

# Multisystem Inflammatory Syndrome in Children Clinical Guideline

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## Care Map Symbols

Links to more information or returns to a previous page.

Start of a Care Map Segment

Decision Point

Stop and Evaluate

Care Map Step  
Blue underlined text is a hyperlink

Progression of care – Patient Improving



Source Reference



Education Module



Hospital Policy



Hospital Reference



Provider Information



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# Clinical Guideline

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[AHA Kawasaki Disease Guidelines](#)

## Suggested Inclusion Criteria for Clinical Guideline

- Fever( >100.4) AND
- Clinical severity is likely to require hospitalization
- AND

### At least 2 of the following

- GI symptoms( severe pain, V/D, enteritis on imaging)
- Suspected cardiac involvement
- Mucocutaneous involvement
- Shock



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# Clinical Guideline

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## Potential Reasons to Avoid Clinical Guideline

- Plausible alternative diagnosis



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# Emergency Department Care: MIS-C



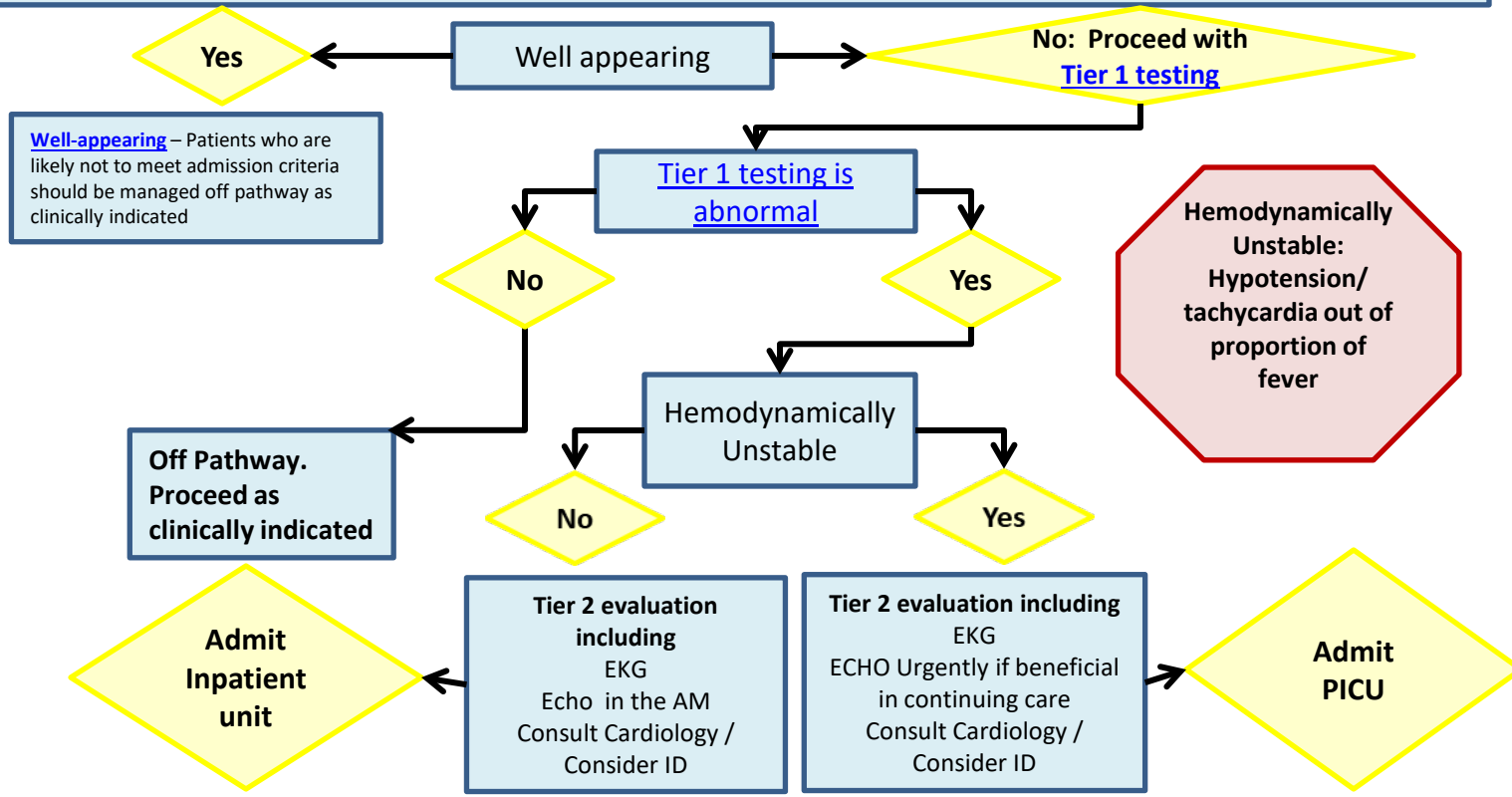
**CAUTION:** Recommendations for diagnosis and treatment of this disease process are rapidly evolving. This guideline has been developed based on consensus recommendations to date and focus on the recognition and early management

**Triage**

- Nurse performs initial assessment and assigns ESI\* level.

\*ESI = Emergency Severity Index

Provider Evaluation: History and Physical Exam suggestive of **MIS-C** (Note: most consistent findings are fever and GI symptoms )without **other plausible explanation** in differential. Typical presentation is 4 weeks after acute infection with COVID-19



**Treatment principles**

For questions concerning this care map, contact: CareMap@etch.com

Last Update:8/24/2023

# Inpatient Care

- Initial consults could include Infectious Disease and Cardiology. Consider Rheumatology based on clinical scenario. Hem/Onc if anticoagulation needed.
- [Assure appropriate infection prevention measures](#)
- Inflammatory markers should be trended daily
- Additional laboratory tests and studies to be obtained/trended as desired by clinical team including BNP/troponin if clinically indicated
- Note: Clinical change and abnormal trends may warrant earlier evaluation as determined by clinical team.
- Repeat Echo in two weeks if initial is abnormal and/or there is a change in clinical condition.
- Multidisciplinary discharge planning.

# High risk Diagnosis to consider

**Table 2.** Percentage of Patients With MIS-C, COVID-19, KD, and TSS Who Met Clinical Criteria for Each Disease\*

Clinical Criteria Included in Case Definitions	Patient Diagnoses			
	MIS-C	COVID-19	KD	TSS
MIS-C clinical criteria	100%	65%	72%	78%
Fever	100%	78%	100%	93%
Inflammation	100%	77%	72%	82%
Multisystem (≥2 organs) involvement	100%	94%	100%	100%
Cardiac	97%	32%	42%	97%
Renal	25%	10%	3%	49%
Respiratory	76%	93%	51%	62%
Hematologic	99%	59%	27%	53%
Gastrointestinal	95%	77%	76%	92%
Dermatologic	73%	13%	100%	92%
Neurologic	51%	26%	6%	43%
COVID-19 clinical criteria	81%	100%	50%	71%
Pneumonia or ARDS	60%	68%	12%	49%
Cough or shortness of breath	49%	87%	44%	34%
At least two of other COVID-19 criteria†	13%	53%	2%	30%
KD clinical criteria	15%	3%	100%	1%
Fever ≥5 days or until IVIG	90%	31%	100%	36%
Rash	50%	12%	97%	88%
Conjunctival injection	62%	3%	96%	26%
Oral mucosal changes	18%	1%	99%	32%
Cervical lymphadenopathy	6%	0%	29%	4%
Peripheral extremity changes‡	-	-	87%	-
Coronary artery abnormalities	15%	3%	29%	3%

\*Clinical criteria for toxic shock syndrome were not considered, as those data were generally not collected for patients with the other diseases.

†At least two of the following symptoms: fever, chills, rigors, myalgia, headache, sore throat and new olfactory or taste disorder.

‡Includes edema, erythema or generalized or periungual desquamation; data were not collected for patients with MIS-C, COVID-19 or TSS. ARDS indicates acute respiratory distress syndrome; IVIG, intravenous immunoglobulin.

# Testing : Laboratory

- 1<sup>st</sup> tier
  - Note: COVID antibody testing may be hard to interpret, history of either recent( within 60 days) COVID infection or exposure is more relevant
  - CBC, CMP, CRP
  - ESR if Kawasaki Disease in differential
  - UA
  - Blood Culture to hold
- 2<sup>nd</sup> Tier
  - Additional labs as clinically indicated by presentation
  - Cardiac testing as clinically indicated

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# Common Laboratory Findings

- Absence of potential causative organism other than COVID -19.

- Abnormal blood cell counts, including:
  - Lymphocytopenia – 80 to 95 percent
  - Neutrophilia – 80 to 90 percent
  - Mild anemia – 70 percent
  - Thrombocytopenia – 30 to 80 percent

- Elevated inflammatory markers, including:
  - C-reactive protein – 90 to 95 percent
  - Erythrocyte sedimentation rate – 80 percent
  - Procalcitonin
  - D-dimer – 80 to 95 percent
  - Fibrinogen – 90 percent
  - Ferritin – 75 percent
  - Interleukin-6 (IL-6)

- Elevated cardiac markers:
  - Troponin – 60 to 90 percent
  - BNP or NT-pro-BNP – 90 to 100 percent
- Hypoalbuminemia – 73 percent
- Mildly elevated liver enzymes – 70 percent
- Elevated lactate dehydrogenase – 50 to 60 percent
- Hypertriglyceridemia – 70 percent

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# Laboratory Characteristics

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Clinical Rheumatology (2022) 41:3807–3816

**Table 1** Clinical, demographic, and laboratory characteristics of MIS-C patients

	All patients (n = 123)	Mild/moderate MIS-C (n = 75)	Severe MIS-C (n = 48)	p value
Gender, male*	78 (63.4)	49 (65.3)	29 (60.4)	0.58 <sup>b</sup>
Age at diagnosis (years) <sup>†</sup>	9.6 ± 4.4	8.9 ± 4.6	10.6 ± 4	0.034 <sup>a</sup>
Duration of symptoms (day) <sup>‡</sup>	4 (3–5) <sup>§</sup>	3 (2–4) <sup>¶</sup>	4 (3–5) <sup>c</sup>	0.005 <sup>c</sup>
Hospitalization time (day) <sup>‡</sup>	12 (8–16.5)	10 (8–13)	15 (12–19)	<0.001 <sup>c</sup>
Intensive care hospitalization n (%)	67 (54.5)	22 (29.3)	45 (93.8)	<0.001 <sup>b</sup>
Intensive care duration (day) <sup>‡</sup>	6 (3–8)	3 (2–6)	7 (4–9)	<0.001 <sup>c</sup>
Kawasaki-like MIS-C n (%)	50 (40.7)	29 (38.7)	21 (43.8)	0.58 <sup>b</sup>
Clinical findings n (%)				
Abdominal pain n (%)	63 (51.2)	38 (50.7)	25 (52.1)	0.88 <sup>b</sup>
Vomiting n (%)	63 (51.2)	36 (48)	27 (56.3)	0.37 <sup>b</sup>
Diarrhea n (%)	40 (32.5)	21 (28)	19 (39.6)	0.18 <sup>b</sup>
Conjunctivitis n (%)	34 (27.6)	19 (25.3)	15 (31.3)	0.47 <sup>b</sup>
Skin rash n (%)	32 (26)	19 (25.3)	13 (27.1)	0.83 <sup>b</sup>
Headache n (%)	18 (14.6)	9 (12)	9 (18.8)	0.30 <sup>b</sup>
Pulmonary symptoms n (%)	16 (13)	6 (8)	10 (20.8)	0.039 <sup>b</sup>
Lymphadenopathy n (%)	13 (10.6)	8 (10.7)	5 (10.4)	0.97 <sup>b</sup>
Laboratory findings				
WBC (10 <sup>9</sup> /L) <sup>‡</sup>	9.4 (6.9–13.7)	9.4 (6.88–13.5)	9.4 (7.2–14.6)	0.63 <sup>c</sup>
Lymphocyte count (10 <sup>9</sup> /L) <sup>‡</sup>	0.92 (0.65–1.36)	1.07 (0.68–1.78)	0.8 (0.54–1.03)	0.005 <sup>c</sup>
Hemoglobin (g/dL) <sup>†</sup>	12.2 ± 1.7	12.4 ± 1.5	12 ± 1.9	0.17 <sup>a</sup>
Platelet (10 <sup>9</sup> /L) <sup>‡</sup>	210 (140–272)	235 (168–298)	153 (111–235)	<0.001 <sup>c</sup>
ESR (mm/h) <sup>†</sup>	43.7 ± 23.7	42.5 ± 22.7	45.4 ± 25.2	0.52 <sup>a</sup>
CRP (mg/dL) <sup>†</sup>	148.6 ± 73.5	127 ± 57.9	182.5 ± 82.7	<0.001 <sup>a</sup>
AST (U/L) <sup>‡</sup>	34 (23–53)	33 (23–44)	36 (23–58)	0.32 <sup>c</sup>
ALT (U/L) <sup>‡</sup>	26 (17–42)	23 (16–40)	30 (22–61)	0.012 <sup>c</sup>
Creatinine (mg/dL) <sup>‡</sup>	0.5 (0.4–0.66) <sup>e</sup>	0.47 (0.37–0.63)	0.59 (0.45–0.89)	0.006 <sup>c</sup>
Ferritin (µg/L) <sup>‡</sup>	252 (147–664) <sup>e</sup>	206 (123–364)	502 (242–1441)	<0.001 <sup>c</sup>
D-dimer (mg/L) <sup>‡</sup>	3.07 (1.54–5.3) <sup>d</sup>	2.04 (1.2–4.3)	4.07 (2.7–6.63)	<0.001 <sup>c</sup>
Troponin (ng/L) <sup>‡</sup>	11 (2.5–86)	2.6 (2.5–26)	91.5 (13–341.8)	<0.001 <sup>c</sup>
Pro-BNP (ng/L) <sup>‡</sup>	1222 (210–4698) <sup>e</sup>	500 (128–1634)	3214 (1630–8072)	<0.001 <sup>c</sup>
IL-6 (pg/mL) <sup>‡</sup>	94.2 (38.6–212) <sup>f</sup>	69.2 (32.2–132.5)	154 (50.6–284)	0.005 <sup>c</sup>

- MIS-C** **Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.**
- Initial Immunomodulatory Therapy*
- **IVIG** 2 g/kg IBW (up to a maximum total dose of 100 g) IV **plus** low to moderate dose **methylprednisolone** (1–2 mg/kg/day) IV<sup>a</sup> or another glucocorticoid at an equivalent dose<sup>a</sup> (**AIIb**).
  - **Glucocorticoid monotherapy, only** if IVIG is unavailable or contraindicated (**BIIa**).
  - **IVIG monotherapy, only** if glucocorticoids are contraindicated (**BIIb**).
- Intensification Immunomodulatory Therapy*
- Intensification therapy is recommended for children with refractory MIS-C who do not improve within 24 hours of receiving initial immunomodulatory therapy (**AIII**). One of the following can be used (listed in alphabetical order):
    - High-dose **anakinra** 5–10 mg/kg IV or SUBQ once daily (**BIIb**)
    - Higher-dose **glucocorticoid** (e.g., **methylprednisolone** 10–30 mg/kg/day IV or equivalent glucocorticoid) (**BIIb**)<sup>b</sup>
    - **Infliximab**<sup>c</sup> 5–10 mg/kg IV for 1 dose (**BIIb**)
- Antithrombotic Therapy*
- Low-dose **aspirin** (3–5 mg/kg/day, up to maximum dose of 81 mg/day) PO for all patients without risk factors for bleeding (**AIII**), **AND**
  - Anticoagulation for patients who fall under 1 of the following clinical scenarios:
    - **Therapeutic anticoagulation** for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease (**AIII**).
    - **Therapeutic anticoagulation** for patients with moderate to severe LV dysfunction who have no risk factors for bleeding (**AIII**).
    - For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider **prophylactic or therapeutic anticoagulation** on an individual basis, taking into consideration risk factors for thrombosis and bleeding. See Table 3e for additional information.

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See [Guidelines Development](#) for more information.

<sup>a</sup> Duration of therapy may vary. For more information, see [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#).

<sup>b</sup> In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids and infliximab or anakinra. Anakinra and infliximab **should not be given** in combination.

<sup>c</sup> Infliximab **should not be used** in patients with macrophage activation syndrome

# Dosing Regimen: NIH Guidelines

Dosing Regimens *For infants, children, and adolescents unless otherwise specified.*

*The doses listed are for FDA-approved indications for other diseases or from reported experiences or clinical trials.*

Adverse Events

Monitoring Parameters

<b>Intravenous Immunoglobulin</b>	<p>IVIg 2 g/kg IBW (up to a maximum total dose of 100 g) IV</p> <p>In the event of cardiac dysfunction or fluid overload, consider administering IVIg in divided doses (1 g/kg IBW per dose IV every 24 hours for 2 doses).</p>	<ul style="list-style-type: none"> <li>•Hypersensitivity</li> <li>•Fever</li> <li>•Chills</li> <li>•Flushing</li> <li>•Hemolytic anemia</li> </ul>	<ul style="list-style-type: none"> <li>•Renal function</li> <li>•Urine output</li> <li>•CBC with differential</li> <li>•Infusion or injection-related AE</li> <li>•Anaphylaxis</li> <li>•Signs and symptoms of hemolysis</li> </ul>
<b>Methylprednisolone</b>	<p>Methylprednisolone 1–2 mg/kg IV every 12 hours</p> <p>If the patient does not respond to 1–2 mg/kg IV every 12 hours, increase the dose to 10–30 mg/kg/day (up to maximum of 1,000 mg/day) IV for 1–3 days.</p>	<ul style="list-style-type: none"> <li>•Adrenal suppression</li> <li>•Hyperglycemia</li> <li>•Sodium retention</li> <li>•Fluid retention</li> <li>•Leukocytosis</li> <li>•Immune suppression</li> </ul>	<ul style="list-style-type: none"> <li>•Blood pressure</li> <li>•CBC with differential</li> <li>•BMP</li> </ul>
<b>Anakinra</b>	<p>Anakinra 5–10 mg/kg/day IV (preferred) or SUBQ in 1 to 4 divided doses</p>	<ul style="list-style-type: none"> <li>•Headache</li> <li>•Fever</li> <li>•Hypersensitivity</li> <li>•Immune suppression</li> <li>•Transaminitis</li> </ul>	<ul style="list-style-type: none"> <li>•CBC with differential</li> <li>•LFTs</li> <li>•SCr</li> </ul>
<b>Infliximab</b>	<p>Infliximab 5–10 mg/kg IV for 1 dose</p>	<ul style="list-style-type: none"> <li>•Infusion-related reaction</li> <li>•Headache</li> <li>•Immune suppression</li> </ul>	<ul style="list-style-type: none"> <li>•Monitor vital signs every 2–10 minutes during infusion.</li> <li>•CBC with differential</li> </ul>
<b>Aspirin</b>	<p>Aspirin 3–5 mg/kg (up to maximum of 81 mg) PO once daily</p>	<ul style="list-style-type: none"> <li>•Gastrointestinal ulcers</li> <li>•Hypersensitivity</li> <li>•Renal dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>•Signs or symptoms of bleeding</li> <li>•Renal function</li> </ul>
<b>Enoxaparin</b>	<p>•<b>Enoxaparin Prophylaxis</b>  <i>Aged &gt;2 Months to &lt;18 Years</i> 0.5 mg/kg (up to maximum of 30 mg) SUBQ every 12 hours</p> <p><b>Enoxaparin Treatment</b>  <i>Aged &gt;2 Months to &lt;18 Years</i></p> <ul style="list-style-type: none"> <li>•1 mg/kg SUBQ every 12 hours</li> <li>•Monitor antifactor Xa activity (treatment goal: 0.5 to 1).</li> </ul>	<ul style="list-style-type: none"> <li>•Increased risk of bleeding</li> <li>•Thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>•CBC with differential</li> <li>•Renal function</li> </ul>

**Key:** AE = adverse effect; BMP = blood mineral panel; CBC = complete blood count; FDA = Food and Drug Administration; IBW = ideal body weight; IV = intravenous; IVIg = intravenous immunoglobulin; LFT = liver function test; MIS-C = multisystem inflammatory syndrome in children; PO = oral; SCr = serum creatinine; SUBQ = subcutaneous

# Discharge/Reporting Definition

## **BOX. Council of State and Territorial Epidemiologists/CDC surveillance case definition for multisystem inflammatory syndrome (MIS-C) in children associated with SARS-CoV-2 infection — United States**

### **Clinical criteria**

- An illness in a person aged <21 years characterized by all of the following, in the absence of a more likely alternative diagnosis\*:
- Subjective or documented fever (temperature  $\geq 38^{\circ}\text{C}$ )
- Clinical severity requiring hospitalization or resulting in death
- Evidence of systemic inflammation (indicated by C-reactive protein of  $\geq 3.0$  mg/dL [30 mg/L])
- New onset manifestations in at least two of the following categories:
  - Cardiac involvement (indicated by left ventricular ejection fraction of  $<55\%$ ; coronary artery dilatation, aneurysm, or ectasia; or troponin elevated above laboratory normal range, or indicated as elevated in a clinical note)
  - Mucocutaneous involvement (indicated by rash, inflammation of the oral mucosa [e.g., mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue], conjunctivitis or conjunctival injection [redness of the eyes], or extremity findings such as erythema [redness] or edema [swelling] of the hands or feet)
  - Shock†

- Gastrointestinal involvement (indicated by abdominal pain, vomiting, or diarrhea)
- Hematologic involvement (indicated by platelet count of  $<150,000$  cells/ $\mu\text{L}$  or absolute lymphocyte count of  $<1,000$  cells/ $\mu\text{L}$ )

### **Laboratory criteria**

- Detection of SARS-CoV-2 RNA in a clinical specimen§ up to 60 days before or during hospitalization, or in a postmortem specimen using a diagnostic molecular amplification test (e.g., polymerase chain reaction); or
- Detection of SARS-CoV-2–specific antigen in a clinical specimen§ up to 60 days before or during hospitalization, or in a postmortem specimen; or
- Detection of SARS-CoV-2–specific antibodies¶ in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization

### **Epidemiologic linkage criteria**

- Close contact\*\* with a confirmed or probable case of COVID-19 disease in the 60 days before hospitalization.

### **Vital records criteria**

- A death of a person aged <21 years whose death certificate lists MIS-C or multisystem inflammatory syndrome as an underlying cause of death or a significant condition contributing to death.

### **Criteria to distinguish a new case from an existing case**

- A case should be enumerated as a new case if the person had never been enumerated as a case or if the person was most recently enumerated as a case with illness onset date (if available) or hospital admission date  $>90$  days previous.

# Infection Prevention

- Isolation per disease/symptom specific guidelines
- FRI precautions only necessary if an acute COVID infection is suspected or confirmed.

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# References/ Institutional Guidelines

- [International Symposium](#)
- [COCA Slides\( CDC consensus report\)](#)
- [Covid-19 Paediatric Multisystem Inflammatory syndrome overview](#)
- [Multisystem Inflammatory Syndrome in Children](#)
- [CHOP Guideline](#)
- [American College Of Rheum guidance](#)
- [Updated ACR guidance](#) and [PDF](#)
- [CDC Guidance](#)
- [AAP Guidance](#)

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# Physician Disclaimers: Clinical Guideline

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# Contact and Revisions Number

- **For questions concerning this care map, contact: [CareMap@etch.com](mailto:CareMap@etch.com)**
- **Last Update: 7/20/21**