UCSF Benioff Children's Hospital

PEDIATRIC COVID/ MIS-C GUIDELINES

How To Use These Guidelines

Acute COVID-19

MIS-C

Anticoagulation

Contributors

References

Click here for ***List of Abbreviations***

This document was developed by the
PEDIATRIC COVID/MIS-C WORKING GROUP
(Version 1 Final Last Updated: 04/01/2021)

How to use these guidelines?

- SARS-CoV-2 infection can result in diverse clinical conditions in children. These guidelines are intended to assist providers in the evaluation and management of the most severe conditions.
- Acute COVID-19 in children can begin as fever and very non-specific “viral” symptoms within different organ systems (e.g. anosmia, rhinorrhea, diarrhea, rash). Some children, especially those who are older with comorbidities like obesity, progress to develop severe lower respiratory tract disease like that seen commonly in adults. The guidance in the Acute COVID-19 section is based primarily on data and principles from the treatment of the respiratory disease in adults.
- Multisystem inflammatory syndrome of children (MIS-C) is a severe syndrome of inflammatory dysregulation that generally occurs weeks after a primary symptomatic or even asymptomatic infection. MIS-C also represents a spectrum of diseases, with younger children often experiencing a vasculitis like that of Kawasaki Disease and older children and adolescents presenting with severe myocarditis and shock.

- How do you decide which pathway to follow?

— This table summarizes characteristics that can be used to distinguish the pathways.

— The timing from exposure may yield a clue. MIS-C classically comes weeks after exposure compared to the shorter incubation period (~ 4-14 days) for acute infection; but note the time windows do overlap.

— Children with mild disease can always be monitored, following symptoms +/- select lab values based on the presentation; but remain alert for acute decline in children with MIS-C.

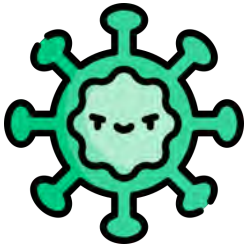
— Some children can have a mix of features from the pathways (e.g. MIS-C and lower respiratory disease). The evaluation and management of children with severe and mixed features should be based on principles of these guidelines and consultation with subspecialties.

— Many children in our care have multiple and complicated chronic medical conditions; their management may fall outside of these guidelines, and should be tailored based on discussion with the relevant subspecialties.

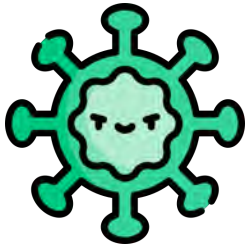
Click here for ***List of Abbreviations***

Main Page

These guidelines were developed by the Pediatric COVID Clinical Working Group, with input from pediatric critical care, hospital medicine, rheumatology, cardiology, gastroenterology, infectious disease, and hematology at Benioff Children’s Hospitals San Francisco and Oakland. These are clinical guidelines only and should not replace clinical judgement. Data about SARS-CoV-2 infection in children continues to evolve; versions of these guidelines will be date stamped and updated. If you have suggestions or questions about these guidelines please email maude.dull@ucsf.edu or theodore.ruel@ucsf.edu.



Distinguishing Acute COVID-19 from MIS-C



Acute COVID-19 and MIS-C have **overlapping features**.
These findings may help to differentiate between them.

Acute COVID-19

COVID exposure within ~2 weeks

Less likely +COVID antibodies

More likely +COVID PCR

Prominent upper and/or lower respiratory symptoms

Acute loss of taste and/or smell

MIS-C

Onset of symptoms 2-6 weeks after infection or exposure

More likely +COVID antibodies

Less likely +COVID PCR

Oral mucosal changes

Swollen hands / feet

Erythema of palms or soles

Extremely elevated ferritin (>10K)

Coronary artery aneurysms

Elevated BNP OR

Evidence of cardiac dysfunction

Main Page

Acute COVID-19 Guidelines

MIS-C Symptoms
Acute COVID-19 Symptoms

ASYMPTOMATIC	No symptoms ascribed to COVID
MILD	Respiratory or other symptoms **not** requiring healthcare without a new or increased supplemental oxygen requirement
MODERATE	Respiratory or other symptoms requiring healthcare **without** a new or increased supplemental oxygen requirement
SEVERE	New or increased requirement for supplemental oxygen (Oxygen saturation < 94% or below patient baseline)
CRITICAL	New or increased requirement for invasive or noninvasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory that does not yet meet these criteria

Main Page

ASYMPTOMATIC

No symptoms ascribed to COVID

If patient meets criteria for HIGH RISK COVID:

Severe obesity (BMI > 99th percentile for age)

Severe immunocompromise as defined by the attached antiviral guidance (not mild-moderate)

Patient dependent on home trach/vent, Bipap, or HFNC

Severe lung disease

Severe cardiac disease

Patients without the above
but with multiple EUA-defined risk factors will also be considered

Consider holding immunosuppression if it can be avoided.
Specific COVID treatment is not recommended.

Main Page

Go back to ***Acute COVID-19 Guidelines Page***

If patient develops oxygen requirement proceed to **SEVERE COVID guidelines**

MILD

Respiratory or other symptoms **not** requiring healthcare without a new or increased supplemental oxygen requirement

If patient meets criteria for HIGH RISK COVID:

Severe obesity (BMI > 99th percentile for age)

Severe immunocompromise as defined by the attached antiviral guidance (not mild-moderate)

Patient dependent on home trach/vent, Bipap, or HFNC

Severe lung disease

Severe cardiac disease

Patients without the above
but with multiple EUA-defined risk factors will also be considered

Monoclonal antibody therapy is not recommended routinely, but may be considered on a case-by-case basis per EUA

Consider holding immunosuppression if it can be avoided. Specific COVID treatment is not recommended.

ID consultation recommended for any treatment questions in patients hospitalized with COVID-19

Main Page

Go back to ***Acute COVID-19 Guidelines Page***

If patient develops oxygen requirement proceed to **SEVERE COVID guidelines**

MODERATE

Respiratory or other symptoms requiring healthcare **without** a new or increased supplemental oxygen requirement

LABS

Recommended if not already done:

- CBC with differential
- C-reactive protein
- Erythrocyte Sedimentation Rate
- Basic Metabolic Panel
- Albumin

Consider based on clinical presentation:

- BNP
- Troponin
- D-dimer
- Ferritin
- Fibrinogen
- INR/PT/PTT
- Specimen storage (red, freeze)
- COVID IgG
- Blood Culture if indicated

Monoclonal antibody therapy is not recommended routinely, but may be considered on a case-by-case basis per EUA

Supportive care is recommended for all patients.

Antiviral therapy may be considered on a case-by-case basis as outlined in pediatric multicenter guidance.

ID consultation recommended for any treatment questions in patients hospitalized with COVID-19

Go back to ***Acute COVID-19 Guidelines Page***

Anticoagulation may be indicated in hospitalized patients

If patient develops oxygen requirement proceed to **SEVERE COVID guidelines**

Main Page

SEVERE

New or increased requirement for supplemental oxygen
(Oxygen saturation < 94% or below patient baseline)

LABS

Recommended if not already done:

- CBC with differential
- C-reactive protein
- Erythrocyte Sedimentation Rate
- Basic Metabolic Panel
- Albumin
- BNP
- Troponin
- D-dimer
- Ferritin
- Fibrinogen
- INR/PT/PTT
- Specimen storage (red, freeze)
- COVID IgG
- Blood Culture if indicated

Remdesivir is indicated

ID Consult required for antivirals

Remdesivir:
Dosage is determined by age and weight of patient

Click here for remdesivir dosing and EUA requirements

Monitoring for Remdesivir:
Monitor hepatic panel at baseline and during therapy
Discontinue remdesivir
ALT elevation > 10X ULN and/or signs or symptoms of liver inflammation:

Consider adding Dexamethasone

Dexamethasone:
0.15 mg/kg/dose (max 6 mg/dose) IV/enterally once daily
Consider risks vs. benefits of dexamethasone in relationship to underlying conditions (e.g. prior immunosuppression, metabolic disease, etc.) *especially in patients with less severe respiratory illness*

Duration of Therapy:

Remdesivir: 5 days in severe illness
Dexamethasone: 10 days
Therapy can be discontinued if patient is well enough for discharge

Antiviral treatment recommendations are based on UCSF IDMP Pediatric Guidelines

Anticoagulation may be indicated in hospitalized patients

At point of hemodynamic instability, revisit **MIS-C recommendations**

Go back to ***Acute COVID-19 Guidelines Page***

Go back to ***Main Page***

CRITICAL

New or increased requirement for invasive or noninvasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory that does not yet meet these criteria

LABS

Recommended if not already done:

- CBC with differential
- C-reactive protein
- Erythrocyte Sedimentation Rate
- Basic Metabolic Panel
- Albumin
- BNP
- Troponin
- D-dimer
- Ferritin
- Fibrinogen
- INR/PT/PTT
- Specimen storage (red, freeze)
- COVID IgG
- Blood Culture if indicated

Remdesivir is indicated

ID Consult required for antivirals

Remdesivir:
Dosage is determined by age and weight of patient

Click here for remdesivir dosing and EUA requirements

Monitoring for Remdesivir:
Monitor hepatic panel at baseline and during therapy
Discontinue remdesivir
ALT elevation > 10X ULN and/or signs or symptoms of liver inflammation:

Consider adding Dexamethasone

Dexamethasone:
0.15 mg/kg/dose (max 6 mg/dose) IV/enterally once daily
Consider risks vs. benefits of dexamethasone in relationship to underlying conditions (e.g. prior immunosuppression, metabolic disease, etc.) *especially in patients with less severe respiratory illness*

Duration of Therapy:

Remdesivir: 5 - 10 days in critical illness, guided by clinical course
Dexamethasone: 10 days or until discharge
Therapy can be discontinued if patient is well enough for discharge

Antiviral treatment recommendations are based on UCSF IDMP Pediatric Guidelines

Anticoagulation may be indicated in hospitalized patients

At point of hemodynamic instability, revisit **MIS-C recommendations**

Go back to ***Acute COVID-19 Guidelines Page***

Go back to ***Main Page***

Remdesivir Therapy

Indicated for Severe and Critical disease

ID Consult required for antivirals

Age < 12 years and/or weight < 40 kg

Remdesivir
Lyophilized powder only

Wt 3.5 - 40 kg:
5 mg/kg/dose IV on day 1,
then 2.5 mg/kg/dose IV q24h

Wt > 40 kg:
200 mg/dose IV on day 1,
then 100 mg/dose IV q24h

Obtain **informed consen**t from caregiver including discussion that medication is not yet FDA approved for patients < 12 years or <40 kg

Age ≥ 12 years and weight > 40 kg

Remdesivir
Lyophilized powder only

Wt >= 40 kg:
200 mg/dose IV on day 1,
then 100 mg/dose IV q24h

Remdesivir is FDA approved for treatment of hospitalized patients ≥ 12 years and ≥ 40kg

Go back to ***Acute COVID-19 Guidelines Page***

Antiviral treatment recommendations are based on UCSF IDMP Pediatric Guidelines

Main Page

At point of hemodynamic instability, revisit **MIS-C recommendations**

MIS-C Evaluation

Consider MIS-C if...

Refer to CDC & WHO case definitions

Fever **AND** Critically Ill
OR
Persistent fever x ≥3 days
AND clinical or lab features of MIS-C
AND ill-appearing
OR
Persistent unexplained fever for ≥5 days

Suspected MIS-C
Ongoing fever, lab evidence of inflammation, multi-system involvement, seriously ill, no alternate diagnosis

Confirmed MIS-C
Above plus +COVID PCR or IgG, or known exposure

Initial Evaluation

Clinical Features

Treatment

Anticoagulation

Main Page

Initial Evaluation

Step 1: Diagnosis

Evidence of Shock

Initiate sepsis evaluation

Initial Labs + Additional Labs
CXR, EKG, POCUS/ECHO

Careful fluid resuscitation
if high suspicion for
cardiac dysfunction

High Suspicion for MIS-C
No evidence of shock

Initial Labs + Additional Labs
+/- CXR if indicated

If lab evidence of MIS-C,
obtain EKG, cardiology consult for
possible ECHO

Low Suspicion for MIS-C
No evidence of shock

Initial Labs +/- CXR if indicated

If lab evidence of MIS-C,
obtain Additional Labs, EKG,
cardiology consult for possible
ECHO

Step 2: Treatment

Meets CDC or WHO case definitions for MIS-C

Manage per
MIS-C treatment protocol

Meets criteria for
Complete or Incomplete KD
AND
Negative or pending COVID PCR/IgG
No known COVID-19 contacts within the past 2 - 4 weeks

Standard KD managment
Monitor for signs of shock
If COVID PCR or IgG becomes
positive, manage per MIS-C
treatment protocol

If clinically stable AND no lab evidence of MIS-C

Consider discharge with close
PCP follow-up

Go back to ***MIS-C Evaluation***

Main Page

Consider alternate diagnoses

Main Page

Clinical Features of MIS-C

- Evidence of current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, **OR**
- Exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms, **AND**
- ≥ 2 organ system involvement:

GI : diarrhea, abdominal pain, appendicitis, pancreatitis, hepatitis, gallbladder hydrops or edema

CV : hypotension or shock, dysrhythmia/arrhythmia, EF <55%, pulmonary edema due to left heart failure coronary artery dilation (z-score ≥2.5) and/or aneurysm, pericarditis, pericardial effusion, valvulitis, BNP > 400, elevated troponin

Heme : WBC <4K, anemia, platelets <150K, DVT, PE, hemolysis, bleeding, prolonged PT/PTT, extremity ischemia

MSK : arthritis, arthralgias, myositis, myalgias

Mucocutaneous : bilateral conjunctival injection, oral mucosal changes, rash or skin ulcers, “COVID toes,” swollen/red/cracked lips, erythema of palms or soles, edema of hands or feet, periungual desquamation

Respiratory : supplemental O2 or mechanical ventilation, severe bronchospasm requiring continuous bronchodilators, pulmonary infiltrates on CXR, lower respiratory infection, PE, pneumothorax, pulmonary hemorrhage, need for chest tube

Neuro : stroke, seizure, encephalitis, aseptic meningitis, demyelinating disorder, AMS, suspected meningitis with negative culture

Renal : acute kidney failure

Go back to ***MIS-C Evaluation***

LABS

Initial Labs:

CBC with Differential

CRP

ESR

BMP

ALT

Albumin

UA with Micro

SARS-CoV2-PCR
(or NAAT as part of RVP)

COVID IgG

RVP

Additional Labs:

BNP

Troponin

Ferritin

D-dimer

PT

PTT

Fibrinogen

LDH

Blood Culture

Red top to hold prior to IVIG

Labs to be Considered with Consultation:

Quantitative Immunoglobins
(IgG/IgA/IgM)

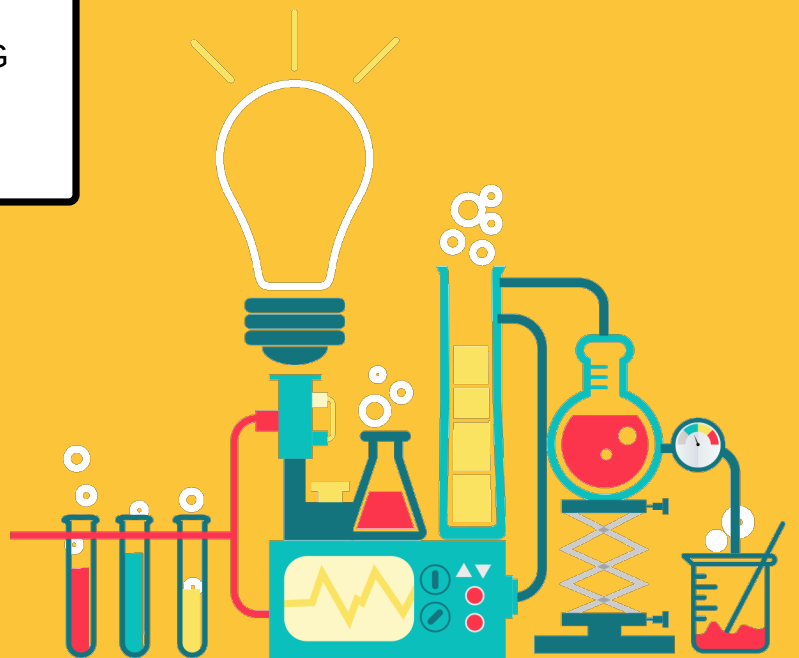
Lymphocyte Subsets

Antiphospholipid Antibodies

Cytokine Panel

Soluble IL-2R

Go back to ***MIS-C Evaluation***



Main Page

Differential Diagnosis

Kawasaki Disease
- More common in younger children
- COVID testing negative
- Less likely shock/cardiac dysfunction

Drug Hypersensitivity Reactions
- Consider SJS, DRESS or serum sickness like reaction
- History of recent or semi-recent exposure to drug
- Arthralgias and diffuse mucositis

Myocarditis:
- May overlap with MIS-C or have alternate cause

Bacterial infection/Sepsis:
- Obtain cultures and evaluate for source
- Consider meningitis

Staphylococcal and streptococcal toxin-mediated diseases
- Diffuse rash and hypotension
- Obtain cultures and evaluate for source, including gynocology or scarlet fever

Staph Scalded Skin Syndrome (SSSS):
- Increasing erythema and bullae
- Younger children
- Obtain cultures

Tick-Borne Illnesses :
- With epidemiologic risk factors
- Rocky Mountain Spotted Fever or Leptospirosis

Viral Infections:
- Active COVID infection, measles, adenovirus, enterovirus

Main Page

Go back to ***MIS-C Evaluation***

MIS-C Treatment

Initial Management

ECHO if not already done
Admit to ICU if shock, hypotension, concern for cardiac dysfunction/dysrhythmia
Consult ID, Rheumatology, Cardiology
Patients with mild disease may receive supportive care only, monitor until clearly improving.
(Mild = normal vital signs apart from fever, only reason for hospitalization is for mild dehydration and/or monitoring).

First-Line Treatment

IVIG 2 g/kg/dose (use ideal body weight) IV X1 dose per infusion protocol
Methylprednisolone 1 mg/kg/dose (max 30 mg/dose) IV q12h
Anti-platelet: ASA 3-5 mg/kg/dose (max 81 mg) enterally qday, if platelets > 80K
Histamine-2 receptor antagonist (H2RA) or Proton pump inhibitors (PPI) while on high-dose steroids

Consider IVIG without steroids if Kawasaki Disease features present (e.g. mucositis, swollen hands and feet) and not critically ill
Consider holding corticosteroids if significant ongoing concern for bacterial sepsis
If concern for MAS or critically ill, *consider* pulse-dose methylprednisolone 30 mg/kg/dose (max 1000 mg/dose) IV q24h for 1-3 days (in consultation with rheumatology)
Consider high-dose methylprednisolone 10 mg/kg/dose IV q24h for patients with severely depressed cardiac function (in consultation with heart failure team)
Consider transitioning to enteral corticosteroid equivalent as patient improves and continue until CRP normalized

Second-Line Treatment

Anakinra IV if not improving with first-line treatment *OR* concern for MAS
Initial dose 2-4 mg/kg/dose (max 100 mg/dose) IV q24h, may increase dose in consultation with rheumatology

Main Page

Click here for ***Post-Discharge Follow-up***

Anticoagulation may be indicated in hospitalized patients

Follow-Up

Rheumatology follow-up:

Labs and medication management

Once CRP normalized, taper steroids over 15 days in 5-day steps (2 mg/kg/day for 5 days, 1 mg/kg/day for 5 days, then 0.5 mg/kg/day for 5 days, then off), per KD RAISE protocol

Cardiology follow up:

ECG & ECHO at 7-14 days and again at 4-6 weeks after presentation or sooner if clinically indicated

Continue ASA until 4-6 week ECHO confirms normal coronary arteries and LV systolic function + normal inflammatory markers + normal platelets

Main Page

Go back to ***MIS-C Evaluation***

Anticoagulation in Patients with COVID-19 and MIS-C

Infection with SARS-CoV-2 is associated with thrombotic complications, particularly in children over the age of 12.

It is recommended that patients > 12 years old hospitalized with COVID-19 or MIS-C be placed on **prophylactic dose** anticoagulation therapy with LMWH or UFH, provided that there are no bleeding contraindications to anticoagulation. Prophylactic anticoagulation should be considered in younger children (≤ 12 years old).

Therapeutic dose anticoagulation may be indicated in some cases (see below). In addition, use mechanical thromboprophylaxis with sequential compression devices, if possible.

- Please see **MIS-C** for use of aspirin and other therapies in children with MIS-C

- **Consult Hematology** for LMWH/UFH anticoagulation treatment recommendations (with ideally a multidisciplinary treatment meeting/plan)

Relative contraindications to anticoagulation:

- Platelet count <50,000
- Fibrinogen <100mg/dL
- Receiving ASA > 5 mg/kg/day
- Underlying bleeding disorder

Active bleeding is a contraindication to anticoagulation

When to use prophylactic (low dose) anticoagulation

(LMWH goal ~0.2-0.4 units/mL
or UFH goal ~0.1-0.3 units/mL)

When to use therapeutic (full dose) anticoagulation

(LMWH goal ~0.5-1 units/mL
or UFH goal ~0.3-0.6 units/mL)

Duration of Anticoagulation

Anticoagulant Drug Doses

Main Page

When to use prophylactic (low dose) anticoagulation

LMWH goal ~0.2-0.4 units/mL or UFH goal ~0.1-0.3 units/mL)

Suggested in patients who are hospitalized with MIS-C or symptomatic COVID-19 AND one or more of the following risk factors:

- ICU admission (including need for mechanical ventilation, inotropic infusion support)
- Central venous catheter (including PICC line)
- D-dimer > 2.5 mcg/mL
- Age > 12 years or post-pubertal
- Obesity (> 95th percentile)
- Concomitant estrogen-containing oral contraceptive use
- First degree family history of unprovoked VTE
- History of thrombosis or acquired or inherited thrombophilia
- Sedated and muscle-relaxed or complete immobility
- Active malignancy, nephrotic syndrome, flare of underlying inflammatory disease, sickle cell VOC
- Congenital or acquired heart disease with venous stasis or impaired venous return (consult cardiology)
- Any rhythm abnormalities, heart block, etc. (consult cardiology)

Main Page

Go back to ***Anticoagulation Main Page***

When to use therapeutic (full dose) anticoagulation
(LMWH goal ~0.5 - 1 units/mL or UFH goal ~0.3 - 0.6 units/mL)

Suggested in patients hospitalized with MIS-C or symptomatic COVID-19
AND one or more of the following:

- Documented thrombosis (Consult Hematology)
- Moderate to severe ventricular dysfunction per Cardiology
- Coronary aneurysm Z score > 10, per Cardiology
- Consider therapeutic anticoagulation for active malignancy, nephrotic syndrome, flare of underlying inflammatory disease state, heart disease with venous stasis or impaired venous return, personal history of thrombosis, or multiple risk factors. (No high quality evidence for therapeutic dosing for these indications).

Discuss with specialist managing underlying condition and/or hematology.

Main Page

Go back to ***Anticoagulation Main Page***

Duration of Anticoagulation

Prophylactic Anticoagulation

- Discontinue prophylactic anticoagulation at discharge in most patients
- Discontinue earlier if patients are improved and risk factors have resolved
- Consider continuation of prophylactic anticoagulation post-discharge for ongoing severe inflammation with other risk factors.

Duration: 30 days post-discharge or when risk factor(s) resolve, whichever is sooner

Therapeutic Anticoagulation

- Continue therapeutic dosing while indicated and formulate outpatient plan with consultants (cardiology, rheumatology and/or hematology)

Main Page

Go back to ***Anticoagulation Main Page***

Anticoagulant Drug Doses

PROPHYLACTIC DOSING

LMWH (clinically stable patients)
Age > 2 months:
Enoxaparin 0.5 mg/kg/dose SubQ q12h

UFH (unstable patients)
Heparin: 10-15 units/kg/hour IV
No loading dose needed

Direct oral anticoagulants
(e.g., rivaroxaban and apixaban)
Not recommended for inpatient VTE prophylaxis because of possible drug interactions with some medications used to treat COVID-19

THERAPEUTIC DOSING

LMWH
Enoxaparin 1 mg/kg/dose SubQ q12h

UFH
Children > 1 yr:
Loading dose 75 units/kg IV over 10 minutes
(range 50-100 units/kg),
followed by 20 units/kg/hr IV
(range 15-25 units/kg/hr).

Main Page

Go back to ***Anticoagulation Main Page***

Main Page

References

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Main Page

List of Abbreviations

AKI	Acute Kidney Injury
ALT	Alanine Aminotransferease
AMS	Altered Mental Status
ASA	Aspirin
BiPAP	Bilevel Positive Airway Pressure
BMI	Body Mass Index
BMP	Basic Metabolic Panel
BNP	B-type Natriuretic Peptide
CBC	Complete Blood Count
COVID-19	Coronavirus Disease 19
CRP	C-Reactive Protein
CXR	Chest XRay
DVT	Deep Vein Thrombosis
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	Electrocardiography
ECHO	Echocardiogram
EF	Ejection Fraction
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
HFNC	High Flow Nasal Cannula
ID	Infectious Diseases
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-2R	Interleukin-2R
INR	International Normalized Ratio
IVIG	Intravenous Immune Globulin
KD	Kawasaki Disease
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
MAS	Macrophage Activate Syndrome
MIS-C	Multisystem Inflammatory Syndrome
NAAT	Nucleic-acid Amplification Test
PCP	Primary Care Physician
PCR	Polymerase Chain Reaction
PICC	Peripherally Inserted Central Catheter
PE	Pulmonary Embolism
POCUS	Point-of-Care Ultrasound
PT	Prothrombin Time
PTT	Partial Thrombopalstin Time
SJS	Steven-Johnson Syndrome
RT-PCR	Reverse Transcriptase PCR
RVP	Respiratory Viral Panel
SubQ	Subcutenous Route
UA	Urinalysis
UFH	Unfractionated Heparin
ULN	Upper Limits of Normal
VOC	Vaso-Occlusive Disease
VTE	Venous Thromboembolism
WBC	White Blood Count

Main Page