

## Original Article

# All hands on deck: A multidisciplinary approach to SARS-CoV-2-associated MIS-C

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### ABSTRACT

**Background:** Multisystem Inflammatory Syndrome in Children (MIS-C) is a post-infectious complication of SARS-CoV-2 infection with overlapping features of Kawasaki disease and toxic shock syndrome. In May 2020, a provincial multidisciplinary working group was established in anticipation of emerging cases following the first wave of SARS-CoV-2 infections.

**Methodology:** Our centre established a multidisciplinary working group for MIS-C cases in British Columbia. The group developed guidelines using the World Health Organization MIS-C case definition. Guidelines were updated using quality improvement methods as new reports and our local experience evolved. We included all children who were evaluated in person or had samples sent to our centre for MIS-C evaluation from May 2020 to April 2021. We prospectively collected patient demographics, clinical and laboratory characteristics, and treatment.

**Results:** Fifty-two children were included. Eleven were diagnosed as confirmed MIS-C. Ten of the 11 MIS-C cases presented with shock. Gastrointestinal and mucocutaneous involvement were also prominent. Common laboratory features included elevated C-reactive protein, D-dimer, troponin, and brain natriuretic peptide. Four out of 11 (36%) had myocardial dysfunction and 3/11 (27%) had coronary artery abnormalities. All 11 patients had evidence of SARS-CoV-2 infection. Ten out of 11 (91%) received intravenous (IV) immunoglobulin and IV corticosteroids.

**Conclusion:** Our provincial cohort of MIS-C patients were more likely to present with shock and cardiac dysfunction, require ICU admission, and be treated with corticosteroids compared to ruled out cases. Our working group's evolving process ensured children with features of MIS-C were rapidly identified, had standardized evaluation, and received appropriate treatment in our province.

**Keywords:** COVID-19; Critical illness; MIS-C; Sepsis; Surveillance.

Multisystem Inflammatory Syndrome in Children (MIS-C) is a recently described condition with overlapping features of Kawasaki disease (KD) and toxic shock syndrome (TSS). It emerged in the setting of the COVID-19 pandemic: a national alert was issued in April 2020 out of the United Kingdom based on a cluster of children with cardiovascular shock, fever, and hyperinflammation temporally related to SARS-CoV-2 infection

(1,2). Although the pathophysiology of MIS-C remains unclear, it is widely accepted to be a post-infectious complication of COVID-19 (3).

In Canada, MIS-C is under active surveillance by numerous programs at provincial and federal levels. In response to this emerging entity, our provincial quaternary paediatric centre established a multidisciplinary working group to evaluate and

provide recommendations for the management of MIS-C cases in British Columbia (BC), Canada. BC contains close to 1 million youth ages 0 to 19 years within a wide geographic area of 944,735 km<sup>2</sup> (4). This report describes how we used the model for improvement to implement a clinical pathway for the evaluation and management of children admitted with suspected MIS-C. Finally, we describe clinical characteristics of 52 BC cases evaluated for MIS-C.

## METHODS

### Establishment of multidisciplinary working group

On May 8, 2020, providers from various specialties at BC Children’s Hospital and Surrey Memorial Hospital (BCCH, SMH) formed the ‘BC MIS-C Working Group’ (BMWG) to establish diagnostic and treatment pathways for this emerging entity. We connected with stakeholders including BC Public Health (PH), the BC Centre for Disease Control (BCCDC), and Child Health BC, a provincial health network. Paediatricians from other BC communities were invited to ensure the BMWG met the needs of children throughout the province.

The immediate challenges faced by the BMWG included (1) lack of diagnostic testing specific for MIS-C, (2) a need to identify possible cases rapidly and appropriately, (3) establishing a case definition and ensuring a systematic timely process for reporting possible cases to PH, and (4) an urgent need to provide guidance on MIS-C to both clinicians and the public.

We utilized the model for improvement with the goal of implementing new diagnostic and management guidance for suspected MIS-C within as fast a timeframe as possible. The number of serology requests and referrals to the BMWG from various regions of the province were the measure of uptake of the tool as compared to the number of cases reported directly to PH. Changes to the process or documentation during study period were made utilizing small, rapid PDSA (plan-do-study-act) cycles (Figure 1).

### Case definition and initial guidance development

The BMWG and key stakeholders initially met weekly to review evidence on MIS-C and to agree on a case definition and guidelines for the initial evaluation of suspected cases. Literature was reviewed and some members participated in the Paediatric COVID-19 International Collaborative meetings where worldwide cases of MIS-C were discussed in detail. BMWG guidelines were approved by the provincial COVID-19 clinical reference group (CRG). The CRG is a provincial entity that is comprised of physicians and PH experts that approves public-facing COVID-19 guidance documents for BC. BC’s case definition derived from the World Health Organization (2) was adapted to only include hospitalized cases and made available to the public through the BCCDC website on June 10, 2020 and to physicians through the College of Physicians and Surgeons of BC on August 28, 2020 (5). Serology testing was performed using the Ortho T VITROS Anti-SARS-CoV-2 Total antibody assay (Ortho IgG;

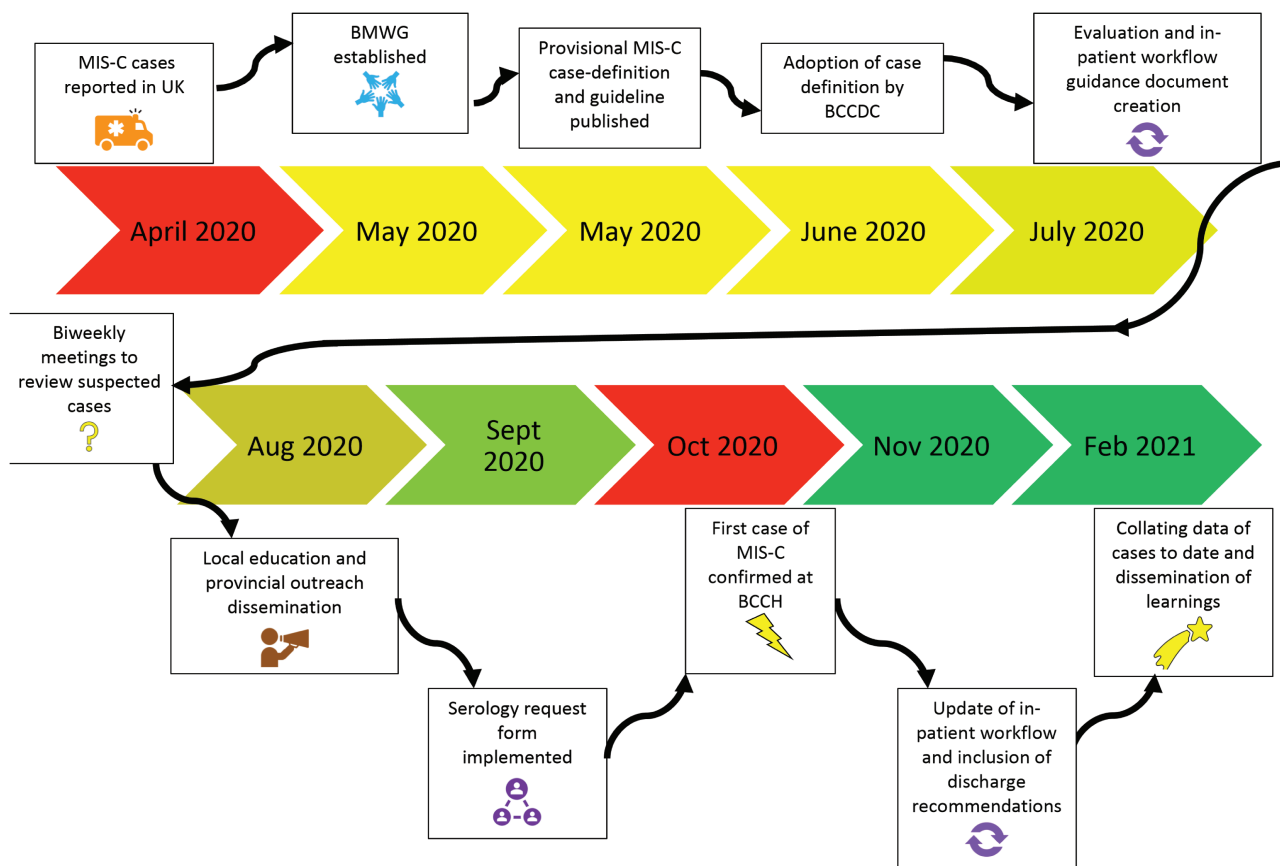


Figure 1. BC MIS-C Working Group evidence-based guideline timeline.

Ortho Clinical Diagnostics, Rochester, NY), a Health Canada and FDA-licensed qualitative assay which detects IgA, IgG, and IgM antibodies (6).

### Case identification and review

A REDCap database was created in June 2020 to track all cases referred for suspected MIS-C. At the time of requesting SARS-CoV-2 serology as part of an evaluation for MIS-C, providers submitted a case report form that was subsequently inputted into the REDCap database by nursing staff. This ensured prompt and accurate reporting to PH and prospective collection of case characteristics. Data were reviewed by the BMWG, and patients were classified as either: (1) a person under investigation, (2) MIS-C confirmed, or (3) MIS-C ruled out. Any case entered as 'person under investigation' or 'MIS-C confirmed' into REDCap triggered an automatic reporting to PH. This project was assessed by the BC Children's and Women's Research Ethics Board and deemed to be a quality improvement (QI)/quality assurance (QA) activity; therefore, REB review was not required.

### Evidence-based guideline (EBG) development process

Once case definitions were disseminated, the BMWG met every 2 weeks. We reviewed cases entered into the REDCap database, followed by review of the most relevant literature regarding MIS-C. We also drafted EBG documents including initial evaluation and inpatient management guidelines for MIS-C at BCCH, and a provincial guidance document ([Supplementary Materials](#)) (5,7,8). Changes to the EBG were tested and revised with stakeholders prior to broader dissemination as a means of quick improvement to the large-scale pathway.

### Statistical analysis

All statistical analyses were performed with Stata 14 (StataCorp, College Station, TX, USA). Data were summarized with nonparametric descriptive statistics (median, interquartile range [IQR]). Between the MIS-C confirmed and MIS-C ruled-out groups, proportions were compared with the Fisher exact test and continuous variables were compared with Wilcoxon rank-sum test. Nominal p-values (not corrected for multiple testing) are reported.

## RESULTS

Utilizing the model for improvement, process mapping and PDSA cycles, the BMWG successfully implemented and disseminated case definitions, evaluation, and management documents and a serology request form process. From May 2020 to April 2021, the BMWG reviewed 52 paediatric patients who underwent evaluation for MIS-C ([Supplementary Figure 1](#)). Eleven children (21%) fulfilled diagnostic criteria for confirmed MIS-C. All confirmed cases were reported via the BMWG with no cases being reported directly to PH outside of this process. Forty-one (79%) children did not meet our case criteria.

### Clinical characteristics and outcomes of evaluated patients

The median age of all 52 evaluated patients was 6.0 years (range: 3 months to 16 years). [Table 1](#) outlines the clinical characteristics and outcomes of confirmed and ruled-out cases. [Supplementary](#)

[Figure 2](#) compares the quantitative laboratory values between the two groups.

### Confirmed MIS-C cases

Of the 11 confirmed cases, 7 had a preceding history of PCR-confirmed acute COVID-19 and/or tested positive on their admission for MIS-C. The remaining 4 tested PCR negative or indeterminate; however, all 11 patients tested positive for SARS-CoV-2 by serology. Ten (91%) patients displayed shock as a clinical feature. Seven children (64%) were admitted to the paediatric intensive care unit (PICU), with 5 (45%) requiring inotropic support and 3 (27%) requiring intubation and ventilation.

Ten (91%) patients received intravenous immunoglobulin (IVIG) and intravenous steroids; five received a second dose of IVIG. One child received no treatment as the disease presentation was mild and quickly self-resolved. Three children received prophylactic anticoagulation with low molecular weight heparin following the newly published International Society on Thrombosis and Haemostasis (ISTH) guidelines (9). Ten (91%) patients received empiric antibiotics on admission.

### Cases where MIS-C was ruled out

Two of these 41 cases tested positive for SARS-CoV-2 by PCR or serology: one was ultimately diagnosed with unrelated *Escherichia coli* urosepsis, and the other did not meet clinical criteria for MIS-C. Six (15%) cases required ICU admission. Twenty-three (56%) patients received IVIG and 15 (37%) received systemic steroids. The indications for those treatments were KD, TSS, and sepsis.

## DISCUSSION

### QI lessons

We describe our single-centre experience of utilizing QI methods to rapidly develop a clinical pathway for a new emerging entity. The involvement of multiple stakeholders early on was vital in our coordinated response to this novel condition during a pandemic. The EBG was frequently revised as data emerged to ensure patients were receiving evidence-based care. A significant change in practice over the study period included the practice of earlier initiation of corticosteroids in severe presentations. With this, we eventually discontinued prescribing a second dose of IVIG in refractory cases. More consideration was also given to anticoagulation and increasing the use of ASA in select patients. We invited clinicians from other regions to participate in the BMWG, which served to improve dissemination of knowledge to other health regions with more cases reported in those regions after involvement of a local champion. The lack of any confirmed MIS-C cases being directly reported to PH outside of the BMWG supports the excellent uptake of the pathway in a very short time frame. We also developed a new reporting system with PH to facilitate provincial and national data sharing.

### Clinical characteristics

To our knowledge, this is the third published case series of MIS-C in Canada (10,11) and the presentation of our cohort

**Table 1.** Patient demographics, clinical features, laboratory features, and interventions

	Total (N=52)	MIS-C confirmed (N=11)	MIS-C ruled out (N=41)	p-value (confirmed vs. ruled out)
<b>Demographics</b>				
Age (years)	6.0 (2.0, 12.5)	6.0 (1.5, 12.0)	6.0 (3.0, 13.0)	0.74
Female (N [%])	28 (53.4)	5 (45.5)	23 (56.1)	0.74
<b>SARS-CoV-2 Testing</b>				
PCR Positive	9 (N=51)	7 (N=11)	2 (N=40)	<0.0001
Serology Positive	12 (N=52)	11 (N=11)	1 (N=41)	<0.0001
<b>Clinical Features (N [%])</b>				
Shock	25 (48.1)	10 (90.9)	15 (36.6)	<b>0.002</b>
Acute abdominal pain	24 (47.1)	6 (54.5)	18 (45.0)	0.74
Vomiting	32 (61.5)	6 (54.5)	26 (63.4)	0.73
Conjunctivitis	30 (57.7)	6 (54.5)	24 (58.5)	0.54
Rash	34 (65.4)	5 (45.5)	29 (70.7)	0.16
Oral mucosal changes	26 (50.0)	5 (45.5)	21 (51.2)	1.0
Erythema/swelling/peeling to peripheral extremities	18 (35.3)	4 (36.4)	14 (35.0)	1.0
Diarrhoea	18 (36.0)	4 (36.4)	14 (35.9)	1.0
<b>Laboratory Features</b>				
Initial CRP (mg/L)	126 (53, 176) (N=52)	88 (78, 157) (N=11)	131 (50, 176) (N=41)	0.86
Peak CRP (mg/L)	159 (59, 209) (N=52)	132 (80, 236) (N=11)	163 (57, 209) (N=41)	0.89
Initial D-dimer (mcg FEU/L)	2335 (946, 3792) (N=45)	3339 (2335, 4270) (N=10)	2050 (860, 3504) (N=35)	<b>0.03</b>
Peak D-dimer (mcg FEU/L)	2708 (1250, 5058) (N=46)	4156 (2919, 5958) (N=11)	2234 (1071, 4575) (N=35)	0.12
Initial Troponin (µg/L)	0 (0,0.06) (N=32)	0.05 (0.04, 0.47) (N=7)	0 (0, 0.05) (N=25)	<b>0.01</b>
Peak Troponin (µg/L)	0.005 (0, 0.21) (N=36)	0.27 (0.13, 0.80) (N=10)	0 (0, 0.09) (N=26)	<b>0.001</b>
Initial BNP (ng/L)	150 (45, 401) (N=33)	470 (240, 1245) (N=10)	102 (30, 297) (N=23)	<b>0.004</b>
Peak BNP (ng/L)	346 (61, 1065) (N=33)	1406 (845, 2049) (N=10)	102 (30, 401) (N=23)	<b>0.0002</b>
<b>Echocardiographic Findings (N [%])</b>				
Myocardial dysfunction	6/46 (13.0)	4/11 (36.4)	2/35 (5.7)	<b>0.02</b>
Coronary artery abnormalities	17/46 (37.0)	3/11 (27.3)	14/35 (40)	0.50
<b>Pharmacologic Interventions (N [%])</b>				
IVIG	33 (63.5)	10 (90.9)	23 (56.1)	<b>0.04</b>
Second IVIG	12 (23.1)	5 (45.5)	7 (17.1)	0.1
Corticosteroid (any dose)	25 (48.1)	10 (90.9)	15 (36.6)	<b>0.002</b>
ASA	28 (53.9)	7 (63.6)	21 (51.2)	0.52
Anticoagulation	6 (11.5)	3 (27.3)	3 (7.3)	0.10
Prophylactic	4 (7.7)	3 (27.3)	1 (2.4)	<b>0.026</b>
Therapeutic	2 (3.85)	0 (0)	2 (4.9)	1.0
Antibiotics	33 (63.5)	10 (90.1)	23 (56.1)	<b>0.04</b>
Antivirals	2 (3.9)	0 (0)	2 (4.9)	1.0
<b>Intensive Care Interventions (N [%])</b>				
Inotropes	12 (23.1)	5 (45.5)	7 (17.1)	0.1
Invasive ventilation	6 (11.5)	3 (27.3)	3 (7.3)	0.10
ECLS	1 (1.9)	0 (0)	1 (2.4)	1.0
<b>Outcomes</b>				
Length of stay (days)	5 (3, 7)	6 (4, 9)	5 (3, 7)	0.19
ICU Admission (N [%])	13 (25.0)	7 (63.6)	6 (14.6)	<b>0.003</b>
Death (N [%])	0 (0)	0 (0)	0 (0)	1.0

Categorical data are presented as n (%). Continuous data are presented as median (interquartile range). P-values are shown for comparison between the confirmed and ruled out groups using Fisher's Exact test (categorical variables) and Wilcoxon Rank Sum (continuous variables). Bold values indicate those with a P<0.05. ASA, acetylsalicylic acid; BNP, brain natriuretic peptide; CRP, C reactive protein; ECLS, extracorporeal life support; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction.

is in keeping with existing literature (10,12–14). Patients with confirmed MIS-C commonly presented with gastrointestinal (GI) and mucocutaneous symptoms, but at a rate comparable to the ruled-out group. This is likely because of the large proportion of KD patients in the ruled-out group, in which mucocutaneous inflammation is a hallmark feature (15). The ruled-out group also included patients with bacterial infections causing fever and GI symptoms, such as *E coli*, *Campylobacter jejuni* and *Salmonella* Typhi. Shock was more frequent in the confirmed MIS-C compared to the ruled-out group. The MIS-C cohort similarly tended to have more cardiac dysfunction, as evidenced by higher levels of BNP and troponin and a greater frequency of myocardial dysfunction seen on echocardiogram. Confirmed MIS-C was also associated with a higher frequency of ICU admission and higher initial D-dimer values. Importantly, inflammatory markers (particularly C-reactive protein) were similar between MIS-C and non-MIS-C cases, suggesting that this biomarker alone may not identify MIS-C cases.

One important finding is the high proportion of bacterial infections in patients who were evaluated for MIS-C. This underscores the need to always consider sepsis in children presenting with features of MIS-C, and to avoid cognitive biases that may predispose clinicians to overlooking other life-threatening causes of shock.

Almost all our MIS-C patients received IVIG and corticosteroids, with 5 given a second dose of IVIG. It is increasingly recognized that early corticosteroids in conjunction with IVIG may be effective in reducing ICU length of stay and clinical severity (16,17). Recent guidelines discourage administration of a second dose of IVIG (18) and we adapted our recommendations accordingly. No thromboembolic events were reported in our cohort, nor bleeding complications in those on prophylactic anticoagulation.

### Limitations

The relatively small sample size of cases limited our ability to identify further differences between confirmed and ruled-out cases of MIS-C. In an attempt to maximize the sensitivity of our analysis for differences between MIS-C ruled-out and MIS-C confirmed groups, we did not correct our statistical analysis for multiple comparisons. This hypothesis-generating strategy increases the risk of type one error, and the p-values reported should be considered nominal. Second, while data were collected prospectively, not all patients evaluated had a full MIS-C workup. We do not feel that this would have impacted their final diagnosis because alternative diagnoses were made. Certain laboratory parameters were not included for all patients thus decreasing the sample size for comparison between the cohorts. Specifically, pro-BNP and high-sensitivity troponin values, measured in a minority of patients, were excluded from the analysis as these cannot be directly compared to BNP and conventional troponin values, respectively. Our definition was limited to hospitalized patients; it is possible that there were mild cases treated as outpatients. Twenty of our non-MIS-C patients with KD or a KD/TSS picture did not meet criteria due to a lack of evidence of SARS-CoV-2 infection or an epidemiologic link to a known case. Some of these cases may have had an unrecognized epidemiologic link to SARS-CoV-2. Further, we did not routinely repeat serology in seronegative patients, although serology is typically positive 2 weeks after SARS-CoV-2 infection (19). Finally,

we did not have a centralized long-term follow-up process for our MIS-C patients apart from routine cardiology follow-up.

### CONCLUSIONS

MIS-C is a rare sequela of SARS-CoV-2 infection that can affect children of all ages. This study presents our centre's quality initiative response to this entity and describes the cases observed. Our working group's surveillance and evolution with the existing literature attempted to ensure that children with features of MIS-C received the appropriate workup and management in our province.

### SUPPLEMENTARY DATA

Supplementary data are available at *Paediatrics & Child Health* Online by searching for pxab110.

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