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Croatian Society for Infectious Diseases recommendations for diagnosis and treatment of multisystem inflammatory syndrome in children

Preporuke Hrvatskog društva za infektivne bolesti za dijagnostiku i liječenje multisistemskog upalnog sindroma u djece

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Summary

Multisystem inflammatory syndrome in children is a novel entity first described in April 2020. It is a complication of COVID-19 that appears with a latency of 2-6 weeks and is characterized by fever, multiorgan involvement, and elevated inflammatory markers. Diagnosis is based on certain diagnostic criteria, and in these recommendations we chose the World Health Organization case definition. Patients should be treated with intravenous immunoglobulin and glucocorticoids together with other symptomatic and supportive measures. Follow-up should be at least a year-long, and even longer in case of cardiac complications. The aim of these recommendations is to help clinicians in diagnosing and treating this disease.

Sažetak

Multisistemski upalni sindrom u djece novi je entitet koji je prvi puta opisan u travnju 2020. To je komplikacija bolesti COVID-19 koja se javlja s latencijom od 2-6 tjedana, karakterizirana vrućicom, zahvaćenosti više organa i povišenim upalnim parametrima. Dijagnoza se temelji na određenim dijagnostičkim kriterijima, a u ovim preporukama odabrali smo definiciju slučaja Svjetske zdravstvene organizacije. Bolesnike treba liječiti intravenskim imunoglobulinom i glukokortikoidima uključujući druge simptomatske i potporne mjere. Praćenje bolesnika treba trajati najmanje godinu dana, a u slučaju kardioloških komplikacija i duže. Cilj ovih preporuka je pomoći kliničarima u dijagnosticiranju i liječenju ove bolesti.

Introduction

During the spring of 2020, at the beginning of the coronavirus disease 2019 (COVID-19) pandemic, pediatricians from different countries noted hospitalization of children who developed fever and multisystem inflammation.[1,2] Some of these children had characteristics that were similar to Kawasaki disease (KD) and some were critically ill with shock and multiorgan failure. Clinical evidence suggested the emergence of a new entity. It was named multisystem inflammatory syndrome in children (MIS-C), also known in the British literature as pediatric inflammatory multisystem syndrome temporally associated with coronavirus disease 2019 (PIMS-TS).[3,4]

MIS-C is a rare complication of COVID-19 in children that develops in less than 1% of infected children.[5] An increase in the number of COVID-19 cases in certain region is followed by an increase of MIS-C cases with the latency of 2 to 6 weeks.[6-8]

Although MIS-C affects children of all ages, the median age is 8-10 years, while half of the cases are between 5 and 13 years of age.[3,6,8,9] The majority of affected children were previously healthy. Comorbidities are rare and if present, the most common are obesity and asthma.[3,9,10] The syndrome affects both sexes equally, although the predominance of boys has been observed in some studies.[6,8,9,11]

The aim of these recommendations is to facilitate the recognition, diagnosis and treatment of MIS-C for all colleagues dealing with these patients, motivated by the fact that a small number of MIS-C related recommendations are available and not fully applicable in our country.[4,12,13]

Clinical characteristics

The interval between COVID-19 and the onset of MIS-C symptoms is usually 2-6 weeks.[6,11] MIS-C can present as a disease similar to KD, fever with elevated inflammatory markers or shock and myocardial dysfunction.[3,4] Younger children are more likely to present with a disease similar to KD, while older children present with hypotension, shock and signs of myocardial dysfunction.[11] All patients have fever.[3,10] Gastrointestinal symptoms (vomiting, diarrhea and abdominal pain) are common.[6,7,11] Abdominal pain can mimic acute appendicitis so children with MIS-C sometimes undergo surgery.[10] Mucocutaneous changes are often found (conjunctivitis, rash, red lips, strawberry tongue).[11] Unlike COVID-19, cough and other respiratory symptoms are uncommon.[3] Tachypnea and difficulty breathing with chest pain may be signs of shock or cardiogenic pulmonary edema. Neurocognitive symptoms are common and include headache, confusion, irritability, lethargy, and positive meningeal signs.[3,9] Myalgia and sore throat may also be present.

A typical patient with MIS-C is a school-age child with fever, rash, conjunctivitis and gastrointestinal symptoms who recently experienced asymptomatic or mild COVID-19.[14] If the disease was asymptomatic there may be information about contact with COVID-19 case and/or the patient should have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in the blood.

Diagnostic evaluation of MIS-C

Laboratory findings include elevated inflammatory markers: C-reactive protein (CRP), procalcitonin (PCT), ferritin, interleukin-6 (IL-6), erythrocyte sedimentation rate (ERS), together with changes in complete blood count (CBC): leukocytosis, neutrophilia lymphopenia, anemia and thrombocytopenia. Other findings include hyponatremia, low serum albumins, hypertriglyceridemia, elevated levels of lactate dehydrogenase (LDH), aminotransferases, fibrinogen (Fg), D-dimers, troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP).[3,11,14]

Chest X-ray may be normal or show cardiomegaly, pleural effusion, signs of pulmonary edema, pulmonary infiltrates or atelectasis.[15,16]

Abdominal ultrasound often shows free fluid in the abdomen, enlarged mesenteric lymph nodes and intestinal wall edema.[16] Liver and spleen may be enlarged but without parenchymal changes.

Electrocardiogram (ECG) changes include non-specific alterations of the ST segment, prolongation of QT interval, arrhythmias and atrioventricular blocks of different degrees.[11,12,14,17]

Reduced ejection fraction (EF) as a sign of impaired left ventricular function is the dominant finding on echocardiogram followed by pericardial effusion and mitral regurgitation.[3,11,14,17] Dilatation or aneurysm of the coronary arteries may also be present, although they occur less frequently than in KD.[18]

This syndrome can resemble sepsis, streptococcal and staphylococcal toxic shock syndrome, appendicitis, central nervous system infection but also some non-infectious diseases such as autoimmune diseases, malignancies, macrophage activation syndrome and others. Therefore, extensive work-up is often necessary to exclude these entities.

Table 1. Diagnostic tests for patients with suspected MIS-C[4,10,12]

Tablica 1. Dijagnostički testovi kod sumnje na MIS-C [4,10,12]

Evaluation of all patients with suspected MIS-C • CBC, CRP, PCT, ESR, ferritin, IL-6*, glucose, urea, creatinine, electrolytes (Na, K, Cl, Ca, P, Mg), liver function tests (T BIL, AST, ALT, GGT), LDH, CK, CPK-MB, troponin, NT-proBNP, total protein, albumin, coagulation (PT, aPTT, Fg) and D-dimers, urine • Chest X-ray, ECG, echocardiogram • Abdominal and pleural ultrasound • Blood cultures • Antigen test or RT-PCR for SARS-CoV-2 from nasopharyngeal swab, SARS-CoV-2 antibodies
Additional evaluation depending on the symptoms • Blood gas analysis, serum lactate • Amylases, triglycerides • Lumbar puncture • Urine culture, stool culture, throat culture, testing for other pathogens • Autoimmune disease markers

* if available

Abbreviations: CBC=complete blood count; Na=sodium; K=potassium; Cl=chloride; Ca=calcium; P=phosphorus; Mg=magnesium; T BIL=total bilirubin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=gamma glutamyl transferase; CK=creatine kinase; CPK-MB=creatine kinase myocardial band; PT=prothrombin time; aPTT=activated partial thromboplastin time; RT-PCR=reverse transcription polymerase chain reaction

Table 1 lists the evaluation we recommend in all patients with suspected MIS-C, as well as the most important additional tests to rule out other diagnoses. The diagnosis of MIS-C is based on diagnostic criteria. There is no pathognomonic symptom, sign or diagnostic test whose positive result would be sufficient to establish the diagnosis. MIS-C is actually

a diagnosis of exclusion – exclusion of other possible causes of the disease is a diagnostic criterion.

Currently, there are three versions of case definition for MIS-C: the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) and the Royal College of Paediatrics and Child Health (RCPCH) case definition.[19-21]

In the Croatian recommendations, we decided to adopt the WHO case definition because we consider it to be the most precise, and because the age limit is 19 years. Also, in the CDC case definition, the criteria of fever duration (one day) is too short, as is the time frame for contact with a person infected with COVID-19 (4 weeks) because MIS-C can develop more than 6 weeks after SARS-CoV-2 infection. The RCPCH criteria are the least accurate of all and are therefore rarely used.

MIS-C diagnostic criteria (WHO)[19]

Children and adolescents 0–19 years of age with fever lasting for at least three days

AND

at least two of the following:

a) Rash, or bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands or feet)
b) Hypotension or shock
c) Cardiac dysfunction, pericarditis, valvulitis, or coronary arteries abnormalities (including echocardiographic findings or elevated troponin/NT-proBNP)
d) Evidence of coagulopathy (prolonged PT or APTT, elevated D-dimer)
e) Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

AND

Elevated inflammatory markers such as ESR, C-reactive protein, or procalcitonin.

AND

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

AND

Evidence of SARS-CoV-2 infection (positive SARS-CoV-2 RT-PCR, or antigen test, or serology, or contact with patient with COVID-19).

It is important to emphasize that often not all symptoms and signs of the disease are present at the same time but clinical manifestations develop over several days. Hence, patient with suspected MIS-C should be monitored (even as outpatient if his condition allows it) until he meets case definition criteria for MIS-C or until another diagnosis is established. However, in seriously ill patients with suspected MIS-C, it is advisable to start immunomodulatory therapy before the diagnostic process is finished and the diagnosis is confirmed.[12]

An increasing number of children who have had COVID-19 as well as a rather small number of children who have been vaccinated make serology less reliable in diagnosing MIS-C. Those who had COVID-19 differ from those vaccinated by the presence of antibodies to both nucleocapsid and spike protein, while those vaccinated have antibodies only to the spike protein. Children who recently had COVID-19 should have not only IgG antibodies present, but also IgM antibodies because they can persist for up to three months after COVID-19.[22]

MIS-C management

Majority of children with suspected or confirmed MIS-C should be admitted to hospital. Exceptions are children with mild disease and normal vital signs who can be closely monitored without the need for hospitalization. All hospitalized children require continuous monitoring of vital signs, including urine output. Children with signs of shock, those who need respiratory support or replacement of some other vital function should be treated in the intensive care unit. We recommend consulting a pediatric cardiologist, (pediatric) infectious disease specialist, and in some cases pediatric rheumatologist and pediatric hematologist.[4,12]

During the diagnostic procedure, and after having taken the microbiological samples, empirical antibiotic therapy should be initiated if there is a clinical suspicion of invasive bacterial disease and it should be continued until the infection is ruled out.[4,14] The drug of choice is a 3rd generation cephalosporin (ceftriaxone at a dose of 50 mg/kg body weight), but therapy should be adjusted to presumptive diagnosis. Clindamycin and antistaphylococcal antibiotic are recommended in case of suspected toxic shock syndrome.

1. Intravenous immune globulin (IVIG) should be given to all MIS-C patients. High dose of 2 g/kg (based on ideal body weight in overweight children) should be used for treatment, up to a maximal dose of 100 g.[4,12,13]
2. Low-moderate doses of glucocorticoids (intravenous methylprednisolone 1-2 mg/kg) should be given for 3-5 days with IVIG in all patients with MIS-C.[12,23-25]

3. In patients who do not respond to IVIG and low-moderate doses of glucocorticoids we recommend using high dose glucocorticoids (intravenous methylprednisolone 10-30 mg/kg up to 1 g/day for 3-5 days) instead of repeating IVIG.[12]

   We recommend high doses of intravenous glucocorticoids as the first treatment choice in most severely ill children (shock, EF<40%, respiratory insufficiency). In all cases, glucocorticoid therapy is continued by oral administration for 2-3 weeks in a gradually decreasing dose (2 mg/kg for 5-7 days, 1mg/kg for 5-7 days, 0.5 mg/kg for 5-7 days).[12]

   In a small number of patients, fever and other symptoms and signs of the disease can persist even 72 hours after IVIG and glucocorticoid therapy. In these cases, we recommend using adjunctive immunomodulatory therapy with infliximab, anakinra or tocilizumab.[4,12] The decision of the choice of drug, dosing and duration of therapy should be made in consultation with a pediatric rheumatologist.[12,13,26]
4. During hospitalization it is necessary to monitor the vital signs of the patient, including ECG monitoring to recognize arrhythmias in time. Maintaining fluid balance monitoring is also important, and in the case of oliguria and/or cardiac dysfunction, diuresis should be stimulated with diuretics.[14] Also, IVIG may be administered at a divided dose of 1g/kg for 2 days.[12]
5. It is necessary to correct the electrolyte imbalance, monitor the metabolic status of the patient, give albumin infusion if hypoalbuminemia occurs.[14] Fever should be reduced with acetaminophen (as the antipyretic of the first choice) and ibuprofen in standard doses. Gastric protection with the proton pump blocker should be given to children receiving glucocorticoid therapy.[4]

   Patients with hypotension and shock should be treated with crystalloid solutions. If hypotension is fluid-resistant, vasopressors should be administered as continuous infusion.[14] Recommendations on the choice of drug and dosage are the same as for other causes of hypotension. Epinephrine or norepinephrine are usually given, but if we expect a short-term administration (2-3 days) dopamine may be administered via peripheral vein.[26,27] In children who have significantly reduced EF, the addition of milrinone to therapy may be helpful. It is administered as continuous infusion at a dose of 0.25-0.75 mcg/kg/min. Some patients will also require respiratory support and in most severe cases extracorporeal membrane oxygenation will be necessary.[14]
6. Antiplatelet and anticoagulant therapy is not indicated in all patients. We recommend using low dose aspirin (3-5 mg/kg/day, up to 100 mg/day) in children with clinical characteristics similar to KD, thrombocytosis (>400x10^9/L) and those with coronary arteries abnormalities.[12,14] Therapy should be continued for 4-6 weeks, until another echocardiogram is done. If there are no changes on coronary arteries and the platelet number is normal, aspirin can be discontinued.[12]

   Treatment with aspirin should be avoided in patients with active bleeding or significant bleeding risk (coagulopathy and/or platelet count ≤80x10^9/L).[12]

   Patients with large or giant coronary artery aneurysm should receive low doses of aspirin and enoxaparin (factor Xa 0.5-1.0).[12]

   Patients with MIS-C and documented thrombosis or EF <35% should receive therapeutic anticoagulation with enoxaparin for at least 2 weeks after discharge from the hospital.[12] Indications for prolonging enoxaparin therapy include: large and giant coronary artery aneurysm, documented thrombosis and ongoing moderate to severe left ventricular dysfunction.[12]

   For MIS-C patients who do not meet the above criteria, the approach to antiplatelet and anticoagulation management should be tailored to the patient's risk for thrombosis.[12] It should be borne in mind that the presence of a central venous catheter increases the risk of thrombosis.[28]

   In most children, antiviral treatment of SARS-CoV-2 is not indicated, even if the virus is detected in the airway by PCR or antigen test.[13] If there is a suspicion that COVID-19 is still active, we recommend a consultation with a paediatric infectious diseases specialist.

Clinical, laboratory and ultrasound monitoring of patients

Regular laboratory evaluation is required during hospitalization.

Patients can be discharged if they are afebrile for at least 24 hours, have normal vital signs with the withdrawal of symptoms and signs of the disease and normalization of inflammatory markers, and if the treatment is finished or can be continued orally.[4]

After discharge from the hospital, we recommend a follow-up check in 4-6 weeks, 6 and 12 months and laboratory test controls until the findings return to normal. In patients who develop complications, longer follow-up may be necessary.

Patients should be advised to avoid physical activity for a period of time defined by the cardiologist.

ECGs should be performed at a minimum of every 48 hours in MIS-C patients who are hospitalized. [12] If conduction abnormalities are present, patients should be placed on continuous telemetry while in the hospital, and Holter monitor during follow-up. After discharge ECG is performed at the same time as echocardiogram.[12]

The frequency of ultrasound examination (abdomen, pleura) depends on symptoms and signs of the disease and findings of previous ultrasounds. They should be repeated until normal.

An echocardiogram should be conducted at diagnosis and should evaluate ventricular/valvular function, pericardial effusion and coronary artery dimensions.[12]

Echocardiogram should be repeated 7-14 days after presentation and earlier in case of clinical indication (clinical condition of the patient or severe cardiac dysfunction).[12])

Echocardiograms should be done 4-6 weeks, 6 months and a year after presentation. Children with left ventricular dysfunction (LV) and/or coronary artery aneurism will require more frequent echocardiograms. [12] It is currently unclear whether cardiac controls are needed beyond one year after the disease.

Cardiac magnetic resonance imaging may be indicated 2-6 months after MIS-C in patients who presented with significant transient left ventricular dysfunction (EF <50%) in the acute phase of illness or in those with persistent LV dysfunction.[12] Cardiac computed tomography should be performed if distal coronary artery aneurism is suspected on echocardiogram.[12]

Vaccination with live vaccines should be delayed for 11 months in all children treated with IVIG, while other vaccines may be given after clinical and laboratory recovery.[29] There are currently no clear recommendations for vaccination against COVID-19 in children with a history of MIS-C, so decision should be made for each patient individually.[13]

These recommendations are based on current knowledge and our experience on treating MIS-C patients and will be updated in accordance with new findings and other guidelines.

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