PEDIATRIC CLINICAL CARE GUIDELINES

Alberta Children's Hospital

Alberta Health Services

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C): CARE GUIDE FOR CHILDREN AND ADOLESCENTS IN ALBERTA

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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) KEY MESSAGES

- MIS-C is a rare complication of SARS-CoV-2 infection
- Consider MIS-C in children or adolescents with any of the following:
  - Fever for 3 or more days, with a recent history of SARS-CoV-2 infection OR known exposure
  - Fever accompanied by abdominal pain or significant vomiting/diarrhea
  - Fever accompanied by shock
  - Signs and symptoms similar to Kawasaki Disease and Toxic Shock Syndrome (TSS)
- Do not delay anti-microbial therapy because you suspect MIS-C, as it is a diagnosis of exclusion

For physicians working at Alberta Level 1 and 2 Emergency Departments - if you suspect a child may have Multi-System Hyperinflammatory Syndrome (MIS-C) - please contact RAAPIDNorth or RAAPID South and ask to speak (for a stable patient) to a Children's Hospital ED physician or (for an unstable patient) a Pediatric Intensivist. Refer to the MIS-C case identification brief poster.

INTRODUCTION

This document addresses Multisystem Inflammatory Syndrome in Children (MIS-C), a condition characterized by fever, inflammation, and multiorgan dysfunction that manifests late in the course of what is often an asymptomatic or mild SARS-CoV-2 infection.[1] These patients present with an acute febrile illness accompanied by a hyper-inflammatory syndrome and often suffer multi-organ failure, particularly acute heart failure, some weeks after an acute COVID-19 infection or exposure to COVID-19.[2] [3] Early recognition and appropriate transfer and management of these patients is critical. Children may present with shock and may not tolerate large volume fluid resuscitation. These patients should be managed at a tertiary pediatric centre. Although these children are often critically ill, most children ultimately will have favorable outcomes. Comprehensive data for Canada is not available but data for the US is available through the Center for Disease Control; as of August 27th, 2021, 4601 children have met CDC's case definition for MIS-C, and 41 have died (0.8%).[4] https://www.cdc.gov/mis/cases/index.html

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Highlights from the CDC data include:

- The median age of children with MIS-C is 9 years, with half between 5 and 13 years of age.
- Of children whose race/ethnicity is known, 61% are either Hispanic/Latino (1,316 cases) or Non- Hispanic Black (1,362 cases).
- 98% of children had a positive test result for SARS CoV-2; the remaining 2% had contact with someone with COVID-19.
- 60% of children are male.[4]

MIS-C CASE DEFINITIONS

Although different terms are used for this condition, e.g. Pediatric Inflammatory Multisystem Syndrome (PIMS), the most common one used is Multisystem Inflammatory Syndrome in Children (MIS-C). Our case definition is that of the World Health Organization Multisystem inflammatory syndrome in children and adolescents with COVID-19.

Children and adolescents 0–19 years of age with fever > 38.0°C for 3 or more days
AND
Two or more of the following:

- Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
- Hypotension or shock
- Features of myocardial dysfunction, myocarditis, pericarditis, valvulitis, or coronary abnormalities including ECHO findings or markers for inflammatory elevated Troponin / N- terminal pro b-type natriuretic peptide (NT-proBNP).
- Evidence of coagulopathy (elevated PT, PTT or d-Dimers)
- Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

AND
Elevated markers of inflammation such as:

- ESR
- C-reactive protein

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 other patients with COVID-19

DIFFERENTIAL DIAGNOSIS

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There is an overlap with various other inflammatory syndromes such as cytokine storm syndrome (CSS) seen in adult and pediatric COVID-19 ARDS, macrophage activating syndrome (MAS), hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome (SIRS), culture-negative sepsis, multi-organ dysfunction syndrome seen in septic shock, cytokine release syndrome (CRS) in oncology CAR-T therapy, and, as already mentioned, KD and TTS. MIS-C overlaps with KD with associated cardiogenic shock/myocarditis (KDSS). Coronary aneurysms have been described in MIS-C.[5]

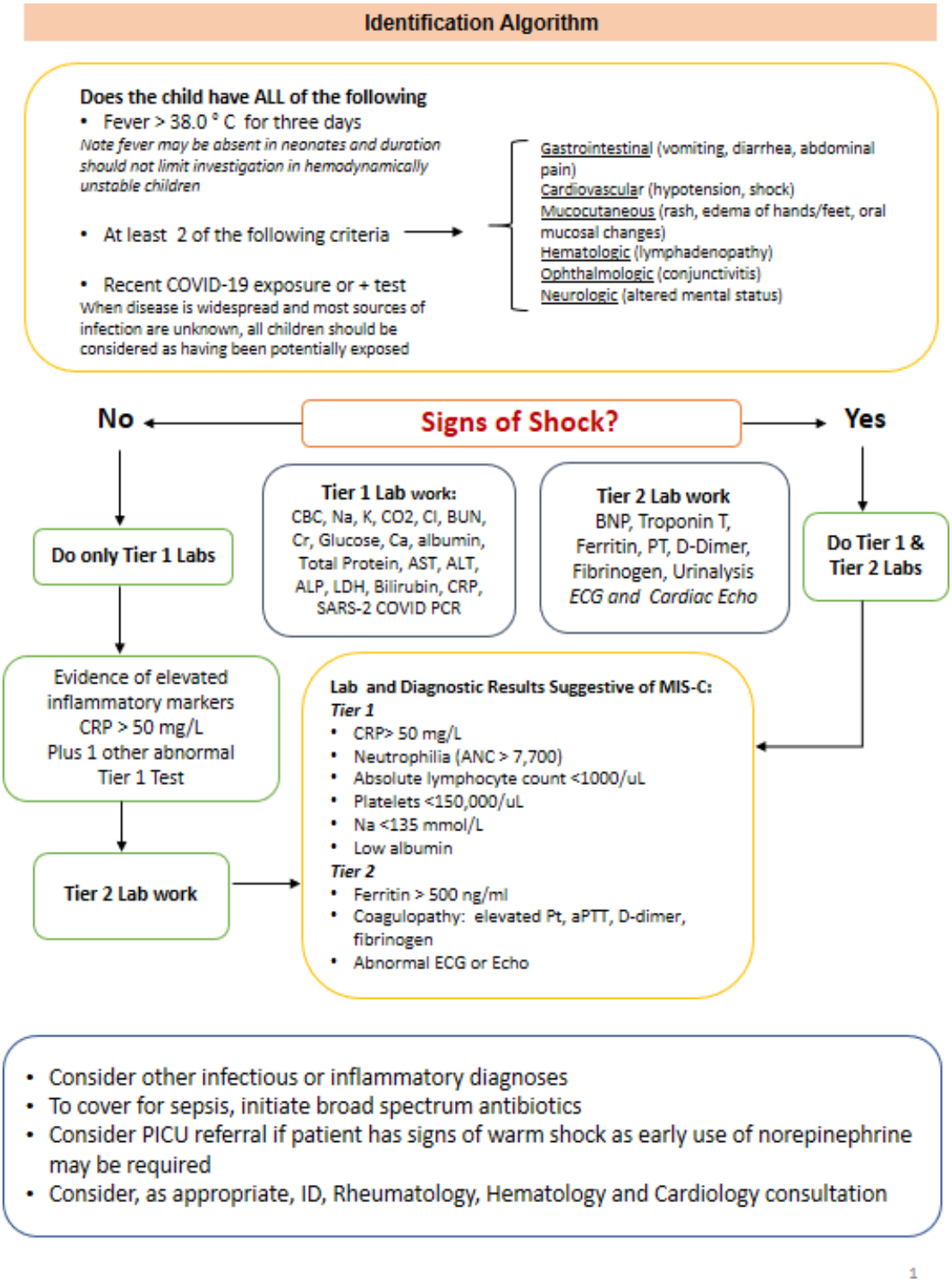
In MIS-C, gastrointestinal symptoms including severe abdominal pain are very common.[3] Cases have been mistakenly managed as surgical emergencies. As such, abdominal ultrasound (US) and/or CT scan may be recommended to rule out appendicitis, intussusception and other acute abdominal pathologies.

Key points that help distinguish MIS-C from KD unrelated to SARS-CoV-2 include:

- MIS-C patients are more commonly of African, Afro-Caribbean, or Hispanic descent, but less likely to be of East Asian descent
- MIS-C patients encompass a broader age range, have more prominent GI and neurologic symptoms, present more frequently in shock, and are more likely to display cardiac dysfunction (arrhythmias and ventricular dysfunction) than children with KD
- At presentation, MIS-C patients tend to have lower platelet counts, lower absolute lymphocyte counts, and higher CRP levels than patients with KD.
- Epidemiologic studies of MIS-C suggest that younger children are more likely to present with KD- like features while older children are more likely to develop myocarditis and shock
- It is unknown if the incidence of coronary artery aneurysms (CAA) is different in MIS-C compared to KD; however, MIS-C patients without KD features can develop CAA[1]

MIS-C IDENTIFICATION AND INITIAL MANAGEMENT ALGORITHMS

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C): CARE GUIDE FOR CHILDREN AND ADOLESCENTS IN ALBERTA



- Consider other infectious or inflammatory diagnoses
- To cover for sepsis, initiate broad spectrum antibiotics
- Consider PICU referral if patient has signs of warm shock as early use of norepinephrine may be required
- Consider, as appropriate, ID, Rheumatology, Hematology and Cardiology consultation

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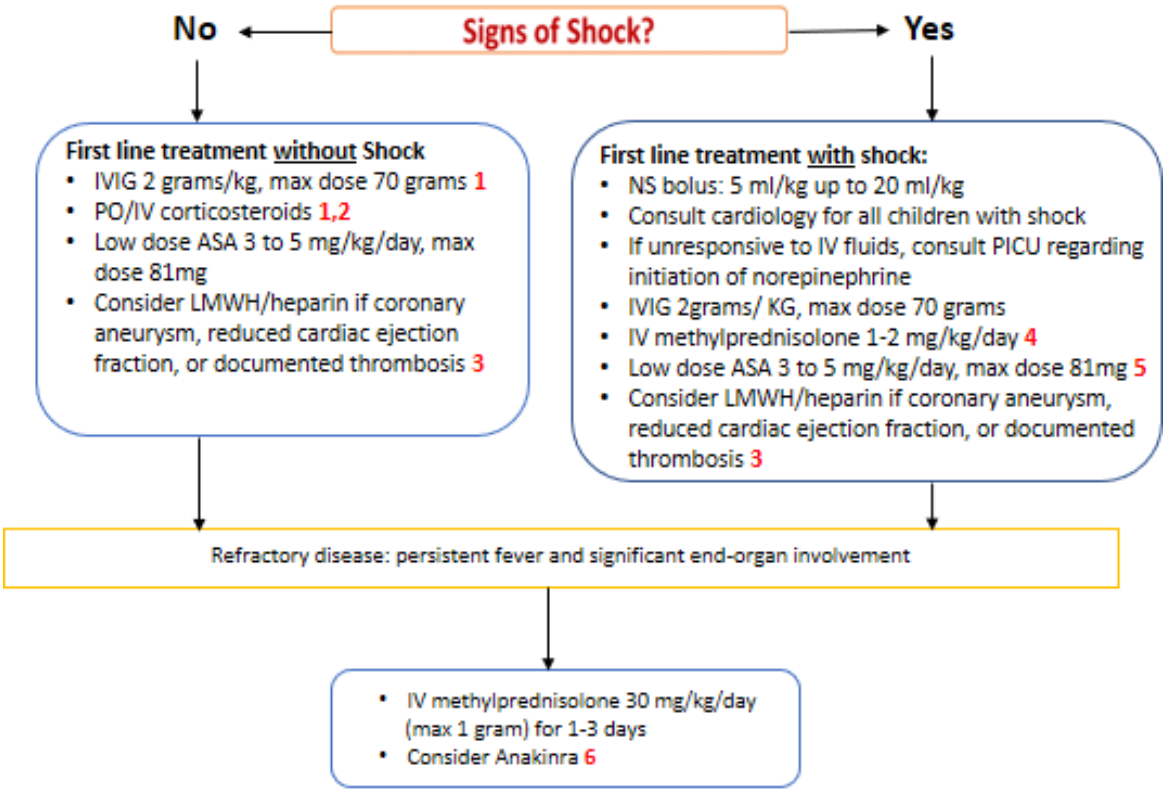
Initial Management Algorithm



1 Consider consulting Rheumatology before initiating IVIG and for recommendations on type and dose of corticosteroids.
2 If corticosteroids are continued beyond seven days, consider consulting Rheumatology regarding the need to taper
3 ***At Stollery***, consult KidsCLOT regarding the need for LWMH/heparin for all children diagnosed with MIS-C.
At Alberta Children's consult cardiology for children with coronary aneurysm or decreased LV ejection fraction, or hematology for children with a documented thrombosis regarding the need for LWMH/Heparin.
4 If there is significant inflammation or cardiac involvement, IV pulse methylprednisolone 30 mg/kg/day (max 1 gram) can be given prior to IVIG.
5 Do not treat with ASA if the patient has significant risk of bleeding
6 Anakinra -- in consultation with rheumatology – can be used in patients refractory to IVIG and prednisone. Initial dosing varies depending on the patient's condition and the rheumatologist's experience.

For confirmed Kawasaki Diagnosis
- Follow Kawasaki protocol
- Consider Cardiology referral +/- Rheumatology
- IVIG 2 gram/kg. Max 70 grams
- ASA: moderate dose 30-50 mg /kg/day

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LABORATORY AND DIAGNOSTIC TESTING

Potential MIS-C Lab Investigations:

Tier 1- MIS-C Symptoms without Hemodynamic Symptoms	
▪ CRP	▪ Glucose
▪ CBC	▪ Ca
▪ Na	▪ BUN
▪ K	▪ Albumin
▪ CO2	▪ Total Protein, AST, ALT, ALP, LDH, Bilirubin
▪ Cl	▪ NP swab/ aspirate throat swab for respiratory panel plus SARS-CoV-2 PCR
▪ Cr	

Tier 2- MIS-C Symptoms with Hemodynamic Symptoms of Positive Tier 1 Labs: Perform all of Tier 1 level tests plus the following:	
▪ Pro BNP*	▪ U/A
▪ Troponin T*	▪ SARS 2 COVID-19 serology
▪ Ferritin	▪ ECG
▪ PT	▪ Echocardiogram
▪ D-Dimer	
▪ Fibrinogen	

*See Appendix for NT-proBNP and Troponin T Normal Values in Children

TREATMENT

Treatment should be guided by consultation (as indicated) with PICU, Infectious Disease, Rheumatology, Cardiology, and Hematology but should be performed with the following considerations in mind:

- Volume resuscitation—should be minimized due to cardiogenic nature of shock and significant capillary leak. We recommend 5 ml/kg aliquots of crystalloid and commencement of vasopressors (initially norepinephrine) once 20 mls/kg volume resuscitation is reached. Volume resuscitation should be ended before the 20 ml/kg volume if hypotension is not responsive to fluid, cardiac function is known to be depressed (e.g.POCUS assessment), and/or the CXR shows evidence of pulmonary edema/effusions
- If clinical concern for sepsis or other localized infection, obtain cultures and initiate antibiotics to cover for bacterial sepsis/TSS with ceftriaxone and clindamycin +/- vancomycin
- Norepinephrine initially for warm shock should be started early rather than excessive use of IV fluids. Consider addition of epinephrine depending on clinical circumstances and cardiac ECHO results
- IVIG 2 grams/kg IV—give slowly if volume load is of concern. Max dose of 70 grams.
- Aspirin Low dose 3-5mg/kg/day, MAX 81mg[1 6]

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- Systemic steroids methyl-prednisone—In patients presenting with shock, early use of IV methylprednisolone and IVIG is associated with a more favorable course. Low to moderate dose of IV methylprednisolone 1-2 mg/KG/day may be considered in patients with MIS-C and signs of shock. If there is significant inflammation or cardiac involvement IV pulse methylprednisolone of 30 mg/kg/day (MAX 1 gram) can be given even prior to IVIG.

Other treatment options to consider (tuberculosis should typically be excluded before initiating these biological agents) – addition recommended only following discussion with appropriate pediatric sub-specialty service:

- Anakinra[7 8 9] —First line treatment for patients with refractory MIS-C and/or with persistent end organ involvement despite treatment with IVIG and systemic steroids.
- Tocalizumab[10] — currently there is not enough evidence to support the use of this agent in patients with MIS-C. This agent is considered a less favorable choice given it has a longer half-life Anakinra.
- Infliximab—refractory hyperinflammation associated with coronary aneurysms or bowel disease[11]
- Plasmapheresis[12] —not widely used

Other therapeutic considerations:

- PTE/DVT prophylaxis—is associated with decreased mortality in adults with COVID ARDS, but indications in children remain uncertain[13 14 15]

Note: Similar therapies have been used in CSS associated with COVID-19 ARDS.[16]

DISCHARGE AND FOLLOW-UP

Follow-up suggested (based on national guidance):

- Cardiology follow-up with ECHO at 2 and 6 weeks after diagnosis for children with uncomplicated cases. For children with significant cardiac involvement, consult cardiology for specific recommendations.
- If needing steroids— a slow steroid taper over 2-4 weeks with close monitoring of symptoms and inflammatory markers is needed to avoid rebound inflammation.
- Peds follow-up with repeat blood work within 2 weeks
- Return if febrile or unwell

REPORTING

MIS-C is a notifiable disease in Alberta.
The current AH reporting requirements are outlined in the MIS-C Notifiable Disease Guideline:
Public Healtth Disease Managment Guidelines: Multisystem Inflammatory Syndrome in Children (MIS-C) (alberta.ca)

All physicians ***shall*** notify the Medical Officer of Health (MOH) (or designate) of the zone, of all cases that meet the preliminary case definition in the prescribed guideline above as determined by the MOH within 48 hours (two business days) and include:

- Age,
- Date of birth,
- Gender,
- Personal health number,

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- Positive laboratory report (if applicable)
- Other relevant clinical/epidemiological information.

*Report here: link to one page form
https://www.alberta.ca/assets/documents/health-ab-mis-children-case-report-form.docx

For Edmonton Zone please report to MOH
Lead Dr Christopher Sikora
Phone: 780-433-3940

For Calgary Zone please report to MOH
Lead Dr Nicholas Etches
Phone: 403-955-3369

RESEARCH

Various research studies are underway in Alberta for COVID related illnesses:
Studies in Alberta- for more information contact Drs. Suzette Cooke, ACH or Joan Robinson, U of A
University of Calgary: https://research.ucalgary.ca/covid-19/collaboration
Canada: CanCOVID

Parent Resource
For Parents: Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 | CDC

APPENDIX

Troponin T and NT-proBNP Normal Values (ng/L):

Table 1. Pediatric reference intervals and cut-offs for high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic protein (NT-proBNP).

Analyte	Age range	n	Lower limit (90% CI[a]) (ng/L)	Upper limit (90% CI) (ng/L)	99th percentile Cut-off (90% CI) (ng/L)	% > 3 ng/L	% > 5 ng/L
hs-cTnT	0–<6 months	64	7 (4, 10)	78 (68, 87)	87 (76, 97)	100%	N/A
	6 months–<1 year	45	6 (5, 7)	34 (28, 42)	39 (32, 47)	100%	N/A
	1–<19 years	131	<3 (<3, <3)	9 (6, 11)	11 (11, 14)	30%	N/A
NT-proBNP	0–<1 year	211	39 (26, 57)	3569 (2188, 4876)	5272 (4788, 6937)	N/A	100%
	1–<19 years	265	<5 (<5, 7)	178 (144, 203)	216 (182, 250)	N/A	97%

[a]CI, confidence interval.

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Definitions from CDC:

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Kawasaki Disease Definition:

For epidemiologic surveillance, CDC defines a case of KD as illness in a patient with fever of 5 or more days duration (or fever until the date of administration of intravenous immunoglobulin if it is given before the fifth day of fever), and the presence of at least 4 of the following 5 clinical signs:

- Rash
- Cervical lymphadenopathy (at least 1.5 cm in diameter)
- Bilateral conjunctival injection
- Oral mucosal changes
- Peripheral extremity changes

Patients whose illness does not meet the above KD case definition but who have fever and coronary artery abnormalities are classified as having atypical or incomplete KD.

Page last reviewed: October 24, 2018
Content source: Centers for Disease Control and Prevention , National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) , Division of High-Consequence Pathogens and Pathology (DHCPP)

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C): CARE GUIDE FOR CHILDREN AND ADOLESCENTS IN ALBERTA

Toxic Shock Syndrome Definition:

Streptococcal Toxic Shock Syndrome (STSS) (*Streptococcus pyogenes*) 2010 Case Definition

NOTE: A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance. Surveillance case definitions enable public health officials to classify and count cases consistently across reporting jurisdictions. Surveillance case definitions are not intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient's health needs.

CSTE Position Statement(s)

09-ID-60

Clinical Description

Streptococcal toxic shock syndrome (STSS) is a severe illness associated with invasive or noninvasive group A streptococcal (*Streptococcus pyogenes*) infection. STSS may occur with infection at any site but most often occurs in association with infection of a cutaneous lesion. Signs of toxicity and a rapidly progressive clinical course are characteristic, and the case fatality rate may exceed 50%.

Clinical Criteria

An illness with the following clinical manifestations*:

- Hypotension defined by a systolic blood pressure less than or equal to 90 mm Hg for adults or less than the fifth percentile by age for children aged less than 16 years.
- Multi-organ involvement characterized by two or more of the following:
  - Renal impairment: Creatinine greater than or equal to 2 mg/dL (greater than or equal to 177 µmol/L) for adults or greater than or equal to twice the upper limit of normal for age. In patients with preexisting renal disease, a greater than twofold elevation over the baseline level.
  - Coagulopathy: Platelets less than or equal to 100,000/mm^3 (less than or equal to 100 x 10^6/L) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.
  - Liver involvement: Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age. In patients with preexisting liver disease, a greater than twofold increase over the baseline level.
  - Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia.
  - A generalized erythematous macular rash that may desquamate.
  - Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.

* Clinical manifestations do not need to be detected within the first 48 hours of hospitalization or illness, as specified in the 1996 case definition. The specification of the 48 hour time constraint was for purposes of assessing whether the case was considered nosocomial, not whether it was a case or not.

Laboratory Criteria for Diagnosis

Isolation of group A *Streptococcus*.

Case Classification

Probable

A case that meets the clinical case definition in the absence of another identified etiology for the illness and with isolation of group A *Streptococcus* from a non-sterile site.

Confirmed

A case that meets the clinical case definition and with isolation of group A *Streptococcus* from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid).

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Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition

NOTE: A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance. Surveillance case definitions enable public health officials to classify and count cases consistently across reporting jurisdictions. Surveillance case definitions are not intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient's health needs.

CSTE Position Statement(s)

10-ID-14

Clinical Criteria

An illness with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C)
- Rash: diffuse macular erythroderma
- Desquamation: 1-2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement (three or more of the following organ systems):
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection
  - Hepatic: total bilirubin, alanine aminotransferase enzyme, or asparate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
  - Hematologic: platelets less than 100,000/mm^3
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria for Diagnosis

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures blood culture may be positive for *Staphylococcus aureus*)
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles

Case Classification

Probable

A case which meets the laboratory criteria and in which four of the five clinical criteria described above are present

Confirmed

A case which meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

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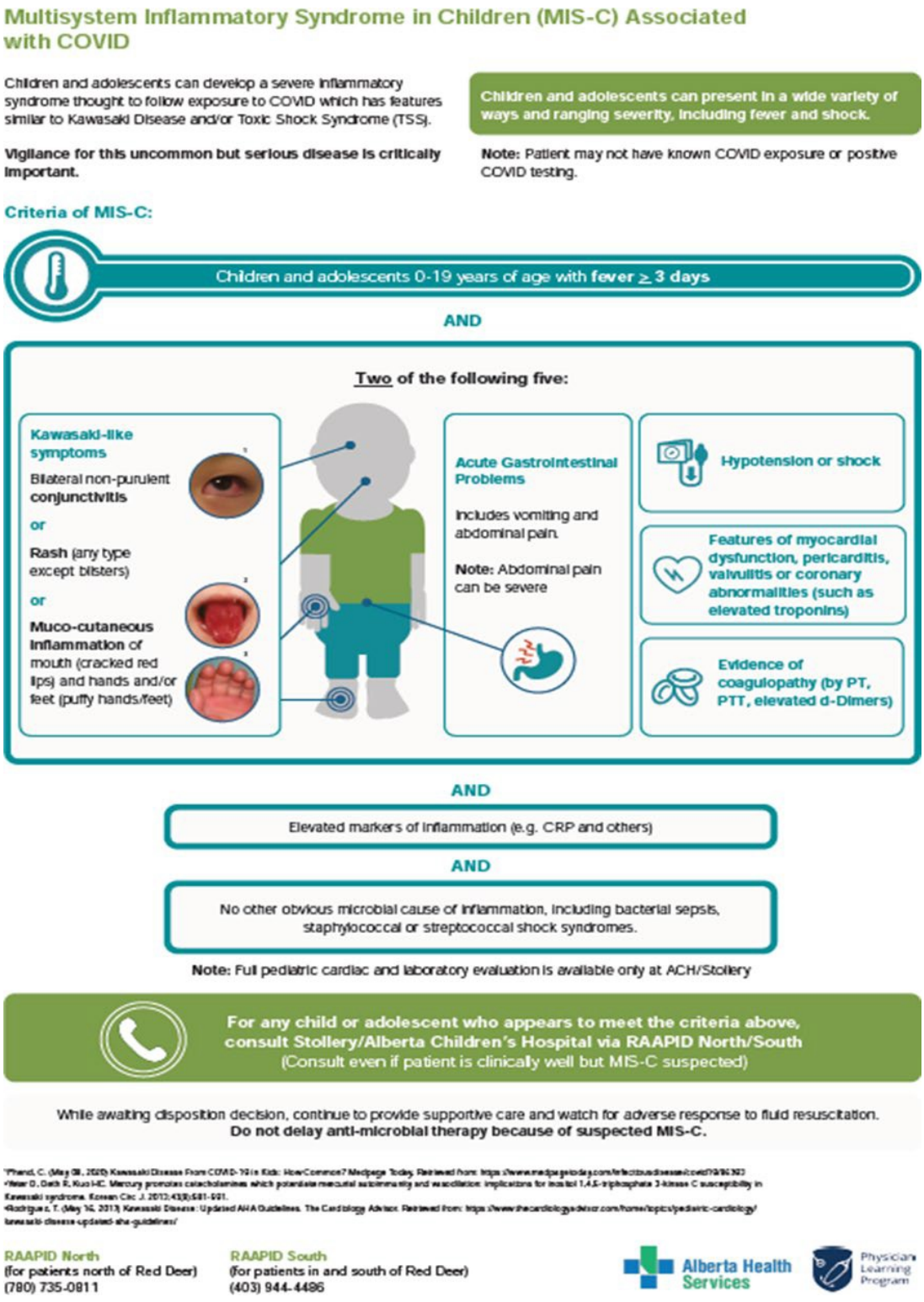
MIS-C Case Identification Poster:



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10. CPS guidance Figure 1. Algorithm for investigations and management in PIMS/MIS-C Source: Spring 2021 Update – Paediatric inflammatory multisystem syndrome temporally associated with COVID-19, Acute Care Committee, May 3, 2021. Available at www.cps.ca Accessed August 1st, 2021