SYNOPSIS
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COVID-19 – What We Know So Far About...Kawasaki Disease-Like Illness

Introduction
Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). “What We Know So Far” documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMED, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All “What We Know So Far” documents are reviewed by PHO subject-matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

Key Points
• Kawasaki disease is a rare multisystem inflammatory vasculitis in children that may be triggered by some viral and bacterial infections.

• There have been reports of an increase in Kawasaki disease-like illness (KD-like illness) from areas with high rates of circulating SARS-CoV-2. However, a causal link between this KD-like illness in children with COVID-19 has not been established. Further investigation, including epidemiological surveillance and serological evaluation of these children, is needed to better understand if a true association exists. Clinicians are encouraged to report cases to the World Health Organization or local surveillance systems.

• Early reports of this KD-like illness have described a several fold higher incidence of disease compared to previous years. Notable clinical differences have included older children than is commonly seen with KD, thrombocytopenia (opposed to thrombocytosis), as well as more severe presentations including toxic shock syndrome, macrophage activation syndrome, and cardiac involvement.

• The majority of COVID-19 infections in children are mild and, in Ontario, approximately 3.2% of all identified cases are in those 19 years old or younger (Ministry of Health). Overall, the risk of children developing KD-like illness is low, however further surveillance efforts are required to better understand this association.
Background

Kawasaki disease (KD) is a multisystem inflammatory vasculitis, and is one of the most common vasculitides in children. In Canada, the estimated annual incidence in children under the age of 5 years is 22 per 100,000 population (28 per 100,000 in Ontario), with a tenfold higher incidence in parts of Asia (Manlhiot et al., Lin and Wu). The etiology of KD is unknown but it may be triggered by some viral and bacterial infections, with susceptibility potentially governed by genetics (Kuo et al.). KD is a clinical diagnosis characterised by fever longer than 5 days, non-purulent bilateral conjunctivitis, unilateral cervical lymphadenopathy, rash, peripheral edema of the hands or feet, cracked or dry lips with a strawberry tongue. The most important long-term effects of KD are cardiovascular complications, most notably coronary artery aneurysms.

Treatment of KD includes intravenous immunoglobulin (IVIG) combined with aspirin. Early clinical recognition and treatment (within 10 days of illness onset) is associated with reduced cardiovascular complications (Heart and Stroke Foundation of Canada). KD management is multidisciplinary including general paediatrics, paediatric infectious diseases, paediatric cardiology and paediatric rheumatology.

On April 7, 2020, researchers published the first case report of a child with classic KD who was also positive for COVID-19 (Jones et al.). On April 27, 2020, the Paediatric Intensive Care Society (PICS) (UK) issued an alert stating they received an “email alert from NHS England highlighting a small rise in the number of cases of critically ill children presenting with an unusual clinical picture. Many of these children had tested positive for COVID-19, while some had not. The alert indicated ‘the cases have in common overlapping features of toxic shock syndrome and atypical Kawasaki disease with blood parameters consistent with severe COVID-19 in children. Abdominal pain and gastrointestinal symptoms have been a common feature as has cardiac inflammation’” (Paediatric Intensive Care Society (PICS)). After these early alerts, physicians in Europe and North America started to report clusters of children with a multisystem inflammatory syndrome, similar to KD, associated with COVID-19 exposure (Viner and Whittaker).

For the purposes of this document, we will use KD-like illness to describe a disease similar to classical and atypical KD that has been described in Italy (Verdoni et al.). The spectrum of this clinical illness is at present not fully delineated and other terms have been used including; multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory syndrome (PID), paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) and pediatric multi-system inflammatory syndrome (PMIS) temporally associated with COVID-19 (Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC), Loomba et al., New York State Department of Health (NYSDOHa), Riphagen et al., Verdoni et al.).

Distribution and Incidence

KD-like illness has been reported throughout Europe and North America, with the highest number of cases from USA (>190 cases), France (≈65 cases) and the UK (≈50 cases) (CDC, ECDC, NYSDOHb, ProMED). To date, there have been no reports of increased KD-like illness in Asia, where KD has historically been more prevalent (ECDC).

- **Canada**: To date, there have been no reported cases of KD-like illness in Ontario; however, more than 15 cases have been reported from Montreal, Quebec (Scott).
• France: 17 patients with KD-like illness were admitted to a hospital over an 11-day period during the epidemic, compared to a mean of one case per two weeks in 2018 and 2019 (Poisson incidence rate ratio = 13.2; 95% confidence interval [CI]: 7.3–24.1, p<0.001) (Toubiana et al., pre-print, not peer reviewed).

• Italy: Verdoni et al. reported a 30-fold increase in incidence of KD-like illness, with 10 cases per month during the epidemic, compared to a monthly incidence of 0.3 before the epidemic.

• USA: Surveillance efforts in New York State have noted 166 cases and 3 deaths, as of 2020 May 24 (NYSDOH). Cases have been reported throughout the USA, including cases from California, Connecticut, Illinois, Iowa, Louisiana, Massachusetts, Michigan, Mississippi, New Jersey, Oregon, Pennsylvania and Washington, DC (ProMED).

Patient Characteristics

There have been four case series (70 patients) (Belhadjer et al.; Riphagen et al.; Toubiana et al. pre-print, not peer reviewed; Verdoni et al.), five case reports (7 patients) (Dallan et al., DeBiasi et al., Jones et al., Licciardi et al., Rivera-Figueroa et al.) and one surveillance system (NYSDOH) that reported on KD-like illness patient characteristics.

The mean and median age of patients with KD-like illness is about 7.5 years (compared to 3 years for typical KD) with an even distribution by sex (Verdoni et al.). While studies are limited and likely not representative of all ethnic backgrounds, most patients in Italy and the UK were of Afro-Caribbean decent. Most patients with KD-like illness do not have underlying conditions.

Age and sex

• UK: The median age of patients was 8.0 years (range: 4–14, n=8) and 3/8 (37.5%) were female (Riphagen et al.).

• France: The median age of patients was 7.5 years (range: 3.7–16.6, n=17) and 10/17 (58.8%) were female (Toubiana et al., pre-print, not peer reviewed).

• Italy: The mean age of patients with KD-like illness was 7.5 years (SD: 3.5, n=10) and 3/10 (30.0%) were female (Verdoni et al.). The two cases from Turin, Italy, were boys aged 7 and 12 years (Licciardi et al.).

• USA: In a case report from California, the patient was a 6-month-old female (Jones et al.). In a case report from Mississippi, the patient was a 5-year-old male (Rivera-Figueroa et al.). In a case report from Washington DC, the patient was a 4-year-old male (DeBiasi et al.). As of 2020 May 24, 28% of 166 cases in New York State were 5–9 years old (NYSDOH).

• Switzerland: The report includes 2 male patients, both 10 years old (Dallan et al.).

• France/Switzerland: The median age of the 35 patients was 10 years (range: 1-16 years) and 17/35 (49%) were female (Belhadjer et al.).
Ethnic background

- **UK:** 6/8 KD-like illness patients were of Afro-Caribbean decent, while one was of Middle Eastern decent and one was Asian (Riphagen et al.).

- **France:** Parental ethnic origin of the 17 patients include Afro-Caribbean (59%), Asian (29%) and European (12%) (Toubiana et al., pre-print, not peer reviewed).

- **USA:** In New York State, as of 2020 May 24, the most common ethnicity/race among cases (n=166) were “black” (31%), “white” (22%) and “unknown” (27%) (NYSDOHb).

- **Switzerland:** One of two patients was “black”, the other patient was of “mixed-race (Asian and white)” (Dallan et al.).

Comorbidities

- **UK:** 2/8 patients had comorbidities (one with autism and ADHD; another had alopecia areata and hay fever) and 7/8 had BMIs above the 75th percentile for their age (Riphagen et al.).

- **Italy:** 1/10 patients had pre-existing congenital adrenal hyperplasia (Verdoni et al.).

- **Switzerland:** Both patients had a BMI > 97th percentile for their age (Dallan et al.).

- **France/Switzerland:** 3/35 patients had asthma, one had lupus and 6 were considered overweight (Belhadjer et al.).

Clinical Characteristics

Most patients with this KD-like illness presented with persistent fever, gastrointestinal symptoms, conjunctivitis and rash; some with abnormal heart function. Classical KD criteria were not always fulfilled. Common laboratory findings include elevated C-reactive protein (CRP), procalcitonin (PCT), ferritin and neutrophils, with decreased platelets and levels of sodium. Patients with KD-like illness generally have a favourable outcome. Deaths due to KD-like illness are uncommon, however they have occurred; i.e., USA (3), UK (2) and France (1) (ECDC, Riphagen et al.).

Common signs and symptoms

- **UK:** Fever (8/8) and shock (8/8) were present in all patients, followed by diarrhea/vomiting (7/8), conjunctivitis (5/8), abdominal pain (6/8), rash (4/8) and odynophagia (3/8) (Riphagen et al.).

- **France:** Gastrointestinal symptoms (17/17) were present in all patients, followed by conjunctivitis (13/17), rash (13/17), myocarditis (12/17), lip and oral cavity changes (12/17), cervical lymphadenopathy (11/17), irritability (11/17), fever (8/17) and swelling in extremities (6/17) (Toubiana et al., pre-print, not peer reviewed).

- **Italy:** Conjunctivitis was experienced by 8/10 patients, followed by rash (8/10), changes in lip or oral cavity (6/10), diarrhea (6/10) and swelling in extremities (5/10) (Verdoni et al.). Fifty percent had incomplete KD. In addition, a Kobayashi score ≥5 (7/10) was common, followed by an abnormal echocardiogram (6/10), pneumonia (5/10), macrophage activation syndrome.
(MAS) (5/10) and Kawasaki disease shock syndrome (KDSS) (5/10). The spectrum of illness was more severe compared to the historical KD cohort. In Turin, Italy, the two patients presented with fever and gastrointestinal symptoms and both developed conjunctivitis and rash (Licciardi et al.).

- **Switzerland:** Both patients presented with persistent fever, conjunctivitis, abdominal pain and vomiting (Dallan et al.). The patients developed acute renal failure and one experienced left anterior descending artery and right coronary aneurysms.

- **France/Switzerland:** All patients presented with fever (35/35) and asthenia (35/35), followed by gastrointestinal symptoms (29/35), respiratory distress (23/35), adenopathy (21/35) and rash (20/35) (Belhadjer et al.). A total of 28 of the 35 patients experienced cardiogenic shock.

**Laboratory findings**

- **UK:** KD-like illness patients showed elevated CRP, PCT, ferritin, triglycerides and D-dimers (Riphagen et al.).

- **France:** Patients had elevated levels of CRP, neutrophils, interleukin-6 (IL-6), D-dimmers and PCT, with low levels of sodium and albumin (Toubiana et al., pre-print, not peer reviewed).

- **Italy:** KD-like illness patients had elevated levels of CRP, neutrophils and ferritin, with decreased white cell count, lymphocytes, platelets and sodium (Verdoni et al.). The two patients from Turin, Italy, had elevated CRP, PCT and ferritin (Licciardi et al.).

- **USA:** In the case report from California, the patient had elevated levels of CRP, with low levels of sodium and albumin (Jones et al.). In the case report from Mississippi, the patient had elevated levels of white blood cells, CRP, PCT and ferritin, with low sodium, albumin and platelet counts (Rivera-Figueroa et al.).

- **Switzerland:** Both patients showed elevated neutrophils, CRP, PCT, D-dimers and ferritin (Dallan et al.).

- **France/Switzerland:** Patients showed elevated neutrophils, white blood cells, CRP, PCT, D-dimers and IL-6 (Belhadjer et al.).

**Severity, treatment and outcomes**

- **UK:** 5/8 patients required mechanical ventilation (MV) via endotracheal tube, followed by non-invasive ventilation (NIV) (2/8), inotropic support (7/8), renal replacement therapy (1/8), high flow nasal cannula (1/8) and veno-arterial extracorporeal membrane oxygenation (ECMO) (1/8). All patients received IVIG (8/8) and steroids (5/10) were commonly used. All patients were admitted to the pediatric intensive care unit (PICU); seven recovered and were discharged from PICU after 4-6 days (one developed a large coronary aneurysm after discharge) and one patient died after a cerebrovascular infarct (Riphagen et al.).

- **France:** All patients received IVIG with aspirin (17/17), 10/17 patients required MV, and 5/17 received steroids. Thirteen patients were admitted to intensive care; 14 were discharged at time of follow-up and no deaths reported (Toubiana et al., pre-print, not peer reviewed).
• **Italy:** All patients received IVIG with aspirin (10/10), 8/10 patients received adjunctive steroid treatment and 2/10 required intropes ([Verdoni et al.](#)). All patients responded to treatment and survived. The two patients reported from Turin, Italy, survived; one received NIV and IVIG, while the other received steroid treatment ([Licciardi et al.](#)).

• **USA:** The patient in Washington DC presented had markedly decreased myocardial function consistent with myocardial injury and required MV, and received IVIG and aspirin ([DeBiasi et al.](#)). The patient in Mississippi was admitted to intensive care and received oxygen through high flow nasal cannula and IVIG ([Rivera-Figueroa et al.](#)). The patient in California had a milder course of illness ([Jones et al.](#)).

• **Switzerland:** One patient received MV and hemodialysis, the other received NIV ([Dallan et al.](#)). Both patients were admitted to the PICU; one was discharged while the other remained hospitalized at last follow-up.

• **France/Switzerland:** 22/35 patients received MV, followed by NIV (11/35), ECMO (10/35) ([Belhadjer et al.](#)). Patients also received inotropes (28/35), IVIG (25/35), heparin (23/35) and steroids (12/35). All patients were admitted to PICU; at last follow-up, most patients (28/35) had been discharged and no patients died.

### Relationship with COVID-19

It is plausible, given the temporal association, that this KD-like illness is a post-infectious disease triggered by SARS-CoV-2. However, a causal link with COVID-19 has not been confirmed and further research is required to establish the etiology of this KD-like illness ([Schroeder et al.](#)).

• **UK:** 2/8 patients tested positive for COVID-19 on bronchoalveolar lavage (BAL) or nasopharyngeal (NP) aspirates after discharge from PICU (including 1 detected post mortem). Among the 6 patients who tested negative, 3 had known family exposure to COVID-19 ([Riphagen et al.](#)). Subsequent to this publication, the Evelina London Children’s Hospital paediatric ICU reported managing > 20 children with a similar clinical presentation. The first 10 have reportedly tested positive for COVID-19 antibody (including the original eight children in the Riphagen cohort).

• **France:** 7/17 patients were RT-PCR positive for COVID-19 on NP swabs; 14/17 were serologically positive for COVID-19 (IgG) ([Toubiana et al.](#), pre-print, not peer reviewed).

  • The median time from potential exposure to COVID-19 patients or initial COVID-19 infection to KD diagnosis was **36 days** (range: 24–38).

• **Italy:** 8/10 patients with KD-like illness presented over a one month period during the COVID-19 epidemic had COVID-19-positive serology (5 of these 8 patients had exposure to a suspected or confirmed COVID-19 case, and 2 of these 8 also tested positive for COVID-19 by nasal swabs) ([Verdoni et al.](#)). The authors hypothesize that COVID-19 is responsible for the 30-fold increase in the incidence of KD-like illness in Bergamo, Italy. Two patients from Turin, Italy were negative for COVID-19 on RT-PCR of NP swabs, but both had positive serology (IgG and IgM) ([Licciardi et al.](#)).
• **USA:** In the case report from California, the patient tested positive for COVID-19 by RT-PCR and was exposed to a sibling with an upper respiratory illness 3-weeks prior to symptom onset (Jones et al.). In the case report from Mississippi, the patient tested positive for COVID-19 by RT-PCR on NP swab (Rivera-Figueroa et al.). For the 166 KD-like illness cases reported in New York State, approximately 92% of patients have tested positive by RT-PCR, serology or both (NYSDOHb).

• **Switzerland:** Both patients were negative for COVID-19 on NP swabs (RT-PCR), but had positive serology (IgG) (Dallan et al.).

• **France/Switzerland:** 31 of 35 patients were positive for COVID-19 by RT-PCR on NP swabs or had positive serology (Belhadjer et al.).

**Proposed Case Definitions for Surveillance**

Further surveillance is needed to better understand this rare but severe syndrome in children. We encourage clinicians to collaborate with the World Health Organization or local surveillance efforts. The World Health Organization has published a preliminary case definition for multisystem inflammatory disorder in children and adolescents to characterize this syndrome and its risk factors:

- A person 19 years of age or under with fever ≥ 3 days. AND
- Two of the following: rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated d-Dimers); acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain). AND
- Elevated markers of inflammation such as ESR, C-reactive protein, 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.

The Royal College of Paediatrics and Child Health (UK) developed a document after expert review of the cases to raise awareness and provide management advice to clinicians. Their proposed case definition includes the following:

- A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for KD.
- Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.
- SARS-CoV-2 PCR testing may be positive or negative.
The **Centers for Disease Control and Prevention (CDC)** (USA) issued a Health Advisory and a case definition for multisystem inflammatory syndrome in children (MIS-C):

- An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological). 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 weeks prior to the onset of symptoms.

The **New York State Department of Health (NYSDOH)** has developed an interim case definition for pediatric multi-system inflammatory syndrome (PMIS) temporally associated with COVID-19. Suspect and confirmed cases of PMIS in those under 21 years of age must be reported. Clinical criteria includes:

- A person under 21 years old with fever and hospitalized.

**Either:** One or more of the following: Hypotension or shock (cardiogenic or vasogenic); features of severe cardiac illness including but not limited to myocarditis, pericarditis, or valvulitis, significantly elevated troponin/pro-BNP, or coronary artery abnormalities; other severe end-organ involvement including but not limited to neurological or renal disease (excluding severe respiratory disease alone).

- **Or:** Two or more of the following: maculopapular rash; bilateral non-purulent conjunctivitis; mucocutaneous inflammatory signs (mouth, hands, or feet); acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain).

- Absence of a more likely diagnosis of the illness, e.g., bacterial sepsis or other viral infection.

**References**


Citation

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This document was developed by Public Health Ontario (PHO). PHO provides scientific and technical advice to Ontario’s government, public health organizations and health care providers. PHO’s work is guided by the current best available evidence at the time of publication.

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