Management of Pediatric Patient with Suspected/Confirmed Covid-19 Infection

Guidelines for Pediatric Critical Care Units in Saudi Arabia

Background:

At this point in time, there is no evidence that children have a greater risk for COVID-19. The greatest number of reported infections are occurring in the adult population. There have, however, been some reported infections in children, most resulting in minor respiratory infections and flu-like symptoms. Still, some children may develop severe disease that warrants PICU admission.

Aims and scope:

To optimize PICUs preparedness and management of pediatric COVID-19 patients, the MOH prepared this guideline in August 2021.

The specific objectives of the COVID-19 clinical pathways are to:

- Guide hospital-based providers on how to evaluate and diagnose children with a possible severe COVID-19 infection.

- Direct hospital-based providers on how to appropriately triage patients with possible COVID-19 infection, including when to consult PICU team.

- Ensure medical staff apply proper isolation and personal protective equipment procedures

Targeted Population:

All pediatric patients who are suspected/ confirmed COVID-19 infection in the ED, hospital wards, and PICUs.

Targeted End User:

- Pediatric Emergency Medicine physicians.
- Pediatric Critical Care Medicine physicians.
- Pediatric Critical Care and Emergency Medicine Nurses.
- Pediatricians

Methodology used:

The guideline was developed by doing a literature review of all pediatric related articles on COVID-19 from 2019 till August 2021 by 3 reviewers and coming up with written document. The key words used for search were: Pediatric, Children, Critical, Pediatric Intensive Care, COVID-19, MIS-C, SARS-CoV-2, Management, Infection Control. The next step was having a meeting with 12 consultants from PICU, rheumatology, Infectious disease, and general pediatricians. Final revision was done with meeting representatives of tertiary PICUs from different area of the kingdom of Saudi Arabia from MOH hospitals and experts from other non-MOH hospitals. Conflict was solved by discussion and voting.

Disclaimer:

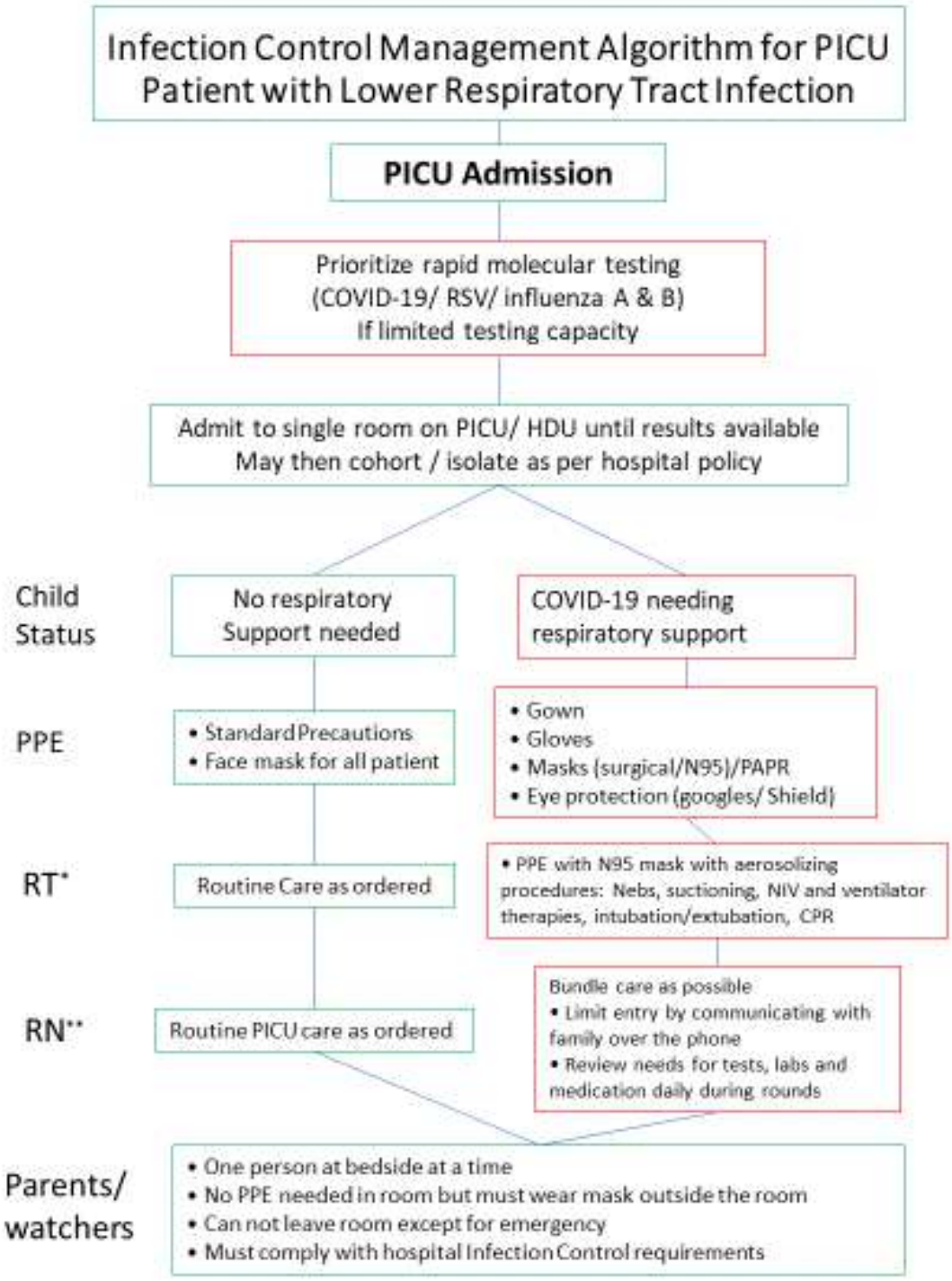
These clinical pathways have been summarized specifically for use at PICUs in Saudi Arabia and are made available for informational and educational purposes only. The clinical pathways are not intended to be, nor are they, a substitute for individualized professional medical judgment, advice, diagnosis, or treatment. Although the designated committee made all efforts to ensure the accuracy of the contents, we make no warranty of any kind as to the completeness of the information or its fitness for use at any particular facility or in any individual case, as the COVID-19 pandemic keeps evolving.

Table of content:

1. **Essential infection control precautions for Pediatric COVID-19 patients:**

- Coronavirus (COVID-19) is mainly transmitted by **droplets** (human to human especially from coughing or sneezing) and by **contact** (when touching contaminated surfaces then touching the mouth, nose or eye) as declared by WHO.
- It strongly recommended to be **handled as air-borne disease** as many infected cases can't be explained by above mechanisms, especially during aerosol generating interventions.
- Coronavirus (COVID-19) is characterized by its ability to spread rapidly among healthcare staff who are not properly protected.
- It can be difficult to rapidly diagnose, and **suspected cases should be handled as confirmed** until proven otherwise.
- The key infection control considerations for all healthcare staff managing critically ill children with suspected/confirmed COVID-19 are:
    - Safe isolation
    - Wearing of Personal Protective Equipment (PPE)
    - Strict adherence to above precaution when transferring suspected/confirmed Covid-19 cases

2. Infection Control Management Algorithm for PICU Patient with LRT Infection:



*RT: Respiratory Therapist, **RN: Registered Nurse

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3. The Golden Rule: Plan ahead (do not rush)

This document serves as a reference only for management of patients admitted to PICU with moderate to severe COVID-19 infection. It can be modified according to individual case scenario and the feasibility of resources in PICU settings.

Infection Control Recommendations for COVID-19 suspected/confirmed cases in PICU
➢ All PICU staff should get fit-tested & trained to use of N95 respirator masks (or PAPR) as they are expected to be assessing or caring for suspected/confirmed cases of COVID-19
➢ All PICU staff should be trained in the safe donning & doffing of Personal Protective Equipment (PPE) & its appropriate use (training minimize errors and reduce staff exposure)
➢ Suspected patients should be placed in respiratory isolation (negative pressure room is strongly recommended when available) or a specified cohort area with HEPA filter
➢ Visitors should be prohibited or extremely restricted. If one parent/caregiver is exceptionally allowed to stay with the child, she/he should remain in the isolation room or cohorted area and should wear surgical mask as per hospital infection control policy.
➢ Transport of COVID-19 suspected/confirmed patient should be minimized and planned for very well and any investigation or procedure outside PICU should be considered carefully (risk to benefit)

Comorbidities with possible increased risk (Early PICU consultations or triaging decision)
➢ **Long term respiratory conditions**, including but not limited to: ○ Severe Asthma ○ Chronic lung disease of prematurity with oxygen dependency ○ Cystic Fibrosis ○ Interstitial Lung diseases ○ Respiratory complications in children with complex medical needs
➢ **Immunocompromised states**, including but not limited to: ○ Malignancy on active treatment with chemotherapy or radiotherapy ○ Post-transplantation ○ Immunosuppressive medication – including long-term steroid use ○ Congenital immunodeficiency ○ Asplenia – structural or functional
➢ **Cyanotic or Hemodynamically significant heart disease**
➢ **Chronic Kidney disease or patient on dialysis**
➢ **Younger age < 2 yrs**
➢ **Obesity**
➢ **Children with diabetes**

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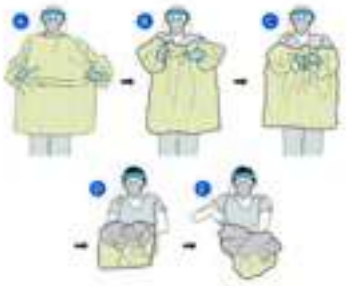
How to manage a pediatric cardiac arrest or pre-arrest in suspected/confirmed cases

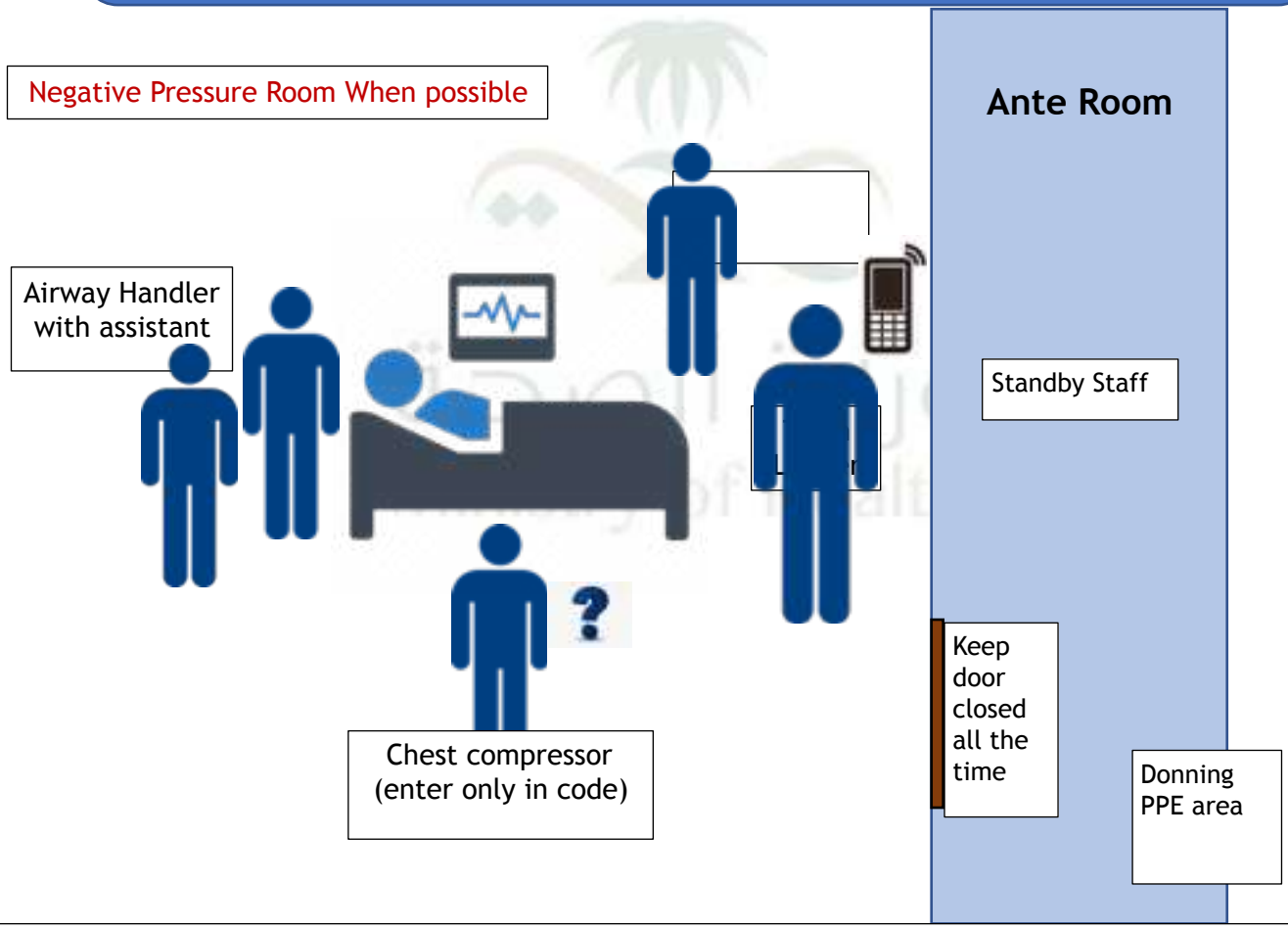
- Do not use the hospital cardiac arrest team and create COVID-19 code team if possible.
- All team members should be mask fit tested and able to don and doff PPE comfortably (practice).
- Lines of communication should be easily available to the team inside the room and the team outside
- Allow the least number of the team to enter the room as determined by code team leader (minimum 4).
- Keep equipment outside the room until needed.
- Most expert intubator undertakes first attempt at intubation.
- Consider airway adjuncts and video laryngoscopy.
- If the child is intubated and ventilated – try not to disconnect from the ventilator when doing CPR
- Cuffed ETT preferable with inflated cuff
- If plan for manual ventilation use small tidal volumes
- Ensure filter is placed between face mask and bag (or ETT and bag)
- If the crash trolley is used – dispose of all disposable contents within the isolation room before taking the trolley out of the room to be cleaned

- **Ensure Proper Donning/Doffing PPE with assistant**
  (someone who observe and guide what you are doing to ensure your safety)



4. Code arrangements for pediatric COVID-19:Golden Rule:

Unstable, pre-arrest or arrest pediatric patients with suspected/ confirmed COVID-19



Suggested COVID-19 Response Team Role distribution in Critical Situation/±Code

Minimize number of team members, Anticipate and prepare ahead

Only essential equipment needed for patient care will be placed inside the patient room

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5. Special considerations for aerosol generating procedures in COVID-19 patients

- Procedures that produce aerosols of respiratory secretions, carry an increased risk of transmission.
- Re-useable equipment should be avoided if possible; if used, it should be decontaminated according to the manufacturer's instructions before removal from the room
- Use dedicated equipment in the isolation room.
- Avoid storing any extraneous equipment in the patient's room
- Dispose of single use equipment as per clinical waste policy inside room
- Ventilators should be protected with a high efficiency filter
- Closed system suction should be used

Aerosol Generating Procedures (AGPs)	Precautions
➢ Intubation, extubation ➢ Bag & mask ventilation ➢ Open suction ➢ NPA swab test ➢ High Flow Nasal Cannula (HFNC) ➢ Non-invasive ventilation – CPAP, BiPAP ➢ Tracheostomy – insertion, removal, suction ➢ Bronchoscopy ➢ Dental procedures	✓ Require full PPE (N95 mask) ✓ Be undertaken in a negative pressure or at least single room with door closed and HEPA filter ✓ Avoided unless essential or proven to be clinically helpful ✓ Only staff required for the procedure or care of the patient should be present ✓ Do not enter or exit room during the procedure or open the door

6. Respiratory Support of children with COVID-19 respiratory distress/failure

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- ➢ Respiratory failure is very unlikely in children (< 5% symptomatic cases)
- ➢ Deterioration usually occurs in the 2nd week with tachypnea, dyspnea and mainly hypoxemia
- ➢ If SpO2 <94%, administer Oxygen via simple nasal cannula or face mask
- ➢ **Connect the cannula to the patient first before turning the flow on to minimize aerosols generation**
- ➢ Avoid HFNC to reduce work of breathing if SpO2 is adequate, as it is associated with significant droplet aerosolization & virus spread
- ➢ If hypoxia persists despite, HFNC can be tried, but should be commenced in a negative pressure room (if available) with full PPE
- ➢ If deterioration despite HFNC consider early intubation preferably done electively inside PICU with full preparation.

Important consideration:

- **Both HFNC and NIV have been used in pediatric COVID-19.**
- **They can be used in suspected/confirmed cases if strict isolation precautions are adhered to – i.e. staff are in full PPE and patient is isolated as per infection control policy.**
- **However, the risk of aerosol generation with HFNC or NIV is considered to be high, and early intubation and invasive ventilation may be necessary in some cases.**

Special Consideration for Mechanical Ventilation in COVID-19 cases
Adult data suggest variable pathophysiology of the disease at different stages and in different population. **Data is lacking for pediatric but generally, consider the following:** • Using high PEEP (8-10) when lung compliance is good is not advised. • When ARDS present then high PEEP (10-15), low tidal volume and lung recruitment will be more suitable). • When using high PEEP monitor mixed venous saturation and its impact on cardiac output • Tidal volume 6-8 ml/Kg per IBW in compliant lung (4-6 in poor compliance) • Prone positioning is recommended early with significant hypoxemia. • HFOV can be used in severe hypoxemia case

7. Management of other manifestations/complications of COVID-19 pediatric patient in PICU

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Shock	No specific recommendations for COVID-19 infected pediatric patients. Please refer to Surviving Sepsis Campaign latest guidelines.
AKI	No specific recommendations
Myocardial involvement	it is emerging as one of most significant and life-threating complication of COVID-19 in children. (see MIS-C section)
Other organ involvement	Supportive PICU care, no specific COVID-19 evidence based recommendations

8. Medication used in PICU for COVID-19 pediatric patients

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Antipyretics	Paracetamol is the 1st line anti-pyretic Avoid Ibuprofen in general especially with poor fluid intake or suspected Acute Kidney Injury

Bronchodilators	Wheeze is not a common problem with COVID-19 as it is not a small airway disease but has been reported. Should not be routinely used unless wheeze or prolonged expiratory phase present. Use bronchodilators with MDI/spacer rather than nebulization, where possible, to minimize droplet spread
Steroids	See MOH COVID-19 guideline
Antimicrobials	Strongly recommended when signs of secondary bacterial infection are present especially with worsening clinical status few days after admission.
COVID-19 specific therapies	Consult ID as the recommendation is changing rapidly with more evidence evolving about the benefit vs harm. ***Reference: Saudi MOH COVID-19 Guidelines Version 3.1 (including Pediatrics) 19 August 2021:*** ***https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/MOH-therapeutic-protocol-for-COVID-19.pdf***

9. PICU and Inpatient Clinical Pathway for Evaluation of Possible Multisystem Inflammatory Syndrome (MIS-C):

9. PICU and Inpatient Clinical Pathway for Evaluation of Possible Multisystem Inflammatory Syndrome (MIS-C):
• **Criteria for diagnosis:**
○ Patient aged < 15 years presenting with fever (>38.0˚C for ≥24 hours, or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation (Including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) ○ No alternative plausible diagnoses ○ Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms
• **Definition:**

- Mild symptoms: patients presenting with fever for ≥3 days and who are well-appearing (i.e., normal vital signs and reassuring physical examination) with only mild symptoms suggestive of MIS-C.
- Moderate to severe symptoms: patients presenting with fever along with one or more organ involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatologic or neurological) or with elevated inflammatory markers.

- Inflammatory markers are measured at the time of admission and then serially to monitor progression based on clinical judgment. Similarly, if cardiac markers are elevated, they should be followed serially to monitor progression according to the clinical judgment.

- Children admitted to the hospital with MIS-C should be managed by a multidisciplinary team that includes general pediatric/ PICU, pediatric rheumatologists, cardiologists, infectious disease, and hematologists.

- **Management:**

- Patients with mild manifestations, as outlined, no further treatment is required and can be managed as outpatient with close follow up (see Appendix 1).
- Patients with moderate to severe manifestations, as outlined, need to be admitted to the ward or PICU as required and should receive IVIG (2 grams per KG), then if no improvement follow treatment pathway (see Appendix 1).

There are no established therapies for COVID-19-associated CSS or MIS-C. These medications are to be used only with guidance from Rheumatology, Cardiology and Infectious Diseases. Patients who are being evaluated for immunomodulatory therapy should also be considered for antiviral therapy if they are not already receiving it.

- Supportive Care: Children with moderate to severe signs and symptoms should be admitted to the hospital. Admission to a pediatric intensive care unit is appropriate for children with hemodynamic instability (shock, arrhythmia), significant respiratory compromise, or other potentially life-threatening complications
- Thromboprophylaxis (please refer to **Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19)**
- Antiviral therapy (please refer to **Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19**)
- Immunomodulator Dosing and Monitoring

Immunomodulator	Dosing	Safety monitoring
IVIG with methylprednisolone see below table *"Medication Related Information"*		
MIS-C with or without features of Kawasaki disease or signs of myocardial dysfunction OR - Severe or critical COVID-19 with evidence of CSS	IVIG 2 g/kg + methylprednisolone at 0.8 to 1 mg/kg every 12 hours (maximum of 30 mg for 12 hours) for 5 days - IVIG 2 g/kg + methylprednisolone bolus of 15 to 30 mg/kg/d for 3 days	Assess cardiac function and fluid status prior to giving to avoid fluid overload - Baseline renal function tests, urine output, IgG level, CBC - Monitor clinically for signs of hemolysis after first dose - Potential adverse reactions: anaphylaxis, - Infusion reaction, hemolysis, transaminitis, aseptic meningitis - Pulmonary adverse reactions; blood pressure (prior to, during, and following infusion); clinical response. - For patients at high risk of hemolysis (dose ≥2 g/kg, given as a single dose or divided over several days, and non-O blood type): Hemoglobin or hematocrit prior to and 36 to 96 hours post-infusion and again at 7 to 10 days post-infusion
Glucocorticoids MIS-C with features of shock or coronary artery dilation/aneurysm OR Severe or critical COVID-19 with evidence of CSS		
- 1-2 mg/kg/day divided BID (prednisone, prednisolone, methylprednisolone) 5 mg/m2 daily (dexamethasone) *Please refer to* ***Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19***		

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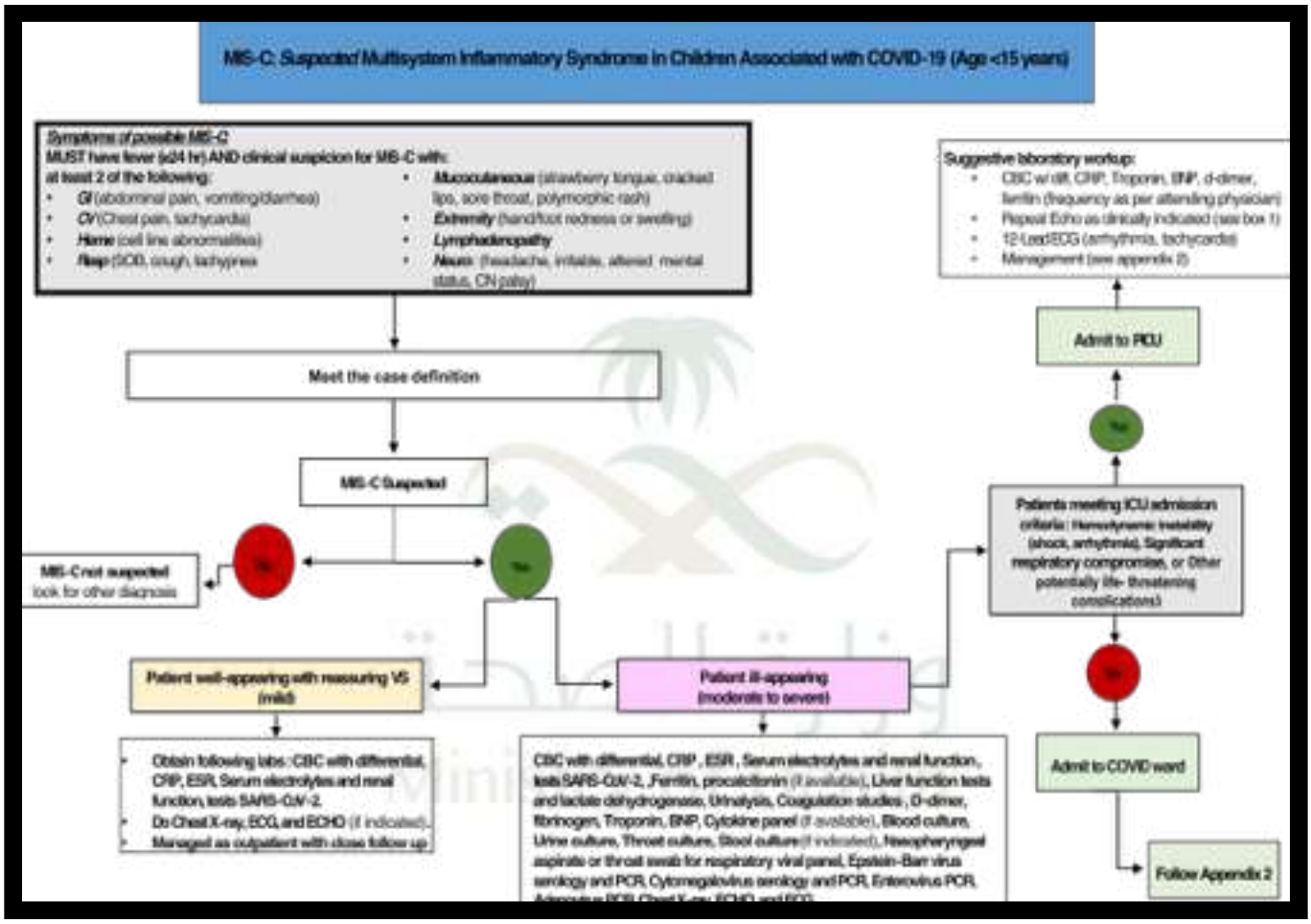
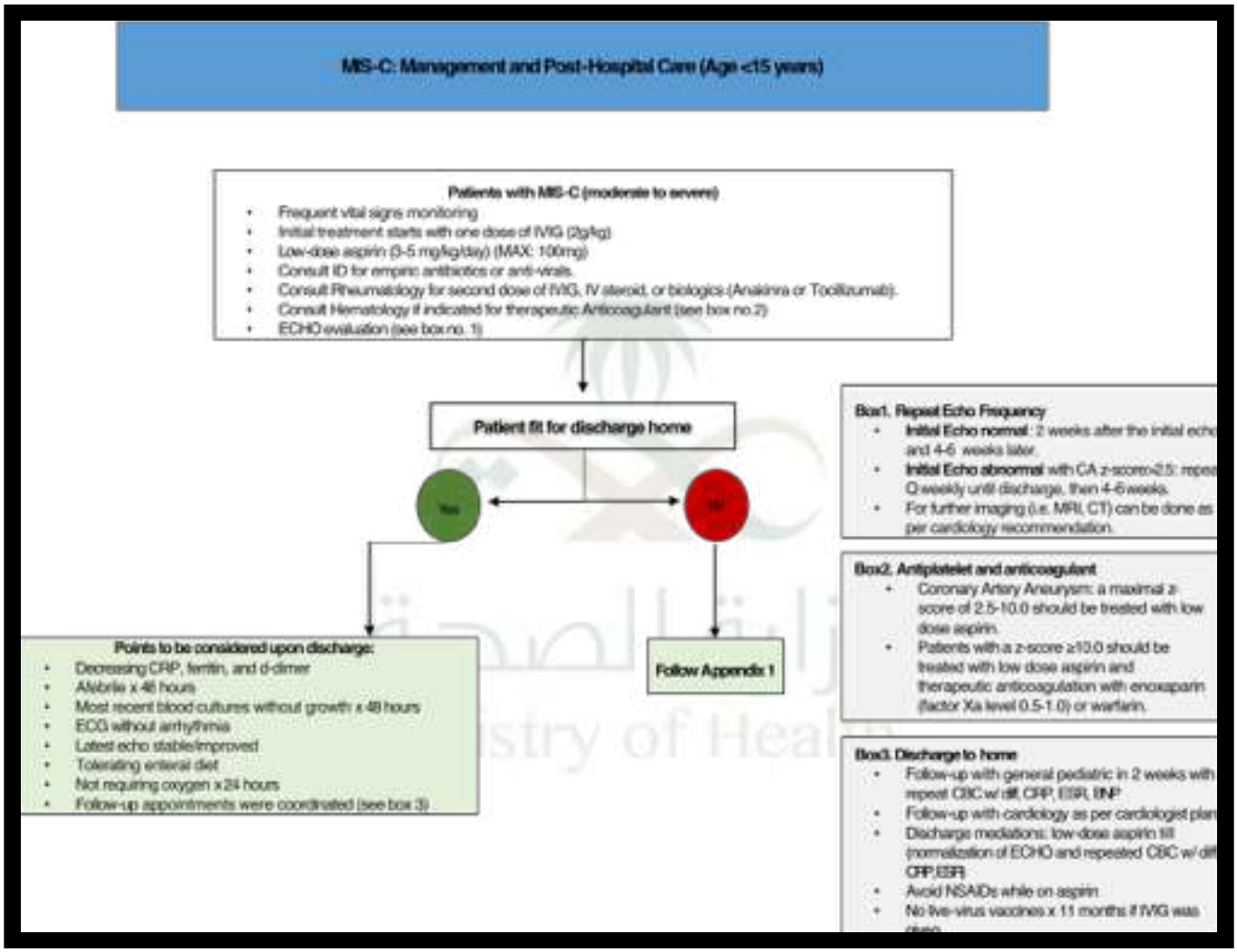
- **HOSPITALIZATION CRITERIA for MIS-C:**

  - Any significant finding/abnormality as per attending team judgment
  - Respiratory distress.
  - Neurologic deficits or change in mental status (including subtle manifestations).
  - Evidence of renal or hepatic injury.
  - Abnormal ECG findings or abnormal levels of BNP or troponin T.
  - Patient aged < 21 years presenting with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation (Including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin), and evidence of clinically severe illness requiring hospitalization, with multi-system (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
  - No alternative plausible diagnoses
  - Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Appendix 1


MIS-C Suspected Multisystem Inflammatory Syndrome in Children Associated with COVID-19 (Age <15 years)
Symptoms of possible MIS-C
MUST have fever (≥24 hr) AND clinical suspicion for MIS-C with:
at least 2 of the following:
GI (abdominal pain, vomiting/diarrhea)
CV (Chest pain, tachycardia)
Heme (cell line abnormalities)
Resp (SOB, cough, tachypnea
Mucocutaneous (strawberry tongue, cracked lips, sore throat, polymorphic rash)
Extremity (hand/foot redness or swelling)
Lymphadenopathy
Neuro (headache, irritable, altered mental status, CN palsy)
Meet the case definition
MIS-C Suspected
MIS-C not suspected
look for other diagnosis
No
Yes
Patient well-appearing with reassuring VS (mild)
Obtain following labs: CBC with differential, CRP, ESR, Serum electrolytes and renal function, tests SARS-CoV-2.
Do Chest X-ray, ECG, and ECHO (if indicated).
Managed as outpatient with close follow up
Patient ill-appearing (moderate to severe)
CBC with differential, CRP , ESR , Serum electrolytes and renal function , tests SARS-CoV-2, Ferritin, procalcitonin (if available), Liver function tests and lactate dehydrogenase, Urinalysis, Coagulation studies , D-dimer, fibrinogen, Troponin, BNP, Cytokine panel (if available), Blood culture, Urine culture, Throat culture, Stool culture (if indicated), Nasopharyngeal aspirate or throat swab for respiratory viral panel, Epstein-Barr virus serology and PCR, Cytomegalovirus serology and PCR, Enterovirus PCR,
Patients meeting ICU admission criteria: Hemodynamic instability (shock, arrhythmia), Significant respiratory compromise, or Other potentially life- threatening complications)
Admit to PICU
Admit to COVID ward
Follow Appendix 2
Suggestive laboratory workup:
CBC w/ diff, CRP, Troponin, BNP, d-dimer, ferritin (frequency as per attending physician)
Repeat Echo as clinically indicated (see box 1)
12-Lead ECG (arrhythmia, tachycardia)
Management (see appendix 2)

Appendix 2


MIS-C: Management and Post-Hospital Care (Age <15 years)
Patients with MIS-C (moderate to severe)
Frequent vital signs monitoring
Initial treatment starts with one dose of IVIG (2g/kg)
Low-dose aspirin (3-5 mg/kg/day) (MAX: 100mg)
Consult ID for empiric antibiotics or anti-virals.
Consult Rheumatology for second dose of IVIG, IV steroid, or biologics (Anakinra or Tocilizumab).
Consult Hematology if indicated for therapeutic Anticoagulant (see box no.2)
ECHO evaluation (see box no. 1)
Patient fit for discharge home
Box1. Repeat Echo Frequency
Initial Echo normal: 2 weeks after the initial echo and 4-6 weeks later.
Initial Echo abnormal with CA z-score>2.5: repeat Q weekly until discharge, then 4-6 weeks.
For further imaging (i.e. MRI, CT) can be done as per cardiology recommendation.
Box2. Antiplatelet and anticoagulant
Coronary Artery Aneurysm: a maximal z-score of 2.5-10.0 should be treated with low dose aspirin.
Patients with a z-score ≥10.0 should be treated with low dose aspirin and therapeutic anticoagulation with enoxaparin (factor Xa level 0.5-1.0) or warfarin.
Points to be considered upon discharge:
Decreasing CRP, ferritin, and d-dimer
Afebrile x 48 hours
Most recent blood cultures without growth x 48 hours
ECG without arrhythmia
Latest echo stable/improved
Tolerating enteral diet
Not requiring oxygen x 24 hours
Follow-up appointments were coordinated (see box 3)
Follow Appendix 1
Box3. Discharge to home
Follow-up with general pediatric in 2 weeks with repeat CBC w/ diff, CRP, ESR, BNP
Follow-up with cardiology as per cardiologist plan
Discharge medications: low-dose aspirin till (normalization of ECHO and repeated CBC w/ diff CRP,ESR)
Avoid NSAIDs while on aspirin
No live-virus vaccines x 11 months if IVIG was

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References:

1. Management of Pediatric COVID 19 in PICU CPG, KFMC, Riyadh, Saudi Arabia
2. https://www.rcpch.ac.uk/resources/national-guidance-management-children-bronchiolitis-during-covid-19
3. https://www.usahealthsystem.com/uploads/pdfs/covid-19/picu-algorithm-management.pdf
4. Jacqueline S. M. et al. Coronavirus Disease 2019 in Critically Ill Children: A Narrative Review of the Literature. Pediatr Crit Care Med 2020; XX:00-00. DOI: 10.1097/PCC.0000000000002376
5. Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19 Supportive care and antiviral treatment of suspected or confirmed COVID-19 infection (version 1.2) April 5th, 2020
6. Paediatric Intensive Care Society UK: PICS Guidance on Management of Critically Ill Children With COVID-19 Infection. Available at: https://picsociety.uk/news/updated-pics-guidance-on-covid-19/. Accessed March 14, 2020
7. Tamburro RF, Kneyber MC. Pulmonary specific ancillary treatment for paediatric acute respiratory distress syndrome: proceedings from the paediatric acute lung injury consensus conference. Paediatr Crit Care Med: June 2015;16(5s): s61–S72.
8. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
9. Saudi center for disease prevention and control: Coronavirus 19 (COVID-19) Guidelines, March 2020: V1.2. Available at: https://covid19.cdc.gov.sa/wpcontent/uploads/2020/03/Coronavirus-Disease-2019-Guidelines-v1.2.pdf.pdf. Cited Mar 24, 2020
10. World Health Organization: Global Surveillance for human infection with coronavirus disease (COVID-19). Available at: https://www.who.int/publicationsdetail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov). Cited Mar 25, 2020
11. World Health Organization: Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acuterespiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected . Cited Mar 25, 2020.
12. Centers for Disease Control and Prevention: Breastfeeding; Coronavirus Disease (COVID-19). Available at: https://www.cdc.gov/breastfeeding/breastfeedingspecial-circumstances/maternal-or-infant-illnesses/covid-19-andbreastfeeding.html. Cited Mar 26, 2020.
13. American Academy of Pediatrics (AAP) guidance on infants born to mothers with suspected or confirmed COVID-19. By Alyson Sulaski Wyckoff. Available at: https://www.aappublications.org/news/2020/04/02/infantcovidguidance040220. Cited Mar April 4, 2020
14. Centers for Disease Control and Prevention: Disposition of Hospitalized patients with COVID-19: Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html. Cited Mar 27, 2020.
15. Karimi A, Rafiei Tabatabaei S, Rajabnejad M, Pourmoghaddas Z, Rahimi H, Armin S et al. An Algorithmic Approach to Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19) in Children: Iranian Expert's Consensus Statement. Archives of Pediatric Infectious Diseases. 2020;In Press(In Press). DOI:10.5812/pedinfect.10240.

16. Gautret P, Lagier J, Parola P, Hoang V, Meddeb L, Mailhe M et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial. International Journal of Antimicrobial Agents. 2020;:105949.

17. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020.

18. Inpatient Guidance For Treatment of COVID-19 in Adults and Children [Internet]. 10th ed. University of Michigan; 2020 [cited 26 March 2020]. Available from: http://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf

19. Cao W, Liu X, Bai T, Fan H, Hong K, Song H et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019. Open Forum Infectious Diseases. 2020.

20. Johns Hopkins Coronavirus COVID-19 Resource Center. Available at: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 . Accessed March 23, 2020

21. Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak. *JAMA* 2020 Feb 24. [online ahead of print]

22. Livingston E, Bucher K: Coronavirus disease 2019 (COVID-19) in Italy. *JAMA* 2020 Mar 17. [online ahead of print]

23. Korean Society of Infectious Diseases; Korean Society of Pediatric Infectious Diseases; Korean Society of Epidemiology; Korean Society for Antimicrobial Therapy; Korean Society for Healthcare-associated Infection Control and Prevention; Korea Centers for Disease Control and Prevention: Report on the epidemiological features of coronavirus disease 2019 (COVID-19) outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci* 2020; 35:e112

24. Lu X, Zhang L, Du H, et al: SARS-CoV-2 infection in children. *N Eng J Med* 2020 Mar 18. [online ahead of print]

25. Liu W, Zhang Q, Chen J, et al: Detection of COVID-19 in children in early January 2020 in Wuhan, China. *N Engl J Med* 2020 Mar 12. [online ahead of print]

26. Xu Y, Li X, Zhu B, et al: Characteristics of pediatric SARS-CoV-2 infection and potential evidence of persistent fecal viral shedding. *Nat Med* 2020 March 13. [online ahead of print]

27. Dong Y, Mo X, Hu Y, et al: Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020 Mar 16. [online ahead of print]

28. Wang XF, Yuan J, Zheng YJ, et al: Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen. *Zhonghua Er Ke Zha Zhi* 2020; 58:E008

29. Zimmerman P, Curtis N: Coronavirus infections in children including COVID-19. *Pediatr Infect Dis J* 2020 Mar 12. [online ahead of print]

30. Wei M, Yuan J, Liu Y: Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA* 2020 Feb 14. [online ahead of print]

31. Cao Q, Chen YC, Chen CL, et al: SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics. *J Formos Med Assoc* 2020; 119:670–673

32. Qin C, Zhou L, Zhang S, et al: Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020 Mar [online ahead of print]

33. Prompetchara E, Ketloy C, Palaga T: Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020; 38:1–9

34. Zhou F, Yu T, Fan G, et al: Clinical course and risk factors for mortality for adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 2020; 395:1054–1062

35. Yang Y, Peng F, Wang R: The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *J Autoimmun* 2020 Mar 3. [online ahead of print]

36. Wang D, Hu B, Hu C, et al: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* 2020; 323:1061–1069

37. Gu H, Xie Z, Li T, et al: Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. *Sci Rep* 2016; 6:19840

38. Lee, PI, Hu YL, Chen PY, et al: Are children less susceptible to COVID-19? *J Microbiol Immunol Infect* 2020 Feb 25. [online ahead of print]

39. Xie X, Xudong X, Chen J, et al: Age- and gender-related difference of ACE2 expression in rat lung. *Life Sci* 2006; 78:2166–2171

40. Xia W, Shao J, Guo Y, et al: Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatr Pulmonol* 2020 Mar 5. [online ahead of print]

41. Heimdal I, Moe N, Krokstad S, et al: Human coronavirus in hospitalized children with respiratory tract infections: A 9-year population based study from Norway. *J Infect Dis* 2019; 219:1198–1206

42. Cheung JC, Ho LT, Cheng JV, et al: Staff safety during emergency airway management for COVID-19 in Hong Kong. *Lancet Respir Med* 2020 Feb 24. [online ahead of print]

43. Faculty of Intensive Care Medicine, The Intensive Care Society, Royal College of Anaesthetists, UK: Information, Guidance and Resources Supporting the Understanding and Management of Coronavirus (COVID-19). 2020. Available at: https://icmanaesthesiacovid-19.org/national-guidance . Accessed April 1, 2020

44. The Alfred ICU Guideline for Intubation of Critically Ill Patients, Appendix on Intubation of Confirmed or Suspected COVID-19 Patients. 2020. Available at: https://intensiveblog.com/covid19-update-for-alfred-icu-guideline-for-intubation-of-critically-ill-patients/ . Accessed March 14, 2020

45. Paediatric Intensive Care Society UK: PICS Guidance on Management of Critically Ill Children With COVID-19 Infection. Available at: https://picsociety.uk/news/updated-pics-guidance-on-covid-19/. Accessed March 14, 2020

46. Mason KE, Urbansky H, Crocker L, et al; Task Force for Pediatric Emergency Mass Critical Care: Pediatric emergency mass critical care: Focus on family-centered care. *Pediatr Crit Care Med* 2011; 12:S157–S162

47. Paediatric Intensive Care Society UK: PICS and ICS Joint Position Statement on Planning for the Pandemic. Available at: https://picsociety.uk/news/pics-and-ics-joint-position-statement-12-mar-2020/ . Accessed March 12, 2020

48. Christian MD, Devereaux AV, Dichter JR, et al: Introduction and executive summary: Care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest* 2014; 146(Suppl 4):8S–34S

49. COVID-19 RELATED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) CPG, KFMC, Riyadh, Saudi Arabia

50. https://www.chop.edu/clinical-pathway/multisystem-inflammatory-syndrome-mis-c-clinical-pathway

51. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020;46(Suppl 1):10–67. doi:10.1007/s00134-019-05878-6 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095013/

52. Children's ED and Inpatient COVID-19 Algorithm (last updated 28 April 2021):

    https://www.connecticutchildrens.org/wp-content/uploads/2021/08/COVID19-Ed-Inpatient-06072021.pdf

53. - Prone Positioning for Pediatric COVID Patients:https://site.cmg.io/scnresearch/Prone_Positioning_for_pediatric_COVID_patients-_V3.0.pdf

54. Schuster JE, de St Maurice A. COVID-19 in Children-Not Just Little Adults. JAMA Network Open. 2021;4(6):e2111441. Doi:10.1001/jamanetworkopen.2021.11441