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The "perfect" storm: Current evidence on pediatric inflammatory multisystem disease during SARS-CoV-2 pandemic

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Summary. Current data suggest that during the global pandemic of COVID 19 children are less affected than adults and most of them are asymptomatic or with mild symptoms. However, recently, cases of pediatric patients who have developed severe inflammatory syndrome temporally related to SARS-CoV-2 have been reported both in USA and Europe. These reports, although sharing features with other pediatric syndromes such as Kawasaki disease (KD), Kawasaki disease shock syndrome (KDSS), macrophage activated syndrome (MAS) and shock toxic syndrome (TSS), seem to outline a novel entity syndrome, characterized by cytokine storm with elevated inflammatory markers and typical clinical finding. Clinical characteristics are greater median age than KD, higher frequency of cardiac involvement and gastrointestinal symptoms, lower frequency of coronary anomalies. We report a summary of the current evidence about clinical features, pathogenesis, therapy strategies and outcome of this novel syndrome.

Background

December 2019, Wuhan, China: a novel virus caused the first cases of pneumonia. Since then, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide, leading the World Health Organization to declare the global pandemic on 11th March 2020. As of 26 July 2020, the WHO reported 15.785.641 cases with over 640.016 deaths.

Compared to adults, children initially seemed to be less affected and to develop a milder disease. Since the end of April 2020, however, several reports have described the occurrence in children of a severe multisystem inflammatory syndrome resembling Kawasaki disease, temporally related to COVID-19 infection. It is not already clear if this is a distinct clinical entity. The present review aims to summarize the recent literature about this topic.

Methods

A literature search was conducted using Pubmed. The terms *Children* AND *COVID-19* OR *coronavirus* AND *inflammatory syndrome* OR *Kawasaki disease* were used, and filters including only articles about the pediatric population. Most of the publications were single case reports, small case series or literature reviews.

Covid-19 in Children

The real prevalence of SARS-COV-2 infection in children is not unknown.

One of the first epidemiologic studies comes from China, the source of the pandemic: of the 2143 pediatric patients reported by Dong et al., the majority were asymptomatic or with mild to moderate symptoms (1). The percentage of patients with severe forms was significantly lower than adults (5.9% vs 18.5%, $p<0,05$) with the highest peak of severe forms in the category 0-5 years and a very low mortality rate (0.1%) (1). It has been supposed that the lower severity of the pediatric forms was associated with environmental factors (lower exposure to pathogenic agents) and immunogenic factors (developing immune system, lower expression of Angiotensin Converting Enzyme 2 receptors, ACE2, on the target tissues) (2), but reasons for this difference remain to be determined.

A more recent systematic review analyzed 18 Chinese studies with 1065 participants (444 patients were younger than 10 years, and 553 were aged 10 to 19 years) with confirmed SARS-CoV-2 infection (3). The authors concluded that the most common pediatric presentation of COVID-19 was an array of signs and symptoms, from completely asymptomatic to symptoms of acute upper respiratory tract infection such as fever, fatigue, cough, sore throat, rhinorrhea and congestion, and shortness of breath. Compared to adults, children rarely progressed to severe upper respiratory symptoms requiring intensive care unit admission. Also, cutaneous features have been described in children in relation to SARS-COV-2 infection, with peculiar attention on chilblains, one of the hallmarks of some rheumatologic disorders (4).

However, data underline that COVID-19 may have a non-negligible rate of severe presentation especially for children with comorbidities, as seen by two Italian research networks published by Parri et al.(5)

Although most children have an uneventful course, reports from Europe and America presented concern about an inflammatory cascade in pediatric patients with COVID-19, whose clinical presentation overlaps with Kawasaki disease (KD), macrophage activated syndrome (MAS), Kawasaki disease shock syndrome (KDSS) or toxic shock syndrome (TSS) (6-11).

Kawasaki Disease

KD is a rare acute vasculitis of the medium and small vessels. According to the Italian guidelines published in 2018, (12) diagnostic criteria of typical or complete KD are the presence of > 5 days of fever and > 4 of the followings: bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in extremities, skin rash and cervical lymphadenopathy.

Incomplete KD occurs in patients presenting a typical fever without a sufficient number of main clinical criteria, while atypical KD presents the typical fever associated to signs and symptoms that differ from the classical ones (meningeal inflammation, gastrointestinal symptoms, acute abdomen, arthritis, pneumonia,…).

A small percentage of patients can develop a more severe form of KD, known as KDSS, and defined on the basis of systolic hypotension for age, sustained decrease in systolic blood pressure from baseline of >20% or clinical signs of poor perfusion.

KD has potential serious cardiac complications, as the coronary artery aneurisms (CAA), and remains the primary cause of acquired heart disease in developed countries.

The etiology is still unclear, although it is believed to be a strong inflammatory response to an infectious trigger in genetically predisposed individuals. Evidence of a viral role in triggering KD is suggested by seasonal epidemic trend (13).

A number of viruses have been implicated in KD etiology, and coronavirus family has been proposed as possible related cause. The identification of a higher percentage of new coronavirus (HCoV-NH) in the respiratory secretions of patients with Kawasaki than controls (72% vs 4,5%) was described by Esper et.al (14), but subsequent studies gave conflicting results (15, 16).

The possible role of SARS-COV-2 in pathogenesis of 'classic' KD is still missing, but current evidence does not seem to support this hypothesis.

Clinical Features: An Overlapping Syndrome

Jones et al. described the first case of concurrent COVID-19 and Kawasaki disease: the authors just detailed the case of a 6-month-old infant, who presented all the criteria for complete KD and also positive RT-PCR testing for COVID-19. The patient was successfully treated with IVIG and acetylsalicylic acid (7).

Since the end of April 2020, several case reports from Europe and US described children presenting a severe inflammatory syndrome temporally related to SARS-CoV 2 infection, and overlapping with KD, MAS[17], KSS(18) and TSS(19) (Table 1).

This occurrence led to alerts and guidelines from various scientific societies, which used different acronyms: the Royal College of Pediatrics and Child Health ((RCPCH)(20) defined PIMS-TS acronym (Pediatric Inflammatory Syndrome Temporally associated with SARS-CoV-2); the Centers for Disease Control and Prevention (CDC)(21) described this syndrome under the label MIS-C (Multisystem Inflammatory Syndrome in Children). Also, the Italian Istituto Superiore di Sanità published recommendations on the topic at the end of May 2020 (22).

Table 2 summarizes case definitions and diagnostic criteria proposed by the scientific societies.

The first reports appeared in UK (8, 23) and Italy (6, 10) followed by France (9, 11, 24, 25), New York and other regions of the US (7, 26).

The first case series from UK showed a cluster of 8 patients with hyperinflammatory shock, which required inotropic support (8). The majority of these cases were of Afro-Caribbean origins; clinical presentations were similar to classic KD, with significant gastrointestinal involvement, while laboratory findings detailed high inflammatory indices and myocardial injury. One of these patients died, due to cerebrovascular accident that followed extracorporeal membrane oxygenation (ECMO).

Moreover, Ramcharan et al. performed a retrospective study, and described 15 cases over 1-month-study period (23). Clinical and biochemical features were similar: median age of 8.8 years, Afro-Caribbean or South Asian origins, predominant gastrointestinal symptoms (87%) cardiac involvement (100%) and shock/hypotension signs (67%). In these series many coronary abnormalities (53%) were detailed, such as prominent, dilated or aneurysmal coronaries, but in about half of the cases, they normalized before discharge.

The Italian case series from Bergamo described 10 patients admitted to the emergency department during COVID-19 pandemic and diagnosed as KD (6). The cases were compared with a historical cohort of KD patients: the first, named Kawasaki-like, were older (mean age 7.5), had respiratory and gastrointestinal involvement, meningeal signs, and signs of cardiovascular impairment. From a biochemical perspective, they had leucopenia with marked lymphopenia, thrombocytopenia, and increased ferritin, as well as elevated markers of myocarditis. Comparing epidemiologic data, the authors reported a monthly incidence at least 30 times greater than the previous 5 years. Kawasaki-like patients had a more severe disease course, with resistance to intravenous immunoglobulin (IVIG) and need of adjunctive steroids, biochemical evidence of MAS and clinical signs of KDSS.

Moreover, Licciardi et al. detailed two case reports, 12-years-old and 7-years-old boys, presented to the Pediatric Department of Turin (Italy) in mid-April 2020, both featuring an hyperinflammatory syndrome and evidence of previous SARS-CoV-2 infection (high IgG titers) (10). These cases share clinical and laboratory findings. The authors tried to divide the syndrome in 3 different clinical phases: in phase 1 the patient had high fever, gastrointestinal symptoms and elevated inflammatory markers, mimicking gastrointestinal bacterial infection; phase 2 was characterized by mucocutaneous involvement resembling KD, but also progressive thrombocytopenia and capillary leak syndrome (not frequent in KD) with hypoalbuminemia, diffuse edema, hypotension requiring fluid resuscitation therapy; lately, myocarditis appeared (phase 3), with slow improvement of cardiac function. Licciardi et al. underlined an overlapping between this disease and KD complicated with MAS, with some differences: absence of coronary involvement, development of myocardial dysfunction and rapidly progressive capillary leak syndrome. Interestingly, authors noted similarities between this syndrome and Feline Infectious Peritonitis, a fatal immune-mediated disease, characterized by fluid accumulation in body cavities,

Table 1: Comparison between syndromes than can overlap with new reported pediatric Covid-19 cases (Paediatric Inflammatory Syndrome Temporally associated with SARS-CoV-2 -PIMS-TS/ Multisystem Inflammatory Syndrome in Children-MIS-C

	Inflammatory Syndrome SARS-CoV-2 Probably Related	**Typical Kawasaki Disease**[12]	**Kawasaki Disease Shock Syndrome**[18]	**MAS syndrome**[17]	**Toxic Shock Syndrome**[19]
Fever	Persistent	Persistent > 5 days	Persistent	High, no remitting	High
Clinical features	Possible fulfils criteria for complete KD, more often incomplete/atypical **(IMPORTANT HIGHER MEDIAN AGE: >5 years)** **Frequent abdominal pain, hypotension** or clinical signs of poor perfusion, **cardiac involvement (myocarditis)** Possible neurological signs (headache/confusion)	**TYPICAL AGE < 5 years** > 4 of the followings: bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in extremities, skin rash, cervical lymphadenopathy	Fulfils criteria for Kawasaki disease (typical/atypical/incomplete) + Systolic hypotension or decrease in systolic blood pressure from baseline of ≥20% or Clinical signs of poor perfusion	Hepatosplenomegaly, Generalized lymphadenopathy, Central nervous system dysfunction, Hemorrhagic manifestations	Nausea/vomiting, Abdominal pain/ diarrhea Myalgia Headache/confusion Rash (diffuse macular erythroderma)/ desquamation/ soft tissue necrosis, Multi-organ involvement (myocardial, renal, ARDS)
Laboratory tests	Elevated CRP, PCT, neutrophilia Frequent elevated ferritin, D-Dimers, I-Troponin Possible: **low platelet counts, lymphopenia** hypoalbuminemia, increased levels of liver enzymes	Elevated WBC, CRP, ERS, Thrombocytosis (second phase), Possible: anemia, hypoalbuminemia, hyponatremia, increased levels of liver enzymes	More elevated WBC, CRP, PCT, BNP, troponin I ferroprotein than KD patients. + Coagulopathy signs: Low platelet counts (<150 × 109 cells per L), High D-dimer results, prolonged partial thromboplastin times for age	Elevated ferritin, liver enzymes, LDH, triglycerides, D-dimers, CRP + Pancytopenia, Low fibrinogen levels	Elevated WBC, CRP, PCT, liver enzymes Low platelet counts (<100 × 109 cells/L) or coagulopathy signs as disseminated intravascular coagulation

Cardiac involvement	**Coronary dilatation less frequent than Kawasaki** **Myocarditis and Hemodynamic instability more frequent than Kawasaki**	Untreated: 25-40% coronary dilations and aneurysm. Pericarditis 18%, myocarditis 3% Hemodynamic instability unusual in acute phase	More-severe abnormalities measures of coronary artery more frequently low ejection fractions and mitral regurgitation/ myocarditis	Uncommon	Hypotension/ Myocardial dysfunction if progressive multiorgan failure
Etiology	Abnormal immune response to SARS-CoV2? Sars-CoV2 with direct trigger action?	Unknown (infectious agent? Host genetic factors?)	Unknown (Overstated inflammatory responses favored by host factors?)	Systemic inflammatory disorders most commonly in systemic juvenile idiopathic arthritis (JIA) or other autoimmune/ auto inflammatory conditions, (SLE, Kawasaki, periodic fever, syndromes), possible infectious trigger EBV, CMV, Mycoplasma.	Super antigenic toxins by Staphylococcus aureus or Streptococcus pyogenes
Therapy	Proposed: IVIG, aspirin, steroids, other immunomodulatory Treatment for shock: volume resuscitation +/- infusions of vasoactive agent	First line: IVIG 2mg/kg + aspirin Second line: second dose IVIG, steroids	Kawasaki therapy + Treatment for shock: volume resuscitation +/- infusions of vasoactive agent	First line: IV methylprednisolone 30mg/kg (max 1 gr) for 3 days Second line: cyclosporine, anakinra, rituximab.	Antibiotic therapy +/- Treatment for shock: volume resuscitation +/- infusions of vasoactive agent
Outcomes	Extremely low death rate	Good if properly treated	Cardiovascular disturbances resolved with therapy, abnormal ventricular diastolic function persisted in chronic phase	Possible evolution with progressive multi-organ failure and eventually a fatal outcome if unrecognized. mortality rate of 8%	Mortality 5-10% with streptococcal TSS, 3–5% for staphylococcal TSS
CRP: C reactive protein; **PCT**: procalcitonin, **WBC**: white blood cells, **ESR**: erythrocyte sedimentation rate; **BNP**: brain natriuretic peptide, **KD**: Kawasaki disease. **IVIG**: intravenous immune globulin					

Table 2: Comparison between guidelines and diagnostic criteria proposed by RCPCH, CDC and ISS.

	Name	Clinical Features	Additional Features	Laboratory Test	Single or Multi-organ Dysfunction	Other Evalu-Ation	Therapy proposed
Royal College of Pediatrics and Child Health (RCPCH)	Pediatric Inflammatory Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS)	Persistent fever >38,5°C +- hypotension +- Oxygen requirement	Rash Conjunctivitis Lymphadenopathy Mucus membrane changes Abdominal pain Diarrhea Headache Confusion	Neutrophilia, lymphopaenia, hypoalbuminemia, elevate CRP, D-dimers, ferritin Abnormal Fibrinogen	PRESENT (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder)	Echocardiogram and ECG Possible finding: Myocarditis, valvulitis pericardial effusion, coronary artery dilatation	Consider IVIG early if fulfils criteria for Kawasaki Disease (+aspirin) or toxic shock syndrome Immunomodulatory therapy should be discussed
Centers for Disease Control and Prevention (CDC)	Multisystem Inflammatory Syndrome in Children (MIS-C)	Fever >38°C for ≥24 hours And fatigue	Evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement	Neutrophilia, lymphopenia, hypoalbuminemia, Elevate CRP, ESR, D-dimer, ferritin fibrinogen, PCT, LDH, or IL-6	PRESENT (Cardiac, gastrointestinal, renal, hematologic, dermatologic, neurologic involvement)	ECG, Echocardiogram, altered cardiac enzyme (troponin) and BNP	Fluid resuscitation; inotropic support; respiratory support; Anti-inflammatory measures (IVIG, steroids)
Italian Istituto Superiore di Sanità (ISS)	acute multisystem inflammatory syndrome in children and adolescents	Fever > 38°C +/- Shock, myocarditis, gastrointestinal involvement, MAS	Classical finding of Kawasaki disease (rash, conjunctivitis, lymphadenopathy, mucus membrane changes)	neutrophilia, lymphopenia, anemia, thrombocytopenia, Elevated CRP, D-dimer, ferritin, BNP	PRESENT (especially cardiac and gastrointestinal involvement)	not specified	Consider IVIG early if fulfils criteria for Kawasaki Disease, additional use of corticosteroids if the state persists
No alternative plausible diagnoses; AND positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.							
CRP: C reactive protein; **PCT:** procalcitonin, **WBC:** white blood cells, **ESR:** erythrocyte sedimentation rate; **BNP:** brain natriuretic peptide, **LDH:** lactic acid dehydrogenase, **IL6:** interleukin 6							

as a consequence of immune complex deposition and macrophage activation. Interestingly, gastrointestinal symptoms in KD have been previously related to a more severe course of the disease, with higher rates of IVIG-resistance (27).

Similar clinical and biochemical characteristics, treatment and outcome are detailed in French case series, which contain information about 21 cases (11) plus 16 cases (25), occurred in Paris. The authors underlined age greater than 5 years and elevated ferritin (> 1400 mcg/l) as features of severe prognostic value (25).

In addition, Belhadjer et al. reported 35 cases of children with acute heart failure and severe inflammatory state from France and Switzerland (9). Despite a similar presentation, comorbidities were found in 28% of the cases, especially asthma and overweight, this latter already reported as risk factor in other reports (11.25). During the same period, 100 cases with similar presentation were identified from the New York State Department of Health.

We also reported here the case series from Chiotos el al. (25). Although the clinical signs similar to the previous case series, this time patients also presented with a high percentage of neurological involvement (4:6 66%) (Table 3).

Myocardial implications seem to be a hallmark of this hyper-inflammatory state, whereas coronary aneurysms are the hallmark of KD.

Therefore, despite some similarities, there are epidemiological clinical and laboratory evidences supporting the concept of a new syndrome, separated from KD and also from MAS and TSS.

Pathogenesis

Almost all of the patients described showed positivity to IgG antibodies for SARS-CoV-2, while only a little percentage was found positive to nasopharyngeal swab: these findings suggest a late onset of the disease compared with the primary infection, due to the host immune response.

Increasing evidence is suggesting that tissue damage in COVID-19 is mostly mediated by the host innate immunity, which activates a cytokine storm resembling the macrophage activation of the viral-induced hemophagocytic lymphohistiocytosis (28, 29). New evidences of the COVID-19 immune response appear to emerge from a recent histopathology study (30) The authors reported the unbalance escalation from Th2 immune response to type 3 hypersensitivity, with the subsequent deposition of antigen-antibody complexes particularly inside the walls of blood vessels, the activation of complement factors (C3a and C5a) and the release of cytokines able to generate an acute necrotizing vasculitis.

A cytokine storm syndrome with increased levels of inflammatory markers such as IL-6 was described in adults with COVID-19, and it has been associated with fatality (31). This storm is reflected clinically by heart failure, pneumonia, gastrointestinal, neurological and renal features, associated with elevated CRP levels, ferritin and cytokines (IL-1, IL-6, TNFalfa).

Genetic studies investigating the susceptibility of patients developing the severe disease triggered by SARS-CoV-2, should be performed.

Epidemiology

Precise epidemiological data regarding the inflammatory syndrome temporally related to SARS-CoV-2 are not yet available, but several countries including Italy, France, Spain and UK have started national registries.

The first results from French national surveillance reported 108 PIMS cases from 1 March to 17 May (24). The epidemic curve revealed a sharp increase in incidence after 13 April, culminating 4-5 weeks after the peak of the COVID-19 epidemic in France, and decreasing thereafter. These results, together with the correlation between geographical distribution of COVID-19 cases and Kawasaki-like patients, support a causal relationship between SARS-CoV-2 infection and PIMS. The timing of 4-5 weeks supports the hypothesis of PIMS being a post-infectious manifestation. One death was recorded in this case series.

The absence of reported cases of Kawasaki-like multisystem inflammatory syndrome associated with SARS-CoV-2 infection in Asia countries where the COVID-19 pandemic started, and where the incidence

Table 3: Comparison between clinical and biological features of reports about inflammatory syndrome SARS-CoV2 probably related

Median CRP (normal <10 mg/L)	303 (169–675)	154 (129–231)	250 (90–520)	CRP >10x normal value (not reported individual values)	253 (89–363)	207 (162–236)	241 (150–311)	222 (83–343)
Coronary artery dilatations/aneurysm	1:8 (12,5%)	8:15 (53%)	2:10 (20%)	None	5:21 (24%)	3:16 (19%)	6:35 (17%)	1:6 (16%)
Cardiac involvement (biochemical/ECG/echo)	7:8 (87%)	15:15 (100%)	6:10 (60%)	2:2 (100%)	17:21 (81%)	7:16 (44%)	35:35 (100%)	4:6 (66%)
Shock/ hypotension	8:8 (100%)	10:15 (67%)	5:10 (50%)	1:2 (50%)	12:21 (57%)	11:16 (69%)	35:35 (100%)	6:6 (100%)
Gastrointestinal Symptoms	7:8 (87%)	13:15 (87%)	6:10 (60%)	2:2 (100%)	21:21 (100%)	13:16 (81%)	29:35 (83%)	6:8 (75%)
Incomplete form of Kawasaki disease*	6:8 (75%)	8:15 (53%)	5:10 (50%)	2:2 (100%)	10:21 (47%)	6:16 (37%)	Not reported	6:6 (100%)
Persistent fever >38°C	All	All	All	All	All	All	All	All
Comorbidities	Weight >75th centile (87%)	/	/	PFAFA syndrome (1.2)	Weight >97th centile (24%)	Overweight (25%)	Overweight (17%) Asthma (8.5%)	None
Median age	8.8	8.8	7.5	9.5	7.9	10	10	8.5
High risk population	Afro-Caribbean (75%)	Afro-Caribbean (40%) South Asian (40%)	Not reported	Not reported	Afro-Caribbean (57%)	Not reported	Not reported	Afro-Caribbean (33%)
Patients numbers	8	15	10	2	21	16	35	6

	Riphagen report[8]	**Ramcharam report[23]**	**Verdoni report[6]**	**Licciardi report[10]**	**Toubiana report[11]**	**Pouletty report[25]**	**Belhadjer report[9]**	**Chiotos report[25]**
Other agents identified	1:8 (adenovirus) (12.5%)	Not reported	None	None	None	None	None	Not reported
Family exposure to Sars-Cov2 suspected or confirmed	4:8 (50%)	3:15 (20%)	5:10 (50%)	1:2 (50%)	10:21 (47%)	Not reported	13:35 (37%)	None
Positive Sars-Cov2 IgG or IgM	2:8 (25%)	12:15 (80%)	8:10 (80%)	2:2 (100%)	19:21 (90%)	87% of tested (7:8)	30:35 (86%)	5:6 (83%)
Positive nasal swab PCR Sars-Cov2	None	2:15 (13,3%)	2:10 (20%)	None	8:21 (38%)	11:16 (69%)	12:35 (34%)	3:6 (50%)
Death	1:8 (12,5%)	None	None	None	None	None	None	
Steroids	5:8 (62,5%)	5:15 (33%)	8:10 (80%)	2:2 (100%)	10:21 (48%)	4:16 (25%)	12:35 (34%)	5:6 (83%)
IVIG	8:8 (100%)	10:15 (67%)	10:10 (100%)	1:2 (50%)	21:21 (100%)	15:16 (93%)	25:35 (71%)	6:6 (100%)
Vasoactive agent	8:8 (100%)	10:15 (67%)	2:10 (20%)	1:2 (50%)	8:21 (38%)	7:16 (44%)	28:35 (80%)	5:6 (83%)
Platelets < 150×10^9 cells per L	4:8 (50%)	Not reported	8:10 (50%)	2:2 (100%)	Not reported	None	Not reported	2:6 (33%)
Median troponin (normal <35 ng/L)	252 (25–813)	396 (100–1280)	1004 (3–4906)	Not reported	282 (10–6900)	58 (36–165)	347 (186–1267)	489 (50–1390)
Median ferritin (normal 14-79 ng/ml)	1.086 (277–4220)	558 (364–1325)	1176 (199–3213)	743 (590–897)	Not reported	1067 (272–1709)	Not reported	889 (512–1267)
	Riphagen report[8]	**Ramcharam report[23]**	**Verdoni report[6]**	**Licciardi report[10]**	**Toubiana report[11]**	**Pouletty report[25]**	**Belhadjer report[9]**	**Chiotos report[25]**

of KD is the highest, is noteworthy. Some authors speculate regarding variation in the virus affecting areas with cases of hyperinflammatory syndrome or increased susceptibility or genomic variation of these populations (32).

Therapy and Outcome

Intravenous immunoglobulins were apparently effective in these patients: their immunomodulatory properties are not specific but result in strong anti-inflammatory effects. Prompt treatment with IVIG 2 gr/kg, however, implies infusion of large amount of fluids: it has been suggested to infuse them divided into two separate doses and to use preferably high concentrated products. In case of obesity (BMI>30), reducing 20% of therapeutic dose may avoid renal complications linked to the increase in oncotic pressure and blood viscosity (4).

In one recent review, Nakra propose to treat all the patients meeting criteria for KD (IVIG+acetylsalicylic acid) (32). Moreover, IVIG could have beneficial immunomodulatory effects also in patients who do not meet these criteria.

Licciardi et al. detailed improvement of both patients described after high-dose steroid use (methylprednisolone iv, followed by prednisone *per os*) (10). In one case also IVIG were administered. Moreover, Verdoni et al. support the need to start adjunctive steroids in patients with features resembling MAS: steroids, on the basis of their experience, are safe and effective (6).

Concerns exist regarding the safety of steroids in the setting of active COVID-19 infection, but no conclusions can be made with the current evidences, although preliminary data suggest that the combination of mechanical ventilation and dexamethasone resulted in lower 28-days mortality in adults compared to those receiving mechanical ventilation alone (33).

Considering this hyperinflammatory syndrome as a post-infectious process, the immunosuppressive effects of the therapy would not risk flaring the infection. Precaution should be used if real-time PCR for SARS-CoV-2 results positive, suggesting active infection.

Only a few children required additional therapies, such as anakinra (recombinant IL-1 antagonist).

Another potential treatment is tocilizumab, an IL-6 inhibitor used in setting of refractory KD, but caution has to be used because of one report that demonstrated rapid development of coronary artery aneurism (CAA) following the therapy (33).

Belhadjer described 35 cases from France and Switzerland: all patients received IVIG, with adjunctive steroids in one third; inotropic support was needed by the majority of critical children, 28% of which were treated with ECMO with good outcome.

Antiviral therapy with remdesivir may be considered for SARS-CoV-2 RT-PCR positive patients, as studies have shown that its benefit is greatest when administered in early disease (34, 35).

Overall mortality has been low, with a single death in the UK cohort (due to cerebrovascular accident while on ECMO) (8), one death reported from French surveillance (24) and four reported deaths in US (36).

Conclusions

The knowledge about the hyperinflammatory syndrome, and its relationship to KD, is evolving. Current evidence underlines some notable differences between this novel syndrome and KD, although they probably share several pathways to activate the so called 'cytokine storm'. Future data and clinical informations will provide insights into the pathophysiology and will increase our understanding of KD. Programs of national surveillance are, consequently, of great importance.

Further studies evaluating predisposing factors and pathogenesis of this hyperinflammatory syndrome are needed to optimally manage this condition, as well as adding insight to long term follow-up of pediatric Covid-19 survivors.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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