Childhood multisystem inflammatory syndrome associated with COVID-19 (MIS-C): a diagnostic and treatment guidance from the Rheumatology Study Group of the Italian Society of Pediatrics

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Abstract

Background: Italy was the first Western country to be hit by the SARS-CoV-2 epidemic. There is now mounting evidence that a minority of children infected with SARS-CoV2 may experience a severe multisystem inflammatory syndrome, called Multisystem inflammatory Syndrome associated with Coronavirus Disease 2019 (MIS-C). To date no universally agreed approach is available for this disease.

Main body: as Italy is now facing a second hit of COVID-19 cases, we fear a recrudescence of MIS-C cases. We have, therefore, decided to prepare a report that will help clinicians to face this novel and challenging disease. We propose a diagnostic algorithm, to help case definition and guide work-up, and a therapeutic approach. MIS-C should be promptly recognized, based on the presence of systemic inflammation and specific organ involvement. Early treatment is crucial, and it will be based on the combined use of corticosteroids, high-dose immunoglobulins and anti-cytokine treatments, depending on the severity of the disease. Ancillary treatments (such as aspirin and thrombo-profilaxis) will be also discussed.

Conclusions: we propose a document that will help physicians to diagnose and treat MIS-C patients. Given the level of evidence available and the methodology used, this document should not be interpreted as a guideline; the final decision about the optimal management should still be taken by the caring physician, on an individual basis.
Introduction
Italy was the first Western country to be hit by the SARS-CoV-2 epidemic. To date, more than 943,000 cases have been diagnosed, with more than 41,192 deaths. Children accounted for around 2% of infections, with an estimated mortality rate of 0.2% [1]. These figures confirm the previous observation in China that children develop milder forms of the illness, compared to adults [2–4]. Nonetheless, there is now mounting evidence that a minority of children infected with SARS-CoV2 may experience a severe multisystem inflammatory syndrome, which has been named Pediatric Multisystem Inflammatory Syndrome temporally associated with Coronavirus Disease 2019 (MIS-C) in the US [5–7]. The latter term will be used in this paper. The clinical spectrum of MIS-C is wide, and children have been treated with a variable association of intravenous immunoglobulin (IV Ig), high-dose glucocorticoids, and anti-cytokine medications [8–13]. To date, although diagnostic and therapeutic recommendations have been proposed by various pediatric societies, no universally agreed approach is available [14, 15].

After the first epidemic peak, which began in late February, the national lockdown policy in Italy led to a drastic reduction of cases, that, however, have restarted growing in the recent weeks. As MIS-C cases have been mostly observed in the regions with the highest impact of SARS-CoV-2 infection, we fear a recrudescence of the disease throughout Italy. We have, therefore, decided to prepare a report that helps clinicians to face this novel and challenging disease. Given the limited information currently available and the methodology employed, this document should not be seen as a guideline, but simply as a set of clinical suggestions based on the existing literature and the personal experience of the authors.

Case definition
There are multiple case definition criteria for MIS-C [16]. We propose to consider MIS-C diagnosis in the presence of:
- A child or adolescent with Fever (> 38 °C) lasting for more than 24 h.
- + Signs/symptoms of at least 2 organs involvement
- + Laboratory work-up showing systemic inflammation (leukocytosis with neutrophilia, ESR and CRP (and PCT) increase, with or without lymphopenia
- + Exclusion of infection

a a recent exposure to SARS-CoV2 may be demonstrated in the majority of patients by means of nasal/pharyngeal swabs or serology. In case of high clinical suspicion, MIS-C diagnosis and treatment should not be delayed by a negative swab or serology. A personal history of close SARS-CoV contact is present in the majority of cases and may be sufficient to substantiate MIS-C hypothesis.

Fig. 1 A proposed diagnostic algorithm for children with suspected MIS-C. Please refer to the main text for further details.
**ORGAN INVOLVEMENT**

**HEART**
- In case of coronary dilation, we recommend to refer to related AHA definitions [17]
  - Hypotension. Please consider that some patients with MIS-C may have SHOCK as the presenting sign, or develop it rapidly during hospitalization. This shock is usually associated with capillary leak syndrome or is cardiogenic, without signs of hyperperfusion.
  - Myocarditis (in some cases there is only cardiac enzyme elevation, without ultrasound abnormalities)
  - Valvular insufficiency
  - Cardiac conduction abnormalities
  - Heart failure
  - Coronary abnormalities

**Respiratory**
- Nasal drip/congestion
- Pharyngodynia/pharyngitis
- Cough
- Thoracic pain
- Respiratory distress
- Acute respiratory failure

**Skin and mucous membranes**
- Polymorphous rash/perineal erythema
- Erythema of the palms and soles
- Induration of the hands and feet
- Cracked lips/strawberry tongue
- Nonexudative conjunctival injection
- Lymphnode enlargement

**Kidney**
- Renal failure
- Oliguria and/or anuria
- Oedema

**Gastrointestinal**
- Severe abdominal pain
- Diarrhea
- Nausea and/or vomiting
- Jaundice

**Musculoskeletal**
- Arthralgia
- Myalgia
- Arthritis

**Central nervous system (CNS)**
- Headache
- Irritability
- Meningism
- Confusion
- Seizures

As many of the signs and symptoms listed are not specific, MIS-C diagnosis should rely on a high index of suspicion and cautious clinical judgement, taking into account the patient’s history, the severity of organ involvement, the inflammatory markers level and other possible mimickers (Fig. 1).

**LABORATORY WORK-UP**

**First Step**
- Complete blood count: leukocytosis with lymphopenia is typical. In case of leukopenia, thrombocytopenia or anemia, consider sHLH*
- CRP: CRP elevation is typical
- Coagulation: Hyperfibrinogenemia

**Second Step**
- Should be performed in case hyperinflammation is confirmed by first step laboratory test, and in the presence of at least one typical clinical finding

**Case definition (Continued)**
- High lactates
- Complement consumption
- Gas
- Low
- Hypertriglyceridemia
- Myopathy

**Ancillary tests**
- As the main differential diagnosis is with sepsis, all possible tests to rule out infection should be performed, according to clinical suspicion. These may include (but should not be limited to) the following.
- **N.B.** MIS-C cases with (presumed) co-infection by EBV, Mycoplasma Pneumoniae, Staphylococcus aureus have been described. A positive test for infection should not exclude MIS-C diagnosis in case of high suspicion
- **Electrolytes:** hyponatremia may occur.
- **Liver function tests:** in case of abnormal liver function tests, consider sHLH*. MIS-C cases with gallbladder hydrops (that may cause hyperbilirubinemia) have been described.
- **Kidney function tests:** MIS-C cases with acute kidney injury have been described.
- **Blood gas analysis:** to assess gas exchange and the presence of metabolic acidosis. High lactates have been described in MIS-C patients without evidence of sepsis
- **Peripheral smear:** to look for schistocytes or Burr cells, denoting microangiopathy
- **Acute phase reactants:** high level of pro-calcitonin has been described in patients with MIS-C, in case of very high ferritin levels (with ESR fall and high CRP) consider sHLH*
- **Troponins and NTpro-BNP:** to rule out myocarditis, which is a very common finding. Troponin and NT pro-BNP should be first step labworks in case myocarditis is suspected.
- **Total protein and albumin levels:** hypoalbuminemia may occur
- **Triglycerides:** consider sHLH* in case of hypertriglyceridemia
- **CPK, LDT:** may indicate myopathy or cytolysis
- **C3, C4:** complement consumption may be seen
- **γGT:** together with LFTs may denote liver involvement
- **Amylase, Lipase:** pancreatitis may occur
- **Blood, urine, stool cultures**
- **Serologies:** for: EBV, Mycoplasma Pneumoniae, Coxsackievirus, Echovirus, Adenovirus, Influenza, VRS.
- In case of positive serologies, PCR testing should be obtained, whenever possible
- **Naso-Pharyngeal swabs** for viruses
Treatment (Continued)
treatment, in case of persistent disease activity 48 h after first-line treatment or in case of shHLH. 
ii. Anakinra: 2 mg/kg (max 100 mg) IV, pulse followed by continuous infusion at a total daily dose of no more than 12 mg/kg or 400 mg mg/dose) × 4/day (to be diluted in 100 sterile saline and administered in no more than 1 h) 
iii. Anakinra: 2 mg/kg (max 100 mg) IV pulse followed by continuous infusion at a total daily dose of no more than 12 mg/kg or 400 mg

Large-spectrum antibiotics: while waiting for microbiology tests
Acetylsalicylic acid: 5 mg/kg for at least 6–8 wks. In case coronary abnormalities are found, refer to AHA recommendations for Kawasaki Disease [17]
Proton Pump Inhibitor: as needed
Thromboprophylaxis with LMWH: since adults with COVID-19 are at high risk of thromboembolism, and given the high inflammatory state of children with MIS-C, it appears reasonable to start prophylaxis with LMWH. As per ISTH recommendations [20], risk stratification should be done based on D-Dimer and other known pro-thrombotic factors. In case of D-Dimer >5X normal values and/or presence of other known pro-thrombotic factors, Enoxaparin 100 UI/kg BID should be administered.
Eculizumab: in case of acute kidney failure and evidence of microangiopathy, consider treatment with eculizumab [21]

Since MIS-C is a post-infectious disease, it is conceivable to assume that symptoms have their onset when the viremic phase is ended. Nonetheless, it is difficult to clearly differentiate these two phases (viremic vs hyperinflammatory) in some clinical scenarios. We recommend to consider carefully the appropriate timing to start immunomodulatory treatment in such cases, to avoid interference with antiviral host response.

Conclusions
Since there is a resurgence of COVID-19 cases throughout Italy, we expect a rise in MIS-C patients over the next weeks. Although MIS-C has variable severity, the majority of patients are seriously ill. The clinical experience indicates that prompt recognition and timely treatment are crucial to achieve good outcomes. Given the frequent overlap of clinical manifestations between MIS-C and Kawasaki disease, patients with the hyperinflammatory syndrome have generally been treated with the therapeutic protocols used in Kawasaki disease. Since the available information does not allow to formulate well-established guidelines or recommendations for MIS-C treatment, and the long-
term sequelae of the illness are not yet known, we agree with the therapeutic regimens proposed and adopted so far. The final decision about the optimal management should be taken by the caring physician, based on the disease characteristics and severity of each individual patient.

Abbreviations
SARS-CoV2: Severe Acute Respiratory Syndrome – CoronaVirus 2; COVID-19: Coronavirus Disease 2019; PIMS-TS: Pediatric Multisystem inflammatory Syndrome temporally associated with COVID-19; MIS-C: Multisystem inflammatory Syndrome associated with Coronavirus Disease 2019

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References
1. Available from: https://www.epicentro.iss.it/proxy/unibs.it/coronavirus/bollettino/Infografica_10giugnoITA.pdf. Accessed 10 June 2020.
2. Garazzo S, Montagnani C, Dona D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Eurosurveillance. 2020;25(18):2000600 Available from: https://www.eurosurveillance.org/content/1028/7560-7917.ES.2020.25.18.2000600. Cited 2020 Jun 8.
3. Parisi N, Lenge M, Buonosono D. Children with Covid-19 in pediatric emergency departments in Italy. N Engl J Med. 2020;383(2):187–90.
4. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020;145(6). https://doi.org/10.1542/peds.2020-0702.
5. Royal College of Pediatrics and Child Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available from: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multiplesystem-inflammation-syndrome-20200501.pdf. Cited 2020 May 8.
6. Preparedness E. Emergency Preparedness and response multisystem in ammatory syndrome in children ( MIS-C ) associated with coronavirus disease 2019. CDCgov. 2020. p. 2019–21. Available from: https://emergency. cdc.gov/han/2020/han00432a.asp. Accessed 10 June 2020.
7. European Centre for Disease Control and Prevention. Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf.
8. Whitaker E, Barnford A, Kenny J, Kafourou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32511692. Cited 2020 Jun 17.
9. Verdino L, Maizza A, Gervasoni A, Martelli L, Ruggeri M, Cuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;0(0). Available from: https://linkinghub.elsevier.com/retrieve/pii/S014067362031103X. Cited 2020 Jun 14.
10. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MFB, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents. N Engl J Med. 2020. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32598831. Cited 2020 Jul 14.
11. Locardi F, Pruccoli G, Derina M, Parodi E, Taglietto M, Rosati S, et al. SARS-CoV-2-Induced Kawasaki-Like Hyperinflammatory Syndrome: A Novel COVID Phenotype in Children. Pediatrics. 2020;20201711. Available from: https://pubmed.ncbi.nlm.nih.gov.proxy.unib.it/32493816/. Cited 2020 Jul 14.
12. Wolff A, Mannarino S, Giaconet V, Camporesi A, Zuccotti G. Acute myocardial injury: a novel clinical pattern in children with COVID-19. Lancet Child Adolesc Health. 2020. Available from: https://pubmed.ncbi.nlm.nih.gov.proxy.unib.it/32497521/. Elsevier B.V. Cited 2020 Jul 14.
13. Belot A, Antona D, Renolleau S, Javouhey E, Hentgen V, Angoulvant F, et al. Diagnosis, treatment, and long-term management of Kawasaki disease 2019: CDCGOV; 2020. p. 2019–21. Available from: https://www.cdc.gov/han/2020/han00432a.asp. Cited 2020 Jun 8.
14. Harwood R, Allin B, Jones CE, Whitaker E, Ramnarayan P, Ramanavv AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2020;Available from: https://pubmed.ncbi.nlm.nih.gov.proxy.unib.it/32493816/. Elsevier B.V. Cited 2020 Oct 28.
15. Henderson LA, Cann SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. Arthritis Rheum. 2020;25(22). https://doi.org/10.2807/1560-7917. ArthritisRheum. 2020;0(0). Available from: https://pubmed.ncbi.nlm.nih.gov.proxy.unib.it/32497521/. Elsevier B.V. Cited 2020 Oct 28.
16. Harwood R, Allin B, Jones CE, Whitaker E, Ramnarayan P, Ramanavv AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health. 2020. Available from: https://linkinghub.elsevier.com/retrieve/pii/S014067362031103X. Cited 2020 Jun 14.
17. Tam H, El Tal T, Go E, Yeung RSM. Pediatric inflammatory multisystem syndrome temporally associated with COVID-19: a spectrum of diseases with many names. CMAJ. 2020;0(0). Available from: https://pubmed.ncbi.nlm.nih.gov.proxy.unib.it/32509809/. Cited 2020 Oct 28.
18. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation. 2017;135(17):e927–99. Available from: https://pubmed.ncbi.nlm.nih.gov.proxy.unib.it/32493816/. Elsevier B.V. Cited 2020 Oct 9.
19. Ravelli A, Minola F, Davi S, Horne AC, Bois F, Pistorio A, et al. Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A European league against rheumatism/Amereican college of rheumatology/Paediatric rheumatology international trials organisation collaborative initiative. Ann Rheum Dis. 2016;75(3):481–9.
20. Hunter JI, Horne AC, Aricò M, Egeler RM, Fillpovich AH, Imaiatsu S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic
lymphohistiocytosis, Pediatric Blood and Cancer. 2007 48:124–131. Available from: https://onlinelibrary-wiley.com.proxy.unibs.it/doi/full/10.1002/pbc.21039. John Wiley & Sons, Ltd. Cited 2020 Nov 23
20. Goldenberg NA, Sochet A, Albisetti M, Biss T, Bonduel M, Jaffray J, et al. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. J Thromb Haemost. 2020;18(11):3099–105 Available from: https://pubmed.ncbi.nlm.nih.gov/33174388/. Cited 2020 Nov 17.
21. Mahajan R, Lipton M, Broglie L, Jain NG, Uy NS. Eculizumab treatment for renal failure in a pediatric patient with COVID-19. J Nephrol. 2020; Available from: https://pubmed.ncbi.nlm.nih.gov/32981025/. Cited 2020 Nov 6.

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