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Multisystem inflammatory syndrome in children and adolescents (temporally related to COVID-19)

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EMA 25 years

Enpr-EMA
Monday 28 September 2020

An agency of the European Union

Nomenclature

PIMS-TS (Paediatric Inflammatory Multisystem Syndrome- Temporally associated with SARS-Cov-2

- **RCPCH:** *persistent fever, inflammation, and evidence of single or multi-organ dysfunction in a child, with exclusion of any other microbial cause, with or without PCR evidence of SARS-CoV-2*

- **ECDC :** *dissemination of UK definition to paediatric surveillance units (May 2020)*

MIS-C (Multi-Inflammatory Syndrome in Children)

- **WHO:** SARS-CoV2 PCR may be positive or negative
- **CDC:** requires confirmation of infection or contact

Currently getting most commonly used terminology

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Approximately 1000 cases reported worldwide (end of June 2020)

World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Whittaker E, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. Published online June 08, 2020.

Epidemiology

- Observational study in children admitted to PICUs in UK between April 1-May 10, 2020
- PIMS-TS ICU admission compared with historical PICU admissions for Kawasaki, TSS, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- 78 PIMS-TS in 21/23 PICUs in UK = avg. 14 admissions/week
- Historical data for similar inflammatory conditions showed average 1 (95% CI 0·85-1·22) admission/week
- Prevalence of afro-Caribbean and Asian ethnicity

Davies P, et al. Lancet Child Adolesc Health. 2020.

	Patients (n=78)
Sex	
Female	26 (33%)
Male	52 (67%)
Age groups	
<1 year	2 (3%)
1–4 years	5 (6%)
5–10 years	29 (37%)
11–15 years	38 (49%)
16–17 years	4 (5%)
Median age, years	11 (8–14)

SARS-CoV-2 antigen PCR positive	17 (22%)
SARS-CoV-2 antigen PCR negative	61 (78%)
SARS-CoV-2 IgG serology in PCR positive patients	
Positive	9/10 (90%)
Negative	1/10 (10%)
Not tested	7/17 (41%)
SARS-CoV2 IgG serology in PCR negative patients	
Positive	24/25 (96%)
Negative	1/25 (4%)
Not tested	36/61 (59%)
PCR negative, serology negative, without known COVID-19 contact (ie, met PIMS-TS criteria, did not meet MIS-C criteria)	1/78 (1%)
PCR negative, serology unknown, without known COVID-19 contact (met PIMS-TS criteria, unknown whether would meet MIS-C criteria)	32/78 (41%)

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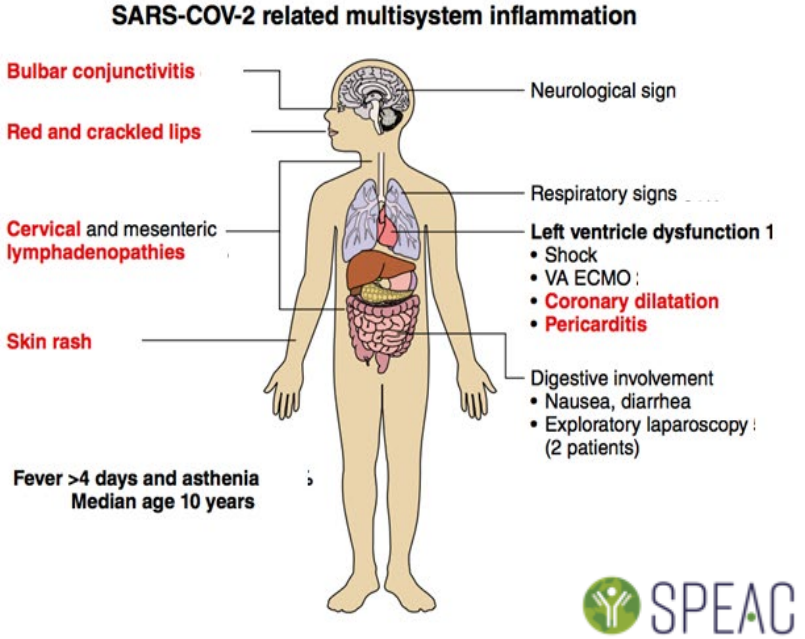
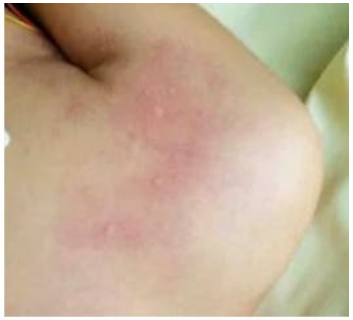
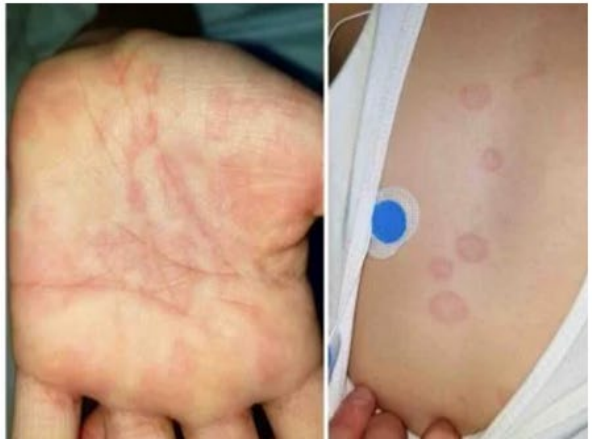
SARS-CoV-2 Related Multisystem Inflammation in Children

(Belhadjer Circulation 2020 May 17; https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.048360)







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Main emerging features

Table 2. Laboratory, Echocardiogram, and Imaging Characteristics of COVID-19–Related Multisystem Inflammatory Syndrome in Children (N = 17)

Characteristic	Value
Echocardiogram findings, No. (%)	
Left ventricular function by echocardiogram at admission, No. (%)	
Normal	6 (35)
Mildly decreased	5 (29)
Mild-moderately decreased	4 (24)
Moderate-severely decreased	2 (12)
Pericardial effusion on admission echocardiogram[a]	8 (47)

- Occurs 2 to 4 weeks after infection with SARS-CoV-2
- uncommon (2 in 100,000 persons <21 years of age) compared with SARS-CoV-2 infection diagnosed in persons younger than 21 years of age over the same period (322 in 100,000)
- Most patients with MIS-C have antibodies against SARS-CoV-2, and virus is detected in a smaller proportion
- relatively high proportion among black, Hispanic, or South Asians
- Critical illness leading to intensive care develops in some patients, with prominent cardiac involvement and coronary-artery aneurysms in 10 to 20
- Cardiac sequelae?

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Laboratory features

- elevated C-reactive protein, D-dimer, and ferritin, troponin, and lymphopenia
- US case series: Serum IL-6 level was elevated in 16/17 patients
- Cytokine profile in 8 patients: elevated IL-2R, IL-18, and CXCL 9 levels in all and mildly increased IFN-γ (n = 3) and IL-8 (n = 2) levels in some. TNF-α, IL-1b, Il-2, IL-4, IL-5, and IL-13 levels were normal

	May not have met MIS-C definition* n=33 (42%)	Met MIS-C definition N=45 (58%)
Age (median)	12 (6-14)	10.25 (8-13)
Male Sex M:F	23/33 (70%)	27/45 (60%)
Non-Caucasian	25/33 (76%)	36/45 (80%)
Highest CRP (mg/L, IQR)	256 [175-319]	251 [192-307]
Lowest Platelet count (x10^9/L)	125 (82-172)	151 (93-208)
Lowest Lymphocyte count (x10^9/L)	0·68 [0·45-0·85]	0·80 [0·41-1·1]
Highest Ferritin (µg/L, IQR))	1112 (548-2059)	958 (516-1554)
Highest Troponin (ng/L, IQR)	72 (26.5-330)	167 (41-1112)
Highest D Dimers (ng/L, IQR))	4635 (2070-7545)	3750 (2106-6958)
Rash	12/33 (36%)	21/45 (47%)
Conjunctivitis	8/33 (24%)	14/45 (31%)
Shock	26/33 (79%)	42/45 (93%)
Invasively ventilated	11/33 (33%)	25/45 (56%)
Inotropic infusion	82/33 (86%)	38/45 (84%)
Given IVIG	26/33 (79%)	33/45 (73%)
Given steroids	22/33 (67%)	35/45 (78%)

*of the 33 patients, 32 were untested, therefore their MIS-C status was indeterminate. 1 patient would definitely not have met MIS-C criteria

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Treatment

- Overall response to existing treatments seems good
- US cases (17): 15 required PICU; vasoactive support in 10. None required MV
- 14 received steroid treatment (methylprednisone 2-30 mg/kg; hydrocortisone (2 mg/kg ; prednisone)
- 13 received IVIG (2-4 g/kg), including 3 who did not receive steroids and 8 who met criteria for KD. One patient received tocilizumab
- Anti-TNF and anti IL1 also reported

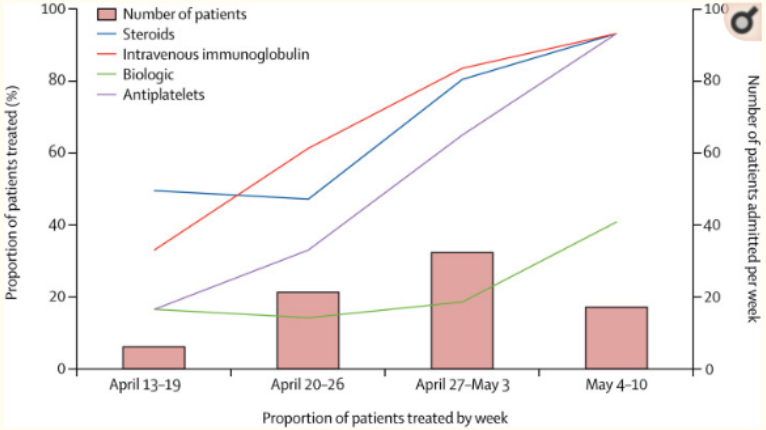

Figure 2

Number of patients with PIMS-TS admitted to UK paediatric intensive care units, and percentage receiving individual treatments over time

Weeks with fewer than three patients were excluded. Biologic refers to any of anakinra, infliximab, tocilizumab, or retiximab. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

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Considerations and Questions

- Need of common definitions/clinical entity (also for monitoring MIS-C as potential adverse event of vaccination)
- Is there any unmet need of treatment in Mis-C?
- If so, which type of treatment, and would clinical trials be feasible?

Differences between children with MIS-C and COVID-19.

	MIS-C	COVID-19
GENERAL INFORMATION		
Total number of patients	662	7780
Dates included	January 1, 2020 - July 25, 2020	December 1, 2019 - May 14, 2020
Number of studies	39	131
Data source	Multi-national	Multi-national
DEMOGRAPHICS		
Age	9.3 ± 0.5	8.9 ± 0.5
mean ± SD	[n = 528]	[n = 4517]
Male gender%	52.3	55.6
	[n = 662]	[n = 4640]
Comorbidity%	48.0	35.6
	[n = 558]	[n = 655]
OUTCOME		
Length of hospitalization	7.9 ± 0.6	11.6 ± 0.3
mean ± SD		
	[n = 423]	[n = 652]
Intensive care unit admission	470 (71.0)	116 (3.3)
In (%)	[n = 662]	[n = 3564]
Shock	398 (60.1)	19 (0.24)
In (%)	[n = 662]	[n = 7780]
Mechanical ventilation	147 (22.2)	42 (0.54)
In (%)	[n = 662]	[n = 7780]
Aneurysm	47 (7.1)	
In (%)	[n = 662]	–
Death	11 (1.7)	7 (0.09)
In (%)	[n = 662]	[n = 7780]

https://www.thelancet.com/action/showPdf?pii=S2589-5370%2820%2930271-6

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Any questions?

Further information

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