



Quality Improvement

Review of MIS-C Clinical Protocols and Diagnostic Pathways: Towards a Consensus Algorithm

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ABSTRACT

Background: The emergence of multisystem inflammatory syndrome in children (MIS-C) during the severe acute respiratory syndrome coronavirus 2 pandemic led to the development of institutional clinical pathways based on expert opinion. We assessed North American paediatric centres' adaptation to MIS-C and analysed the degree of agreement between algorithms on tiered clinical investigations.

Methods: This study evaluated MIS-C diagnostic algorithms from 50 tertiary centres developed between May 2020 and December 2021 in the United States and Canada obtained online and through colleagues in various institutions. Descriptive statistics were used to analyse results.

RÉSUMÉ

Contexte : L'émergence du syndrome inflammatoire multisystémique chez les enfants (SIME) pendant la pandémie de SARS-CoV-2 a amené les établissements de soins pédiatriques à concevoir des approches cliniques fondées sur l'opinion d'experts. Nous avons évalué l'adaptation des établissements de soins pédiatriques nord-américains à la réalité du SIME et analysé le degré de concordance des algorithmes au niveau des paliers d'investigation clinique.

Méthodologie : Cette étude a permis d'évaluer les algorithmes de prise en charge du SIME développés entre mai 2020 et décembre 2021 dans 50 établissements de soins tertiaires aux États-Unis et au Canada. Les algorithmes ont été obtenus en ligne et par l'intermédiaire de collègues

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a global pandemic on March 11, 2020. In the spring of 2020, clusters of cases of a shock-like inflammatory syndrome in paediatric patients were observed among various centres across Europe and the United States.¹⁻⁶ Reports of a novel clinical syndrome described a clinical picture consistent with shared features of Kawasaki disease and/or toxic shock syndrome, and significant systemic hyperinflammation and cardiovascular involvement.⁷⁻¹¹ Although most cases described were of mild-to-moderate severity, cases of severe shock requiring intensive care admission were also reported,^{12,13} rarely resulting in patient demise. An epidemiologic link with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was established, leading to several case definitions determined by the WHO,¹⁴ the Centers for Disease Control and Prevention (CDC),¹⁵ the

Royal College of Pediatrics and Child Health,¹⁶ and the Canadian Paediatric Surveillance Program.^{17,18} Since the onset of the COVID-19 pandemic, an alarming rate of cases have been reported. Although specific case definitions vary, the terms multisystem inflammatory syndrome in children (MIS-C),^{14,15} paediatric inflammatory multisystem syndrome,¹⁸ and paediatric inflammatory multisystem syndrome temporally associated with COVID-19¹⁶ describe a postinfectious hyperinflammatory syndrome associated with the COVID-19 virus.

The emergence of novel clinical entities poses a diagnostic and therapeutic challenge for physicians and health professionals. Globally, paediatric experts were faced with the dilemma related to the diagnosis and management of patients presenting with symptoms suggestive of MIS-C.¹⁹ Given its novelty, a lack of literature limited the creation of evidence-based recommendations. Despite limited studies at the time, several paediatric societies released clinical guidance documents in summer 2020 based on clinical experience available. The American Academy of Pediatrics issued interim guidance on July 13, 2020.²⁰ Specific guidelines for the proposed investigations and treatment of MIS-C were published by the American College of Rheumatology (ACR), with the initial

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Results: All clinical pathways used a tiered approach, and most required coronavirus disease 2019 polymerase chain reaction testing on presentation. Over one-quarter used a 24-hour fever to initiate investigations, and another quarter used 3 days. Basic biochemical workup was performed in all centres on presentation (complete blood count, inflammatory markers, hepatic, and renal functions). Specialized investigation was generally reserved for secondary testing (cardiac biomarkers, electrocardiogram and echo, and coagulation panel). Institutions were divided on several investigations for tier distribution, including urine studies, blood cultures, chest radiograph, and severe acute respiratory syndrome coronavirus 2 serology. Subspecialty consultations were reserved for second-line testing, including cardiology, infectious disease, and rheumatology. Finally, we propose a composite algorithm representative of the consulted pathways.

Conclusions: Faced with an unprecedented clinical challenge, paediatric institutions responded swiftly with evaluation standardization, adapting to evolving knowledge. Most pathways agreed on initial basic screening tests followed by secondary workup including cardiac investigations. These protocols, developed during a high level of uncertainty, require comparative assessment on efficacy and superiority.

version available online as of July 23, 2020,²¹ and the final version published on December 5, 2020.²² The Canadian Paediatric Society published a practice point on July 6, 2020, as well as an update on May 3, 2021.¹⁸

Despite this challenge faced by paediatricians across the globe, centre-specific protocols and algorithms were developed based on available and emerging literature. Protocols varied based on location, centre preferences, and accessibility and availability of investigations and treatments. Consequently, a comparison of MIS-C algorithms across paediatric centres internationally needs to be studied to better understand where paediatric centres agree and disagree. Consequently, the objective of this observational study was to review common elements in MIS-C protocols across various tertiary paediatric centres in North America.

Methods

We screened MIS-C protocols and clinical pathways of 50 available paediatric tertiary centres in North America. Protocols were obtained through internet search (“MIS-C protocol,” “algorithm” “clinical pathway,” or slight variations) or through colleagues within a specific institution up until December 2021. Centres were chosen based on protocol availability and centre expertise. Characteristics of each clinical pathway were analysed and compared. Descriptive statistics were used. A protocol was excluded if it contained insufficient information on the evaluation of potential MIS-C cases, for

example, if the institutional protocol included case definitions for suspected cases but no clear algorithm or list of investigations. We scanned for protocol updates in search of a potential time point when such updates would have occurred the most and considered this as a possible indicator for impactful shift in management.

Résultats : Tous les algorithmes comportaient des paliers d’investigation, et la plupart réclamaient un test de détection moléculaire du SARS-CoV-2 par réaction en chaîne de la polymérase (PCR) lors de la consultation initiale. Plus du quart des établissements amorçaient des investigations lorsqu’une fièvre se manifestait depuis 24 heures; un autre quart des établissements faisaient de même lorsque la fièvre était présente depuis trois jours. Des analyses biochimiques de base étaient demandées dans tous les établissements lors de la consultation initiale (hémogramme, bilans inflammatoire, hépatique et rénal). Les investigations spécialisées étaient généralement réservées aux analyses et examens secondaires (dosage des biomarqueurs cardiaques, électrocardiographie, échocardiographie, tableau de coagulation). Les établissements étaient mitigés quant à la distribution de plusieurs investigations par paliers, dont les analyses d’urine, les hémocultures, les radiographies thoraciques et les tests sérologiques de détection des anticorps dirigés contre le SARS-CoV-2. Les consultations surspécialisées étaient réservées aux investigations de deuxième ligne, notamment en cardiologie, en infectiologie et en rhumatologie. Pour résumer nos observations, nous proposons un algorithme représentatif des différents algorithmes consultés.

Conclusions : Face à un défi clinique sans précédent, les établissements de soins pédiatriques ont rapidement réagi en normalisant l’évaluation des patients et en s’adaptant à l’évolution des connaissances. La plupart des algorithmes concordaient en ce qu’ils prévoyaient un dépistage de base lors de la consultation initiale, suivi d’un bilan secondaire relevant notamment de la cardiologie. Ces protocoles, conçus dans un contexte de grande incertitude, doivent être l’objet d’une évaluation comparative de l’efficacité et de la supériorité.

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Data including basic bloodwork, infectious studies, imaging, amongst others, were collected. Tier 1 investigations included tests or consultations systematically ordered for all patients with a clinical suspicion for MIS-C, regardless of clinical stability on initial presentation. Tier 2 included investigations ordered based on abnormal tier 1 results or clinical instability (eg, for patients presenting with shock). A specific test was not included if only written as “to consider” without being systematically ordered; however, this information was noted for each protocol when possible. Tier 3 investigations included tests ordered according to consultant or subspecialist evaluation. Other tests ordered based solely on presenting symptoms (eg, diarrhoea or vomiting, respiratory symptoms) were also noted when possible. Where multiple versions of protocols from a single institution were available, only the most recent protocol was included. Where clinical pathways contained a statement for consultation with a specialty “as needed,” “if clinical concerns,” or “to consider,” without further details available, these consultations were considered in a separate category (and not tier 2), as to avoid overestimation.

We finally created a common representative algorithm based on our results from the 50 clinical pathways. An

investigation was incorporated in this final algorithm if included by many centres (ie, $\geq 30\%$ of protocols), with a distinction between investigations included in $\geq 30\%$ but $< 50\%$ (discontinued line boxes) vs $> 50\%$ (solid line boxes) as displayed in Figure 1. A test was considered as tier 2 if the difference between tiers was $\geq 20\%$ (ie, in the case where there was more than 20% disagreement between algorithms). The test was considered in a grey zone (between tier 1 and tier 2) if the disagreement between algorithms was $< 20\%$. For example, although all institutions include the use of troponin, 32% included these tests at the tier 1 level vs 68% at the tier 2 level. For the tests in the grey zone, we performed a test for proportions and used $P < 0.05$ for statistical significance.

Results

Clinical pathways for the diagnosis and management of MIS-C from 55 paediatric centres were reviewed. A total of 5 protocols were excluded because of insufficient information; 50 protocols were included in our analysis.

A map detailing centre locations across North America is included in Figure 2 with superimposed cumulative cases of MIS-C by state (as of November 30, 2021²³) and by province (as of May 31, 2021^{17,24}). Clinical pathway information and Web site sources

(when available) are provided in Supplemental Appendix S1. A timeline of last available protocol versions, according to issuing dates, is shown in Figure 3. In total, 39 protocols had indications of updates/previous versions; the remaining protocols were either original versions or the status of potential updates was undisclosed. The latter protocols were considered as original versions. Three protocols were publications.²⁵⁻²⁷

Of the pathways reviewed, 49 were from tertiary or quaternary care institutions, with one being a provincial guideline used at a Canadian institution. Six protocols were from Canada, and 44 were from the United States. The CDC definition of MIS-C was used in 19 protocols (38.0%), whereas 6 protocols used a mix of CDC and WHO definitions. The definition used was unclear/undisclosed in 21 protocols (42%). One centre used the WHO definition, and 3 centres used an institution-defined case definition. All clinical pathways used a tiered investigational approach. A minimum duration of fever of 24 hours was a cutoff to start workup for a possible diagnosis of MIS-C in one-quarter (14 of 50 [28.0%]) of protocols, and 3 days of fever another quarter of protocols (14 of 50 [28.0%]). The presence of any fever was used in 7 protocols (14.0%). Eleven protocols (22.0%) used 3 days if mild symptoms and any duration (or 1 day) if severe symptoms on presentation. One protocol used a 2-day duration of fever, and 1 protocol used a 3-day duration if

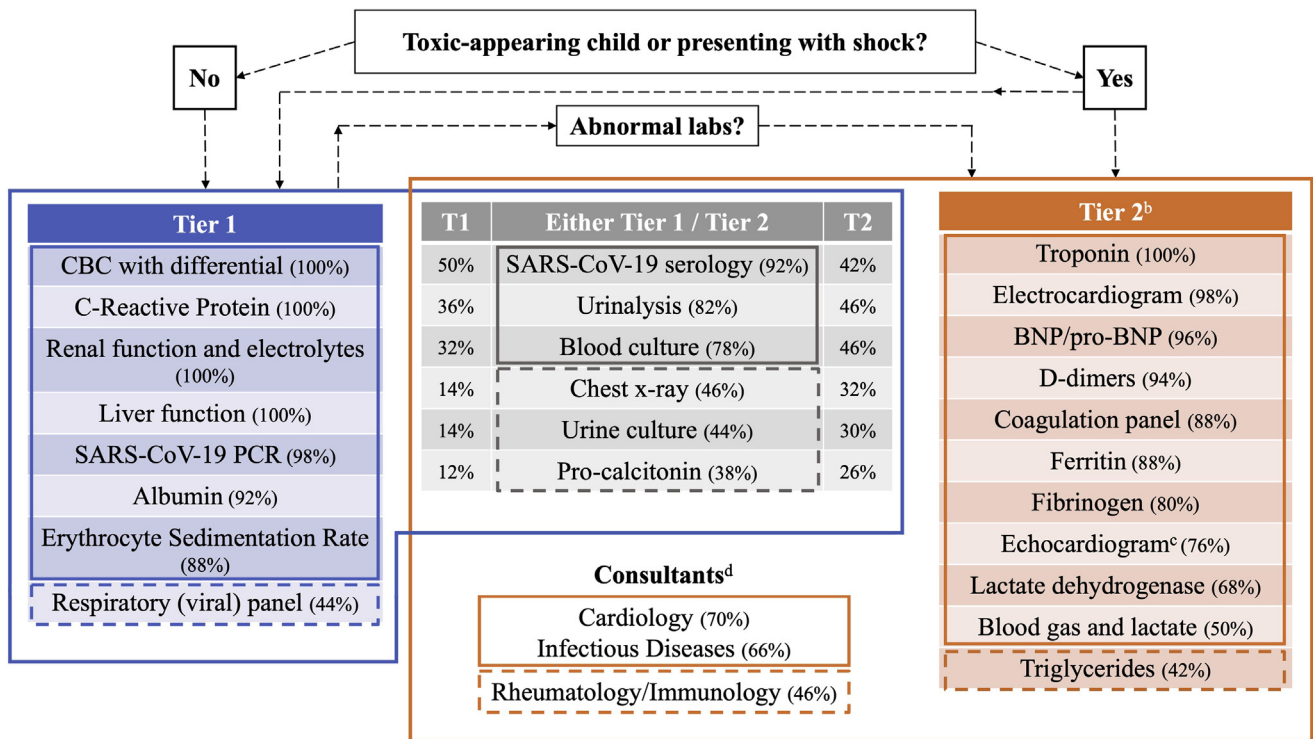


Figure 1. Common proposed algorithm for the evaluation of possible MIS-C cases according to results of 50 North American clinical pathways. A **solid line** boxes investigations performed in $\geq 50\%$ of protocols; a **dashed line** boxes investigations included in $\geq 30\%$ of protocols but $\leq 50\%$. Percentages (%) are proportions of algorithms suggesting that test. Tier 2 category if the difference between tiers $\geq 20\%$, or mitigated tiers (**gray shade table**) if difference between tiers $< 20\%$. BNP, brain natriuretic peptide; CBC, complete blood count; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. ^aSerology test based on results or PCR test or lack of confirmed documented exposure to coronavirus disease 2019. ^bThe most common Tier 2 tests used in the protocols analysed are included here; however, others can be added depending on clinical suspicion and/or risk factors. ^cEchocardiography can either be performed directly as a second-line test, or as a third-line depending on consultant (often cardiology) recommendation. ^dAdditional consultants, such as haematology, can be included as needed.

inpatient and a 1-day duration if outpatient. The duration of fever was unclear in 2 protocols. Overall, 38 of 50 clinical pathways (76.0%) included a statement for consideration of additional workup according to clinical indication and/or the differential diagnosis. The majority (62.0%) of protocols were dated in 2021.

A detailed list of investigations of all 50 clinical pathways is included in [Supplemental Table S1](#). Most centres (76.0%) included a nasopharyngeal COVID-19 polymerase chain reaction (PCR) test on presentation, whereas the remaining protocols included it as a second-tier investigation. One protocol did not mention COVID-19 PCR testing. Half of protocols (50.0%) systematically asked for COVID-19 serology initially and another 21 centres (42.0%) as a second-line test. Three protocols included a COVID-19 stool PCR in the presence of gastrointestinal symptoms and/or consultant recommendations. All pathways included a complete blood count and c-reactive protein on presentation. Almost three-quarters of protocols (74.0%) included an erythrocyte sedimentation rate as a first-line test. Renal and liver function tests were included as initial investigations in most protocols (100% and 96.0%, respectively). Almost

two-thirds of protocols (64.0%) included ferritin as a second-line investigation. Coagulation panel, fibrinogen, and d-dimers were ordered routinely as second tier tests in over one-half of protocols (70.0%, 60.0%, and 70.0%, respectively), whereas only some centres requested these tests on presentation (18.0%, 20.0%, and 24.0%, respectively). Troponin levels were obtained systematically as tier 1 tests in one-third of clinical pathways (16 of 50 [32.0%]) and as tier 2 tests in the remaining two-thirds (34 of 50 [68.0%]). Results were similar for brain natriuretic peptide/pro-brain natriuretic peptide testing (28.0% as tier 1 and 68.0% as tier 2).

Further infectious, haematology, and rheumatology workup considerations are listed in [Supplemental Table S1](#). Blood cultures were included as a primary test in one-third (32.0%) of clinical pathways and as a secondary test in another half (46.0%). Almost one-third (16 of 50 [32.0%]) of clinical pathways included a respiratory pathogen panel on presentation. Urinalysis was ordered on presentation in over one-third (36.0%) of pathways and as a second-tier test in another 23 centres (46.0%). Urine cultures were ordered as tier 2 tests in one-third (30.0%) of protocols. One-quarter of pathways (11 of 50 [22.0%]) included a cytokine panel as a routine second-tier investigation. Other

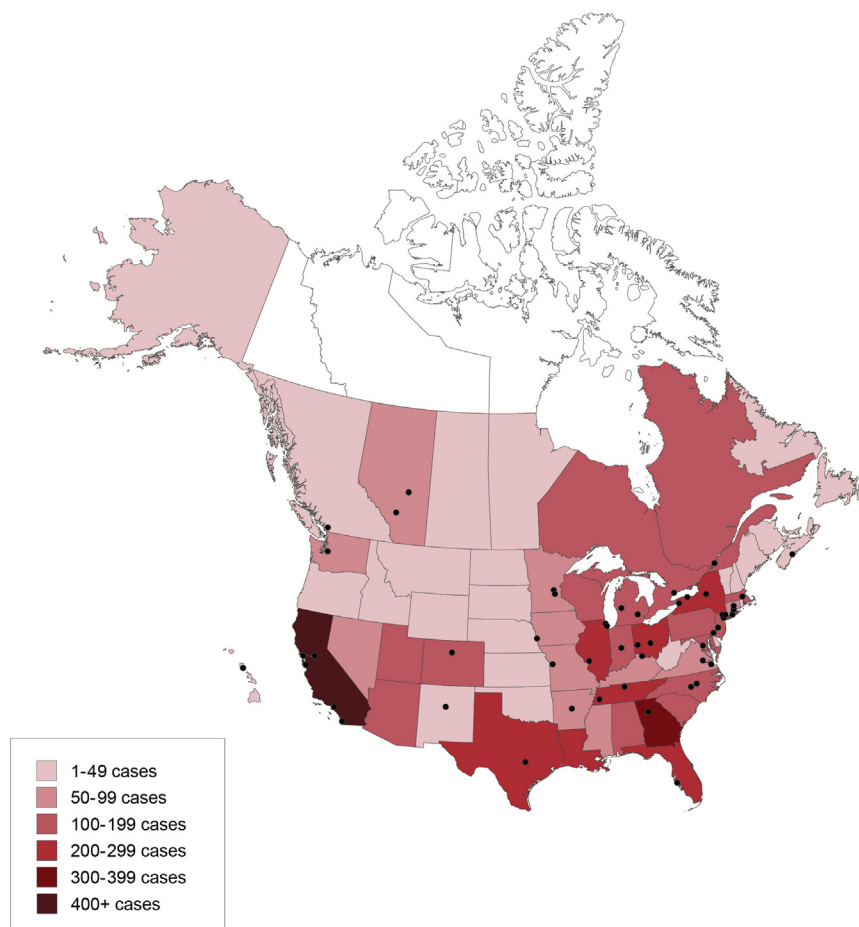


Figure 2. Geographical distribution of 50 multisystem inflammatory syndrome in children (MIS-C) clinical pathways' North American paediatric centres. Centres included in study are shown as **filled circles**. Reported MIS-C cases by state are shown up to November 30, 2021, according to Centers for Disease Control and Prevention data.²³ Canadian cases, by province, are shown up to May 31, 2021, according to the Canadian Paediatric Surveillance Program (the Canadian Pediatric Society).^{17,24}

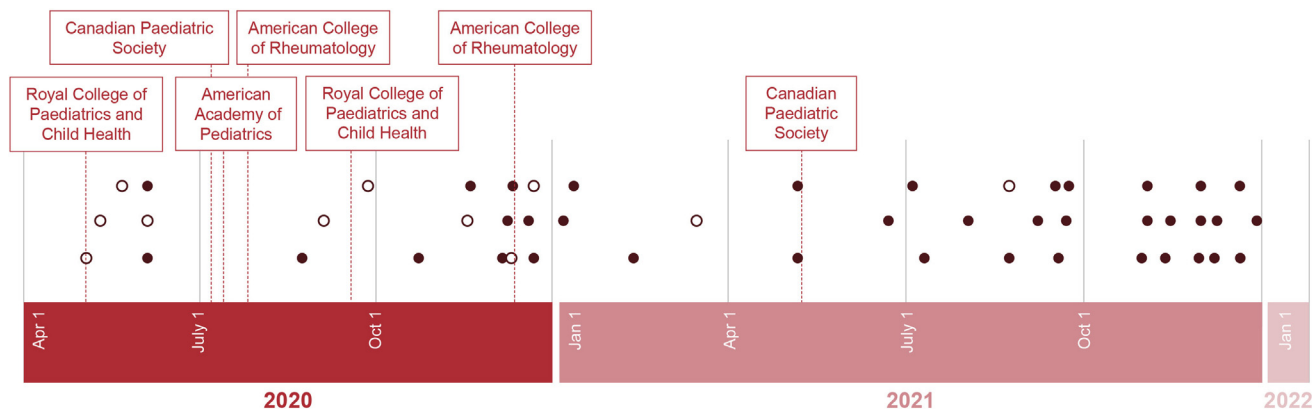


Figure 3. Timeline from 50 North American multisystem inflammatory syndrome in children clinical pathways. Guidelines and practice points from the American Academy of Pediatrics,²⁰ Canadian Paediatric Society,¹⁸ Royal College of Paediatrics and Child Health,^{16,28} and American College of Rheumatology.^{21,22} Filled circles represent clinical pathways with confirmed updates, whereas original pathways or pathways whose version was unknown are shown in white circles.

investigations included viral serologies, blood PCR for pathogen-specific infections, antiphospholipid panels, complement workup, and quantitative serum immunoglobulins.

Few pathways (8 of 50 [16.0%]) of protocols included an electrocardiogram systematically at presentation, whereas the majority (41 of 50 [82.0%]) included it as a second-line test. One pathway that did not include routine electrocardiogram nor echocardiography included an indication based on presenting symptoms. Two clinical pathways (4.0%) included cardiac echocardiography on initial presentation; however, routine echocardiography studies were included in the majority (72.0%) of clinical pathways as second-line. Another 6 pathways (12.0%) included echocardiography after discussion with cardiology. Five pathways did not mention echocardiography in their algorithms. One-third of protocols (32.0%) included chest radiographs as secondary tests. Abdominal echography, in the presence gastrointestinal symptoms, was mentioned in almost one-quarter of protocols (11 of 50 [22.0%]).

The evolution and management of MIS-C included an interdisciplinary team of various subspecialties in most centres. A consultation in infectious diseases on presentation was included in very few pathways (4.0%), whereas as second-line in almost two-thirds of protocols (62.0%) and for specific conditions in another 6 protocols (12.0%). No institutions requested cardiology consultation as an initial investigation; however, the majority (70.0%) included a routine cardiology consultation as second-line. Specific considerations for cardiology consultation were noted in another 6 pathways (12.0%). Rheumatology service was requested only as a second-line investigation in almost half of protocols (23 of 50 [46.0%]); however, 14 centres (28.0%) noted specific conditions for rheumatology consultation. Specific indications/conditions for haematology consultation were noted in one-quarter of pathways (26.0%), for example, for consideration of anticoagulation; however, only 8 centres (16.0%) included routine consultation (all as second-line). Nephrology, gastroenterology, and neurology consultations were included in several pathways based on specific conditions in several protocols (12.0%, 8.0%, and 8.0%, respectively). Details regarding subspecialty consultations are listed in [Supplemental](#)

Table S2. A final common algorithm was created based on cumulative results, as shown in [Figure 1](#).

Most of these updates appeared after October 31, 2020, which was set as the point in time when a cluster of new and updated protocols were observed. Of the 10 protocols before October 2020, 4 (40.0%) were updated versions, in contrast to most protocols (87.5%) after October 2020. Among the 6 tests in the grey zone between tier 1 and tier 2 ([Fig. 1](#)), more centres dated after October 31, 2020, included SARS-CoV-2 serology (50.0% vs 10.0%, $P = 0.02$), procalcitonin (32.5% vs 0.0%, $P = 0.04$), and urinalysis (50.0% vs 30.0%, $P = 0.03$) in tier 2 vs centres with protocols dated before October 31, 2020. The rest of the tests in the grey zone were not statistically significant.

Discussion

This qualitative study of North American MIS-C protocols contributes a consensus summary of 50 clinical protocols in the evaluation of MIS-C. Its results reflect the practical approach with which institutions with paediatric expertise adapted to an unprecedented and untimely clinical entity with only emerging literature. Despite a lack of evidence-based data due to limited clinical experience, the protocols reflect the adaptability of paediatric institutions and urgency to make clinical decisions despite debatable research on MIS-C. This study should be viewed from the perspective illustrating how paediatric centres adapted in response to MIS-C. The inclusion of recent protocols provides refined algorithms based on centre experience and emerging knowledge. However, a systematic review of tertiary centres' clinical pathways was not possible because most protocols were not published in peer-reviewed scientific journals and were not listed in traditional reference databases (eg, PubMed).

Our timeline in [Figure 3](#) demonstrates that a substantial number of updated versions of clinical pathways (coloured circles) were issued after October 31, 2020, whereas original clinical pathways were predominantly present before. Despite several tests in the grey zone between tier 1 and tier 2, the shift of SARS-CoV-2 serology, procalcitonin, and urinalysis to

second line in protocols dated after October 31, 2020, suggests increased confidence in establishing a diagnosis of MIS-C or case severity with less investigations needed. This is consistent with Bayesian clinical learning that occurred as cumulative knowledge about MIS-C becomes available. Our findings suggest that the updated clinical pathways represent matured versions of original protocols, possibly reflecting responses of paediatric institutions based on experience, emerging literature, and guidelines,^{16,18,20,28} whereas earlier protocols were best-guess adjustments (given the lack of literature) based on limited available science and on extrapolated knowledge from other disease conditions.

Other research has surveyed paediatric experts from various centres regarding institutional protocols for the evaluation of MIS-C. A study analysing hospital protocols for the diagnosis and management of MIS-C between June and July 2020 used a questionnaire that was sent via a web-based platform to collect data on hospital information and protocol characteristics.²⁹ Our study differs from the previous study in our inclusion of protocols spanning a 20-month period (ie, from May 2020 to December 2021), with over half of protocols (50.0%) after June 2021. Less than half of protocols (20 of 50) were common to both studies. Overall, rates of COVID-19 PCR and serology testing appeared to be similar in both studies, as was basic bloodwork including complete blood count, inflammatory markers, liver function tests, and chemistry panels. We found that the majority of centres included troponin as second-line and only one-third on presentation; however, in the previous study, the majority of centres included troponin for all patients with potential MIS-C. We also noted a more selective use of electrocardiograms and echocardiography on presentation. In contrast with the initial shared opinions on the evaluation of MIS-C with near immediate consultation with cardiology, the present data showed that most cardiology consultations were part of tier 2 investigations. Similar findings were observed for infectious disease and rheumatology subspecialty consultations in comparison with a previous study.²⁹ This shift in paradigm reflects the emergence of more robust supportive literature along with advancing clinical experience. The lack of routine rheumatology consultation in nearly half of protocols suggests either an increased clinical confidence among general paediatricians in the management of MIS-C or a direct admission to rheumatology services. However, an additional 28% of protocols included rheumatology consultation for specific conditions, such as refractory disease ([Supplemental Table S2](#)). These latter observations suggest that rheumatology service is unlikely to be a first-line consulting service and more of a supportive role for potentially complex MIS-C cases.

Our common algorithm based on cumulative pathways simplifies the stepping-up towards the tier 2 level as it displays tests where various institutions disagree between each other (tier 1 vs tier 2). Whereas the ACR recommendations are the resultant of experts' opinion,²² our comparative analysis and deduced algorithm represents a consensus analysis considering a range of multidisciplinary expert groups' clinical practice pathways originating from multiple tertiary institutions in geographical areas where the largest MIS-C experience was recorded. To our knowledge, neither the ACR nor other algorithms have undergone cost-benefit

assessment or efficacy evaluation. We therefore suggest an optimized investigation algorithm summarizing various preferences from the analysed algorithms, which may be used as a common denominator for the sake of comparing individual algorithms to this "consensus" algorithm.

Our study has several limitations. First, given that most institutional protocols are often for internal use, only protocols available through a public Web site and/or private contact were collected. Protocols from other tertiary paediatric centres whose pathways were not available through these collection methods were excluded and may influence our data. Second, several clinical pathways referenced one another, reflecting potential overlap between protocols, complicating analysis. Third, we did not control for number of cases of MIS-C seen at each institution, and this may affect our results as hospitals with a higher volume of MIS-C patients seen may modify their pathways based on clinical experience. However, as shown in the mapped display, the algorithms essentially originate from the most affected (and experienced) states and provinces. Our study does not analyse therapeutic approach as this was not its scope or the scope of the algorithms. Hence we did not control for success rates vs failure potentials of the protocols, which is, again, beyond the scope of this project. However, we aimed to overcome this by targeting tertiary and quaternary care institutions. In addition, in order to address the potential rapid evolution of institutional protocols, we contacted all centres to validate current protocol use and inquire for newer versions when possible. To the best of our knowledge, we were able to validate current use in the majority (92.0%) of centres, either through direct contact or through the centre's Web site. For protocols dated >6 months old, we were able to confirm current versions in 22 of 25 protocols (88.0%) by this same method. Finally, the protocols used in the study were compared qualitatively and not systematically, and thus, the results must be interpreted in this limited context.

Despite these limitations, our study contributes to existing literature by providing a simplified algorithm for the evaluation of MIS-C based on pathways from 50 centres across North America, using updated pathways that reflect emerging evidence and clinical experience. Our findings may provide supplementary information (in addition to established guidelines set forth by clinical societies) to help guide centres with fewer resources. In particular, given the risk of cardiac complications in MIS-C, our findings suggest that most clinical pathways reserve cardiac investigations as second-line testing when evaluating cardiovascular involvement in suspected cases. Directions for future research include cost-benefit analysis and systematic review of protocols including assessment of superiority between pathways. The MIS-C experience represents an important lesson and a case study for potential unexpected novel clinical entities in the future.

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Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Pediatric and Congenital Heart Disease* at <https://www.cjcpc.ca/> and at <https://doi.org/10.1016/j.cjcpc.2022.01.003>.