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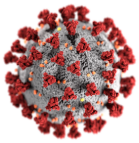
vACCine covid-19  monitoring readinESS

EVENT DEFINITION FORM

Event: multisystem inflammatory syndrome in children
Outcome/covariate: outcome
Version: 1
Status: final

Contributing authors

authors	Role	Date
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Carlos Durán	Rev. narrow/possible assignment	29-03-2021
Miriam Sturkenboom	Inclusion of codes used in final report	23-08-2021

1. Event definition

Multisystem inflammatory syndrome in children, also known as MIS-C, is a syndrome that appears to be a rare complication of COVID-19 in children. Where we first thought COVID-19 didn't affect children, it seems that children who were previously healthy can get severe ill from COVID-19. The syndrome is similar to incomplete Kawasaki disease (KD), a febrile illness of young childhood involving inflammation of the blood vessels that can result in coronary artery aneurysms. Symptoms often occur 1-6 weeks following infection with COVID-19 and may overlap with an acute respiratory COVID-19 presentation. [1]
If we look at the diagnostic criteria for KD and compare this with MIS-C there are some similarities and differences.

Diagnostic criteria for Kawasaki disease

The diagnosis of Kawasaki disease requires the presence of fever lasting at least 5 days* without any other explanation combined with at least 4 of the 5 following criteria:
Bilateral bulbar conjunctival injection
Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase)
Polymorphous rash
Cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter)

* If ≥4 of the above criteria are present, Kawasaki disease can be made on day 4 of illness.

Table 1. Diagnostic criteria for Kawasaki disease. [1]

MIS-C can be present similar to the criteria above, or at least some of them. Besides these symptoms, children can present with evidence of multi-organ failure. [3]
The main difference between KD and MIS-C is that classic KD typically affects infants and young children, whereas MIS-C affects mostly older children and adolescents. Children with MIS-C have a median age of 9 years old, which is 2.7 years for those with KD. Gastrointestinal symptoms are often dominant in children with MIS, whereas these symptoms are less prominent in classic KD. This also applies to myocardial dysfunction and shock, which occurs more commonly in MIS-C than in classic KD.
It is unclear if the risk of developing MIS-C varies by race. It seems to affect primarily people of African American, Caribbean and Hispanic ancestry, which is different from KD that mostly affects children of Asian ancestry. [5]

The presenting symptoms of MIS-C are the following: [1]

- Persistent fever
- Gastrointestinal symptoms like abdominal pain, vomiting and diarrhoea
- Rash
- Conjunctivitis
- Mucous membrane involvement
- Neurocognitive symptoms like headache, lethargy and confusion
- Respiratory symptoms, not prominent in most of the cases
- Swollen hands/feet
- Sore throat

Clinical findings when children are admitted to the hospital are the following: [1]

- Shock
- Criteria met for complete Kawasaki disease
- Myocardial dysfunction
- Acute respiratory failure requiring non-invasive or invasive ventilation
- Acute kidney injury
- Serositis (small pleural, pericardial and ascitic effusions)
- Acute hepatic failure

The distinction between KD and MIS-C can be made by the fact that MIS-C is COVID-19 associated. Some children have a positive serology for SARS-CoV-2 but have a negative PCR testing. Some children have it the other way around. [1,2]

The pathophysiology of MIS-C is not well understood. It has been suggested that the syndrome results from an abnormal immune response to the virus, with some similarities to KD, macrophage activation syndrome (MAS), and cytokine release syndrome. A post infectious process is suggested based on the timing of the rise of these cases relative to the peak of COVID-19 cases in communities. [6]

The WHO, the Center for Disease Control and Prevention (CDC) and Royal College of Paediatrics and Child Health (UK) came up with a case definition for MIS-C. There are some differences between these definitions. The CDC requires that the child has to have severe symptoms requiring hospitalisation, whereas the WHO case does not. An advantage of the WHO definition is that it provides more detail regarding clinical signs of multisystem involvement.
Another difference is that the WHO states that the child has to have fever for 3 or more days, whereas CDC states to have fever for 24 hours or more. [1,2]

The case definition put forth by the WHO is as follows: [2]
Age 0 to 19 years old
AND
Fever for ≥3 days
AND
Elevated markers of inflammation (e.g., erythrocyte sedimentation rate, C-reactive protein, or procalcitonin)
AND
No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal shock syndromes
AND
Evidence of SARS-CoV-2 infection (positive reverse transcription PCR [RT-PCR], antigen test, or serology) or contact with an individual with COVID-19
AND
Clinical signs of multisystem involvement (at least two of the following):

- Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
- Hypotension or shock
- Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/brain natriuretic peptide [BNP])
- Evidence of coagulopathy (prolonged prothrombin time or partial thromboplastin time; elevated D-dimer)
- Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

Note: after start of the study, the Brighton Collaboration was published (8)

3. Synonyms / lay terms for the event

Synonyms of multisystem inflammatory syndrome in children are: [1,3]

- MIS-C
- Pediatric multisystem inflammatory syndrome (PMIS)
- Pediatric inflammatory multisystem syndrome (PIMS)
- Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)
- Pediatric hyperinflammatory syndrome
- Pediatric hyperinflammatory shock
- Pediatric COVID-19 associated inflammatory disorder (PCAID)
- Kawasaki like disease
- Hyperinflammatory shock in children with COVID-19

4. Laboratory tests that are specific for event

Laboratory findings with reference ranges expressed in SI units, specified for children: [1]
Abnormal blood cell counts, including:

- Lymphocytopenia (1500-3000 x 10^6/L)
- Neutrophilia (3000-5800 x 10^6/L)
- Thrombocytopenia (150-400 × 10^9/L)

Elevated inflammatory markers, including:

- C-reactive protein (< 10 mg/L)
- Erythrocyte sedimentation rate (0-15 mm/h)
- D-dimer (<500 ng/mL)
- Fibrinogen (2.0-4.0 g/L)
- Ferritin (20-200 ug/L)
- Procalcitonin (0.01 ng/mL)
- Interleukin-6 (IL-6) (< 42 pg/mL)

These markers appear to correlate with severity of illness.

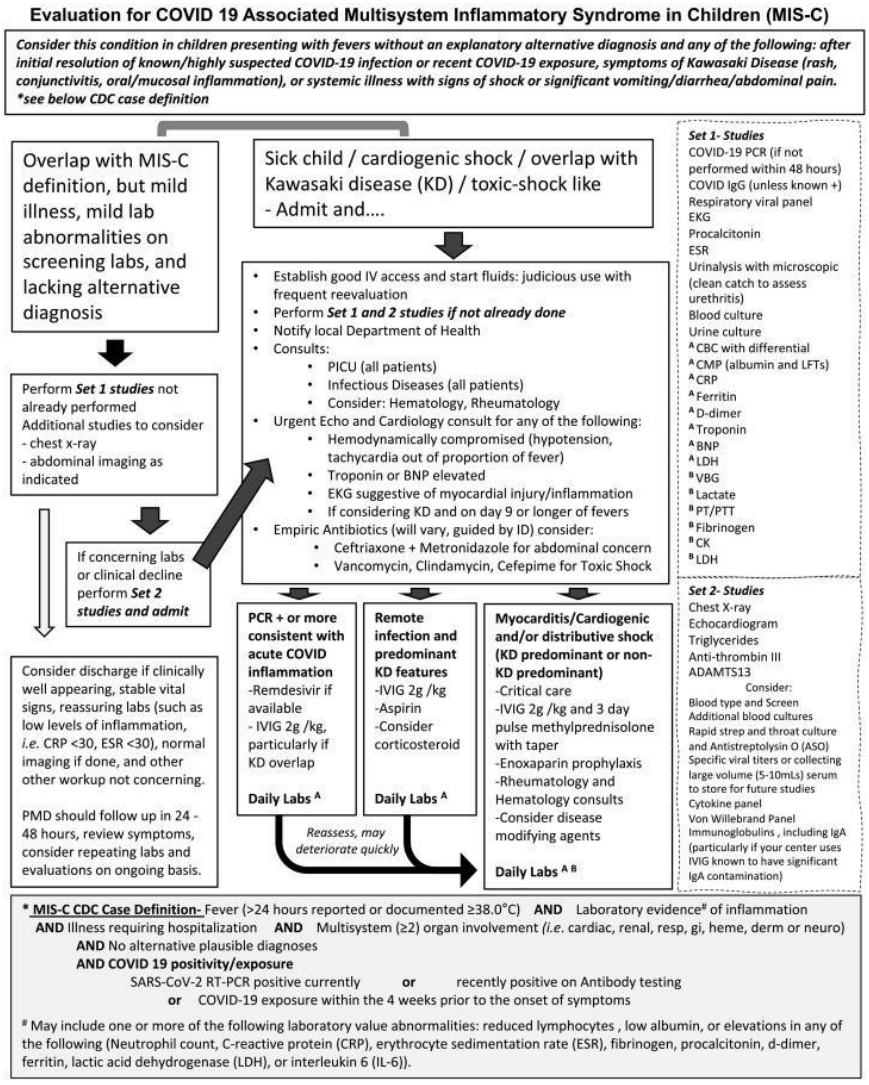
Elevated cardiac markers:

- Troponin (< 30 ng/L)
- BNP or NT-pro-BNP (<10 – 22 pmol/L or <15 pmol/L)

Hypoalbuminemia (35-55 g/L)
Mildly elevated liver enzymes (ALAT man: <50 E/L, vrouw: < 40 E/L, ASAT: <45 E/L)
Elevated lactate dehydrogenase (60-170 IU/L)
Hypertriglyceridemia (0.45-1.71 mmol/L)
Positive reverse transcription PCR [RT-PCR], antigen test, or serology to test for SARS-CoV-2 infection.
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 and/or adenovirus PCR.

5. Diagnostic tests that are specific for event

There has been created a guideline to diagnose MIS-C, which is shown below. It shows the different steps that have to be taken for diagnosis. [3]



Diagnostic tests used for MIS-C: [1]

Echocardiogram

- Depressed LV function: normal left ventricular ejection fraction ranges from 55% to 70%.
- Coronary artery dilatation/aneurysm, classified based on the classification of coronary artery abnormalities in children also used in KD. Dilatation only if Z score is 2 to <2.5 or initially <2 and a ≥ 1 decrease in Z-score during follow-up. Small aneurysm ≥2.5 to <5, medium aneurysm ≥5 to <10 and absolute dimension <8 mm and large aneurysm ≥10 or absolute dimension ≥8 mm. [7]
- Other findings can include mitral regurgitation and pericardial effusion.

Chest radiograph:

- Normal in many patients
- Abnormal findings included small pleural effusions, patchy consolidations, focal consolidation and atelectasis

Chest CT:

- Findings generally similar to those on chest radiograph
- A few patients have nodular ground-glass opacification

Abdominal imaging (ultrasound and/or CT):

- Findings are nonspecific, including free fluid, ascites, bowel and mesenteric inflammation, including terminal ileitis, mesenteric adenopathy/adenitis, and pericholecystic edema.

3. Drugs that are used to treat event

Antibiotic therapy: broad spectrum because symptoms overlap with severe bacterial infections.

- Milder illness: ceftriaxone
- GI symptoms predominant: ceftriaxone and metronidazole
- Severe illness or shock: vancomycin, clindamycin and cefepime or vancomyin, meropenem and gentamicin.

Add antiviral therapy especially when PCR positive for COVID-19 or symptoms similar to COVID-19: remdesivir IV, current proposed dose for children is 5 mg/kg load IV once (max dose 200 mg) on day 1, then 2.5 mg/kg (100 mg max dose) IV daily for nine days.
Adjunct therapies have been used because of the profound inflammatory response and KD-like features: IVIG, corticosteroids, anakinra (IL-1 inhibitor) and tocilizumab (IL-5 inhibitor).
For all patients with KD-like illness, evidence of excessive inflammation (ferritin >700 ng/mL, CRP >30 g/dL, or multisystem organ failure), or cardiac involvement we can give a therapy similar used for KD: aspirin 20-25 mg/kg/dose every 6 h (80-100 mg/kg/day) and IVIG 2g/kg. Children with KD-like illness in high-risk categories (infants, KD shock syndrome, CRP > 130 g/dL, admission echo Z score >2.5 or aneurysms, Asian race) should receive IVIG 2 g/kg as single infusion with a three-day pulse methylprednisolone. [3]

Treatment with intravenous diuretics and inotropic agents is necessary in patients with significant ventricular dysfunction, such as milrinone, dopamine and dobutamine.
Patients are at risk of experiencing thrombotic complications. Antithrombotic therapy is needed which includes low-dose aspirin and additional antiplatelet and/or anticoagulant therapy. [1]

6. Procedures used specific for event treatment

Children presenting predominantly with shock benefit from cardiac and respiratory support. [3]

7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

The setting patients present themselves with MIS-C is in the emergency room.

8. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA: seek literature for papers that have studied this event, and see how they extracted/measured the event.

There is no specific code for MIS-C yet. The disease is similar to Kawasaki disease and the code for this disease is the following:
ICD-10-CM M30.3 mucocutaneous lymph node syndrome (Kawasaki)

9. Codes used in ACCESS

Coding system	Code	Code name	Concept	Concept name	Algorithm
ICD10/CM	M30.3	Mucocutaneous lymph node syndrome [Kawasaki]	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
ICD10/CM	R57.9	Shock, unspecified	C0036974	Shock	Possible
ICD9CM	446.1	Acute febrile mucocutaneous lymph node syndrome [MCLS]	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
ICD9CM	785.50	Shock, unspecified	C0036974	Shock	Possible
ICPC2P	B99022	Disease;Kawasaki	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
RCD	G7510	Kawasaki's disease	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
RCD	G751z	Acute febrile MCLS NOS	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
RCD	R0550	[D]Failure of peripheral circulation	C0036974	Shock	Possible
RCD	XM00r	Shock - physiological	C0036974	Shock	Possible
RCD	XM1C7	Shock, unspecified	C0036974	Shock	Possible
RCD2	G7510	Kawasaki disease	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
RCD2	G751z	Acute febrile MCLS NOS	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
RCD2	R0550	[D]Failure/peripheral circul.	C0036974	Shock	Possible
SCTSPA	27942005	choque	C0036974	Shock	Possible
SCTSPA	75053002	enfermedad de Kawasaki	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
SCTSPA	195349001	síndrome ganglionar mucocutáneo febril agudo, SAI	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
SCTSPA	207026006	[D]insuficiencia circulatoria periférica	C0036974	Shock	Possible
SCTSPA	274729009	choque, no especificado	C0036974	Shock	Possible
SNOMEDCT_US	27942005	Shock	C0036974	Shock	Possible
SNOMEDCT_US	39419009	[D]Hypovolaemic shock			possible
SNOMEDCT_US	75053002	Acute febrile mucocutaneous lymph node syndrome	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
SNOMEDCT_US	155444003	Kawasaki's disease	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
SNOMEDCT_US	158354004	[D]Failure of peripheral circulation	C0036974	Shock	Possible
SNOMEDCT_US	195348009	Kawasaki's disease	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
SNOMEDCT_US	195349001	Acute febrile mucocutaneous lymph node syndrome NOS	C0026691	Mucocutaneous Lymph Node Syndrome	Narrow
SNOMEDCT_US	207026006	[D]Failure of peripheral circulation	C0036974	Shock	Possible
SNOMEDCT_US	267302008	Shock	C0036974	Shock	Possible
SNOMEDCT_US	274729009	Shock, unspecified	C0036974	Shock	Possible

11. Algorithm proposal

Broad algorithm:

- Code from concept sets (Kawasaki, Shock) those classified as possible and narrow
- Index date = date of the first occurrence of a code

Narrow algorithm:

- Code from concept sets classified as narrow
- Index date = date of the first occurrence of a code from the concept set Kawasaki 12. Background rates

We used the following search string: *"pediatric multisystem inflammatory disease, COVID-19 related" [supplementary concept] OR "MIS-C" [tw] OR "pediatric multisystem inflammatory syndrome" [tw] OR "PMIS" [tw] OR "PIMS" [tw] OR "PIMS-TS" [tw] OR "Kawasaki like disease" [tw] AND ("incidence" [tw]) NOT (Comment [ptyp] OR Editorial[ptyp] OR News[ptyp] OR Newspaper Article[ptyp]) NOT ("animals"[Mesh] NOT "humans" [Mesh]) AND English [lang].* Filters: abstract, English and from 2010 – 2020.

MIS-C is related the SARS-CoV-2 and therefore there are no incidence rates known before this time period.

13. References

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