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 multi-system 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 hypoaubuminemia, 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)

| Clinical features | 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            |
|                  | Possible fulfils criteria for complete KD,     | TYPICAL AGE < 5 years          | 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 |
|                  | 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) |                                |                                |                  |                  |
|                  | Elevated CRP, PCT, neutrophilia                | Elevated WBC, CRP, ERS,        | More elevated WBC, CRP, PCT, BNP, troponin I ferritin protein than KD patients. + Pancytopenia, Low fibrinogen levels |
|                  | Frequent elevated ferritin, D-Dimers, I-Troponin | Thrombocytosis (second phase), | Possible: anemia, hypoalbuminemia, hyponatremia, increased levels of liver enzymes | Elevated ferritin, liver enzymes, LDH, triglycerides, D-dimers, CRP |
|                  | Possible: low platelet counts, lymphopenia     | Possible: anemia, hypoalbuminemia, hyponatremia, increased levels of liver enzymes | Low platelet counts (<150 × 109 cells per L), High D-dimer results, prolonged partial thromboplastin times for age | Elevated WBC, CRP, PCT, liver enzymes |
|                  | hypoalbuminemia, increased levels of liver enzymes |                                |                                |                  | Low platelet counts (<100 × 109 cells/L) or coagulopathy signs as disseminated intravascular coagulation |

\(^{12}\) Possible fulfils criteria for complete KD, more often incomplete/atypical

\(^{17}\) Elevated WBC, CRP, PCT, liver enzymes

\(^{18}\) Possible 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

\(^{19}\) Elevated ferritin, liver enzymes, LDH, triglycerides, D-dimers, CRP + Pancytopenia, Low fibrinogen levels
| Cardiac involvement | Coronary dilatation less frequent than Kawasaki | Myocarditis and Hemodynamic instability more frequent than Kawasaki | Uncommon | Hypotension/ Myocardial dysfunction if progressive multiorgan failure |
|---------------------|------------------------------------------------|-------------------------------------------------|----------|---------------------------------------------------------------|
| Etiology            | Abnormal immune response to SARS-CoV2?         | Sars-CoV2 with direct trigger action?           | Unknown  | 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 Evaluation                        | 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, lymphopenia, hypoalbuminemia,  
elevate CRP, D-dimers, ferritin | 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 fulfills 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 fulfills 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

| Clinical/Biological Feature                                      | Afro-Caribbean (75%) | Afro-Caribbean (40%) | South Asian (40%) |
|-----------------------------------------------------------------|-----------------------|----------------------|-------------------|
| **Median CRP (normal <10 mg/L)**                                | 303 (169–675)         | 154 (129–231)        | 250 (90–520)      |
| **Coronary artery dilatations/aneurysm**                        | 1:8 (12,5%)           | 8:15 (53%)           | 2:10 (20%)        |
| **Cardiac involvement (biochemical/ECG/echo)**                  | 7:8 (87%)             | 15:15 (100%)         | 6:10 (60%)        |
| **Shock/hypotension**                                           | 8:8 (100%)            | 10:15 (67%)          | 5:10 (50%)        |
| **Gastrointestinal Symptoms**                                   | 7:8 (87%)             | 13:15 (87%)          | 6:10 (60%)        |
| **Incomplete form of Kawasaki disease**                         | 6:8 (75%)             | 8:15 (53%)           | 5:10 (50%)        |
| **Persistent fever >38°C**                                      | All                   | All                  | All               |
| **Comorbidities**                                               | Weight >75th centile (87%) | /                   | PFAFA syndrome (1.2) |
| **Median age**                                                  | 8.8                   | 8.8                  | 7.5               |
| **High risk population**                                        | Afro-Caribbean (40%) | /                    | /                 |
| **Patients numbers**                                            | 8                     | 15                   | 10                |
| Other agents identified | Riphagen report⁸ | Ramcharam report²¹ | Verdoni report⁴ | Licciardi report⁹ | Toubiana report¹¹ | Pouletty report²⁵ | Belhadjer report⁹ | Chiotos report²⁵ |
|-------------------------|------------------|-------------------|----------------|------------------|------------------|------------------|------------------|------------------|
| 1:8 (adenovirus)        | Not reported     | None              | None           | None             | None             | None             | None             | None             |
| (12.5%)                 |                  |                   |                |                  |                  |                  |                  |                  |
| 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             | 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 x 10⁹ 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) |

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1:8 (adenovirus)
(12.5%)

Not reported

Not reported

Not reported

None

None

None

None

Riphagen report⁸

Ramcharam report²¹

Verdoni report⁴

Licciardi report⁹

Toubiana report¹¹

Pouletty report²⁵

Belhadjer report⁹

Chiotos report²⁵
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 divide 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, Verdini 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.

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References

1. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020; 145(6): e20200702. doi: 10.1542/peds.2020-0702.
2. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450–454.
3. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronaviruses 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr 2020 April 22. doi: 10.1001/jamapediatrics.2020.1467. Online ahead of print.
4. Koné-Paut I, Cimaz R. Is it Kawasaki shock syndrome, Kawasaki-like disease or pediatric inflammatory multisystem disease? The importance of semantic in the era of COVID-19 pandemic. RMD Open 2020;6:e001333.
5. Parri, N., Magistà, A.M., Marchetti, F. et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. Eur J Pediatr 179, 1315–1323 (2020). https://doi.org/10.1007/s00431-020-03683-8
6. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395(10239):1771–1778.
7. Jones VG, Mills M, Suárez D, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hosp Pediatr 2020; 10:537–540
8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 23;395(10237):1607–1608.
9. Belhadjer Z, Méot M, Bajolle F, et al.; Acute heart failure in multisystem inflammatory syndrome children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 2020 doi.org/10.1161/CIRCULATIONAHA.120.048360 Online ahead of print.
10. Licciardi F, Pruccoli G, Denina M, et al. SARS-CoV-2–induced Kawasaki-like hyperinflammatory syndrome: a novel COVID phenotype in children. Pediatrics. 2020; May 21:e20201711. doi: 10.1542/peds.2020-1711
11. Toubiana J, Poirault C., Corsia A., Bajolle F., Fourgeaud J., Angoulvant F. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020; Jun 3;369:m2094. doi: 10.1136/bmj.m2094.
12. Marchesi A, Tarissi de Jacobis I, Rigante D. Kawasaki disease: guidelines of the Italian Society of Pediatrics, part I - definition, epidemiology, etiopathogenesis, clinical expression and management of the acute phase. Ital J Pediatr. 2018;44:102
13. Makino N, Nakamura Y, Yashiro M et al. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. J Epidemiol. 2015; 25: 239–245
14. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005; 191: 499–502.
15. Ebihara T, Endo R, Ma X, Ishiguro N, Kikuta H. Lack of association between New Haven coronavirus and Kawasaki disease. J Infect Dis. 2005; 192: 351–352
16. Shirato K, Imada Y, Kawase M, Nakagaki K, Matsuyama S, Taguchi F Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. J Med Virol. 2014; 86: 2146–2153
17. Ravelli A, Minoa F, Davi S, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis. 2016; 75: 481–489
18. Kanegaye JT, Wilder MS, Molkara D. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123:e783–e789
19. Chuang, Y-Y, Huang, Y-C,Lin T-Y Toxic Shock Syndrome in Children. Pediatric Drugs. 2005; 7(1): 11–25.
20. 2015. https://www.cdc.gov/mis-c/hcp/last access July 30, 2020
21. Royal College of Paediatrics and Child Health (RCPCH). Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. May 2020 https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric multisystem-%20inflammatory%20syndrome-20200501.pdf last access July 30, 2020
22. Centers for Disease Control and Prevention: Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). 14 May 2020. https://www.cdc.gov/mis-c/hcp/last access July 30, 2020
23. Istituto Superiore di Sanità. Indicazioni ad interim su malattia di Kawasaki e sindrome infiammatoria acuta multisistemica in età pediatrica e adolescenziale nell’attuale scenario emergenziale da infezione Sars-CoV-2. 2020, Rapporto ISS COVID-19 n. 29/2020
24. Ramcharan T, Nolan O, Lai CY et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediart Cardiol 2020 Jun 12;1-11. doi: 10.1007/s00246-020-02391-2. Online ahead of print.
25. Belot A, Antona D, Renolleau S et al. SARS-CoV-2–related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. Euro Surveill. 2020 Jun;25(22):2001010. doi: 10.2807/1560-7917.ES.2020.25.22.2001010. (22) (2020)
26. Pouletty M, Borocco C, Ouldali N et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa- COVID-19): a multicenter cohort. Ann Rheum Dis 2020 Aug;79(8):999–1006.
27. Chiotos K, Bassiri H, Behrens E M, et al. Multisystem Inflammatory Syndrome in Children During The Coronavirus 2019 Pandemic: A Case Series. J Pediatric Infect Dis Soc. 2020 Jul 13;9(3):393–398.
27. Fabi M, Corinaldesi E, Pierantoni L, Mazzoni E, Landini C, Bigucci B, et al. Gastrointestinal presentation of Kawasaki disease: A red flag for severe disease? PloSone. 2018;13(9): e0202658. doi: 10.1371/journal.pone.0202658
28. Henderson LA, Canna SW, Schulert GS. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheum. 2020 Jul;72(7):1059–1063
29. Molloy EJ, Bearer CF. COVID-19 in children and altered inflammatory responses. Pediatr Res. 2020 doi: 10.1038/s41390-020-0881-y. published online April 3
30. Roncati L., Ligabue G., Fabbiani L., Malagoli C. Type 3 hypersensitivity in COVID-19 vasculitis. Clin Immunol. 2020;217
31. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. doi:10.1016/S0140-6736(20)30183 5
32. Nakra, NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed management. Children 2020, 7, 69
33. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2021436.
34. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020, 30, 269–271
35. Wang Y, Zhang, D.; Du, G.; Du, R.; Zhao, J.; Jin, Y.; Fu, S.; Gao, L.; Cheng, Z.; Lu, Q.; et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020, 395, 1569–1578
36. Feldstein LR, Rose EB, Horwitz SM et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020 Jul 23;383(4):334–346.

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