	Task Force Votes								
	1	2	3	4	5	6	7	8	9
	Disagree								Agree

Supplementary Table 1: Evaluation of Multisystem Inflammatory Syndrome in Children (MIS-C)		
MIS-C in Children		
The vast majority of children with SARS-CoV-2 infections have mild symptoms with excellent outcomes. MIS-C remains a rare complication of SARS-CoV-2 infections.		9 ***
To date, MIS-C has been identified in communities following the peak of COVID-19 cases in adults. Therefore, the prevalence of SARS-CoV-2 infections in a given geographic location, which may change over time, should inform diagnostic and treatment decisions.		9 **
Diagnostic Evaluation of MIS-C		
A child under investigation for MIS-C should also be evaluated for other infectious and non-infectious (e.g. malignancy) etiologies that may explain the clinical presentation.		9 ***
In the absence of a clearly identified infectious etiology, patients presenting with shock and any duration of fever should undergo a complete diagnostic evaluation for MIS-C.		9 ***
In the absence of shock, children presenting with sustained fever >38.0^{o} C and the following features should be considered a patient under investigation for MIS-C and additional diagnostic studies should be pursued.		9 ***
	Patient has an epidemiologic link to SARS-CoV-2 infection defined as ANY of the following criteria:	9 **
	• Child is SARS-CoV-2 PCR positive	9 **
	• Child has positive SARS-CoV-2 serologies	9 **
	• Child has a preceding history of disease resembling COVID-19	7.5 **
	• Child has close contact with others with confirmed or suspected COVID-19 in the past 4 weeks	8 **
	AND patient displays 2 of the following features:	8.5 ***
	• Rash (polymorphic, maculopapular, or petechial, but not vesicular)	9 ***
	• Gastrointestinal symptoms (diarrhea, abdominal pain, vomiting)	9 ***
	• Edema of hands and feet	8 **
	• Oral mucosal changes (erythematous or cracked lips, strawberry tongue, erythema of oroharyngeal mucosa)	8 **
*	• Conjunctivitis (bilateral bulbar conjunctival injection without exudate)	8 **
	• Lymphadenopathy (cervical > 1.5 cm, unilateral)	8 **
	• Neurological symptoms (altered mental status, encephalopathy, focal neurologic deficits, meningismus, papilledema)	8 ***
Patients under investigation for MIS-C should receive further testing in a tiered fashion. In Tier 1, the initial diagnostic evaluation for MIS-C should include CBC, CMP, ESR, CRP, and SARS-CoV-2 testing by PCR, antigen or serologies.		9 ***
Patients with the following laboratory parameters on the initial diagnostic		8.5 ***

Supplementary Table 1: Evaluation of Multisystem Inflammatory Syndrome in Children (MIS-C)	
evaluation (Tier 1) should undergo a complete Tier 2 diagnostic evaluation for MIS-C.	
• CRP ≥ 3 mg/dL – or – ESR ≥ 40 mm/hr	9 **
AND any one of the following:	8 **
• Absolute lymphocyte count < 1.0 Kcell/uL	8 **
• Platelet count < 150 Kcells/uL	8 ***
• Na < 135 mmol/L	7.5 **
• Neutrophilia	8 **
• Hypoalbuminemia	8 **
A complete (Tier 2) diagnostic investigation includes the following:	9 **
• Elevated brain natiruretic peptide	9 ***
• Elevated troponin T	9 ***
• Procalcitonin	8 **
• Ferritin	9 ***
• Coagulation studies (PT, PTT, D-dimer, fibrinogen)	9 ***
• Lactic dehydrogenase	8 ***
• Urinalysis	8 **
• Cytokine panel (if available)	8 **
• If not performed previously, antibody testing to SARS-CoV-2 (preferably IgG/IgA/IgM)	9 ***
• Triglycerides (if concern for MAS)	8 **
• EKG	9 ***
• Echocardiogram	9 ***
Patients under investigation for MIS-C may display individual clinical manifestations that could require directed additional diagnostic studies including, but not limited to, chest imaging, abdominal imaging, neurologic imaging, and lumbar puncture.	9 ***
A well appearing child who is under investigation for MIS-C and presents with stable vital signs and a reassuring physical exam may be eligible to undergo a diagnostic evaluation as an outpatient with close clinical follow up.	8 **
Patients presenting with shock, significant respiratory distress, neurologic changes (altered mental status, encephalopathy, focal neurologic deficits, meningismus, papilledema), dehydration, or features of KD should be admitted for further work-up, regardless of MIS-C status, per standard of care.	9 ***
Patients with possible MIS-C may also be considered for admission to the hospital for further observation and serial monitoring, while awaiting results of extended laboratory and possible cardiac evaluation, especially if they display the following:	9 ***
• Mild pertubations in vital signs (tachycardia, tachypnea)	8 ***
• Mild respiratory distress	8 ***
• Neurologic deficits or change in mental status, including more subtle manifestations	9 ***
• Evidence of acute renal or hepatic injury, including if mild	8 ***
• Markedly elevated inflammatory makers	8 **
• Abnormal EKG, BNP, and/or troponin T	9 ***
Children admitted to the hospital with MIS-C typically require care by a multi-disciplinary team including pediatric rheumatologist, pediatric cardiologists,	9 **

Supplementary Table 1: Evaluation of Multisystem Inflammatory Syndrome in Children (MIS-C)	
pediatric infectious disease specialists, and pediatric hematologists.	
Depending on clinical manifestations other subspecialties may also need to be consulted. These include but are not limited to pediatric neurology, nephrology, hepatology, and gastroenterology.	9 ***
Comparing and Contrasting Clinical and Laboratory Features of MIS-C and Kawasaki Disease (KD)?	
Patients with KD that is unrelated to SARS-CoV-2 will continue to require evaluation, diagnosis and treatment during the SARS-CoV-2 pandemic.	9 ***
MIS-C and KD unrelated to SARS-CoV-2 infections can present with overlapping clinical features:	9 ***
• Conjunctival injection	9 **
• Oropharyngeal findings including strawberry tongue and red, cracked lips	9 ***
• Rash	9 ***
• Swollen and/or erythematous hands and feet	9 ***
• Unilateral cervical lymphadenopathy (>1.5 cm)	8 **
Clinical features of MIS-C that may differ from KD include the following:	8.5 **
• Children with MIS-C tend to be older than children with KD	8 **
• Children with MIS-C may have more prominent GI symptoms than children with KD	9 **
• Children with MIS-C may have more neurologic symptoms than children with KD	8 **
• Children with MIS-C present more frequently in shock than children with KD	9 **
• Children with MIS-C may have cardiac dysfunction including arrhythmias and valvular abnormalities, which are not commonly reported in KD	9 **
• The racial demographic of patients with MIS-C differs from patients with KD with increased incidence of MISC-C in children of African, Afro-Caribbean, and possibly Hispanic descent, but a lower incidence in those of East Asian descent	8.5 **
Patients with MIS-C present with laboratory studies that may differ from patients with KD including:	9 **
• MIS-C patients have more thrombocytopenia than KD	8 **
• MIS-C patients have more lymphopenia than KD	8 **
• MIS-C patients have higher CRP than KD	8 **
• MIS-C patients have, on average, higher ferritin levels than KD patients	8 **
A pressing clinical concern is to determine if the incidence of coronary artery aneurysms (CAA) is different in MIS-C vs KD, which is currently unknown.	9 ***
MIS-C patients without KD features can develop CAA.	8 **

** Moderate consensus; *** High consensus (all votes in upper tertile)

Abbreviations: Multisystem Inflammatory Syndrome in Children (MIS-C), coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), polymerase chain reaction (PCR), complete blood count (CBC), comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), c-reactive protein(CRP), prothrombin time (PT), partial thromboplastin time (PTT), Immunoglobulin (Ig), Macrophage Activation Syndrome (MAS), Kawasaki's Disease (KD), electrocardiogram (EKG), brain natriuretic peptide (BNP), coronary artery aneurysms (CAA)

Supplementary Table 2: Cardiac Evaluation and Management	
Cardiac Evaluation in MIS-C	
Children with MIS-C and abnormal BNP and/or troponin T at baseline should have these laboratory parameters trended over time.	9 ***
All children with MIS-C should have an EKG at diagnosis due to risk for conduction abnormalities as well as ST/T-wave changes.	9 ***
If conduction abnormalities are present in children with MISC at diagnosis, then patients should be placed on continuous telemetry.	9 ***
Echocardiograms conducted during the diagnostic evaluation of MIS-C should include evaluation of ventricular function, valvar function, pericardial effusion, and coronary artery dimensions with measurements indexed to body surface area using z-scores.	9 ***
Cardiac Follow Up in MIS-C	
Patients with MIS-C and cardiac involvement will require ongoing monitoring and care with a pediatric cardiologist after discharge from the hospital.	9 ***
Troponin and BNP level should be obtained at the first outpatient visit if not normalized at time of discharge.	9 ***
EKGs should be performed every 48 hours during hospitalization and at all follow-up visits to monitor for arrhythmias and conduction abnormalities.	9 ***
Holter monitors should be considered during outpatient follow-up for patients who had conduction abnormalities during the acute hospital stay including but not limited to bradycardia, heart block and bundle branch block.	9 **
Echocardiograms should be performed for all patients at (but not limited to):	
• 7-14 days post diagnosis	9 ***
• 4-6 weeks post diagnosis	9 **
• 1 year post diagnosis	8 **
Patients with LV dysfunction and/or coronary artery aneurysms will require more frequent echocardiograms.	9 **
Follow up echocardiograms should be focused on assessment of coronary artery size, ventricular/valvar function including strain and pericardial effusion.	9 ***
Cardiac Magnetic Resonance Imaging may be indicated at 2-6 months post diagnosis in patients with significant transient or persistent LV dysfunction in the acute phase of illness (LV ejection fraction < 50%).	8 ***
In patients who require cardiac MRI, the imaging should be focused on myocardial characterization including functional assessment, T1/T2 weighted imaging, T1 mapping and extracellular volume (ECV) quantification, early and late gadolinium enhancement.	8 ***
Cardiac Computed Tomography with contrast (CCT) should be performed in patients in whom echocardiographic images raise suspicion of distal coronary artery aneurysms that are not well seen by echocardiogram and if a CCT will alter clinical management decisions.	9 **
Antiplatelet and Anticoagulation Therapy in MIS-C	
Patients with MIS-C and KD-like features with a platelet count ≥ 80,000 Kcells/uL should be on low-dose aspirin (3-5 mg/kg/day) and continue aspirin until normalization of platelet count and confirmed normal coronary arteries at > 4 weeks post diagnosis.	8.5 **
The following antiplatelet and anticoagulation therapies are recommended for MIS-C patients with coronary artery aneurysms:	9 ***

Supplementary Table 2: Cardiac Evaluation and Management	
• Maximal CAA z-score 2.5 to 10: low dose aspirin	**8.5 ****
• Maximal z-score ≥ 10: low dose aspirin + therapeutic anticoagulation with enoxaparin or warfarin	**9 *****
For patients with MIS-C and documented thrombosis or > mild LV dysfunction (EF < 35%) therapeutic anticoagulation with enoxaparin during hospitalization and at least 2 weeks post discharge.	**8.5 *****
Indications for longer outpatient therapeutic enoxaparin dosing include: CAA with z-score > 10 (indefinite dosing), documented thrombosis (3 months pending thrombus resolution), ongoing > mild LV dysfunction.	**8.5 *****
For MIS-C patients who do not meet the above criteria, approach to antiplatelet and anticoagulation management should be tailored to the patient's risk factors and laboratory evidence of hypercoagulability and/or bleeding risk.	**9 *****

** Moderate consensus; *** High consensus (all votes in upper tertile)

Abbreviations: Multisystem Inflammatory Syndrome in Children (MIS-C), brain natriuretic peptide (BNP), electrocardiogram (EKG), left ventricle (LV), magnetic resonance imaging (MRI), extracellular volume (ECV), Cardiac Computed Tomography (CCT), Kawasaki's Disease (KD), coronary artery aneurysms (CAA), ejection fraction (EF)

Supplementary Table 3: Treatment of MIS-C	
Immunomodulatory Treatment of MIS-C	
Patients under investigation for MIS-C without shock or significant myocardial dysfunction should undergo a complete diagnostic evaluation for MIS-C and other possible infectious and non-infectious etiologies of the presentation before treatment is initiated.	**9 ****
Patients under investigation for MIS-C with shock and severe myocardial dysfunction may require treatment for MIS-C before the full diagnostic evaluation can be completed.	**9 *****
After an evaluation by specialists with expertise in MIS-C, some patients with mild symptoms may require only close monitoring without immunomodulatory treatment.	**8 ****
A stepwise progression of immunomodulatory therapies should be used to treat MIS-C.	**8 *****
IVIG should be used as first-line immunomodulatory treatment in MIS-C.	**8 ****
Cardiac function and fluid status should be assessed in MIS-C patients with shock before IVIG treatment is provided.	**9 ****
Glucocorticoids should be used as first-line immunomodulatory treatment in MIS-C.	**8 ****
High dose glucocorticoids can be considered in MIS-C patients with shock.	**8 ****
Cytokine blockade can be considered for treatment of MIS-C refractory to IVIG and steroids or in patients with a contraindication to these treatments.	**8.5 *****
Anakinra (IV or SQ) is the preferred anti-cytokine therapy for patients with MIS-C.	**8 ****
Patients treated with immunomodulatory treatments such as steroids will often require a 2-3 week taper following discharge.	**9 *****
Sequential laboratory testing and cardiac assessment should be used to guide treatment response and treatment tapering.	**9 *****

** Moderate consensus; *** High consensus (all votes in upper tertile)

Abbreviations: Multisystem Inflammatory Syndrome in Children (MIS-C), intravenous immunoglobulin (IVIG)

Supplementary Table 4: Management of Hyperinflammation in COVID-19	
Management of Hyperinflammation in Children with COVID-19	
Children with severe respiratory symptoms due to COVID-19 with any of the following features should be considered for immunomodulatory therapy:	9 ***
• Shock or cardiac dysfunction	9 ***
• ARDS	8 **
• Elevation of LDH, D-Dimer, IL-6, IL-2R, and/or ferritin	8 ***
• Depression of lymphocyte count, albumin, and/or platelet count	7.5 **
In patients with COVID-19 and signs of hyperinflammation, glucocorticoids should be considered for use as immunomodulatory therapy.	8 **
Anakinra is safe in severe infections and in children with hyperinflammatory syndromes.	8.5 ***
In patients with COVID-19 and signs of hyperinflammation, high dose (>4 mg/kg/day IV or SQ) anakinra should be considered for use as immunomodulatory therapy.	8.5 ***
Initiation of anakinra before invasive mechanical ventilation may be beneficial.	8 ***
Patients with COVID-19 treated with anakinra should be monitored for LFT abnormalities.	9 **
Patients treated with tocilizumab may be at higher risk for secondary bacterial and fungal infections than patients treated with standard of care.	8 **
Tocilizumab appears to be effective at reducing mortality and ICU admission in patients with severe COVID-19 pneumonia and signs of systemic hyperinflammation.	8 **
Tocilizumab treatment in COVID-19 should be dosed at 8mg/kg (max 800mg) and can be repeated 12 hours later if desired.	8 **
Tocilizumab may be more effective when given to COVID-19 patients with signs of hyperinflammation but earlier in disease course / pre-ICU.	8 **
COVID-19 patients treated with tocilizumab should be monitored for infusion reactions, LFT abnormalities, and hypertriglyceridemia	9 **
In the absence of RCT or comparative effectiveness studies, the balance of risk and benefit suggests anakinra as firstline immunomodulatory treatment of pediatric patients with COVID-19 and hyperinflammation.	8 **
There is insufficient evidence to support the use of other immunomodulatory agents unless corticosteroids, IL-1, and/or IL-6 blocking therapies are contraindicated or have failed.	9 **
COVID-19 in Children	
Medically complex children, including those with rheumatic diseases on immunosuppression, may be at higher risk for severe outcomes in COVID-19.	8 **
Patients on moderate to high dose corticosteroids may be at risk for more severe outcomes in COVID-19.	8 **
Compared to adults, children admitted to the hospital are much less likely to have severe outcomes from COVID-19 defined as ICU admission, mechanical ventilation, and mortality.	9 ***
As in adults, children admitted to the hospital with COVID-19 present with similar symptoms such as fever, upper respiratory tract symptoms, tachypnea, abdominal pain, and diarrhea.	8.5 **

** Moderate consensus; *** High consensus (all votes in upper tertile)

Abbreviations: Coronavirus disease 2019 (COVID-19), acute respiratory syndrome (ARDS), lactate dehydrogenase (LDH), interleukin (IL), liver function test (LFT), intensive care unit (ICU), randomized controlled trial (RCT)

Supplementary Table 5: Voting Statements for Guidance Version 2.0	
General statements for MIS-C:	
The approach to testing for SARS-CoV-2 infections will evolve over the course of the COVID-19 pandemic. Seropositivity for SARS-CoV-2 antibodies will become more prevalent and may not be indicative or recent SARS-CoV-2 infection. It is therefore important to interpret testing results in the context of the prevalence of viral transmission in the community.	9**
Diagnostic Evaluation of MIS-C	
Patients with the following should undergo a diagnostic evaluation for MIS-C:	
• Unremitting fever >38C	8**
A complete tier diagnostic investigation for MIS-C includes the following studies (tier 2 evaluation)	
• Cytokine panel with abnormally elevated IL-10	7**
• Blood smear to evaluate for evidence of microangiopathy	7.5**
Comparing and Contrasting Features of MIS-C and Kawasaki Disease	
Younger children with MIS-C are more likely to present with KD-like features while older children with MIS-C are more likely to develop myocarditis and shock.	8**
Immunomodulatory Treatment in MIS-C	
A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG considered first tier therapy. Glucocorticoids should be used as adjunctive therapy in patients with severe disease or as intensification therapy in patients with refractory disease.	8**
• IVIG should be given to MIS-C patients who are hospitalized and/or fulfill KD criteria.	9***
• High dose IVIG (typically 2 gm/kg, dosed based on ideal body weight) should be used for treatment of MIS-C.	8***
• Cardiac function and fluid status should be assessed in MIS-C patients before IVIG treatment is provided. Patients with depressed cardiac function may require close monitoring and diuretics with IVIG administration.	9***
• In some patients with cardiac dysfunction, IVIG may be given as in divided doses (1 gm/kg daily over 2 days).	9**
• Low-moderate dose glucocorticoids should be given with IVIG as adjunctive therapy for treatment of MIS-C in patients with shock and/or organ threatening disease.	8**
• In patients who do not respond to IVIG and low-moderate dose glucocorticoids, high dose, IV pulse glucocorticoids may be considered, especially, if a patient requires high dose or multiple inotropes and/or vasopressors.	9***

	• In patients with refractory MIS-C despite a single dose of IVIG, a second dose of IVIG is not recommend given the risk of volume overload and hemolytic anemia associated with large doses of IVIG.	7***
	• Low-moderate dose steroids may also be considered in patients with milder forms of MIS-C who are persistently febrile and symptomatic despite a single dose of IVIG.	9**
Serial laboratory testing and cardiac assessment should guide immunomodulatory treatment response and tapering. Patients may require a 2-3-week, or even longer, taper of immunomodulatory medications.		9***
Anakinra (IV or SQ) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids, in patients with MIS-C and features of macrophage activation syndrome (MAS), or in patients with contraindications to long-term use of glucocorticoids.		9**
Antiplatelet and Anticoagulation Therapy in MIS-C		
	Low dose aspirin (3-5 mg/kg/day; max 81 mg/day) should be used in patients with MIS-C and continued until normalization of platelet count and confirmed normal coronary arteries at ≥4 weeks after diagnosis. Treatment with aspirin should be avoided in patients with active bleeding, significant bleeding risk, and/or platelet count ≤80,000/μL.	9**
Management of Hyperinflammation in Children with COVID-19		
Immunomodulatory treatment in children with COVID-19:		
	• Glucocorticoids should be used as first tier immunomodulatory treatment in patients with COVID-19 and hyperinflammation.	9***
	• In children with COVID-19 and hyperinflammation, anakinra (>4mg/kg/day IV or SQ) should be considered for immunomodulatory therapy in patients with refractory disease despite glucocorticoid treatment or in patients with contraindications to steroids.	8***
	• Tocilizumab is not recommended for a majority of pediatric patients with COVID-19 and hyperinflammation given the lack of benefit reported in randomized, double-blind, placebo-controlled trials in adults with COVID-19 pneumonia.	9***
	• In addition, the effects of tocilizumab are long-lasting, which leaves little recourse if a patient does not respond favorably to the medication.	9**
	• There is insufficient evidence to support the use of other immunomodulatory agents unless glucocorticoids, IL-1 blocking, and/or IL-6 blocking therapies are contraindicated or have failed.	8**

** Moderate consensus; *** High consensus (all votes in upper tertile)

Abbreviations: Multisystem Inflammatory Syndrome in Children (MIS-C), coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, Macrophage Activation Syndrome (MAS), Kawasaki's Disease (KD), intravenous immunoglobulin (IVIG)