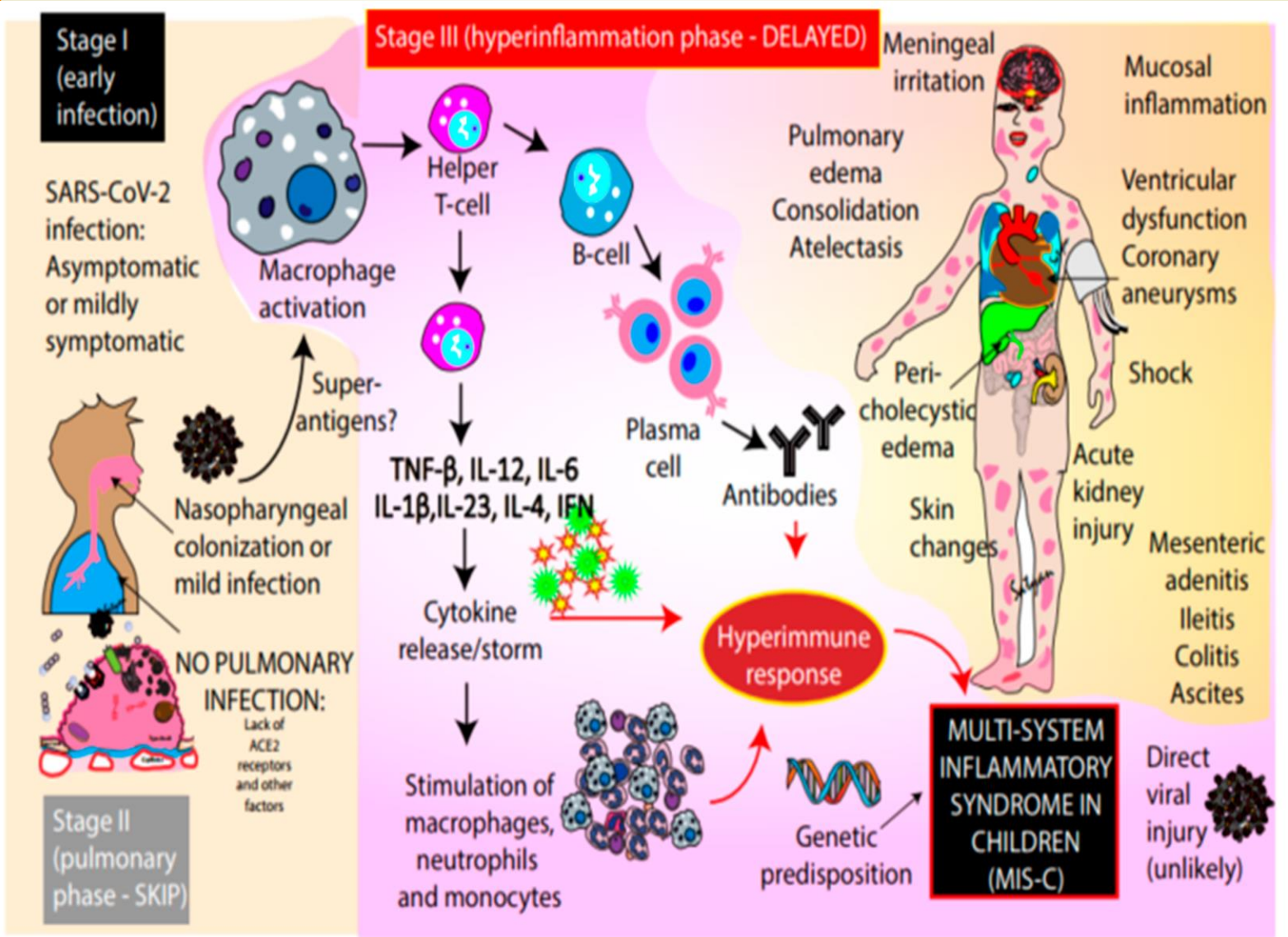


PATHOPHYSIOLOGY

60 percent had positive serology with negative PCR,
34 percent were positive on both tests,
and 5 percent were negative on both tests.

abnormal inflammatory response or Immune
dysregulation

A post-infectious process is suggested,



CLINICAL MANIFESTATIONS

Persistent fevers (median duration four to six days) – 100 percent

Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) – 60 to 100 percent

Rash – 45 to 76 percent

Conjunctivitis – 30 to 81 percent

Mucous membrane involvement – 27 to 76 percent

Neurocognitive symptoms (headache, lethargy, confusion) – 29 to 58 percent

Respiratory symptoms – 21 to 65 percent

Sore throat – 10 to 16 percent

Myalgia – 8 to 17 percent

Swollen hands/feet – 9 to 16 percent

Lymphadenopathy – 6 to 16 percent

Clinical finding:

Criteria met for complete Kawasaki disease (KD) 22 to 64 percent

- **Myocardial dysfunction** (by echocardiogram and/or elevated troponin or brain natriuretic peptide [BNP]) – 51 to 90 percent

- **Shock** – 32 to 76 percent

Arrhythmia – 12 percent

- Acute respiratory failure requiring noninvasive or invasive ventilation – 28 to 52 percent

- Acute kidney injury (most cases were mild) – 8 to 52 percent

- Serositis (small pleural, pericardial, and ascitic effusions) – 24 to 57 percent

- Hepatitis or hepatomegaly – 5 to 21 percent

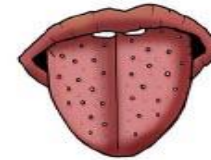
- Encephalopathy, seizures, coma, or meningoencephalitis – 6 to 7 percent

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



Red or Pink Eyes
(Conjunctivitis)

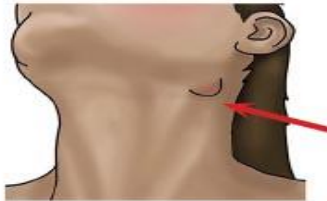
Loss of
Appetite



Red, Cracked Lips
or Red Tongue
(looks like a
strawberry)

Enlarged Gland
(lymph node on
one side of neck)

Fever Lasting
Several Days
(100.4F or more)



Diarrhea and/or
Vomiting



Hive-like
Skin Rash

Abdominal
Pain

Swollen Hands
and Feet
(may also be red)



Irritability or
Sluggishness







Laboratory findings:

Abnormal blood cell counts, including: ▶

Lymphocytopenia – 80 to 95 percent ▶

Neutrophilia – 68 to 90 percent ▶

- Mild anemia – 70 percent ▶

- Thrombocytopenia – 31 to 80 percent ▶

Laboratory findings:

Elevated inflammatory markers, including: ➤

C-reactive protein (CRP) – 90 to 100 percent ➤

• Erythrocyte sedimentation rate – 75 to 80 percent ➤

• D-dimer – 67 to 100 percent

• Fibrinogen – 80 to 100 percent ➤

• Ferritin – 55 to 76 percent ➤

• Procalcitonin – 80 to 95 percent ➤

• Interleukin-6 (IL-6) – 80 to 100 percent ➤

Laboratory findings:

Elevated cardiac markers: ➤

- Troponin – 50 to 90 percent ➤
- BNP or N-terminal pro-BNP (NT-pro-BNP) – 73 to 90 percent ➤
- Hypoalbuminemia – 48 to 95 percent ➤
- Mildly elevated liver enzymes – 62 to 70 percent ➤
- Elevated lactate dehydrogenase – 10 to 60 percent ➤
- Hypertriglyceridemia – 70 percent ➤



Echocardiography

Depressed LV function

- Coronary artery (CA) abnormalities, including dilation or aneurysm
- Mitral valve regurgitation
- Pericardial effusion

Imaging finding

Chest radiograph – Many patients had **normal** chest radiographs. Abnormal findings included pleural effusions, patchy consolidations, focal consolidation, and atelectasis

Computed tomography (CT) of chest – Chest CT (when obtained) generally had findings similar to those on chest radiograph. A few patients had nodular ground-glass opacification.

abdominal ultrasound or CT included free fluid, ascites, and bowel and mesenteric inflammation including terminal ileitis, mesenteric adenopathy/adenitis, and pericholecystic edema



EVALUATION

Mild symptoms

- CBC with differential
- CRP
- Serum electrolytes and renal function test

EVALUATION

moderate to severe symptoms:

- Complete blood count (CBC) with differential
- C-reactive protein (CRP) and erythrocyte sedimentation rate (optional: procalcitonin)
- Ferritin
- Liver function tests and lactate dehydrogenase
- Serum electrolytes and renal function tests
- Urinalysis

Coagulation studies Troponin

Brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP)

- Cytokine panel



Testing for other pathogens

- Blood culture
- Urine culture
- Throat culture
- Stool culture
- Nasopharyngeal aspirate or throat swab for respiratory viral panel
- Epstein-Barr virus serology and PCR
- Cytomegalovirus serology and PCR
- Enterovirus PCR
- Adenovirus PCR

Spectrum of disease

the spectrum of COVID-19-associated disease ranges from mild to severe.

MIS-C without overlap with acute COVID-19 or Kawasaki disease (KD)

35 percent

Nearly all patients in this group had **cardiovascular and gastrointestinal involvement**

one-half had ≥ 4 additional organ systems involved.
shock, cardiac dysfunction

markedly elevated C-reactive protein (CRP) and ferritin
Nearly all patients in this group had positive SARS-CoV-2 serology (with or without positive polymerase chain reaction [PCR]).

Spectrum of disease

MIS-C overlapping with severe acute COVID-19

30 percent.

Many children in this group presented with **respiratory involvement**, including cough, shortness of breath, pneumonia, and acute respiratory distress syndrome.

positive SARS-CoV-2 PCR without seropositivity.

The mortality rate was higher in this subgroup compared with the other two subgroups (5.3 versus 0.5 and 0 percent, respectively)

older than those with KD-like features and they more commonly have comorbidities.



Spectrum of disease

MIS-C overlapping with KD

35 percent of the cohort.

Children in this group were younger than the other two groups (median age 6 versus 9 and 10 years, respectively).

They more commonly had rash and mucocutaneous involvement and less commonly had shock or myocardial dysfunction.

Approximately two-thirds of patients in this group had positive SARS-CoV-2 serology with negative PCR, and one-third were positive on both tests.



Differentiating MIS-C and Kawasaki disease

MIS-C commonly affects **older** children and adolescents

- In MIS-C, **black and Hispanic** children appear to be disproportionately affected and Asian children account for only a small number of cases.
- **Gastrointestinal symptoms** (particularly abdominal pain) are very common in MIS-C
- **Myocardial dysfunction and shock** occur more commonly in MIS-C compared with classic KD .
- **Inflammatory markers** (especially CRP, ferritin, and D-dimer) tend to be more elevated in MIS-C compared with classic KD and KDSS . In addition, **absolute lymphocyte and platelet counts** tend to be lower in MIS-C compared with KD
- It is unclear if the risk of CA involvement in MIS-C is comparable with the risk in classic KD. Among patients with KD, those with KDSS more frequently have CA abnormalities and intravenous immune globulin (IVIG) resistance compared with those without shock. It is unclear if MIS-C is similar to KDSS in



DIFFERENTIAL DIAGNOSIS

Bacterial sepsis

Kawasaki

Toxic shock syndrome

Appendicitis

Other viral infections

Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)

Systemic lupus erythematosus (SLE)

Vasculitis



Management

Abnormal vital signs (tachycardia, tachypnea)

- Shock

Respiratory distress

- Evidence of cardiac involvement (eg, elevated troponin or brain natriuretic peptide, depressed ventricular function or coronary artery [CA] abnormality on echocardiogram, abnormal electrocardiogram)
- Features of Kawasaki disease (KD)

Neurologic changes (eg, depressed mental status, abnormal neurologic examination, seizures)

- Severe abdominal pain or vomiting, especially if unable to tolerate oral feeding
- Clinical or laboratory evidence of dehydration
- Laboratory evidence of acute kidney injury, acute hepatic injury, or coagulopathy
- Underlying medical condition that may place the child at increased risk for complications (eg, immunodeficiency, cardiac or pulmonary conditions)
- Inability to return for followup

Management

Shock

Children presenting with shock should be resuscitated according to standard protocols

most children with MIS-C presented with **vasodilatory shock** that was refractory to volume expansion.

Epinephrine or norepinephrine are the preferred vasoactive agents for the management of fluid-refractory shock in children. Epinephrine is preferred when there is evidence of left ventricular (LV) dysfunction.

In children presenting with severe LV dysfunction, the addition of **milrinone** may be helpful.

Management

Features of Kawasaki disease

standard therapies for KD, including **IVIg**, **aspirin**, and, if there are persistent signs of inflammation or coronary artery (CA) dilation/aneurysm, **glucocorticoids**.

As it will be increasingly difficult to distinguish patients with incident KD who have seroconverted from prior SARS Co-V2 infections from patients with MIS-C who meet KD criteria, it is important to intensify treatment if KD high-risk criteria are present.

Management

Cardiac dysfunction

children with cardiac involvement may present with **arrhythmias** and **hemodynamic compromise**.

Serial echocardiographic assessment of cardiac function and monitoring of brain natriuretic peptide and troponin levels can help guide therapy.

Management focuses on **supportive care** to maintain hemodynamic stability and ensure adequate systemic perfusion. **IVIg** is often used, though conclusive evidence of benefit is lacking.

Continuous cardiac monitoring is essential so that arrhythmias are promptly detected and treated.

Patients with significant LV dysfunction are treated with intravenous **diuretics** and inotropic agents, such as **milrinone, dopamine, and dobutamine**.

In cases of fulminant disease, mechanical hemodynamic support



Management

Antibiotic therapy

Ceftriaxon-vancomycin

Antiviral therapy

Severe MIS-C with active infection

Immune-modifying therapies

Intravenous immune globulin

Management

We recommend **IVIg** for

1- all patients who meet criteria for complete or incomplete KD

2-Shock

3-Cardiac involvement, including any of the following:

Depressed LV function on echocardiography

CA abnormalities (dilation or aneurysm) on echocardiography

Arrhythmia

Elevated brain natriuretic peptide and/or troponin

4-Other severe manifestations requiring PICU

Management

Glucocorticoid therapy may be given concomitantly with IVIG if severe or life-threatening illness is present. It also may be given as a second-line treatment in patients who do not respond to IVIG.

- Dosing – Glucocorticoid therapy is initially given intravenously (IV) with methylprednisolone at a dose of **2 mg/kg/day** in two divided doses .

Once the patient has defervesced and is improved clinically, this can be transitioned to an equivalent oral dose of prednisolone or prednisone by the time of discharge and then tapered off over **three to four weeks**.

In life-threatening circumstances, pulse doses of glucocorticoids are sometimes used (IV methylprednisolone **30 mg/kg/dose**, with a maximum of 1 g)



Management

The benefits and risks of adjunctive therapies (interleukin-1 [IL-1] inhibitors [eg, anakinra, canakinumab], IL-6 inhibitors [eg, tocilizumab], convalescent plasma from recovered COVID-19 patients) are uncertain.

Consultation with pediatric infectious disease and rheumatology specialists is advised.

Management

Antithrombotic therapy

Patients with MIS-C are at risk of experiencing thrombotic complications

For example, patients with severe **LV dysfunction** are at risk for apical LV thrombus and those with **KD who have large or giant CA aneurysms** are at risk for myocardial infarction.

In addition, patients may be at risk for venous thromboembolism (VTE), including pulmonary embolus, due to **hypercoagulability associated with COVID-19**.



Management

Antithrombotic therapy

KD :At a minimum low dose aspirin

LV dysfunction: Moderate to severe

Other patients Is individualized



Management

Patients with **mild** symptoms who lack KD-like features, shock, and cardiac involvement can be monitored **conservatively** initially.

However, if the patient's clinical status worsens or they remain persistently febrile with elevated inflammatory markers, including rising ferritin levels, we typically administer **IVIG**.



outcome

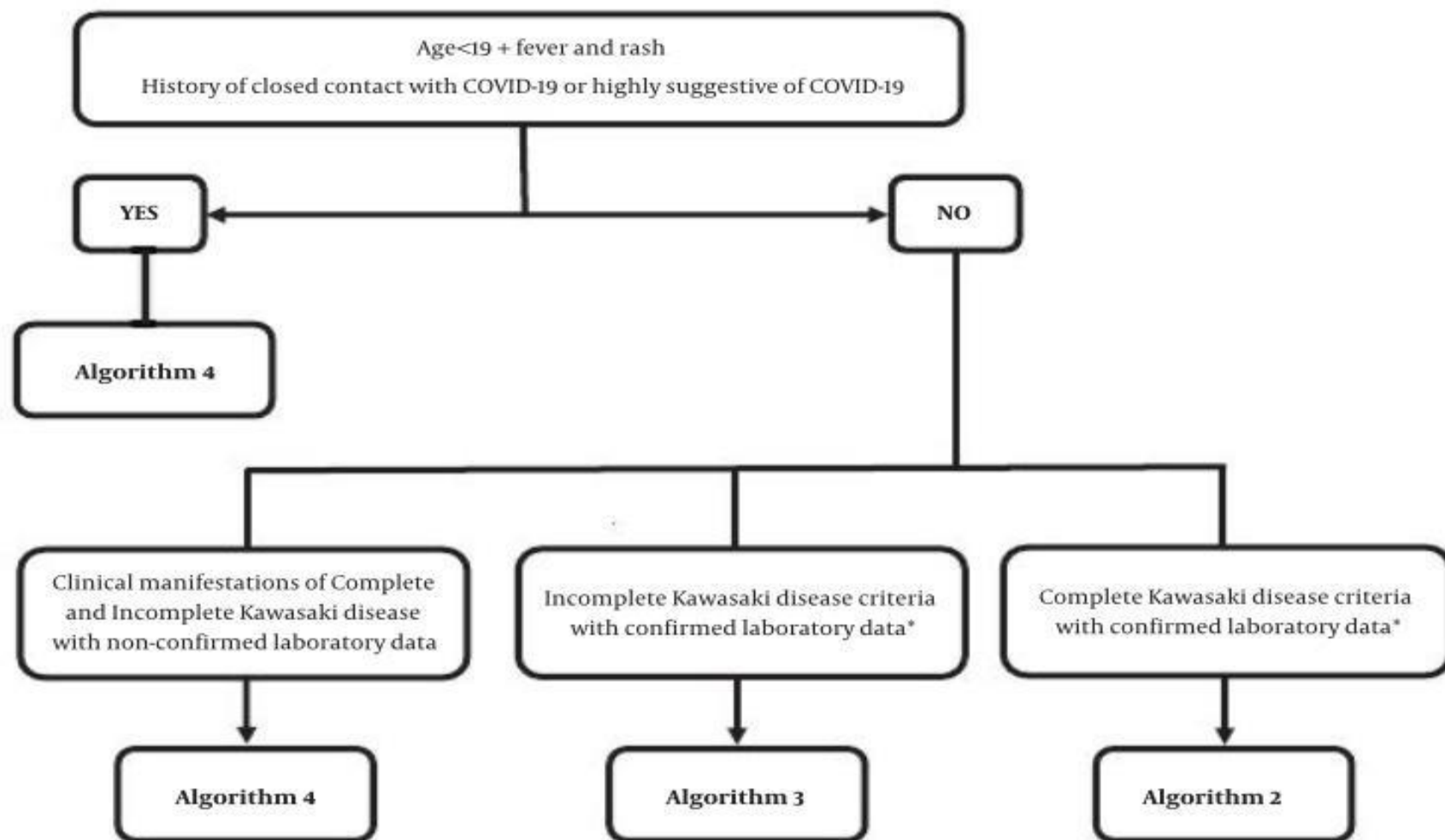
Prognosis is uncertain

In 655 patients with MIS-C there were 11 death.(1.7 %)

Most patient with cardiac involvement had recovery

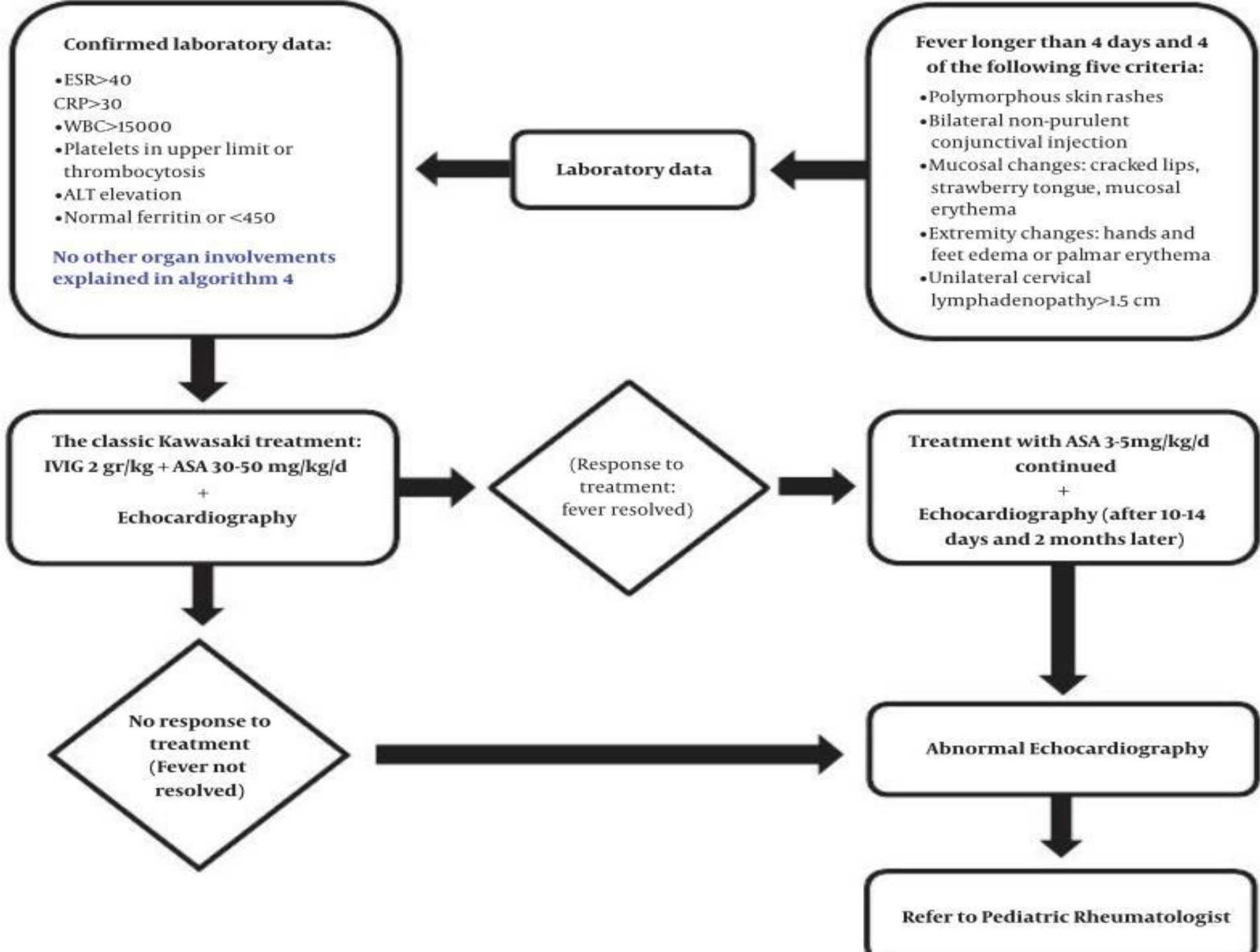


Algorithm 1: A pproach to children with fever and rash <19 years old

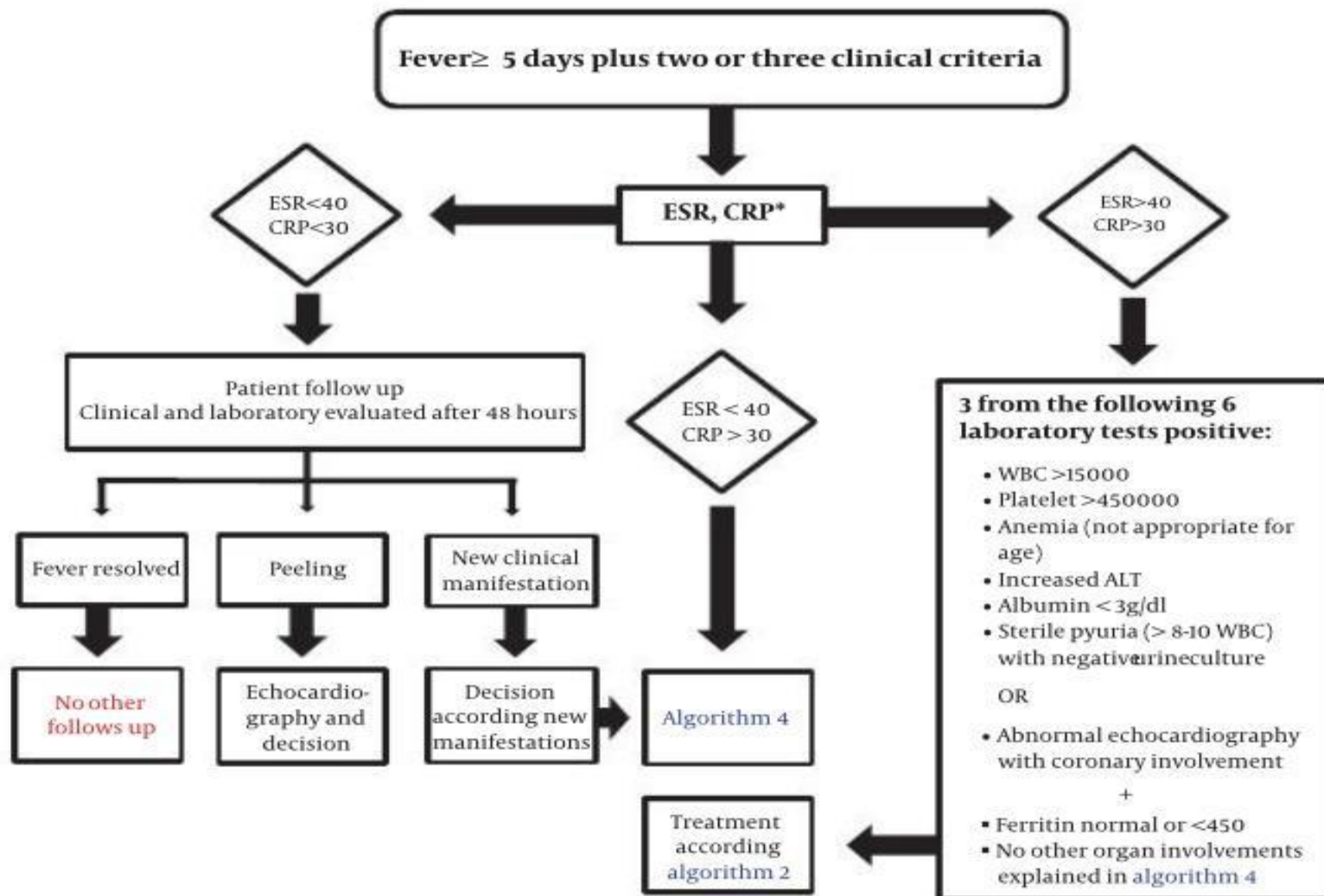


*According to American Heart Association 2017 diagnostic criteria for complete and incomplete Kawasaki disease.

Figure 1. Approach to Kawasaki-like syndromes in pandemic COVID-19: The Tehran Children's Medical Center Protocol (algorithm 1); designed by Pediatric Rheumatology Department confirmed by Pediatric Infectious Diseases, Pediatric Intensive Care, Pediatric Cardiology, and Pediatric Emergency Departments.

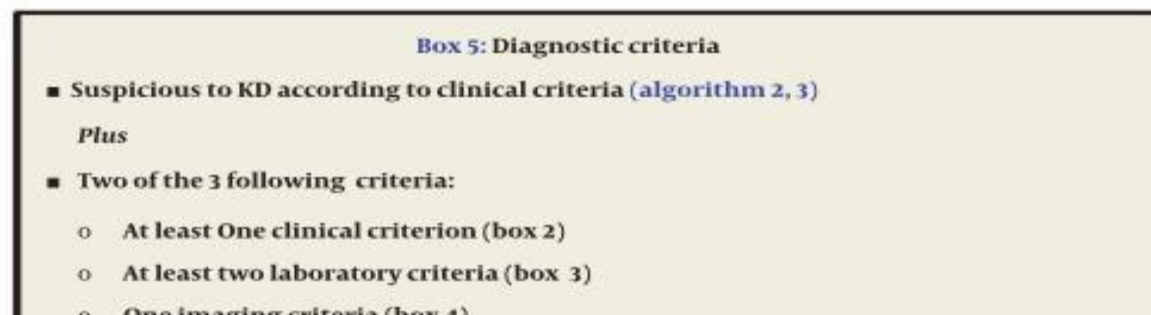
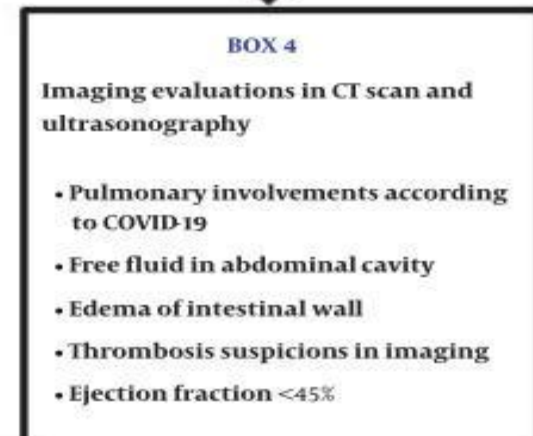
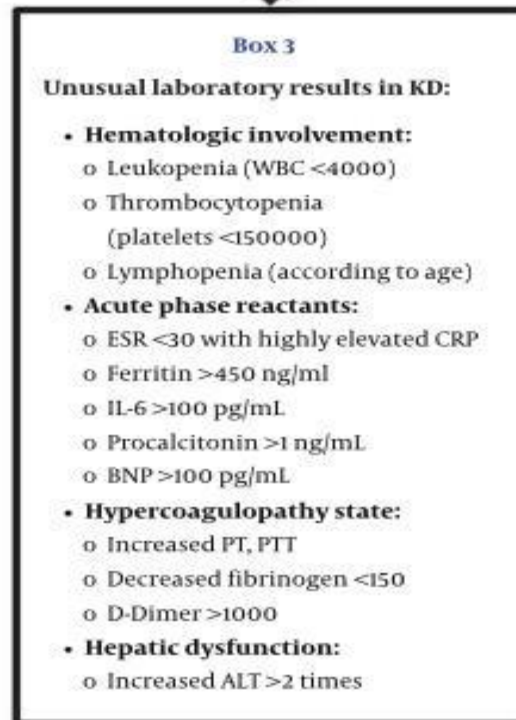
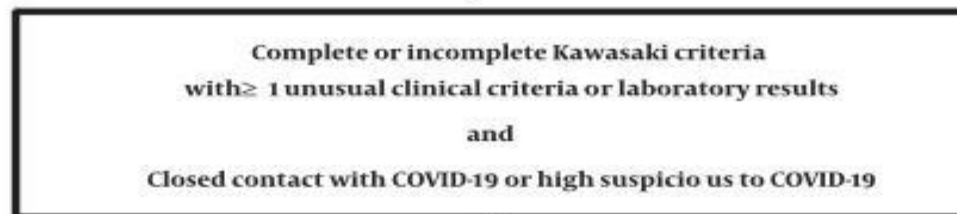


Algorithm 3: Incomplete Kawasaki according to American Heart Association criteria



BOX 1: Para-clinic evaluation for all suspicious patients:

- CBC, ESR, CRP, B/C, U/A, U/C
- Liver function test, PT, PTT, INR, serum albumin and serum Ferritin
- D-Dimer, BNP, IL6, Procalcitonin (if available)
- Pancreatic and Cardiac Enzymes (in selective patients)
- Abdominal ultrasonography
- Echocardiography



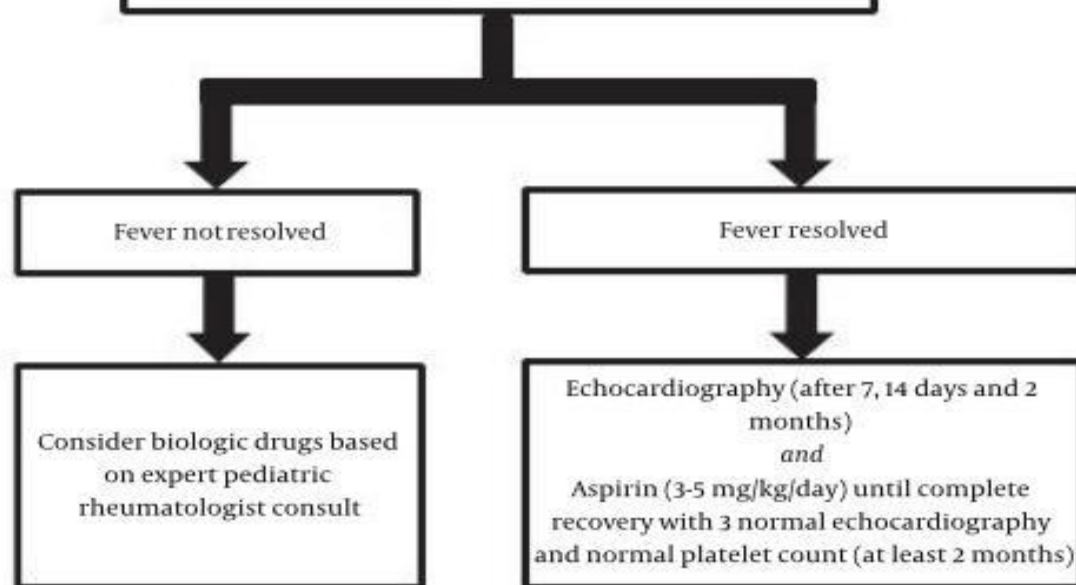
Algorithm 5: Therapeutic approach to Kawasaki-like syndrome or multisystem inflammatory syndrome in children (MIS-C) by SARS-COV2

Box 6: Treatment of cytokine storm*:

- Treatment with methylprednisolone pulses (20-30 mg/kg/day) for 3 consecutive days.
 - +
 - Treatment with IVIG 2gr/kg single dose after the first MTP (If coronary arteries involved)
 - +
 - Enaxaparin in critical patients (admitted in ICU) 0.5 mg/kg/dose every 12 hours
 - +
 - Aspirin 3-5 mg/kg
- IVIg should be infused with blood pressure and pulse rate monitoring in a prolonged time of about 18-24 hours with complete hydration
- * Consult pediatric rheumatologist

Box 7: Suspicious to infectious disease*

- Antibiotic therapy (if necessary)
 - Anti viral therapy (if necessary)
 - Hydroxychloroquine treatment
 - Treatment of other symptoms
- * The above mentioned approaches should be performed parallel cytokine storm treatment with pediatric infectious disease consultation



List of Abbreviations:

- IVIg: Intravenous Immunoglobulin
- ASA: Acetylsalicylic Acid
- ESR: Erythrocyte Sedimentation Rate
- CRP: C-Reactive Protein (mg/L)
- KD: Kawasaki Disease
- IL-6: Interleukine-6
- BNP: Brain natriuretic peptide
- CNS: Central Nervous System
- PT: Prothrombin Time
- PIT: Partial thromboplastin time
- ALT: Alanine Aminotransferase

Figure 5. Approach to Kawasaki-like syndromes in pandemic COVID-19: The Tehran Children's Medical Center Protocol (algorithm 5); designed by Pediatric Rheumatology Department confirmed by Pediatric Infectious Diseases, Pediatric Intensive Care, Pediatric Cardiology, and Pediatric Emergency Departments.

بیمار با تب بالا و یا مساوی ۳۸ درجه برای بیش از ۴ روز با ۲ تا ۵ علامت بیماری کاوازاکی مراجعه می کند:

بثورات جلدی (پلئ مورفیک و یا ماکولوپاپولار)

اریتم و ادم دست و پا

اریتم و ترک خوردگی لب ها زبان توت فرنگی و اریتم مخاط دهان و حلق

لنفادنوپاتی گردن یکطرفه با اندازه بیش از ۱/۵ سانتیمتر

کنژنکتویت دو طرفه غیر چرکی

و $CRP \geq 30$, $ESR \geq 40$

در ضمن بیمار یافته غیر طبیعی به نفع بیماری دیگری غیر از KD نداشته باشد و تشخیص های افتراقی رد شده باشد.

در آن صورت:

- اکوکاردیوگرافی برای بیمار انجام شود.
- در صورت مطرح شدن کاوازاکی آنتیبیوتیک یا کلاسیک درمان استاندارد با IVIG و اسپیرین شروع شود.
- در صورت داشتن سابقه مبتلا بودن به کوید-۱۹ یا تماس با بیمار بهبود یافته طی دو هفته اخیر از نظر ابتلا به کوید-۱۹ بررسی شود و اقدامات درمانی و پیشگیرانه مطابق با دستورالعمل کشوری کووید در اطفال به عمل آید.

بیمار سیر بیماری کاوازاکی را طی و با اولین دز IVIG تب قطع می شود و طبق پروتکل درمان کاوازاکی پس از ۴۸-۷۲ ساعت بدون تب بودن، دز ضد التهاب اسپیرین به ضد ترومبوز تبدیل شده و از نظر قلبی با ثبات است.

بله

خیر

ترخیص با توصیه های لازم شامل هشدار
علامت خطر

تشخیص افتراقی های مثل، سپتی سمی، TSS ناشی از استرپ گروه A و یا استافیلوکوک، KD-Shock syndrome، تب های هموراژیک (به خصوص CCHF) و سندرم التهابی چند سیستمی ناشی از کرونا ویروس (MIS-C) و MAS مد نظر باشد و آزمایشات مرتبط طبق کتب مرجع بعمل آید.

در صورت وجود یکی و یا بیشتر از علائم ناسازگار با کاوازاکی:

- شوک یا فشار خون پایین
- نارسایی قلبی و یا کاردیت
- شواهد دال بر شکم حاد، گاسترو انتریت حاد
- اسیت غیر قابل توجه
- هپاتیت با و یا بدون زردی
- اسپلنومگالی
- بثورات جلدی پاستولار، وزیکولار و یا پتشی و پورپورا
- شواهد بالینی به نفع کوآرگولوپاتی
- شواهد به نفع انفالیت (مثل کاهش سطح هوشیاری، تشنج و درگیری اعصاب کرانیال و ...)

اگر معیارهای زیر وجود داشته باشد بیمار به عنوان MIS-C در نظر گرفته شود:

A. سن ۱۹-۰ سال

B. تظاهرات بالینی شامل تمام موارد زیر:

۱. تب ثابت شده بالای ۳۸ درجه برای بیش از ۲۴ ساعت

۲. درگیری دو ارگان یا بیشتر شامل: کاردیو واسکولار (مثل شوک، افزایش troponin، BNP، اکوی غیر طبیعی و آرتمی، $F.E < 45\%$)؛ درگیری تنفسی (مثل پنومونی، ARDS، آمبولی ریه)، درگیری کلیه ها (مثل AKI و نارسایی کلیوی)؛ گرفتاری اعصاب (تشنج، مننژیت آسپتیک، کاهش سطح هوشیاری و Stroke)؛ هماتولوژیک مثل کوآگولوپاتی؛ درگیری گوارشی (مثل افزایش آنزیم های کبدی، ایکتز، اسهال و استفراغ، ایلئوس، شکم حاد، خونریزی گوارشی و علائم و نشانه های مرتبط با پانکراتیت) و پوستی (مثل اریترودرمی، موکوزیت و سایر راش ها)

۳. بیماری شدید منجر به بستری

۴. شواهد از مایشگاهی به نفع التهاب شامل موارد زیر:

- غیر طبیعی شدن مارکرهايي مثل ESR، CRP < 30 و همزمان افت غیر قابل توجه ESR > 40 ، فیبرینوژن زیر ۱۵۰، PCT، فریپین، LDH < 500 ، > 100 IL6، نوئروفیلی، لنفوپنی و هیپوآلبومینمی

C. رد سایر تشخیص های افتراقی مطرح شده در همین الگوریتم

D. شواهد بنفع عفونت SARS-CoV2 شامل هر کدام از موارد زیر:

وس کرونا

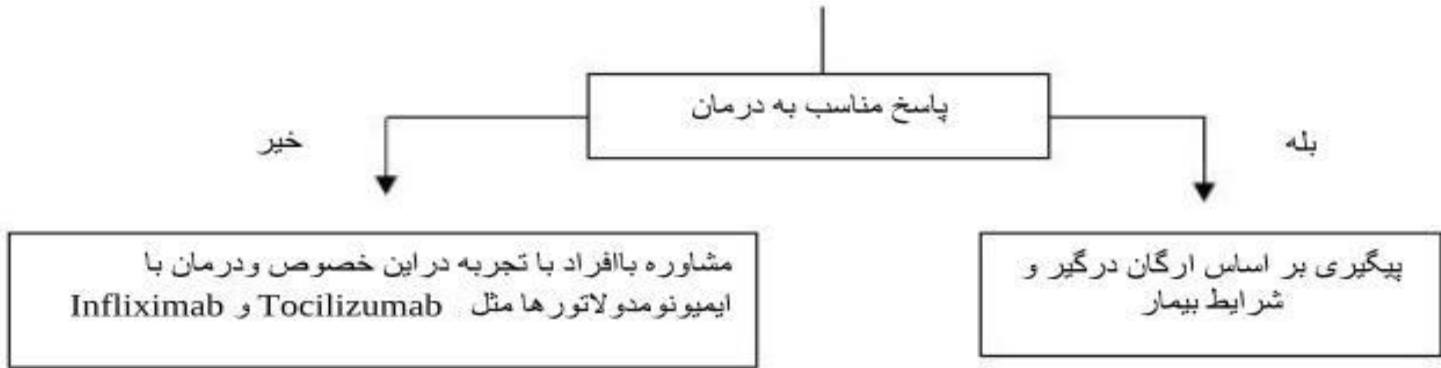
CO و یا فرد در قرنطینه

SARS-CoV2 و یا تماس با مورد COVID-19 و یا فرد در قرنطینه

بیمار با شرح حال تب بیش از ۳۸ درجه به همراه شوک یا اختلال عملکرد میوکارد و یا نیازمند آزو پروسور و یا نارسایی شدید یکی از ارگان های بدن در PICU و در غیر این صورت در بخش بستری شود. (مطابق دستورالعمل کشوری کودکان)



- مانیتور علائم و نشانه های مرتبط صورت بگیرد و احتمال موضع عفونی رد شود.
- انجام اکوکاردیوگرافی و سونوگرافی (در صورت وجود علائم شکمی)، مانیتور با EKG و گازهای خون شریانی
- ایجاد ثبات همودینامیک منطبق با وضعیت بیمار (از نظر شوک، اختلال عملکرد قلبی و...)
- شروع آنتی بیوتیک مناسب بسته به وضعیت بیمار
- شروع IVIG در صورت وجود شواهد دال بر TSS؛ Kawasaki Shock Syndrome و MIS-C
- شروع پالس میتل پردنیزولون با دز 20-30 mg/kg/day برای سه روز متوالی
- شروع LMWH (آنوکسپارین) با دز پایین برای پیشگیری از ایجاد ترومبوز
- ارسال کشت از محیط های استریل مثل خون، مایع مغزی نخاعی و مایع آسیت و نیز گلو و زخم در صورت وجود .
- بررسی آزمایش های عملکرد کبدی، گازهای خون شریانی، تری گلیسیرید، فریتین، فیبرینوژن، تروپونین، آلبومین ، الکترولیت ها، کلسیم، منیزیم، (مارکرهای التهابی حاد) APR ها و ..
- تصمیم جهت تکرار آزمایشات بر اساس شرایط بیمار و تاریخ آزمایشات
- ارسال PCR نازوفارنکس جهت ویروس کرونا و نیز سرولوژی
- نمره دهی بالینی و پاراکلینکی برای CCHF بر اساس پروتکل کشوری کریمه کنگو و درمان در صورت شک بالینی قوی
- با توجه به درگیری چند ارگان، تیمی متشکل از تخصص های مرتبط بیمار را اداره می کنند.



نکته:

