



A. MIS-C CRITERIA:

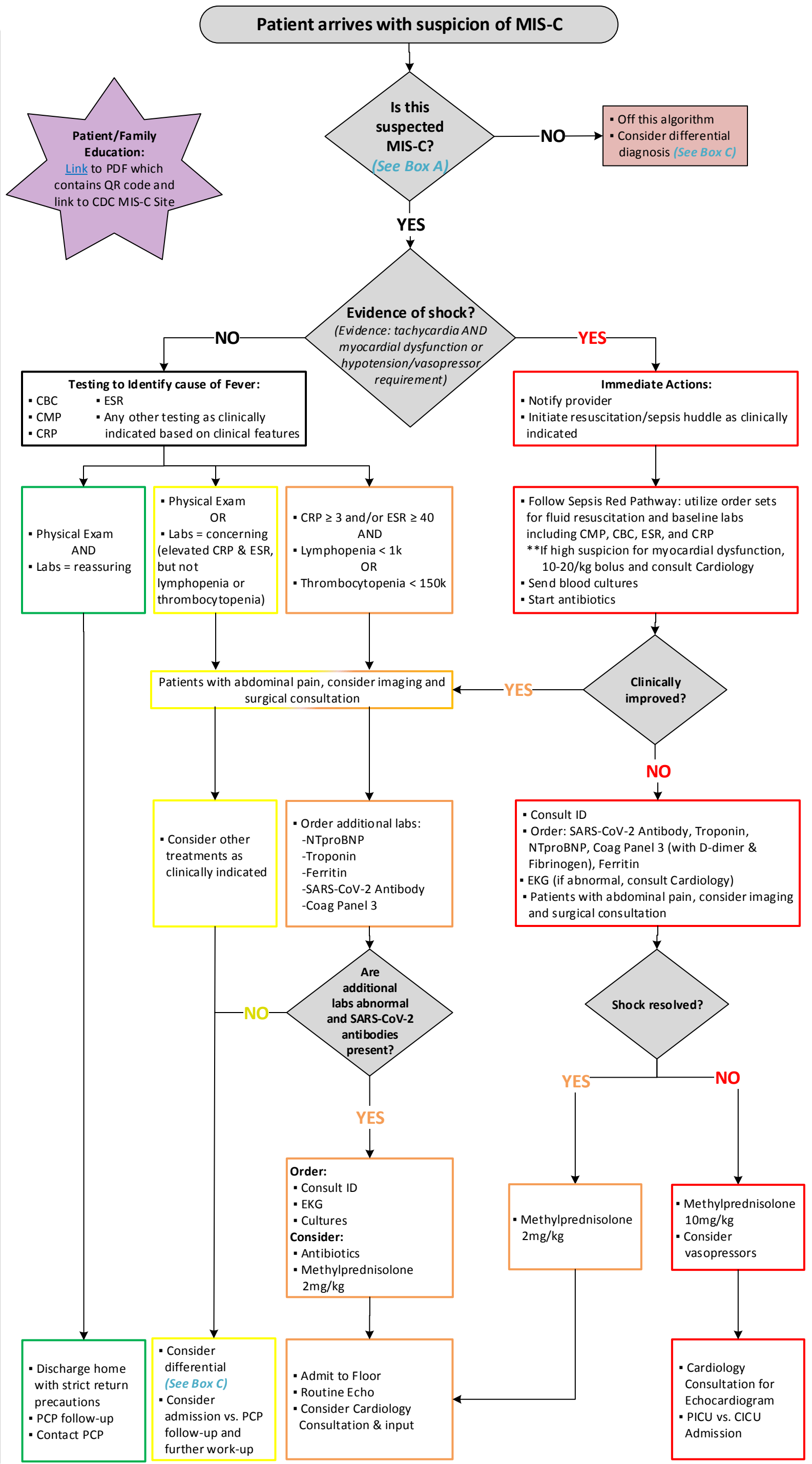
- History & Physical Exam**
 - ✓ Fever ≥ 38.5 C for ≥ 2 days AND
 - ✓ Tachycardia for age AND
 - ✓ Presence of 2 or more Clinical/Historical Features (See Box B)
- Heightened Suspicion of MIS-C if**
 - ✓ Exposure history/prior SARS-CoV-2 positivity within 8 weeks
 - ✓ History of loss of smell & taste
 - ✓ Abdominal pain

B. CLINICAL/HISTORICAL FEATURES:

- GI Symptoms**
Abdominal pain (mild/severe), vomiting, and/or diarrhea
- Rash**
Polymorphic, maculopapular, petechial, NOT vesicular
- Extremity changes**
Erythema and edema of the hands and feet
- Oral Mucosal changes**
Erythema of oropharyngeal mucosa
- Conjunctivitis**
Bilateral bulbar conjunctival injection without exudate
- Lymphadenopathy**
Cervical > 1.5 cm
- Neurologic Symptoms**
Headache, irritability, lethargy, altered mental status
- Epidemiologic Link to SARS-CoV-2**
Patient with history of COVID-19 disease or close contact with known positive SARS-CoV-2 case in past 8 weeks, or person placed in quarantine

C. CONSIDER DIFFERENTIAL DIAGNOSIS FOR MIS-C:

- Acute SARS-CoV-2
- Kawasaki Disease
- Other viral or bacterial infection
- Toxic Shock Syndrome
- Systemic Onset Juvenile Idiopathic Arthritis (JIA)
- Macrophage Activation Syndrome (MAS)
- Hemophagocytic Lymphohistiocytosis (HLHH)
- Myocarditis



Patient/Family Education:
Link to PDF which contains QR code and link to CDC MIS-C Site



A. CASE DEFINITION:

- < 21 years of age
- Fever
- Lab evidence of inflammation
- Multi-system involvement
- Positive SARS-CoV-2 antibody

B. INITIAL CONSIDERATIONS FOR ALL PATIENTS:

- Appropriate antibiotic rule-out while cultures are pending (i.e. sepsis rule out or SBI rule out)
- General ID consult for treatment considerations based on clinical severity
- Use GI prophylaxis IV or PO while patient is receiving steroids
- Hematology consult to consider anti-thrombotic prophylaxis: Lovenox and/or low-dose aspirin
- Cardiology consult for abnormal echo, EKG, or troponin results
- Abdominal imaging and Pediatric Surgery consult for focal abdominal findings
- Head imaging and Neurology consult for focal neurologic findings, altered mental status, seizure, and/or severe headache with meningeal signs
- Supportive care per clinical scenario

C. CLASSIFICATION OF CLINICAL SEVERITY:

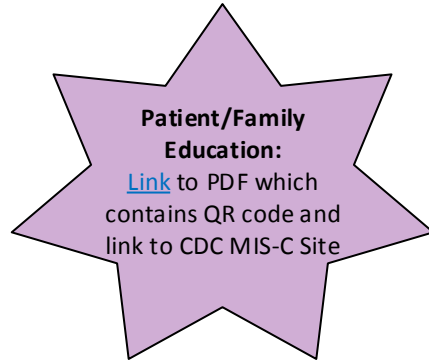
- **MILD:**
 - ✓ No vasoactive requirement
 - ✓ Minimal/no respiratory support
- **MODERATE:**
 - ✓ Single vasoactive requirement
 - ✓ Respiratory support required
- **SEVERE:**
 - ✓ High-dose or persistent vasoactive requirement
 - ✓ NIPPV or invasive respiratory support
 - ✓ Refractory to initial therapies

****IMPORTANT: patients may progress and need additional therapies: frequent reassessment of clinical severity is recommended**

Confirm patient meets case definition of MIS-C

(See Box A)

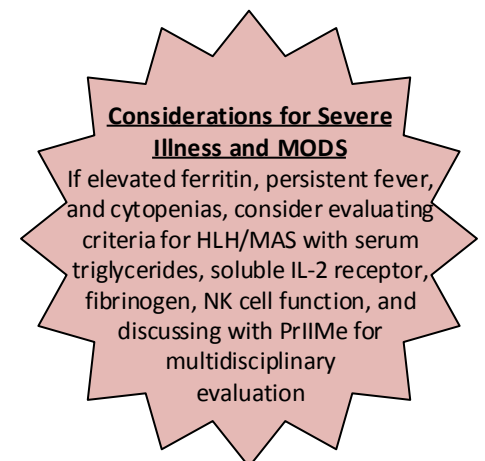
Review the Initial Considerations for All Patients
(See Box B)



Which Classification of Clinical Severity does this patient meet?
(See Box C)

	MILD	MODERATE	SEVERE
Therapeutics	<ul style="list-style-type: none"> ▪ IVIG 2g/kg once ▪ Methylprednisolone 2mg/kg/day 	<ul style="list-style-type: none"> ▪ IVIG 2g/kg once ▪ Methylprednisolone 10mg/kg/day -If improved, 2mg/kg/day 	<ul style="list-style-type: none"> ▪ IVIG 2g/kg once ▪ Methylprednisolone 10mg/kg/day ▪ Consider Anakinra 4mg/kg/day
Anti-Coagulation Therapy	<ul style="list-style-type: none"> ▪ Consider compression stockings (age > 12 y/o) ▪ Consideration for anti-coagulation prophylaxis should be tailored to patient's risk for thrombus 	<ul style="list-style-type: none"> ▪ Consider compression stockings (age > 12 y/o) ▪ Consideration for anti-coagulation prophylaxis should be tailored to patient's risk for thrombus 	<ul style="list-style-type: none"> ▪ Patients with documented thrombosis or an EF < 35% should receive therapeutic anticoagulation with Lovenox¹ ▪ Consider prophylactic LMWH for reduced cardiac function
Anti-Platelet Therapy	<ul style="list-style-type: none"> ▪ Consider low dose aspirin if coronary artery z-score > 2.5 (3-5mg/kg/day given as 40mg, 80mg, or a max of 160mg)² 	<ul style="list-style-type: none"> ▪ Consider low dose aspirin if coronary artery z-score > 2.5 (3-5mg/kg/day given as 40mg, 80mg, or a max of 160mg)² 	<ul style="list-style-type: none"> ▪ Consider low dose aspirin if coronary artery z-score > 2.5 (3-5mg/kg/day given as 40mg, 80mg, or a max of 160mg)²
Lab Monitoring	<ul style="list-style-type: none"> ▪ At least Every Other Day³: -BMP -CRP -CBC -Troponin⁴ ▪ One time & PRN: NTproBNP 	<ul style="list-style-type: none"> ▪ Daily³: -Troponin⁴ -CMP -CBC -Coag panel 3 -CRP -Ferritin -Lactate ▪ Weekly & PRN: NTproBNP 	<ul style="list-style-type: none"> ▪ Daily³: -Troponin⁴ -CMP -CBC -Coag panel 3 -CRP -Ferritin -Lactate ▪ Bi-weekly & PRN: NTproBNP
Cardiac Monitoring	<ul style="list-style-type: none"> ▪ Echo twice weekly ▪ Baseline EKG 	<ul style="list-style-type: none"> ▪ Echo at least twice weekly ▪ EKG twice weekly 	<ul style="list-style-type: none"> ▪ Echo at least twice weekly ▪ EKG per Cardiology
Consulting Services	<ul style="list-style-type: none"> ▪ ID ▪ Consider Cardiology ▪ Consider Hematology 	<ul style="list-style-type: none"> ▪ ID ▪ Cardiology ▪ Hematology 	<ul style="list-style-type: none"> ▪ ID ▪ Cardiology ▪ Hematology ▪ PrIIME

¹ Indications for longer outpatient therapeutic dosing include: documented thrombosis, treatment for ≥ 3 months pending thrombus resolution, or ongoing moderate-to-severe LV dysfunction
² Platelet counts should be > 50 x 10³/μl if patient also requires Lovenox therapy
³ Decrease frequency of labs once clinically appropriate
⁴ Troponin:
 -If initial troponin abnormal, trend q12-24 hours until normalized
 -If initial troponin normal, no repeat necessary unless clinical concerns



Preparing for Discharge:

Discharge Readiness: <ul style="list-style-type: none"> ▪ Hemodynamically stable ▪ Afebrile ▪ Steadily down-trending CRP 	Medications: <ul style="list-style-type: none"> ▪ Transition to PO steroids and taper per ID - expect discharge with prednisone taper based on CRP ▪ Continue GI prophylaxis while on steroids ▪ Discontinue Lovenox at discharge ▪ Continue low-dose aspirin (if started) until seen by Cardiology at 6 week appointment or until instructed by Heme or Cardiology 	Outpatient Labs: <ul style="list-style-type: none"> ▪ CRP will be trended on the 5th day of each steroid dose to determine wean schedule ▪ Other labs as needed 	Follow-up: <ul style="list-style-type: none"> ▪ If ventricular dysfunction, consult Cardiology for follow-up plan ▪ ID department will schedule appointment 2 weeks post-discharge along with echocardiogram ▪ Cardiology at 6 weeks post-discharge with echocardiogram ▪ Consider outpatient neurology follow-up if any significant neurologic symptoms while inpatient
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This guideline is developed based on the best available evidence and local expert consensus for elements of which evidence are inconclusive. Please refer to recommendation table below for further details.

MIS-C Overview

Background & Problem:

The COVID-19 pandemic was declared in March 2020. Children were initially recognized as overall having mild disease compared to adults. In April and May of 2020, reports emerged from around the world describing a new multi-system inflammatory syndrome affecting children in the post-viral period after SARS-CoV-2 infection, some with very severe illness including cardiorespiratory failure, systemic inflammation, and varied involvement of multiple organ systems. This was later termed Multisystem Inflammatory Syndrome in Children (MIS-C) by the CDC, and was thought to be temporally related to SARS-CoV-2 infection and a post-viral hyperinflammatory reaction. MIS-C has significant overlap with other syndromes including sepsis, Toxic Shock Syndrome, Kawasaki Disease, and HLH/MAS. Patient presentation and acuity is varied and subject to change rapidly. This affects resource use, time to diagnosis, and treatment planning. Given the recent development of this syndrome, data on MIS-C pathogenesis and management is limited. Little is known about clinical outcomes. This guideline is subject to change as evidence from this pandemic continues to grow.

Outcome Measure:

- Length of stay (Observed over Expected (O:E))

Process Measures:

- MIS-C order set utilization
- Cultures or RVP sent for febrile patients
- COVID PCR and COVID antibody testing sent
- Follow up appointments made with ID and cardiology

Balancing Measures:

- Readmitted within 30 days
- Return to ED within 72 hours of discharge
- Sepsis order set utilization

Inclusion:

All patients in the Lurie ED or inpatient areas including intensive care units with suspected or known MIS-C.

Exclusion:

None

*See page 4 for literature review grading details

Recommendation	Strength of recommendation	Quality of evidence
Patients meeting criteria for MIS-C ¹ should be evaluated for common clinical/historical features and lab findings of MIS-C ²⁻⁵ , especially if SARS-CoV-2 antibody positive which would be consistent with the timing of MIS-C occurring 4-6 weeks out from SARS-CoV-2 exposure ⁶ .	Strong, consensus	Moderate
Other infectious or non-infectious etiologies that may explain the clinical presentation must be evaluated, including but not limited to sepsis, Kawasaki disease, or toxic shock syndrome ^{4,5} .	Strong, consensus	Low to moderate
For patients presenting with concern for sepsis, even if also concerned for MIS-C, the sepsis guideline should be followed including drawing cultures and starting antibiotics. (link)	Strong, consensus	N/A
Patients with MIS-C usually have multiple markers of inflammation and multiple organ involvement, recommend lab evaluation similar to sepsis work-up, plus inflammatory markers CRP, ESR, and cardiac markers troponin and NTproBNP ⁴ . Lab markers should be repeated serially until normalized or no longer clinically applicable ⁸ .	Strong, consensus	Moderate
For all patients with confirmed or strongly suspected MIS-C, give IVIG 2g/kg once and methylprednisolone dosing based on acuity ^{7,8} .	Strong, consensus	Low to Moderate
Anticoagulation and anti-platelet therapy should be tailored to the patient's platelet count and coronary artery z-score ⁸ .	Strong, consensus	Low
Anakinra is an IL-1 receptor antagonist that has been used in children with severe infections and hyperinflammatory syndromes. Anakinra may be used for severe refractory MIS-C at a dose of 4mg/kg/day ⁸ .	Strong, consensus	Low
Until more is known about the long-term sequelae of MIS-C, recommend following outpatient evaluation similar to Kawasaki disease protocol, including cardiology follow up with echocardiogram at 2 weeks and 6 weeks post-discharge ^{4,8} , and ID follow up to monitor resolution of symptoms and inflammation.	Strong, consensus	Low

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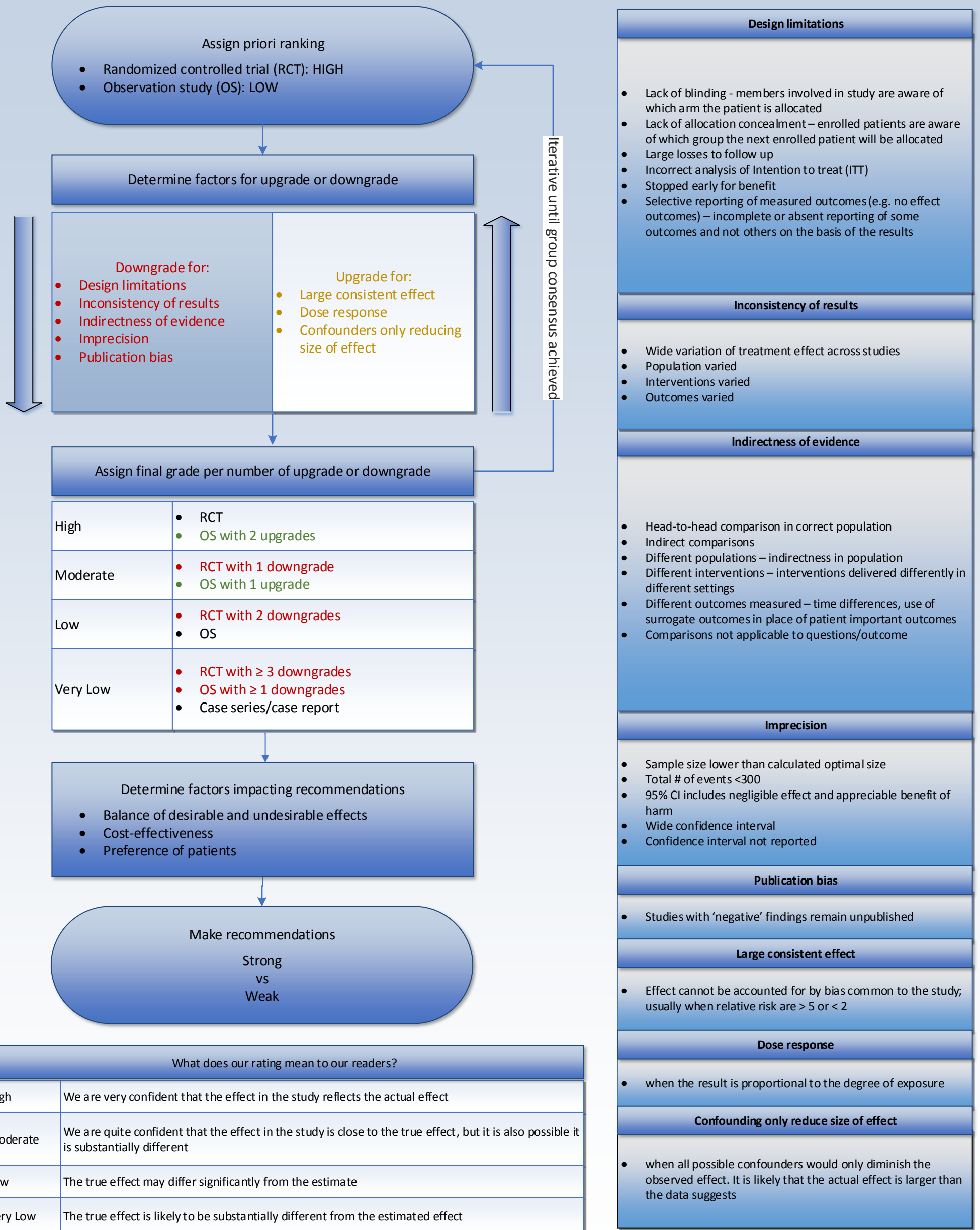
Dan Healy

References

1. <https://www.cdc.gov/mis-c/hcp/>
2. Aronoff, Stephen C., Ashleigh Hall, and Michael T. Del Vecchio. "The Natural History of Severe Acute Respiratory Syndrome Coronavirus 2–Related Multisystem Inflammatory Syndrome in Children: A Systematic Review." *Journal of the Pediatric Infectious Diseases Society* (2020).
3. Bautista-Rodriguez, Carles, et al. "Multisystem inflammatory syndrome in children: an international survey." *Pediatrics* 147.2 (2021).
4. Feldstein, Leora R., et al. "Multisystem inflammatory syndrome in US children and adolescents." *New England Journal of Medicine* 383.4 (2020): 334-346.
5. Nakra, Natasha A., et al. "Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management." *Children* 7.7 (2020): 69.
6. Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. *JAMA*. 2020;323(22):2249–2251. doi:10.1001/jama.2020.8259
7. Ouldali, Naïm, et al. "Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children." *JAMA* (2021).
8. Henderson, Lauren A., et al. "American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 2." *Arthritis & Rheumatology* (2020).



Rating the Quality of Evidence using GRADE



What does our rating mean to our readers?

High	We are very confident that the effect in the study reflects the actual effect
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different
Low	The true effect may differ significantly from the estimate
Very Low	The true effect is likely to be substantially different from the estimated effect

References
 1. Goldet, G., & Howick, J. (2013) Understanding GRADE: an introduction. Journal of Evidence-Based Medicine, 6(1): 50-54. <https://doi.org/10.1111/jebm.12018>
 2. Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013). GRADE Handbook. Retrieved from: <https://gdt.grade.org/app/handbook/handbook.html#h.svwngs6pm0f2>