RAPID ADVICE ON PULMONARY CARE IN PEDIATRIC COVID-19

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EXECUTIVE SUMMARY

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus. There are few data on the clinical presentation of COVID-19 in specific populations, such as infants and children. While clinical data available to date are based largely on the disease experience in China, Europe, and the United States, the pediatric literature on COVID-19 is still in its infancy. Acquisition of new data in the regional, national, and international guidance is still rapidly evolving.

This guidance was made from meager resources available in children and will serve as a foundation for optimized respiratory supportive care for pediatric COVID-19 patients. The purpose of this document is to complement with the WHO, CDC and the other subspecialty guidelines in providing respiratory care for children with acute respiratory infections when COVID-19 is suspected. This guidance should be used alongside with infection prevention control guideline.

This novel virus involves the respiratory system in the progressive stage of the disease. The considerations for pediatric patients with respiratory involvement is highlighted throughout the text. It is not meant to replace clinical judgment or specialist consultation but rather to strengthen clinical management of these patients and to provide up-to-date guidance. Best practices for optimized respiratory supportive care ie., aerosolized procedures, proning in children, and airway therapies and management of asthma in pediatric COVID-19 patients.

We recognize the unsettling nature of these changing recommendations and we want to provide pediatric health care providers with more data to better understand the shifting landscape surrounding respiratory care in COVID-19. The evidence is rapidly changing and this guidance will be updated to reflect the same as evidence becomes available.

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Guideline Methodology

This Guideline was prepared in accordance with the general rules of WHO Rapid Advice Guidelines and DOH Manual for Clinical Practice Guideline Development 2018.

The End-User of The Guideline

The guideline is intended for clinicians involved in the care of pediatric patients with or at risk for severe acute respiratory infection (SARI) when infection with the COVID-19 virus is suspected.

Declaration of Conflict of Interests

Written inquiry for financial interests of relevant personal was conducted after the first meeting prior to the start of this guideline. Relevant financial as well as nonfinancial interests were surveyed and disclosed and subsequently assessed in consensus conference in order to minimize potential bias in guideline development. Finally, there is no conflict of interests for all the personnel participating to prepare this guideline.

Literature Searching and Preparation of Evidence Profiles

Draft of the proposed scope and list of potential priority topics was performed. This was subsequently refined to the list of priority topics and identifying key issues. The Pediatric Pulmonology COVID task Force Committee members concentrated on the management of respiratory care and the topic list was utilized to formulate the key questions. These questions were used as a guide in the search of evidence and are developed using the PICO format. In addition, we have an independent literature searching team to search available indirect evidence from systematic reviews and/or RCTs (randomized controlled trials), of the existing evidence. We addressed topics or questions covered by the guideline, then its quality assessed. If there is a lack of higher-level quality evidence, our panel considered observational studies and case series. We identified relevant literature up to April 15,2020.

We Searched the literature to identify relevant information, including existing guidelines and systematic reviews. The bibliographic databases and concepts were defined with search terms that include both medical subject headings (MeSH) and text words. We also searched following websites: the WHO (https://www.who.int/), CDC(Centers for Disease Control and Prevention, https://www.cdc.gov/) and DOH (Department of health, https://www.doh.gov.ph)

Grading the Evidences and Recommendations

We accorded to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) basic approaches and rules and particularly considered experts' evidence to assess the quality of a body of evidence to make recommendations.

The quality of evidence reflects whether the extent to which our confidence estimating the effect is adequate to support a particular recommendation. The level of evidence was categorized as "high quality", "moderate quality", "low quality", or "very low quality";

The recommendations were classified as "strong" or "weak." In specific recommendations, we used "*should" or "strongly recommend*" for **strong** recommendations; whereas, "*suggest" or "consider"* was used for **weak ones**.

Updating the Guideline

Because clinical information about the optimal management of COVID-19 is evolving quickly, this Guideline will be updated frequently as published data and other authoritative information becomes available. If there is a reason to believe one or more recommendations need updating, and plans should be made to start that process. In situation ie. new controversial areas, those in which new evidence has emerged or if there are concerns that one or more recommendations in a guideline may no longer be valid, the committee will make every effort to ensure to update the recommendations.

Disclaimer: The evidence is rapidly changing and this guidance will be updated to reflect the same as evidence becomes available. Please take note that this rapid advice will have to undergo revisions and editing as new evidence will set in before it will be published in the final form. Due to the unavailability of reliable current sources on pediatric COVID-19 infection, the following evidence summaries are developed from the existing pool of available data obtained by the researchers, which were scrutinized further, and the final articles registered in this document were those that were warranted valid enough for citation (systematic reviews and meta-analyses were prioritized among other articles as they grant the most accurate findings). There is a need to conduct more systematic reviews of the available data with further specification on exposure and outcome variables which will be of great help in the determination of quality evidence for the consequent development of accurate clinical practice guidelines. Moreover, for the PECO questions which do not have scientific evidence yet, there should be at least observational studies done to answer these questions especially during this pandemic period.

Contents

RECOMMENDATIONS AT A GLANCE

I. Clinical Presentation of COVID-19

Recommendation 1: Children presenting with any of the following : fever, cough, sore throat, shortness of breath and/or gastrointestinal symptoms without any plausible etiology should be further investigated for possible exposure to COVID – 19 and be considered as COVID suspect.

II. Clinical Classification of COVID-19 Based on Severity of Pneumonia

Recommendation 2: Pneumonia in COVID-19 Children should be classified as non-severe or severe pneumonia.

III. Laboratory Examination

Recommendation 3:

Consider the use of laboratory tests to support the diagnosis and monitor COVID – 19 patients especially in evaluating for co-infections and multi-organ dysfunctions.

Laboratory tests that may be requested:

1. Complete Blood Count
2. C Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR)
3. Procalcitonin

Laboratory tests that may be requested in severe cases:

1. Alanine Aminotransferase (ALT),
2. Aspartate aminotransferase (AST),
3. PT PTT
4. LDH
5. Creatinine,
6. Blood Urea Nitrogen (BUN), serum electrolytes
7. Creatinine kinase – MB (CK-MB)
8. D Dimer
9. Arterial Blood gases

IV. Chest Imaging in Pediatric COVID-19 Patient

A Chest Radiography

Recommendation 4

Chest imaging should be requested

a. For medical triage of patients with suspected COVID-19 who present with **moderate to severe** clinical features and a high-test probability of disease in resource-limited settings.

b. When a child requires hospitalization, or is suspected of having hospital acquired pneumonia, CXR is the most appropriate step in imaging evaluation.

c. Chest xray should not be requested in patients with suspected early stages of pediatric COVID-19 and mild clinical features at outpatient setting unless they are at risk for disease progression.

Recommendation 5

The following should be the structured reporting of CXR findings for pediatric COVID- 19 patients[10]

1. **Typical Findings Of Pediatric COVID-19**
   Bilateral distribution peripheral and/or subpleural GGOs and/or consolidation.

2. **Indeterminate Findings Of Pediatric COVID-19**
   Unilateral peripheral or peripheral and central GGOs and/or consolidation, bilateral peribronchial thickening and/or peribronchial opacities, or multifocal or diffuse GGOs and/or consolidation without specific distribution.

3. **Atypical Findings Of Pediatric COVID-19**
   Unilateral segmental or lobar consolidation, central unilateral or bilateral GGOs and/or consolidation, single round consolidation i.e., round pneumonia with or without air bronchogram, pleural effusion, or lymphadenopathy.

4. **Negative for Pediatric COVID-19**
   No CXR findings suggestive of pneumonia

V. Chest Computed Tomography

Recommendation 6

The following should be in the structured reporting for CT findings for pediatric COVID-19 patients[10]

1. **Typical findings of pediatric COVID-19**
   Bilateral, peripheral and/or subpleural GGOs and/or consolidation in lower lobe predominant pattern
2. **Indeterminate findings of pediatric COVID-19**
   Unilateral peripheral or peripheral and central GGOs and/or consolidation, bilateral peribronchial thickening and/or peribronchial opacities, multifocal or diffuse GGOs and/or consolidation without specific distribution, or the “crazy paving” sign.
3. **Atypical findings of pediatric COVID-19**
   Unilateral segmental or lobar consolidation, central unilateral or bilateral GGOs and/or consolidation, discrete small nodules, lung cavitation, plural effusion, or lymphadenopathy.
4. **Negative for pediatric COVID-19**:
   No Chest CT findings suggestive of suggestive of pneumonia in children

VI. Chest Ultrasound

Recommendation 7

Chest ultrasound can be considered as an alternative to CXR and Chest CT in the diagnosis of pneumonia in COVID 19 patients. It is a tool that could be used at bedside avoiding the need for shifting infected patients to the Radiology suite [101 103]

VII. Respiratory Support for COVID-19 Patients

Management of Hypoxemia in the Spectrum of the COVID-19 Illness

A. Precaution

Recommendation 8

The use of High Flow Nasal Cannula (HFNC), CPAP/BiPAP and Non Invasive Ventilation (NIV) theoretically increase the risk of viral spread through aerosol generation. Therefore, we suggest to observe the following precautions.[19]

1. Preferably in an appropriate Airborne Infection Isolation Room (AIIR)
2. Use of a surgical mask over HFNC, to reduce droplet spread
3. Use an appropriate viral exhalation filter for CPAP/BiPAP
4. Healthcare providers shall be in proper Personal Protective Equipment (PPE)

B. First line Approach

Recommendation 9

Children with suspected or confirmed severe pneumonia COVID-19 will need supplemental oxygen to achieve target sp02 ≥94%. We suggest to use:

1. A Low Flow Nasal Cannula (LFNC) at 1 to 6L/minute may be started with a surgical mask worn over the patient's face to reduce droplet spread.
   1–2 L/min in infants
   2–4 L/min in young children
   4–6 L/min in older children and adolescents
   Titrate supplemental oxygen based on patient's saturation
2. The use of CPAP or a bi-level NIV is the approach recommended if SPO2/FiO2 ratio >221 and < 264.

Recommendation 10

In low-resource settings or in facilities where ventilators are not available, we suggest that an improvised CPAP (iCPAP), using locally available equipment, may be used.

VIII. Airway Management and Tracheal Intubation Specific to COVID-19 Patient Group

A. Precaution

Recommendation 11

We strongly recommend an appropriate environment for airway management of suspected or confirmed COVID-19 pediatric patients as follows;

1. The use of a negative pressure ventilation room is ideal to minimize exposure to aerosols and droplets from pediatric COVID-19 patients
2. Normal pressure rooms with closed doors are an alternative setting in low-resource facilities
3. The use of airway devices providing 6L/min or more of oxygen shall be discouraged as this procedure is considered aerosol-generating, unless it is performed under an AIIR.
4. Strict hand hygiene and compliance to the minimum PPE requirement is necessary in handling pediatric COVID-19 patients
5. Double gloving as a standard practice for handling pediatric COVID-19 patients

B. Intubation

Recommendation 12

We strongly recommend that intubation should not be further delayed if SpO2/FiO2 ratio < 221 in pediatric patients on bi-level NIV or CPAP and if there is no improvement in oxygenation (target SpO_2 92-97% and FiO_2) within 60-90 minutes.

Recommendation 13

The use of Bag Valve Mask (BVM) prior to intubation is not advised for suspected or confirmed COVID-19 patients due to its capacity to generate aerosols. However, if the bag/mask ventilation is necessary for pre-oxygenation, it is strongly recommended to follow safety measures to minimize aerosolization:

a. Two-Person technique/Two handed vice grip, use of a viral filter, and gentle ventilation
b. A clear drape should be placed over the patient's face to minimize aerosolization.

Recommendation 14

Rapid Sequence Intubation (RSI) is should be the treatment of choice for endotracheal intubation of suspected or confirmed COVID-19 patients as inadequate sedation and paralysis can produce coughing during laryngoscopy, which is an aerosol-generating procedure.

It is strongly recommended that cuffed endotracheal tubes be used to avoid peri-tubal leak and dissemination of secretions.[30]

IX. Ventilator Management and Strategies

A. Lung Protective Strategies

Recommendation 15

The general principles of management of child with ARDS apply to a child with COVID-19 related ARDS. The lung protective strategies suggested are as follows: [6 32]

1. Low tidal volume (3-6ml/kg IBW) if poor respiratory compliance
   Low tidal volume (5-8ml/kg) if better preserved respiratory compliance
2. High PEEP (>10cmH2O)
3. Target plateau pressure <28cmH2O

4. Permissive hypercapnia (pH >7.20)

B. Proning for Pediatric Covid-19 Patients

Recommendation 16

Prone positioning may be considered as part of treatment regimen for pediatric COVID-19 patients with moderate to severe ARDS.

X. Airway Therapies and Respiratory Mechanics

Recommendation 17: The use of pMDI for the delivery of B2 agonists via spacer or valve holding chamber (VHC) should strongly considered as means of drug delivery over nebulizers among non-intubated children suspected or confirmed to have COVID-19 with signs of bronchoconstriction.

Recommendation 18: The use of pressurized metered dose inhaler (pMDI) is strongly recommended among mechanically ventilated COVID-19 suspect or confirmed children the use of pressurized metered dose inhaler (pMDI) is strongly recommended over nebulization.

Recommendation 19: The use of nebulization for the delivery of B2 agonists among children having bronchospasm should only be used for limited specific situations under strict aerosol generating procedure protective measures and should be avoided as much as possible. The Limited Indications of Nebulization Include [50]

1. Severe life-threatening respiratory distress,
2. Patients with compromised ventilation,
3. Uncooperative patients
4. Children with poor response to pMDI

Pressurized metered dose inhaler (pMDI) and Administration Techniques

Recommendation 20: It is strongly recommended that for suspected or confirmed COVID-19 children presenting with bronchospasm initial dose of salbutamol 2 puffs for children ≤ 5yo; 4 puffs children 6-11 yo and adolescent (100mcg/actuation) delivered is strongly recommended.

If symptoms persist after initial bronchodilator: a further 2–6 puffs of salbutamol for <5 yo 4-10 puffs (>6 yo) may be repeated every 20 minutes until good clinical response is achieved.

Recommendation 21: In ventilator-supported children, clinicians should consider using bidirectional in-line adapter when administering pMDI. This should be connected to the inspiratory limb of the ventilator tubing before the Y-piece. Unidirectional in-line and elbow adapters may be used as alternatives but are less effective.

XI. AIRWAY CLEARANCE THERAPIES RATIONALE FOR USE FOR COVID-19

Recommendation 22: For airway clearance procedures, we strongly recommend the following strategies among pediatric COVID-19 patients:

- Ensuring adequate oxygenation, keeping the respiratory tract unobstructed
- Appropriate inhalation therapy
- Appropriate reassessment of airway patency
- Non-invasive/invasive respiratory support and mechanical ventilation
- Judicious use of fluids and vasoactive medications

ASTHMA IN CHILDREN DURING THE COVID-19 PANDEMIC

Recommendation 23: The administration of existing medications for asthma controller medications should be continued for pediatric patients with asthma during the COVID-19 pandemic.

DISCHARGE and ENDING ISOLATION OF PEDIATRIC COVID-19 PATIENTS

Recommendation 24: We strongly recommend that based on the latest DOH updated guidelines, symptomatic patients COVID-19 Patients (suspect/ probable/ confirmed) who have fulfilled completion of 14 days isolation, clinically recovered and no longer symptomatic can be discharged and tagged as recovered without RT-PCR or antibody testing and provided that there is a clearance from licensed physician.
(Strong recommendation, low-grade evidence).

Recommendation 25: We strongly recommend, home isolation should be discontinued based on the guidance for Symptom based-strategy with the following conditions: patient has completed 14 days quarantine OR patient has at least 3 days (72 hours) have passed since recovery (based on resolution of fever without use of antipyretics and improvement of respiratory symptoms) and has at least 10 days have passed since symptoms first appeared ,whichever is longer.
(Strong-recommendation, low-grade evidence)

Chapter 1

1 Background

Medical professionals require an up-to-date guideline to follow when an urgent healthcare problem emerge. We developed this rapid advance guideline for respiratory care of pediatric suspect and confirmed COVID-19 cases.

Due to the necessary speed in which this guidance has been drawn up, recent evidences from different countries were gathered with the aim to provide an overview of principles of respiratory care in children.

Pediatric Burden of COVID – 19

In the early days of COVID – 19, affected children were rather rare, there are relatively fewer cases, milder symptoms and better prognosis, with children having less frequent exposure to the main sources of transmission. However with familial ingathering, a rise in the number of children were affected. From mild to severe cases and atypical clinical presentation patterns continue to evolve. However, with the substantial rise in the number of cases globally, this necessitates early planning in consideration of a rise in pediatric cases.

Confirmed cases of COVID-19 in children are relatively fewer than adults. In the United States 2%, China 2.2%, Italy 1.2% of confirmed cases of COVID -19 were among persons < 18 years. In the Philippines, recent data (as of June 18, 2020) from the Department of Health revealed pediatric patients comprise 6.85% (1,895 out of 27,663) of the total confirmed COVID-19 patients in the Philippines. There are 25 deaths among the pediatric patients. Case fatality rate is 1.33% as compared to 4.03% in general population.

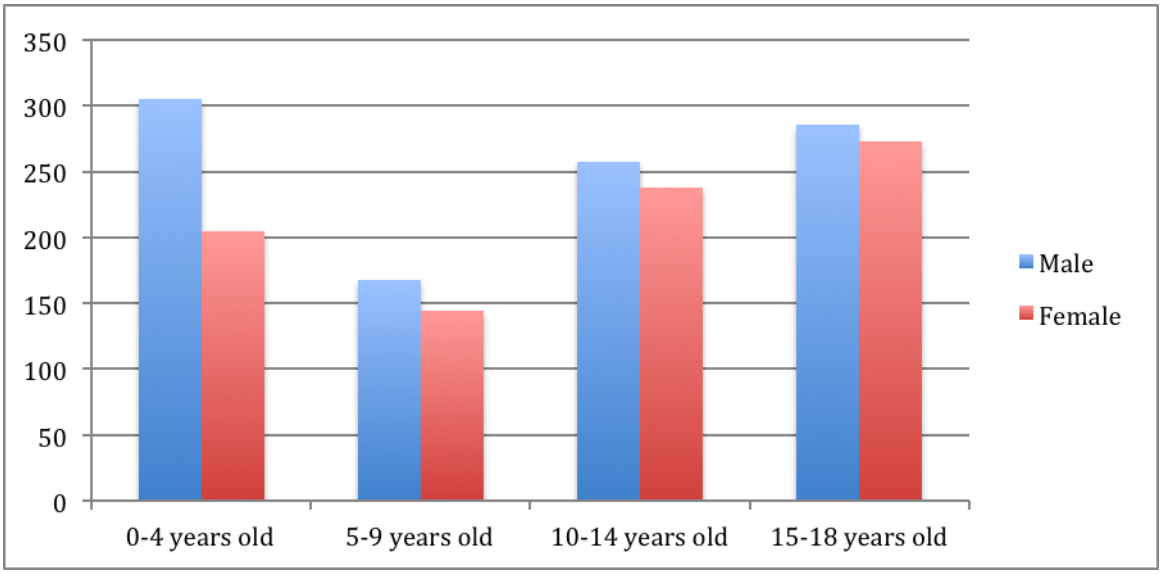


Figure 1. Age and Sex distribution of Symptomatic Pediatric COVID-19 Cases in the Philippines

The table below shows the total and distributed numbers based on age group of the confirmed pediatric COVID-19 cases and deaths.

Table 1. June 18, 2020 Data Drop of COVID-19 Pediatric Cases from the Department of Health Case Report https://ncovtracker.doh.gov.ph

27,663 TOTAL CASES (NATIONWIDE)	
Confirmed Pediatric Cases **1,876**	**Reported Number of Deaths** **25**
0-4 years old: 510 **5-9 years old: 312** **10-14 years old: 495** **15-18 years old: 559**	<1 year old, male <1 year old, male <1 year old, male <1 year old, male <1 year old, male <1 year old, male <1 year old, female 1 year old, female 1 year old, female 1 year old, female 1 year old, male 1 year old, male 1 year old, male 7 year old, female 7 year old, female 9 year old, female 10 year old, female 13 year old, male 15 year old, female 17 year old, male 17 year old, male 18 year old, male 18 year old, male 18 year old, male 18 year old, male

Asymptomatic: 19 cases	Recovered: 241 cases

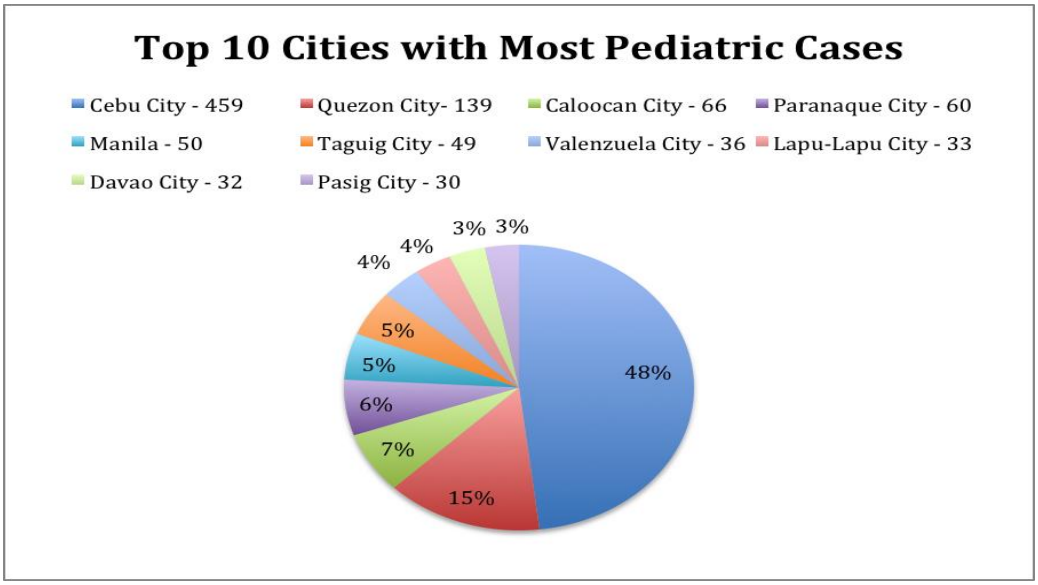


Figure 2. Top 5 cities with most Pediatric COVID-19 cases as of June 18, 2020

Clinical Features

1.1 Etiology, Pathogenesis, Incubation Period

Etiology

Coronaviruses (CoVs) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope.

SARS-CoV-2, the causative agent of COVID-19 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. It is sensitive to ultraviolet rays and heat and can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.[109]

Pathogenesis

Coronavirus S protein has been reported as a significant determinant of virus entry into host cells. The envelope spike glycoprotein (S1) binds to the cellular receptor of Angiotensin Converting Enzyme 2(ACE2) for SARS-CoV and SARS-CoV-2. ACE2 is present in epithelium in the nose, mouth, lungs, heart, blood vessels, kidneys, liver and gastrointestinal tract. In the lungs, ACE2 is highly abundant on type 2 pneumocytes, an important cell type present in chambers within the lung called alveoli, where oxygen is absorbed and waste carbon dioxide is released.

Belouzard et al. found that a critical proteolytic cleavage event occurred at SARS-CoV S protein at position (S2) mediated the membrane fusion and viral infectivity. After cell entry, the viral RNA genome is released into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate.[129] During this process of rapid viral replication, the affected pneumocytes will be damaged subsequently stimulating the body's humoral and cellular immunity, which are mediated

by virus-specific B and T cells. Inflammatory mediators (Interleukin 1, Interleukin 6 and Tumor Necrosis Factor Alpha) will be released causing vasodilation and increased capillary permeability. This in turn may lead to alveolar edema and atelectasis leading to impaired gas exchange and eventual hypoxemia.

The main pathogenesis of COVID-19 infection as a respiratory system targeting virus is severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury.

ARDS is the main death cause of COVID-19. ARDS is the common immunopathological event for SARS-CoV-2. The cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines and chemokines. The cytokine storm will trigger a violent attack on respiratory cellular structure including the pneumocytes and the endothelial cells, cause ARDS leading to multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection. [129]

Incubation Period

The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset.[12]
Rationale:
Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18). This data also showed that this novel epidemic doubled about every seven days.
There is currently no data on the specific incubation period of SARS-CoV2 among pediatric patients, though a current study suggests the median incubation to be at 5.1 days (95% CI, 4.5-5.8 days) and the development of symptoms start within 11.5 days (95% CI, 8.2-15.6 days) of infection[12.] There is also an implication that, under conservative assumptions, 101 out of every 10,000 cases will develop symptoms after 14 days of active monitoring or quarantine[12.]

1.2 Mode of Transmission of COVID-19

Household or direct contact is the major transmission route for COVID-19 infection in children [4,14.] Having close contact with persons with a positive exposure history to COVID-19 pointed as another route for its infection in children [4,14.] There is no risk of vertical transmission of COVID-19 from infected pregnant mothers to their fetuses [4.]

According to the World Health Organization (WHO) report, SARS COV2 which spreads via oral and nasal droplets[111] WHO believes that further evidence is needed to assess the possibility of aerosol transmission. Some observations suggest that aerosol propagation is possible under the condition of long exposure to high concentrations of aerosols in a relatively closed environment[112.]

1.3 Clinical Presentation of COVID-19

1.3.1 Early recognition and Clinical presentation

The main symptoms in children are fever, flu like illness (nasal obstruction, runny nose), dry cough, myalgia and fatigue. Some children only present with low to moderate grade fever in their entire course of disease, and some do not show fever at all.[6 17] It is important for pediatric providers to have an appropriate suspicion of COVID-19, but also to continue to consider and test for other diagnoses, such as influenza.

Recommendation 1: Children presenting with any of the following: fever , cough sore throat, shortness of breath and/or gastrointestinal symptoms without any plausible etiology should be further investigated for possible exposure to COVID–19 and be considered as COVID suspect. [4 14]

(Strong recommendation, moderate grade of evidence).

Signs and Symptoms

Signs and Symptoms	Physical examination
Fever range is usually > 38^0C Cough Nasal Congestion or Rhinorrhea Sore throat Gastrointestinal symptoms Shortness of breath Fatigue Headache Myalgia Poor Feeding or poor appetite	Tachypnea and tachycardia Minimal rales or wheezing *Other findings*: Digital swelling Cutaneous manifestations Kawasaki disease like manifestations (gastrointestinal symptoms, conjunctivitis, rashes and mucosal changes).

Rationale:
Fever and cough, remain as the most common symptoms of pediatric COVID - 19, amongst all epidemiological studies around the globe. Fever range is usually above 38^0C (38.1^0C to 39^0C)[4,14]. Other symptoms are variable when it comes to rate of occurrence. These may include shortness of breath, gastrointestinal symptoms, rhinorrhea and sore throat[4,14].

Physical examination may reveal tachypnea and tachycardia[14]. Auscultatory findings may reveal minimal rales or wheezing[5 14,]. Recently, there have been reports of dermatologic manifestations in children especially amongst teens with mild disease. The cutaneous manifestations consisted of an acral eruption of erythemo-violaceous papules and macules, with possible bullous evolution or digital swelling (see figure 3). These are benign self-limiting lesions that would tend to appear late in the course of disease[114]

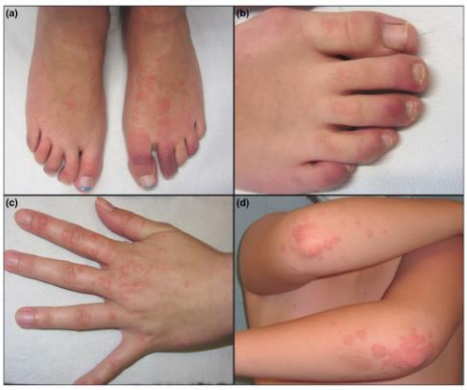


Figure 3. Erythematous violaceous maculopapular rashes seen on fingers and elbows

Not so common presentations of the disease, include kawasaki disease-like illness and myocarditis[115]. Kawasaki disease has been linked to coronaviruses of the past particularly SARS Cov 1[116]. At present, in London and in New York, there had been reports of critically ill children positive for COVID – 19 who are presenting with gastrointestinal symptoms, conjunctivitis, rashes and mucosal changes (atypical Kawasaki/toxic shock syndrome). Case reports have been published but clear association between SARS Cov 2 virus and Kawasaki disease is still unknown.[116 117]
It is in Europe and Northern America that these cases were first recognized and they presented with signs and symptoms similar to atypical Kawasaki Disease and Toxic Shock Syndrome. To date, there were 230 cases reported across the European countries (U.K., France, Italy and Spain). All children had prolonged fever, abdominal pain and other gastrointestinal symptoms (50–60%) as well as conjunctivitis, rash, irritability and, in some cases, shock, usually of myocardial origin. However, some respiratory symptoms could be present, and dyspnea was usually correlated with concurrent shock**.**

Some children were positive for SARS-CoV-2 by PCR, while others were positive for IgG antibodies. COVID-19 history or COVID-19-compatible symptoms could be either elicited in the history of the child or a household member. Markers of inflammation were elevated: neutrophilia with lymphopenia, significantly increased C-reactive protein, D-dimer, IL-6 and ferritin levels, and hypoalbuminaemia.[130]

The Centers for Disease Control and Prevention (CDC) is calling the condition **Multisystem Inflammatory Syndrome in Children (MIS-C)** and is urging clinicians to report suspected cases.

The European Centre for Disease Prevention and Control on the other hand, has coined the term, **Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-Cov-2 infection in children or PIMS-TS** to describe these cases.

1.3.2 Spectrum of Illness Severity

For the severity of pediatric COVID-19 patients of the 2143 patients reported from China the Illness severity ranged from asymptomatic to critical.[98]

- Asymptomatic 4.4 %

- Mild 50.9 %
- Moderate 38.8 %
- Severe disease 5.2 %
- Critical disease 0.6%

In a systematic review and meta-analysis done included all age groups, from neonates to adolescents, majority of patients were categorized as having mild to moderate disease (98%)[4]

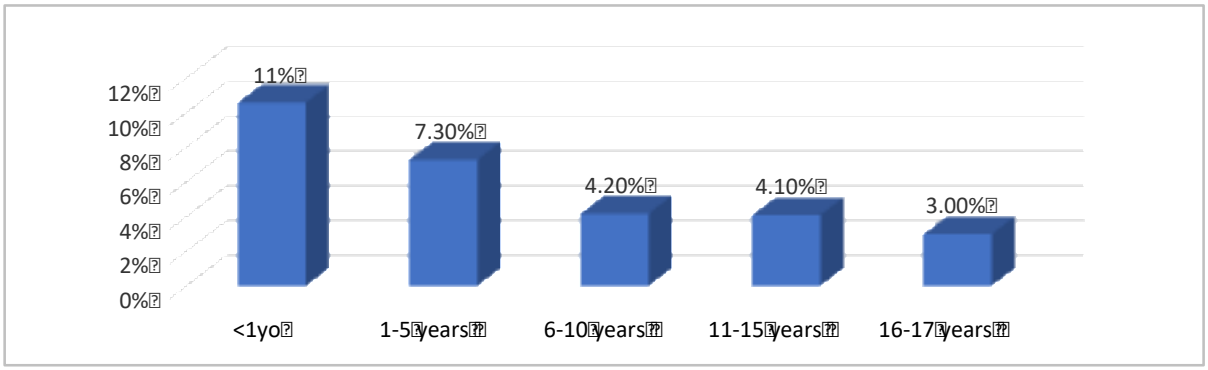


Fig 4. Prevalence of Severe and Critical Disease in Children

The severity of illness by age showed that young children, particularly infants, were vulnerable and that half of the children with critical COVID-19 in this study were less than one year of age.[5.]

Severe disease is usually seen among infants or those with underlying conditions such as asthma, congenital heart disease or immunosuppression[14]. None of those who recovered from disease had permanent disability because of infection. Prognosis in children is generally good. Even if hospitalized, most will recover in two weeks.

Theories on as to why children are less affected and have better outcomes include[4,14,**119**]:

- Humoral and cellular immune development in children is not fully developed. This may be one of the mechanisms that lead to the absence of severe immune responses after viral infection.
- As COVID-19 virus exploits the ACE2 receptors to gain entry inside the cells, under expression, immaturity of ACE2 receptors in children is another hypothesis in this regard.
- Trained innate immunity from BCG vaccine, less exposure to smoke and less occurrence of co morbidities such as hypertension. Further studies need to be done to prove these claims since these are purely observational studies.

1.3.3 Clinical Classification of Confirmed COVID-19

A. <u>Clinical Classification of COVID-19 Based on Severity of Clinical features:</u>

Table 2. Clinical Classification of COVID-19 Based on Severity of Clinical features: [5]

Asymptomatic	Symptomatic			
	Mild	**Moderate**	**Severe**	**Critical**
Absence of any clinical symptoms and signs chest imaging is normal RT-PCR (+)	Acute URTI fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Congested pharynx No auscultatory abnormalities Other cases no fever, or only GI symptoms ie. as nausea, vomiting, abdominal pain and diarrhea.	Pneumonia fever, dry cough followed by productive cough, with fast breathing (according to age) some may have wheezing No hypoxemia CXR- pneumonia Chest CT shows lung lesions, which are subclinical.	Early severe respiratory distress Fever, cough, +/- GI Sx dyspnea with central cyanosis Grunting, chest indrawing Oxygen saturation is < 90% at room air with other hypoxia manifestations Disease progresses around 1 week	Children can quickly progress to acute respiratory distress syndrome (ARDS) or respiratory failure, May also have shock, encephalopathy, myocardial injury or heart failure, Coagulation dysfunction, and acute kidney injury. Organ dysfunction can be life threatening.

B. Clinical Classification of COVID-19 Based on Severity of Pneumonia

Recommendation 2: Pneumonia in COVID-19 Children should be classified as non-severe or severe pneumonia
(Strong recommendation, Low-grade evidence)[6]

Pneumonia is considered a clinical syndrome associated with COVID-19 in children, with the following specifications [6]:

a. **Non-severe pneumonia** with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing: < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 in breaths/min) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air (and no signs of severe pneumonia
b. **Severe pneumonia** presenting with cough or plus at least one of the following:
   1) Central cyanosis or SpO2 < 90%;
   2) Severe respiratory distress (e.g. grunting, very severe chest indrawing)
   3) Signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.
   4) Fast breathing

SARS-COV2 is a pathogen causing a high prevalence of pneumonia in infected individuals. A study showed that the main clinical features of COVID-19 in children include pneumonia comprising about a fifth of the cases. Compared with children with H1N1 influenza, pediatric patients with COVID-19 had fewer upper respiratory symptoms but pneumonia was more frequent.[17]

Severe to Critical Disease in Pediatric COVID 19

Clinically, it would be difficult to differentiate the manifestations of a sick child presenting with severe pneumonia, a critically ill child suffering from septic shock and a child with pediatric acute respiratory distress syndrome (pARDS). All will have some form of respiratory distress that may be related to a direct lung injury caused by an infectious process such as pneumonia, an uncontrolled inflammatory cascade causing alveolar edema and decreased lung compliance secondary to ARDS or the distress could be due to a compensatory mechanism from a metabolic acidosis brought about by severe sepsis.

Although it is difficult to delineate each spectrum by signs and symptoms alone, it is still of paramount importance to differentiate them using other parameters because management will vary. A SARS Cov2 infected pediatric patient may have any of these disease spectrum but special emphasis would be made on ARDS as this is thought to be the central pathophysiologic mechanism of its progression to critical disease.

COVID 19 Pediatric Acute Respiratory Syndrome (pARDS) vs classical pARDS

While pediatric data are scarce, it is worth mentioning the findings related to adult COVID – 19. The ARDS Berlin criteria defined that for a patient to be diagnosed as having ARDS, the onset must be within 1 week of a known clinical insult or new or worsening respiratory symptoms. As the onset time of COVID-19-related ARDS was 8–12 days, it suggested that the 1-week onset limit defined by ARDS Berlin criteria did not apply to COVID-19-related ARDS.[132]

Lung compliance might also be relatively normal in some COVID-19-related ARDS patients who met ARDS Berlin criteria. This was obviously inconsistent with ARDS caused by other factors. In addition, the lung compliance was relatively high in some COVID-19-related ARDS patients, which was inconsistent with the severity of hypoxemia.[133]

Table 3: Pediatric Acute Respiratory Distress Syndrome [6]

Onset	Within 1 week of a known clinical insult (i.e. Pneumonia) or new or worsening respiratory symptoms
Chest Imaging	Radiograph, CT scan, or lung ultrasound: bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules
Origin of pulmonary infiltrates	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. Echocardiography) to exclude hydrostatic cause of infiltrates/edema if no risk factor

	present		
Oxygen impairment	Bilevel (NIV or CPAP) ≥ 5 cmH2O via full face mask PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264 Use OI when available. If PaO2 not available, wean FiO2 to maintain SpO2 ≤ 97% to calculate OSI or SpO2/FiO2 ratio OI- Oxygen Index OSI- Oxygen Saturation Index		
	Mild ARDS (invasively ventilated)	**Moderate ARDS (invasively ventilated)**	**Severe ARDS (invasively ventilated)**
	4 ≤ OI < 8 or 5 ≤ OSI < 7.5	8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3	OI ≥ 16 or OSI ≥ 12.3

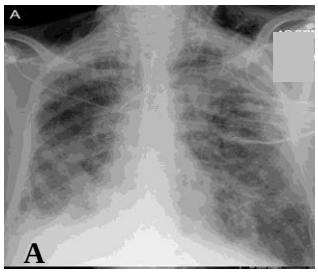
Radiographic Findings in COVID – 19 Pediatric ARDS

Based on the Berlin ARDS Definition, chest radiograph criterion include bilateral opacities consistent with pulmonary edema that are not fully explained by effusions, lobar/lung collapse, or nodules/masses on chest radiograph, there is also absence of cardiomegaly and septal lines.[134]

CT has been shown to be helpful, not only as a confirmatory and problem-solving tool, but emerging studies have shown the potential for classifying and prognosticating ARDS. The classical CT appearance of acute phase ARDS is that of opacification that demonstrates an anterio-posterior density gradient within the lung, with dense consolidation in the most dependent regions, merging into a background of widespread ground-glass attenuation and then normal or hyperexpanded lung in the non-dependent regions (see Figure 6). Ground-glass opacification on CT is a non-specific sign that reflects an overall reduction in the air content of the affected lung. In the case of acute ARDS, this is likely to represent edema and protein within the interstitium and alveoli. Another important observed feature in acute ARDS is bronchial dilatation within areas of ground-glass opacification.[135]

A case report of pediatric COVID – 19 shows interlobular and intralobular septal thickening and rounded ground-glass opacities, predominantly in a peripheral distribution in both lungs; small peripheral or subpleural areas of subsegmental collapse or consolidation are noted, particularly at the bases.[136]

Lung ultrasound findings may facilitate the diagnosis in acute respiratory failure (ARF) patients. In particular, ARDS presents multiple B lines, typically with a non-homogeneous non-gravity-dependent distribution, pleural thickening, subpleural consolidations, decreased or abolished lung sliding, spared areas especially in anterior regions and in the early stage of the disease.[137]



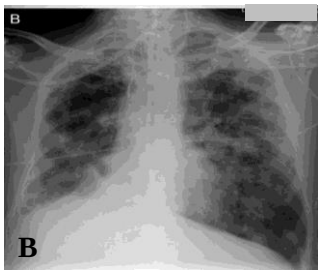


Fig. 5. A: Chest radiograph of patient with ARDS shows bilateral infiltrates. There is bilateral consolidation and a right pleural effusion.
B: Chest radiograph of the same patient shows persistent bilateral infiltrates after 7 days[132]

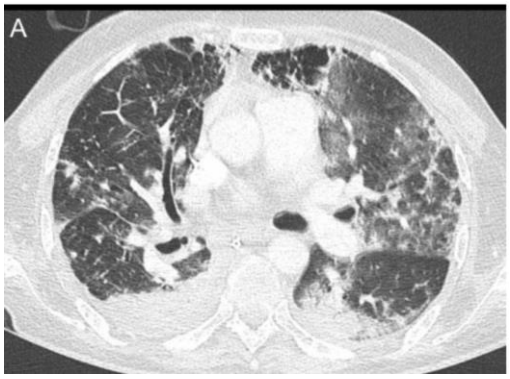


Fig.6 Computed tomogram shows bilateral dependent consolidation in a patient with ARDS, as well as ground-glass opacities in the non-dependent lung [133]

1.4 Case Definition

During the early part of COVID-19 pandemic the classification was changed. To guide transformation in database of terminologies comparison of old and new classification are tabulated below.

Table 4. Comparison of Old and New DOH Classification of COVID-19 Cases

OLD CLASSIFICATION	NEW CLASSIFICATION
Neither a Person under monitoring (PUM) or Person under Investigation	Non-COVID case
PUM	Not included in new classification
PUI (mild, severe, critical) who was not tested or awaiting test results	SUSPECT
PUI (mild, severe, critical) with inconclusive test results	PROBABLE
COVID Positive	CONFIRMED

Table 5. New DOH COVID-19 Case Definition Administrative Order No. 2020-0013 April 9, 2020

All Severe acute respiratory infection (SARI) cases with NO other etiology explaining the clinical presentation	

Influenza-like illness (ILI) cases **with** any of the following: 1.) with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in areas with reported local transmission of COVID-19 disease during the 14 days prior to symptom onset OR 2.) with contact to a confirmed or probable case of COVID-19 in two days prior to onset of illness of the probable/confirmed COVID-19 case until the time the probable/confirmed COVID-19 case became negative on repeat testing	SUSPECT CASE
Individuals with fever or cough or shortness of breath or other respiratory signs or symptoms fulfilling **any one** of the following conditions: 1.) Aged 60 years and above 2.) With a comorbidity 3.) Assessed as having high-risk pregnancy 4.) Health worker	
Suspect case whom testing for COVID-19 is inconclusive	PROBABLE CASE
Suspect who tested positive for COVID-19 but whose test was not conducted in national or subnational reference laboratory or officially accredited laboratory for COVID-19 laboratory testing	
Any individual, irrespective of presence or absence of clinical signs and symptoms, who was laboratory confirmed for COVID-19 in a test conducted at the national reference laboratory, a subnational reference laboratory, and/or DOH-certified laboratory testing facility.	CONFIRMED CASE

Rationale: Initially, the case definition classifies individuals as either Patients Under Investigation (PUI) or Persons under Monitoring (PUM). The evidence of local and community transmission necessitated a new classification with the aim of early detection and laboratory confirmation, especially among high risk and vulnerable population, to guide appropriate clinical management. [113]

1.5 Diagnostic Confirmation

1) **Real-Time Reverse Transcriptase (RT)-PCR** determination of SARS CoV 2 from oropharyngeal or nasopharyngeal specimen remains as the reference standard for the diagnosis of pediatric COVID 19. Viral load is not parallel with clinical severity[120]. The average number of days before negative conversion in children is 12 days, usually 4 to 5 days after symptoms resolve[17]. RT PCR using blood sample can also be done and if positive may be indicative of viremia, hence severe disease[14 121]

2) **Serology**: Rapid antibody test using lateral flow immunoassay to detect IgM and IgG can also be used with an overall testing sensitivity of 88.66% and specificity of 90.63%[122]. We must take into account that IgM can only start to appear in 3 to 6 days from infection while IgG will appear after 8 days from infection. Therefore, if rapid antibody testing will be done, it should be requested at least 4 days from the onset of symptoms.[123]A false positive result may occur as the test is known to cross react with

flu viruses. Even if patients have already recovered, these tests may remain positive as long as antibodies are present. Likewise, a false negative result can also be misleading especially if the patient has not mounted enough immune response when the assay was done.

The key is that the results of RT-PCR and IgM/IgG serological tests do not necessarily need to agree. A disagreement between the two tests, if any, can often be traced to the after-infection time points at which the tests were performed. RT-PCR testing may be appropriate for the detection of the SARS-CoV-2 virus during the acute phase, IgM/IgG is an appropriate test during the chronic phase. Since the exact time of infection is often unknown, combining RT-PCR and IgM/IgG testing can improve the accuracy of the COVID-19 diagnosis.

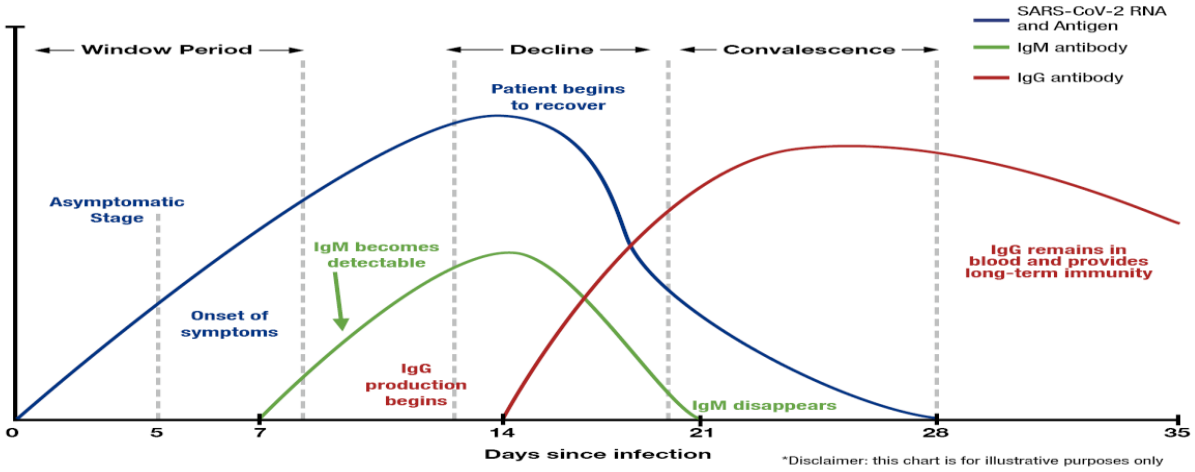


Fig 7 Variation of the Levels of SARS-CoV-2 RNA and Antigen, IgM and IgG after infection. [12]
http://www.diazyme.com/covid-19-antibody-tests

Techniques in doing RT PCR [106 107]

At present, Reverse Transcriptase Polymerase Chain Reaction (RT- PCR) of respiratory specimens for detection of SARS CoV 2 is the reference standard in confirming COVID – 19 infection. Detection of the virus is achieved by identifying the viral RNA through nucleic acid amplification, usually using a polymerase chain reaction. The most commonly tested sample types are swabs taken from the nasopharynx (more sensitive) and/or oropharynx. Swabs are then placed into a liquid to release viral RNA into the solution and subsequently amplified using reverse transcription-PCR.

Indications for testing

Ideally, all individuals suspected of having the disease should be subjected for confirmatory testing using RT – PCR. However, due to global shortage of testing kits and limitation in local capacity for testing, there is a need to rationalize available tests and prioritize the following groups (in order of greatest to least priority):

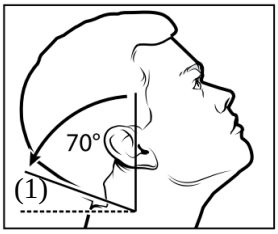
1. Patients or healthcare workers with severe/critical symptoms, relevant history of travel/contact
2. Patients or healthcare workers with mild symptoms, relevant history of travel/contact, and considered vulnerable
3. Patients or healthcare workers with mild symptoms, relevant history of travel/contact
4. Patients or healthcare workers with no symptoms but relevant history of travel/contact

General Guidelines:

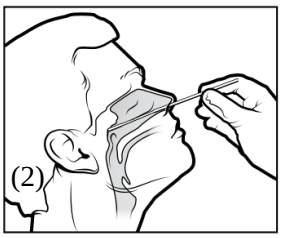
Among most parts of the world, decisions about testing are left at the discretion of state and local health departments and/or individual clinicians but each test should be conducted in consultation with a healthcare provider. Specimens should be collected immediately once the decision to test is made regardless of the time of symptom onset.

A trained healthcare professional may collect from any of the following specimens:

1. **A Nasopharyngeal (NP) Specimen**
   Tilt the patient's head back 70^0 (1). Insert mini tip swab with a flexible shaft (wire or plastic) through the nostril parallel to the palate (not upwards) until resistance is encountered or the distance is equivalent to that from the ear to the nostril of the patient, indicating contact with the nasopharynx.
   Swab should reach depth equal to distance from nostrils to outer opening of the ear (2). Gently rub and roll the swab. Leave swab in place for several seconds to absorb secretions.

   Slowly remove swab while rotating it. Specimens can be collected from both sides using the same swab, but it is not necessary to collect specimens from both sides if the mini tip is saturated with fluid from the first collection. If a deviated septum blockage create difficulty in obtaining the specimen from one nostril, use the same swab to obtain the specimen from the other nostril.

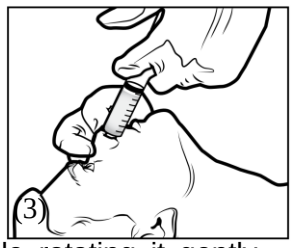
   or

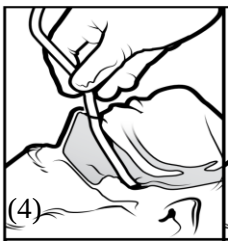
2. **An Oropharyngeal (OP) Specimen**
   Insert swab into the posterior pharynx and tonsillar areas. Rub swab over both tonsillar pillars and posterior oropharynx and avoid touching the tongue, teeth, and gums.

3. **A Nasal Mid-turbinate Swab or Deep Nasal Swab**
   This maybe self collected as long as supervised by a healthcare professional on site using a flocked tapered swab.
   Tilt patient's head back 70 degrees. While gently rotating the swab, insert swab less than one inch (about 2 cm) into nostril (until resistance is met at the turbinates). Rotate the swab several times against nasal wall and repeat in other nostril using the same swab.

4. **An Anterior Nares (nasal swab) Specimen**
   This maybe self collected as long as supervised by a healthcare professional on site using a flocked or spun polyester swab. Insert the swab at least 1 cm (0.5 inch) inside the nostril (naris) and firmly sample the nasal membrane by rotating the swab and leaving in place for 10 to 15 seconds. Sample both nostrils with same swab.

5. **Nasopharyngeal Wash/Aspirate or Nasal Wash/Aspirate (NW) Specimen**
   Attach catheter to suction apparatus. Have the patient sit with head tilted slightly backward. Instill 1 mL-1.5 mL of non-bacteriostatic saline (pH 7.0) into one nostril (3). Insert the tubing into the nostril parallel to the palate (not upwards). Catheter should reach depth equal to distance from nostrils to outer opening of ear (4). Begin gentle suction/aspiration and remove catheter while rotating it gently. Place specimen in a sterile viral transport media tube.

6. **Sputum**
   If patient can expectorate or has productive cough, sputum sample can be collected. However, induction of sputum to acquire a quality specimen is not recommended.
   Educate the patient about the difference between sputum and oral secretions (saliva). Have the patient rinse the mouth with water and then expectorate deep cough sputum directly into a sterile, leak-proof, screw-cap collection cup or sterile dry container.

7. **Bronchoalveolar Lavage, Tracheal Aspirate, Pleural Fluid, Lung Biopsy**
   Collect 2-3 mL into a sterile, leak-proof, screw-cap sputum collection cup or sterile dry container. These may be limited to patients presenting with more severe disease, including patients who are admitted to the hospital and/or intubated.

Storing:
Once specimen is collected, swab/wash/aspirate should be placed immediately into a sterile transport tube containing 2-3mL of either viral transport medium (VTM), Amies transport medium, or sterile saline.

- Specimens should be placed into sterile viral transport media and immediately placed on refrigerant gel packs or at 4 degrees Celsius (refrigerator) for transport to the state public health laboratory.
- Keep specimens refrigerated (2-8 degrees Celsius, 26-46 degrees Fahrenheit) prior to shipping.

Collecting and Handling Specimens Safely
Healthcare professionals who will collect the specimen should maintain proper infection control and use recommended personal protective equipment, which includes an N95 or higher-level respirator (or facemask if a respirator is not available), eye protection, gloves, and a gown, when collecting specimens.

For providers who are handling specimens, but are not directly involved in collection (e.g. self-collection) and not working within 6 feet of the patient, gloves are recommended. They are also recommended to wear facemask or cloth face covering at all times while in the healthcare facility. PPE use can be minimized through patient self-collection while the healthcare provider maintains at least 6 feet of separation.

Bulk-packaged swabs may be used for sample collection; however, care must be exercised to avoid SARS-CoV-2 contamination of any of the swabs in the bulk-packaged container.

- Before engaging with patients and while wearing a clean set of protective gloves, distribute individual swabs from the bulk container into individual disposable plastic bags.
- If bulk-packaged swabs cannot be individually packaged:
  a. Use only fresh, clean gloves to retrieve a single new swab from the bulk container.
  b. Close the bulk swab container after each swab removal and leave it closed when not in use to avoid inadvertent contamination.
  c. Store opened packages in a closed, airtight container to minimize contamination.
  d. Keep all used swabs away from the bulk swab container to avoid contamination.
- As with all swabs, only grasp the swab by the distal end of the handle, using gloved hands only.

Use only synthetic fiber swabs with plastic or wire shafts. Do not use calcium alginate swabs or swabs with wooden shafts, as they may contain substances that inactivate some viruses and inhibit PCR testing. CDC is now recommending collecting only the NP swab, although OP swabs remain an acceptable specimen type. If both NP and OP swabs are

collected, they should be combined in a single tube to maximize test sensitivity and limit use of testing resources. Proper labeling is a must and should include complete name, hospital number, type of specimen and date of collection.

Shipping:
If delivery will be delayed for more than 3-4 days, specimen should be frozen at -70 degrees Celsius (-94 degrees Fahrenheit). Ensure that the specimen will be received by the public health laboratory personnel during normal business hours. Specimens that can be delivered promptly to the laboratory can be stored and shipped at 2-8°C. When there is likely to be a delay in specimens reaching the laboratory, the use of viral transport medium is strongly recommended and specimens may be frozen to - 20°C or ideally -70°C and shipped on dry ice. It is important to avoid repeated freezing and thawing of specimens**.**

1.6 Laboratory Examination

Recommendation 3:
Consider the use of laboratory tests to support the diagnosis and monitor COVID – 19 patients especially in evaluating for co-infections and multi-organ dysfunctions.
(Weak recommendation, low grade of evidence) [6,22,23]

Laboratory tests that may be requested:

1. Complete Blood Count
2. C Reactive Protein (CRP),
3. Erythrocyte Sedimentation Rate (ESR)
4. Procalcitonin

Laboratory tests that may be requested in severe cases:

1. Alanine Aminotransferase (ALT),
2. Aspartate aminotransferase (AST),
3. PT PTT
4. LDH
5. Creatinine,
6. Blood Urea Nitrogen (BUN), serum electrolytes
7. Creatinine kinase – MB (CK-MB)
8. D Dimer
9. Arterial Blood gases
10. Serum Ferritin

Rationale:

CBC: Leukopenia, and lymphopenia have been reported.
A handful of sick children may reveal lymphopenia (less than 1500 x 10^9), but still, a normal CBC is the most likely finding[14]. Leukopenia may also be seen in pediatric

patients[14]. On the contrary to adult data, it was noted that there is increased leukocyte and neutrophil counts especially in patients with unfavorable COVID-19 progression[124] Mild thrombocytopenia is commonly seen.

Inflammatory Markers: CRP, ESR may be elevated by as much as 30 to 100%[124]. Procalcitonin may be used to determine secondary bacterial infection which is common among severe cases[124]

Liver Function Tests: Alanine Aminotransferase (ALT), Aspartate aminotransferase (AST) Elevated liver enzymes (ALT, AST) are observed in up to 1/3rd patients and need to be monitored.

Serum Electrolytes and Renal Function Tests: These may be normal but are deranged in critical patients. Creatinine, Blood Urea Nitrogen (BUN) are also increased and needs to be monitored.

Lactate Dehydrogenase (LDH) may increase and is a predictive factor for early recognition of lung injury.

Serum Ferritin elevation indicates cytokine storm syndrome or organ damage.

Recently, pediatric COVID - 19 has been linked to myocarditis therefore requesting for cardiac enzymes such as CK-MB in patients with tachycardia without any known cause may be prudent[17].

1.7 Chest Imaging in Pediatric COVID-19 Patient

1.7.1 Chest Radiograph

A. <u>Indication of Chest Imaging</u>

Recommendation 4

1. Chest imaging should be requested
   1.1 For medical triage of patients with suspected COVID-19 who present with **moderate to severe** clinical features and a high pre-test probability of disease in resource-limited settings

   1.2 When a child requires hospitalization, or is suspected of having hospital acquired pneumonia, CXR is the most appropriate step in imaging evaluation

2. Chest xray should not be requested in patients with suspected early stages of pediatric COVID-19 and mild clinical features at outpatient setting unless they are at risk for disease progression [10,20]
   (Strong Recommendation, Low-Grade Evidence)

Rationale: CXR is frequently used as the first imaging in the evaluation of pediatric patient presenting with cough, fever and difficulty of breathing. The findings on CXR are not specific, it is insensitive in mild or early COVID-19 infection.

According to the American College of Radiology (ACR) appropriate criteria, imaging is not indicated in a well appearing immunocompetent child > 3 months of age who does not require hospitalization. However, if the child is not responding to outpatient management, requires hospitalization, or is suspected of having hospital acquired pneumonia, CXR is considered the most appropriate first step in imaging evaluation.[10] Initial chest radiographs should be considered in pediatric patients with suspected COVID-19 presenting with moderate to severe acute respiratory illness symptoms. However, due to limited sensitivity and specificity, a negative CXR does not exclude pulmonary involvement in patients with laboratory confirmed COVID-19 nor does it indicate absence of infection in cases of suspected COVID-19 not yet confirmed by RT-PCR. CXR had a median sensitivity of 25% and median specificity of 90% for identifying lung opacities identified on same day chest CT.[20]

B. <u>Common Radiographic Findings In Pediatric Patients with COVID-19</u>

1. Bilateral distribution peripheral and/or subpleural ground glass opacities GGOs and halo sign or consolidation were the most common feature
2. Local or bilateral patchy shadowing
3. Viral pneumonia-like changes [4 14]

In a systematic review and meta-analysis done the most common radiographic features among 31% patchy consolidation and 48% of these patients were halo signs with ground glass opacities. In 27% of the patients, there was no definite lung lesion.[4] Similarly, ground glass opacity was seen in 33% of diagnosed children. Local or bilateral patchy shadowing was seen in 18.7% and 12.3%, respectively. Viral pneumonia-like changes in 70.4% children undergoing chest imaging were seen. [4,14]

In the International Expert Consensus Statement on Chest Imaging in Pediatric COVID-19 from United States, Spain, Hong Kong, Brazil, South Africa, and United Emirates they cited similar findings typical of COVID-19 pneumonia as multiple unilateral and bilateral opacities with peripheral and lower lung zones predominance seen both on CXR and Chest CT.[10]

C. <u>Structured Reporting of CXR findings for pediatric COVID-19 patients</u>

Recommendation 5 [4 14]

The following should be the structured reporting of CXR findings for pediatric COVID-19 patients[10]

1. **Typical Findings Of Pediatric COVID-19**
   Bilateral distribution peripheral and/or subpleural GGOs and/or consolidation.
2. **Indeterminate Findings Of Pediatric COVID-19**
   Unilateral peripheral or peripheral and central GGOs and/or consolidation, bilateral peribronchial thickening and/or peribronchial opacities, or multifocal or diffuse GGOs and/or consolidation without specific distribution.

3. **Atypical Findings Of Pediatric COVID-19**
   Unilateral segmental or lobar consolidation, central unilateral or bilateral GGOs and/or consolidation, single round consolidation i.e., round pneumonia with or without air bronchogram, pleural effusion, or lymphadenopathy.
4. **Negative for Pediatric COVID-19**
   No CXR findings suggestive of pneumonia

   (Strong Recommendation, Moderate-Grade Evidence)

Table 6. Structured CXR Reporting for Pediatric COVID-19

Classification	Rationale	CXR Finding(s)	Suggested Reporting Language
Typical	Commonly reported CXR findings of COVID-19 pneumonia in children	• Bilateral distribution peripheral and/or subpleural GGOs and/or consolidation	Imaging findings are commonly seen with COVID-19 pneumonia in children. Differential diagnosis also includes other viral or atypical pneumonia.
Indeterminate	Non-specific CXR findings of pediatric COVID- 19 pneumonia	• Unilateral peripheral or peripheral and central GGOs and/or consolidation • Bilateral peribronchial thickening and/or peribronchial opacities • Multifocal or diffuse GGOs and/or consolidation without specific distribution	Imaging findings can be seen with COVID-19 pneumonia in children. However, they are non-specific and differential diagnosis includes both infectious and non-infectious etiologies.
Atypical	Uncommon or not reported CXR findings of pediatric COVID- 19 pneumonia	• Unilateral segmental or lobar consolidation • Central unilateral or bilateral GGOs and/or consolidation • Single round consolidation (i.e., round pneumonia ± air bronchogram) • Pleural effusion Lymphadenopathy	Imaging findings are atypical or uncommonly reported in cases of COVID-19 pneumonia in children. Recommend consideration of alternative diagnosis.
Negative	No CXR findings suggestive of pneumonia in children	• No CXR findings suggestive of pneumonia	No CXR findings present to suggest pneumonia (Note: CXR has limited sensitivity for COVID-19, especially in early stages).

CXR = Chest Xray
GGO = Ground glass opacity
COVID -19 = Coronavirus Disease of 2019

1.7.2 Chest Computed Tomography

Recommendation 6

The following shall be considered in the structured reporting for CT findings for pediatric COVID-19 patients[10]

1. **Typical findings of pediatric COVID-19**
   Bilateral, peripheral and/or subpleural GGOs and/or consolidation in lower lobe predominant pattern

2. **Indeterminate findings of pediatric COVID-19**
   Unilateral peripheral or peripheral and central GGOs and/or consolidation, bilateral peribronchial thickening and/or peribronchial opacities, multifocal or diffuse GGOs and/or consolidation without specific distribution, or the "crazy paving" sign.

3. **Atypical findings of pediatric COVID-19**
   Unilateral segmental or lobar consolidation, central unilateral or bilateral GGOs and/or consolidation, discrete small nodules, lung cavitation, plural effusion, or lymphadenopathy.

4. **Negative for pediatric COVID-19**:No chest CT findings suggestive of suggestive of pneumonia in children

(Strong Recommendation, Moderate-Grade Evidence)

Table 7 Structured Reporting for CT Findings For Pediatric COVID-19 patients

Classification	Rationale	CT Finding(s)	Suggested Reporting Language
Typical	Commonly reported CT findings of COVID-19 pneumonia in children	• Bilateral, peripheral and/or subpleural GGOs and/or consolidation in lower lobe predominant pattern • Halo" sign (early)	Imaging findings are commonly seen with COVID-19 pneumonia in children. Differential diagnosis also includes other viral or atypical pneumonia, hypersensitive pneumonitis, and eosinophilic lung disease. In addition, fungal infection in immunocompromised children when "halo" sign is present.
Indeterminate	Non-specific CT findings of pediatric COVID- 19 pneumonia	• Unilateral peripheral or peripheral and central GGOs and/or consolidation • Bilateral peribronchial thickening and/or	Imaging findings can be seen with COVID-19 pneumonia in children. However, non-specific and differential diagnosis includes infectious and non-infectious etiologies.

		peribronchial opacities • Multifocal or diffuse GGOs and/or consolidation without specific distribution “Crazy paving” sign	
Atypical	Uncommon or not reported CT findings of pediatric COVID- 19 pneumonia	• Unilateral segmental or lobar consolidation *Central unilateral or bilateral GGOs and/or consolidation *Discrete small nodules (centrilobular, tree-in-bud) *Lung cavitation *Pleural effusion *Lymphadenopathy	Imaging findings are atypical or uncommonly reported in cases of COVID-19 pneumonia in children. Recommend consideration of alternative diagnosis.
Negative		*No CT findings suggestive of pneumonia	No CT findings present to suggest pneumonia (Note: CT may be negative in the early stages of COVID-19).

CT = Computed Tomography

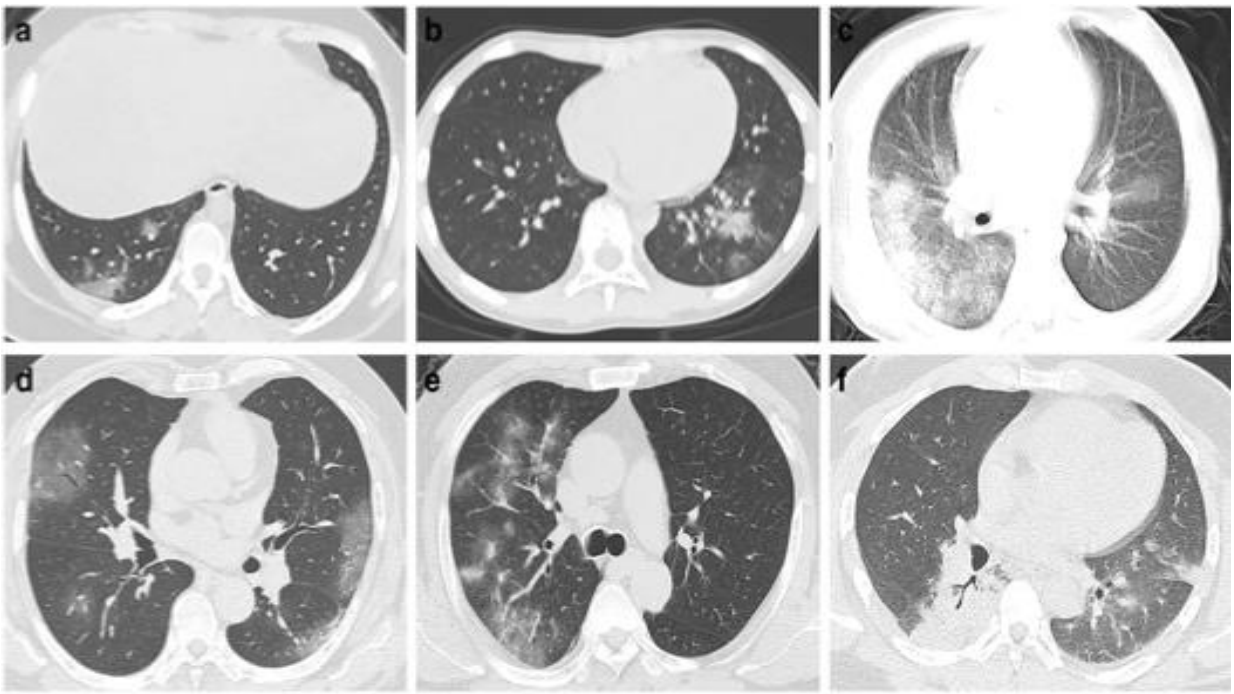


Fig 8a Chest CT imaging of coronavirus disease 2019 (COVID-19) pneumonia in children and adults. a Female, 14 years old. Chest CT showed scattered GGO in the inferior lobe of the right lung, located subpleural or extended

from subpleural lesions. **b** Male, 10 years old. Chest CT showed consolidation with halo sign in the inferior lobe of the left lung surrounded by GGO. **c** Male, 1 year old. Chest CT showed diffused consolidations and GGO in both lungs, with a "white lung" appearance of the right lung. **d** Male, 49 years old. Chest CT showed multiple subpleural GGO in both lungs. **e** Male, 64 years old. Chest CT showed multiple GGO and consolidations in the right upper lobe. **f** Male, 34 years old. Chest CT showed diffused consolidation in the right lower lobe and left lung with fewer GGO surrounded.[127]

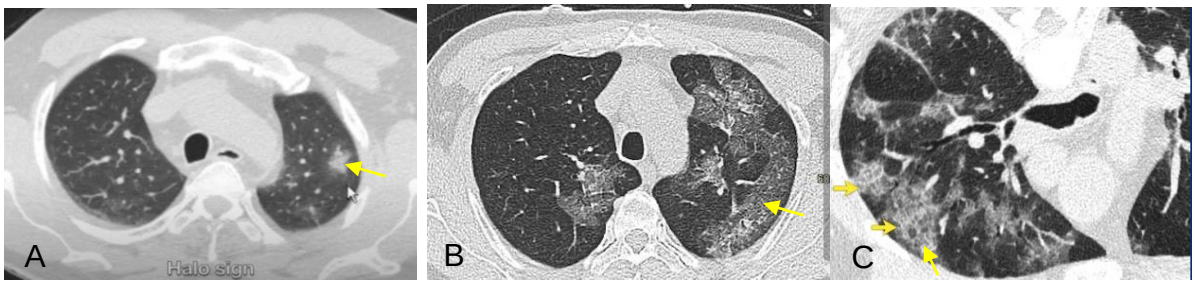


Fig 8.b A) Focal consolidation with a rim of surrounding ground glass opacity "halo sign"
B) Bilateral ground-glass opacities c) Thickened interlobular and intralobular lines in combination with a ground glass pattern called "crazy paving"

1.7.3 Chest Ultrasound

Recommendation 7
Chest ultrasound can be considered as an alternative to CXR and Chest CT in the diagnosis of pneumonia in COVID 19 patients. It is a tool that could be used at bedside avoiding the need for shifting infected patients to the Radiology suite [125 126]
(Weak Recommendation, Low-Grade Evidence)

Through the years, chest ultrasound has been proven to be a useful tool for the evaluation of a wide variety of chest diseases particularly when pleural cavity is involved. Lung Ultrasound (LUS) is commonly used in the emergency department at the bedside for early diagnosis of non-COVID pneumonia. It is a highly sensitive and specific technique considered as an alternative to chest radiography or Chest CT scan. Chest CT scan performed in COVID -19 patients and showed a strong correlation with chest ultrasound[30]

The well-known **Advantages of LUS** in terms of: [103]

1. Portability, Bedside Evaluation - It is a tool that could be used at bedside avoiding the need for transferring infected patients to Radiology suite.
2. Safety
3. Low risk of further infection spreading within the healthcare personnel.

4. Low cost and no radiation exposure as compared to Chest CT.

Ultrasonographic features of nCoV pneumonia:[127]

1. Thickening of the pleural line with pleural line irregularity
2. B lines in a variety of patterns including focal, multi- focal, and confluent
3. Consolidations in a variety of patterns including multifocal small, non-translobar, and translobar with occasional mobile air bronchograms
4. Appearance of A lines during recovery phase
5. Pleural effusions are uncommon.

Chest ultrasound performed on COVID-19 pneumonia patients and showed thickened pleural lines, B lines organized in different patterns & patchy consolidation; Ultrasound along with Chest CT was done demonstrating an association with CT findings of GGO and consolidation. These findings confirm the important Role of chest ultrasound in the management of patients with SARS COV-2 allowing to rapidly diagnose and monitor COVID-19 pneumonia and its evolution towards ARDS.[102]

The lung ultrasound on patients with COVID-19 was performed using 12-zone method (table 8) . The observational patterns occurred across a continuum from mild alveolar interstitial pattern to lung consolidation. The findings of lung ultrasound features of SARS COV-2 pneumonia/ARDS are related to the stage of the disease and the severity of lung injury and co-morbidities. The predominant pattern is of varying degrees of interstitial syndrome and alveolar consolidation, the degree of which is correlated to lung injury.

Table 8 CT and ultrasonographic features of COVID-19 pneumonia[99]

Lung CT	Lung ultrasound
Thickened pleura	Thickened pleural line
Ground glass shadow and effusion	B lines (multifocal, discrete, or confluent)
Pulmonary infiltrating shadow	Confluent B lines
Subpleural consolidation	Small (centomeric) consolidations)
Translobar consolidation	Both non-translobar and translobar consolidation
Pleural effusion is rare.	Pleural effusion is rare
More than two lobes affected	Multilobar distribution of abnormalities

Negative or atypical in lung CT images in the super-early stage, then diffuse scattered or ground glass shadow with the progress of the disease, further lung consolidation	Focal B lines is the main feature in the early stage and in mild infection; alveolar interstitial syndrome is the main feature in the progressive stage and in critically ill patients; A lines can be found in the convalescence

However, articles on its use in diagnosing COVID-19 pneumonia especially in children were very limited. Data are preliminary and further studies are necessary to confirm the role of lung US in the diagnosis and management of COVID-19 pneumonia in children.

Chapter 2

2 Respiratory Support for COVID-19 Patients

2.1 Management of Hypoxemia in the Spectrum of the COVID-19 Illness

A. Precaution

Recommendation 8

The use of High Flow Nasal Cannula (HFNC), CPAP/BiPAP and Non Invasive Ventilation (NIV) theoretically increase the risk of viral spread through aerosol generation. Therefore, we suggest to observe the following precautions.[19]

1. Preferably in an appropriate Airborne Infection Isolation Room (AIIR)
2. Use of a surgical mask over HFNC (figure 1) to reduce droplet spread
3. Use an appropriate viral exhalation filter for CPAP/BiPAP

4. Healthcare providers shall be in proper Personal Protective Equipment (PPE)
(Weak recommendation, low quality evidence)

B. First line Approach

Recommendation 9[6 19 30 32]

Children with suspected or confirmed severe COVID-19 will need supplemental oxygen to achieve target sp02 ≥90%. We suggest to use:

1. A Low Flow Nasal Cannula (LFNC) at 1 to 6L/minute may be started with a surgical mask worn over the patient's face to reduce droplet spread.
    a. *1–2 L/min in infants*
    b. *2–4 L/min in young children*
    c. *5*4–6 L/min in older children and adolescents*
    d. Titrate supplemental oxygen based on patient's saturation
2. The use of CPAP or a bi-level NIV is the approach recommended when SPO2/FiO2 ratio >221 and < 264.
(Weak recommendation, low quality evidence)

Remarks: The rationale of the use of a surgical mask to be worn over the patient's face when giving any form of respiratory support is to prevent droplet spread during aerosol generating procedures. In a study by Hui et. al., substantial exposure to exhaled air occurs within 0.3-0.42 meters from patients receiving oxygen support via nasal cannula. This increases to 1 meter from patients receiving NIV. This occurs even in an isolation room with negative pressure. Hence, surgical masks can reduce such spread.[138 139]
The recommendation by CDC (COVID-19 and Children. https://www.cdc.gov/coronavirus/2019-ncov/faq.html#COVID-19-and-Children. Accessed on June 7, 2020) which states that cloth face coverings should not be placed on children younger than 2 because of the danger of suffocation, is meant for well children going out into the community. The recommendation of the use of surgical masks while on any respiratory support is meant for children with hypoxemia, needing hospital admission, and is under oxygen supplementation and close clinical monitoring.

The use of CPAP or a bi-level NIV is the approach recommended over HFNC in patients SPO2/FiO2 ratio >221 and < 264. The rationale is that a higher pressure level might be obtained when using CPAP/NIV. HFNC, on the other hand, might be considered an option if CPAP or NIV is unavailable for patients with and SPO2/FiO2 ratio < 264.[32]

Titrate supplemental oxygen based on patient's saturation. Child should be monitored frequently including for SpO_2, change in respiratory rate and heart rate, hemodynamic parameters, sensorium and urine output.

The optimal mode of respiratory support for individuals with severe COVID-19 before invasive mechanical ventilation (IMV) is a subject of much debate.

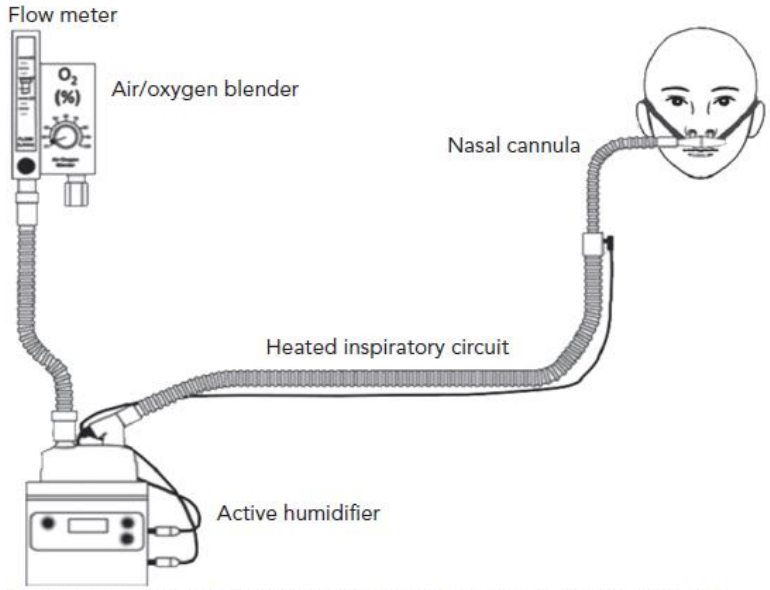
Recommendation 10

In low-resource settings or in facilities where ventilators are not available, we suggest that an improvised CPAP (iCPAP), using locally available equipment, may be used. [19]

(Weak recommendation, low quality evidence)

Remarks: The iCPAP is much like the Pediatric Bubble CPAP (figure 10), a simple and effective means of generating airway pressure by bubbling expired air or oxygen through a fixed amount of water.[34]

In order to address the demand for standard ventilators, an improvised CPAP system using a facemask has been considered which provides a potentially more benign form of breathing assistance than invasive ventilation. In a pilot study among adults with ARDS, it was shown that limited experimentation with higher pressure values could be reliably maintained by this device.[33]



An air/oxygen blender, allowing 90% fractional inspired oxygen, ranging from 0.21 to 1.0, generates flows of up to 60 l/min. The gas is heated and humidified by an active heated humidifier and delivered via a single limb.

Fig.9. High Flow Nasal Cannula (HFNC) Reprinted from: High Flow Nasal Cannula Oxygenation revisited in COVID-19. https://www.cfrjournal.com/journals/editions/cfr-volume-6-2020. Permission requested.

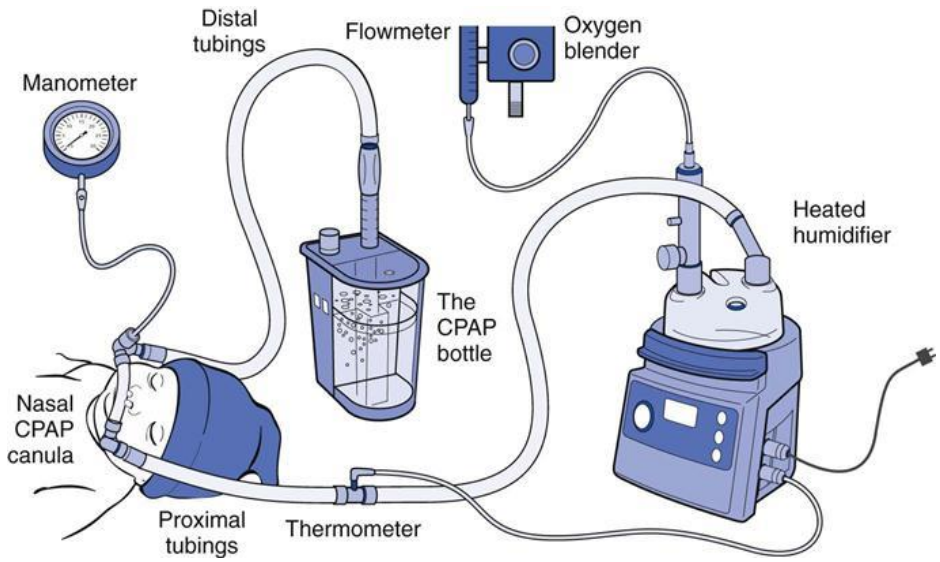


Figure 10 Diagram of Bubble CPAP delivery system. DiBlasi, R. M. (2016). Neonatal and Pediatric Mechanical Ventilation. In *Thoracic Key*. Retrieved from https://thoracickey.com/neonatal-and-pediatric-mechanical-ventilation/. Reprinted with permission.

2.2 Airway Management and Tracheal Intubation Spe e COVID-19 Patient Group

A. Precaution

Recommendation 11

We strongly recommend an appropriate environment for airway management of suspected or confirmed COVID-19 pediatric patients as follows;

1. The use of a negative pressure ventilation room is ideal to minimize exposure to aerosols and droplets from pediatric COVID-19 patients
2. Normal pressure rooms with closed doors are an alternative setting in low-resource facilities
3. The use of airway devices providing 6L/min or more of oxygen shall be discouraged as this procedure is considered aerosol-generating, unless it is performed under an AIIR.
4. Strict hand hygiene and compliance to the minimum PPE requirement is necessary in handling pediatric COVID-19 patients
5. Double gloving as a standard practice for handling pediatric COVID-19 patients[19]

(Strong recommendation, low quality evidence)

B. Indication for Intubation

Recommendation 12

We strongly recommend that intubation should not be further delayed if SpO2/FiO2 ratio < 221 in pediatric patients on bi-level NIV or CPAP and if there is no improvement in oxygenation (target SpO_2 92-97% and FiO_2) within 60 minutes.[32]

(Strong recommendation, Moderate quality evidence)

Monitoring SpO2/FiO2 ratio in patients on non-invasive respiratory and the oxygenation saturation index (OSI) or the oxygenation index (OI) in invasively ventilated children for disease severity grading. The level of FiO2 should be guided by targeting SpO2 $\geq$ 97% to allow for valid measurement of the SpO2/FiO2 ratio and the OSI.

Recommendation 13

The use of Bag Valve Mask (BVM) prior to intubation is not advised for suspected or confirmed COVID-19 patients due to its capacity to generate aerosols. However, if the bag/mask ventilation is necessary for pre-oxygenation, It is strongly recommended to follow safety measures to minimize aerosolization: [19 32]

a. Two-Person technique/Two handed vice grip (figure 9), use of a viral filter, and gentle ventilation

b. A clear drape should be placed over the patient's face to minimize aerosolization. (Strong recommendation, low quality evidence)

Remarks: Optimize preoxygenation by placing the patient's bed up, the head elevated, use of end expiratory airway valves and airway adjuncts. The "two person/two handed vice grip" technique will ensure a better seal of the mask around the mouth. Aside from a clear drape, some centers also make use of an "aerosol box" (figure 11) to decrease aerosolization risks.[28] Another option for pre-oxygenation, if time allows, is to use 100% FiO2 for 3–5 minutes, using a well-fitting mask with reservoir, preferably using a closed circuit.[140]

Figure 11. Two-handed vice grip during BVM (right).
Reprinted from Australian Safe Airway Society Consensus Statement. Permission requested

One person manages the mask and the airway, while the second person squeezes the bag to ventilate the chest. The person responsible for the mask stands at the head of the bed and places his thumbs on the top surface of the mask. The remaining fingers are then used to grip the mandible on either side. The mask is squeezed between the thumbs and the fingers to create a seal and at the same time the mandible is elevated to open the airway. This technique is considerably easier, but again, the physicians must be constantly checking that air is flowing easily into the patient and that the chest is rising and falling.

Figure 12 Aerosol box aerosol box.

Photo by Wang Chun Chi published in Taipei Times on March 2020 showing the designer of the aerosol box Taiwanese doctor. Lai Hsien-Yung. Permission requested.

Recommendation 14

Rapid Sequence Intubation or rapid sequence induction and intubation (RSI) is should be the treatment of choice for endotracheal intubation of suspected or confirmed COVID-19 patients as inadequate sedation and paralysis can produce coughing during laryngoscopy, which is an aerosol-generating procedure.

It is strongly recommended that cuffed endotracheal tubes be used to avoid peri-tubal leak and dissemination of secretions.[30]
(Strong recommendation, low quality evidence)

Remarks: Children with ARDS may desaturate quickly during endotracheal intubation hence, it is ideal for the most skilled and experienced person to perform it. This will also help to minimize the attempts. The use of video laryngoscopy is recommended over direct laryngoscopy.[30]

2.3 Ventilator Management and Strategies

Preliminary pediatric data shows that severe COVID-19 disease appears uncommon in young children although those < 1 year of age may experience greater disease severity.[32]

Recommendation 15

The general principles of management of child with ARDS apply to a child with COVID-19 related ARDS. The lung protective strategies suggested are as follows: [6 32]

a. Low tidal volume (3-6ml/kg IBW) if poor respiratory compliance
   Low tidal volume (5-8ml/kg) if better preserved respiratory compliance
b. High PEEP (>10cmH2O)
c. Target plateau pressure <28cmH2O
d. Permissive hypercapnia (pH >7.20)

(Weak recommendation, low quality evidence)

Initial PEEP should be around 10cmH2O and might need for further increase depending on the severity. It can reach to as high as > 15cmH2O, although attention should be paid to limiting plateau pressure. Balancing oxygenation and hemodynamics is of utmost importance when titrating PEEP.

FiO2, on the other hand, can be titrated to maintain SpO2 of 92 – 96% but for patients with severe disease, the minimal acceptable SpO2 should be 88%.[32]

Prone Positioning For Mechanically Ventilated Confirmed Covid-19 Children

Recommendation 16: Prone positioning may be considered as part of treatment regimen for pediatric COVID-19 patients with moderate to severe ARDS

(Weak recommendation, low quality evidence). [32]

Remarks: The Pediatric Mechanical Ventilation Consensus Conference (PEMVECC) and European Society for Pediatric and Neonatal Intensive Care (ESPNIC) recommends early and prolonged prone positioning of moderate to severe ARDS among children with suspected and proven COVID-19.[32] A review by Orloff, et. al on pediatric ARDS also reported that prone positioning may be considered as part of the treatment regimen for severe ARDS in children.[85] Both of these articles stated prone positioning as adjunctive therapy as part of the Pediatric Acute Lung Injury Consensus Collaborative (PALICC) guidelines. While the World Health Organization (WHO) Interim guidance on the management of COVID-19 states that prone positioning may be considered for pediatric patients with severe ARDS, but the proning maneuver requires sufficient health care manpower and expertise for safety.[6] Alternating supine and prone positioning in COVID-19 patients with ARDS reported favorable results with improvement in lung recruitability.[83]

INDICATIONS

- PEDIATRIC COVID-19 patient
- On invasive mechanical ventilation with attached ETT or tracheal tube access
- Received mechanical ventilation for at least 24 hours at the Acute Phase of ALI/ARDS
- *Patient has the* *<u>Pediatric ARDS (PARDS) Baseline Criteria (PALLIC Guidelines)</u>*
    1. Onset within 7 days of known clinical insult
    2. New pulmonary infiltrates on CXR/CT Scan
    3. Absence of cardiac failure
    4. Sudden deterioration in oxygenation

    * Exclusion: Perinatal Lung disease
- Patient has moderate to Severe Pediatric ARDS based on

    * Moderate PARDS : OI 8-16 / OSI 7.5-12.3

    * Severe PARDS : OI ≥16 / OSI ≥12.3

Contraindications for PRONE POSITIONING

- Hemodynamic instability despite the administration of adequate inotropic agents.
- Patients with bronchospasms
- Patients with tracheal lesions (congenital tracheomalacia, tracheal infections)
- Unstable spinal cord injuries.
- Increased intracranial pressure
- Recent abdominal or thoracic injuries or surgeries
- Inability to tolerate Proning (*eg*, pelvic fracture, unstable long bone fracture).
- Patients without consent for proning

A comprehensive Cochrane review, involving 24 studies among hospitalized infants and children with Acute Respiratory Distress Syndrome (ARDS) was published by Gilles, et al. The outcome measures included were the following respiratory and oxygenation parameters: improvement in oxygen saturation, arterial oxygen, and oxygenation index.[82]Proning is considered safe among the critically ill children. Furthermore, there was also statistically beneficial improvement in decreasing the respiratory rate in infants who underwent the prone positioning procedure.[84, 86]

There are no standard proning techniques for children with ARDS as different proning protocols were used in different trials. A team coordinated approach with pre-positioning, turning [108,101] and post positioning protocol have been described. [101,105,108] Providing adequate sedation and preoxygenation with a fraction of inspired oxygen (FiO_2) of 1 is recommended prior to moving the patient to prevent transient hemodynamic instability and desaturation related to turning the patient.

Duration of proning practices vary between 12 – 18 hrs per day with the patient in prone protocol. Prolonged prone positioning (>24 hrs) may be considered early in the disease trajectory. Improvements in the oxygenation was noted 2 hours after prone positioning

in the study by Kornecki et al., but the reduction in Oxygenation Index was maintained among children with acute respiratory failure for a duration of until 12 hours.[105]

Prone positioning can be discontinued if PaO2/FiO2 ≥150; OI < 12; OSI < 10. [32] The clinical experience of the First Affiliated Hospital, China reported that that they ceased the proning procedure once the patient demonstrated improvement of PaO2/FiO2 ratio to > 150.[87] The assisted proning procedure may be considered safe for critically ill children with no serious adverse events noted. [82,105, 86]The evolving data of benefit of self proning in non-ventilated COVID-19 confirmed adults cannot however, be safely extrapolated to children as of this present time.

Presently, there are no available studies to determine standard steps for proning and the duration of use of proning among mechanically ventilated children with COVID-19 who develop ARDS. However, prone positioning for COVID-19 patients videos especially to support healthcare workers are freely available for review. (https://youtube.com/watch?v=E_6jT9R7WJs). Below is an adapted preparation and prone positioning steps for proning among COVID-19 confirmed children using local institution practices in child proning among the critically ill and from gathered data during this literature search.

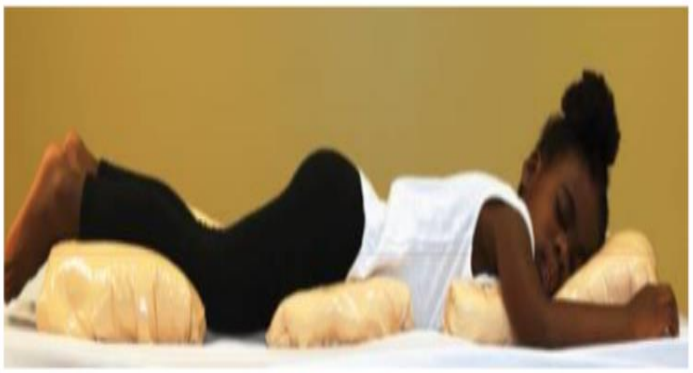


Figure 11 Child on Prone: The main goal is to have a free floating abdomen and adjustments to Z Flo sizes (or cushions) or additional pillows may be done.
Adapted with permission from Tracy Fulkerson,BSN RN CCRN

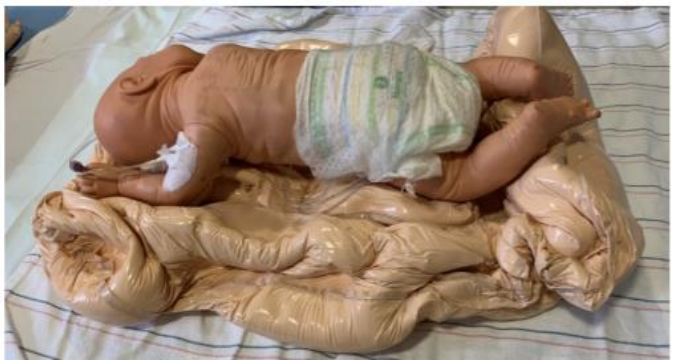


Figure 12 Infant on Prone Position :
Adapted with permission from Tracy Fulkerson,BSN RN CCRN

Preparation and the Prone Positioning Steps for Pediatric COVID-19 patients

1. Prepare cushions available in the PICU unit: memory foam (egg crate material) or rolled blankets to cushion the head, the chest and the pelvis to allow free movement of the patient's abdomen.
2. Identify the Pediatric Proning team dependent on the patient size:
   - Physician: in-charge of the airway access and possible reintubation
   - At least 2 nurse team assigned to facilitate the roll/turning of patient

   One (1) nurse assigned to support mid section and (1) to the lower extremities
   - Once identified , team lead (physician) discusses turning technique for patient

   SUPINE – PRONE TURN TECHNIQUE:

   * It is Important to plan to do the turn TOWARDS the ventilator side WITHOUT disconnecting the ventilator support from the patient to ensure safety & avoidance of aerosolization.

   Smaller Children (infants/ Toddlers) : body elevated, turned to side (about 45degrees) Placed on prone over prepared cushions

   Bigger Children: Turn by log roll using linens draped around each side of the patient; initially move towards the edge of the bed away from the ventilator, then turn to side (about 45 degrees) , place on prone using drape linens with prepared cushions placed on designated areas

   PRONE – SUPINE TURN TECHNIQUE:

   Smaller Children (infants/ Toddlers) : body elevated, turned to side (about 45 degrees) Placed on SUPINE with the head and shoulder supported then elevate bed to 30 degrees head elevation

   Bigger children: initially move towards the edge of the bed nearest from to the ventilator, then turn to side (45 degrees) ,turn patient to SUPINE by log roll using draped linens from each side of the patient . Adjust patients position to elevate head part to 30 degrees elevation
3. Ensure complete PPE is worn by team members during each procedure. Do hand washing.
4. Cap the nasogastric tube, secure the Foley Bag Catheter
5. Move ECG electrodes to the lateral aspects of the patient's trunk. Reposition tubings /lines to allow sufficient mobility of proning team and patient during the turn.
6. Consider giving scheduled sedation or Neuromuscular blockade agents (NMA) prior to each turn
7. Apply cover or plastic drape over patient's head
8. Suction the oropharynx, recheck level of ETT placement and secure plasters ; reposition drape
9. Team lead then reviews turning techniques out loud, team prepares for turning on his count
10. During the turn, the team should be mindful to keep the head aligned with the patients body to ensure avoidance of disconnection from the ventilator and any untoward injuries
11. Once patient is on prone position, recheck ETT /IV lines placement and patency, remove drape
12. Gently place the patient's head on the side over a cushion lined with an underpad for draining oronasal secretions, then one elbow is folded over the head level, the other stretched, a cushion supporting the upper shoulders, hips and the abdomen is repositioned in a suspended placement to achieve a "swimmer's position" of the *patient as seen in Figure 1 and Figure 2*
13. Place patient on prone for at least 12 hours per day. Proning may be extended for 18-24 hours during the early course of the disease trajectory[32].
14. Assess patient tolerance to the prone position for around 10-15 minutes.

    *If well tolerated ; move the ECG leads to the chest of the patient support pressure points with gel pads or watered gloves continue monitoring, feeding and care
15. *To return to the supine position*, do handwashing, recheck that PPE worn by the team should be level 4 PPE for AGMP procedures. Team lead reviews the prone to supine procedure aloud.
16. Recheck and secure airway patency and Iv access, reposition the ECG lead, cap NGT
17. Place drape over the patients head part, wipe oral secretions if any
18. Gently turn patient from PRONE to SUPINE while supporting the midtorso and leg portion of patient
19. Recheck airway access, patency and secure ETT and attachments. Ensure proper placements of IV access ECG monitor leads, pulse oximeter.
20. Adjust patient to most comfortable position with head part elevated to 30 degrees. Continue care. Repeat cycle till patient has achieved *PaO2/FiO2 ≥150; OI < 12; OSI < 10*[32]. If not tolerated, do not proceed with proning.

Chapter 3

3. Airway Therapies and Respiratory Mechanics

3.1 Aerosol and Delivery Devices

3.1.1 Aerosol Therapy Among Spontaneously Breathing Children

Supportive therapies are presently given to confirmed COVID-19 patients which includes respiratory care especially for the critically ill. Children with COVID-19 often present with respiratory symptoms and there will be a need to deliver aerosol therapy for those with signs and symptoms of bronchoconstriction while carefully ensuring prevention of further viral transmission to others.

There are four primary types of aerosol devices used for drug delivery to children:

1. Nebulizer
2. Pressurized metered-dose inhaler (pMDI)
3. Dry powder inhaler (DPI
4. Liquid metered-dose inhaler (LMDI).[36]

Devices used for the delivery of bronchodilators and steroids can be equally efficacious comparing use of nebulizers, pMDI, DPI in the emergency department, inpatient and out patient settings [37,38,39,40]

Aerosol-Generating Medical Procedure (AGMP) involved in nosocomial virus transmission [41,42,43,44]

1. Nebulizers
2. Oxygen masks - Facemasks and mouthpiece

Evidence from recommendations as early as the start of the Pandemic from China till the present guidelines and expert opinions from different countries indicate the avoidance of aerosol generating procedures like nebulization and to use of dry powder inhaler, metered dose inhaler with spacer for spontaneously breathing patients.[8, 47-52]

Recommendation 17: The use of pMDI for the delivery of B2 agonists via spacer or valve holding chamber (VHC) should be used as a means of drug delivery over nebulizers among non-intubated children suspected or confirmed to have COVID-19 with signs of bronchoconstriction.

(Strong recommendations, Low grade evidence)[7]

Practice Points

- Avoid unnecessary aerosol drug delivery to patients with COVID-19 [2,52]

- Use pMDIs with valve holding chambers for aerosol drug delivery instead of nebulizers, if the patients is awake and can perform specific breathing patterns (tidal breathing) among spontaneously breathing children suspected or confirmed to have COVID-19.
- The selection of device is best based upon, (1) the pediatric patient's pathophysiology and the severity of the lung disease (2) the pharmacological aspects of the various drugs that can be used for the treatment, (3) about the technical qualities of the delivery devices. This includes literature on the aerosol characteristics of the delivery device both in vitro as in vivo. Furthermore, about the efficacy studies for the drug of choice in different age categories. (4) about the abilities of the child and parents. [40]
- There is no literature available recommending the specific device and interface for age among children with COVID-19, however, standing guideline recommendations will be best adhered to for the time being.
- Should aerosol therapy be done, it is important to note that the success of the drug delivery is based on the proper technique in the use of the chosen device. [51] (Further discussion regarding use of device techniques in Section 3.2)

Table 9 Choosing an inhaler device suited for age for suspected or confirmed COVID-19 children

	AGE			
	0-3 years old	***4-5 years old***	***6 years old to 11 years***	***13 years old & above***
Preferred device	pMDI plus dedicated spacer	pMDI plus dedicated spacer	pMDI with VHC, DPI or breath actuated pMDI	
Alternate device only when necessary	Nebulizer	Nebulizer	Nebulizer	
Interface	Tightly sealed Face mask	Tightly sealed Face mask or Mouthpiece	Mouthpiece	Mouthpiece

Combined reference : GINA 2020 Report & Arzu Ari and James B. Fink.Journal of Aerosol Medicine and Pulmonary Drug Delivery.Apr 2016.95-106 [51,52]

Procedure of Pressured Metered Dose Inhaler with VHC

1. "Prime" the pMDI by releasing into the air or into the delivery chamber if it is new or has not been used for several days to provide adequate dose.
2. A single pMDI actuation should be delivered at a time, with the inhaler shaken in between. Multiple actuations into the spacer before inhalation may markedly reduce the

amount of drug inhaled.

3. Static charge may accumulate on some delivery devices like plastic spacers, attracting drug particles and reducing lung delivery. This charge can be reduced by washing the spacer with detergent (without rinsing) and allowing it to air dry. Spacers made of anti-static materials or metals are less subject to this problem. If a patient or health care provider carries a new plastic spacer for emergency use, it should be regularly washed with detergent (e.g. monthly) to reduce static charge. [51]
4. Cleaning of pMDI delivery device is necessary according to the manufacturer's advise

3.1.2 Aerosol Therapy Among Children on Non-Invasive Ventilation

Among children with COVID-19 who are benefitting from non-invasive ventilation (NIV) either by CPAP, BIPAP NIV and or HFNC but are experiencing bronchoconstriction, inhaled drug delivery is necessary. While the Data on aerosol therapy selection in children on noninvasive ventilation in general is quite small. In a review by Berlinski, 2017, included in vivo and in vitro studies in child lung models for NIV inhaled drug delivery via nebulizers, with an inclusion of an adult based and in vitro study for pMDI use, the review indicates the study summary for pediatric aerosol therapy in NIV:

(1) placing a vibrating mesh nebulizer in the mask after the leak improved aerosol delivery when using a single-limb circuit,

(2) placing a vibrating mesh nebulizer between the Y-piece and the unvented mask improved aerosol delivery when using a double-limb circuit;

(3) the vibrating mesh nebulizer is 3.5–5-fold more efficient that the jet nebulizer in a double- limb circuit;

(4) high flows with a heated flow attached to the mask result in decreased aerosol delivery, and

(5) pMDI with a spacer should be actuated during inhalation. [68]

To date, there is also no data of which aerosol therapy is best and safest to use for inhaled drug delivery among children with COVID19 on NIV support. The practitioner should strongly consider the availability of aerosol therapy devices and interface to be used, the negative pressure rooms with full PPE supply in the practice setting, as both non-invasive ventilation and aerosol therapy are aerosol generating procedures.

Practice Points

Avoid unnecessary aerosol drug delivery to patients with COVID-19 [2,52]

1. Use pMDIs with valve holding chambers for aerosol drug delivery instead of nebulizers, if the patients is awake and can perform specific breathing patterns (tidal breathing) among spontaneously breathing children suspected or confirmed to have COVID-19.
2. There is no literature available recommending the specific device and interface for age among children with COVID-19, however, standing guideline

recommendations will be best adhered to for the time being.

3. Should aerosol therapy be done, it is important to note that the success of the drug delivery is based on the proper technique in the use of the chosen device.[51] (Further discussion regarding use of device techniques in Section 3.2)

4. The selection of device is best based upon, (1) the pediatric patient's pathophysiology and the severity of the lung disease (2) the pharmacological aspects of the various drugs that can be used for the treatment, (3) about the technical qualities of the delivery devices. This includes literature on the aerosol characteristics of the delivery device both in vitro as in vivo. Furthermore, about the efficacy studies for the drug of choice in different age categories. (4) about the abilities of the child and parents.[40] While for children improving on Non-invasive ventilation (NIV), selection of aerosol therapy to be used is dependent on the *interface* type (Helmet device, full face or half faced mask and *circuit* (dual limb or single limb circuit) used depending on what is available in practice settings.

3.1.2. Aerosol Therapy Among Intubated Mechanically Ventilated Suspected or

Recommendation 18: The use of pressurized metered dose inhaler (pMDI) is strongly recommended among mechanically ventilated COVID-19 suspect or confirmed children the use of pressurized metered dose inhaler (pMDI) is strongly recommended over nebulization. (Strong recommendations Low grade evidence)[9]

Confirmed Covid-19 Children

Recommendations on aerosol therapy in ventilator-supported patients with COVID-19 are made to reduce the risk of aerosolized viral transmission to healthcare providers. These were based on experience gathered from different countries [47,48,49] recommending the avoidance unnecessary use of aerosol therapy for COVID-19 patients.

A mesh nebulizer is positioned before the humidifier tank without removing the virus filter over the exhalation end of the nebulizer for mechanically ventilated patients in delivery of aerosolized medications[47 52] The Australian Physiotherapy management of COVID-19 recommends to minimize aerosolization (eg, use of a PariSprint with inline viral filter) should nebulization be performed[57]

In pandemics involving a highly contagious virus like Sars-Cov2, it is ideal to use inline closed-system nebulizers. An example is the "inline closed system vibrating mesh nebulizer" (*eg.* Magnair, developed by PARI) to achieve treatment without viral transmission risks.[16]

However, in the local settings, should this device be unavailable, clinicians should

consider using pMDI delivered via actuator devices that are connected to the ventilator circuit *(Further details in next section 3.2B2)*

Practice Points for Mechanically Ventilated Patients with COVID-19

1. Avoid unnecessary aerosol drug delivery to mechanically ventilated patients with COVID-19
2. Use pMDIs with valve holding chambers for aerosol drug delivery instead of nebulizers
3. In cases warranting nebulization, use in-line, or closed system nebulization if the patient with COVID-19
4. Viral /HEPA filter should be place in both the inhalation and exhalation port of the ventilator. Should nebulization be done, keep the viral filter at the expiratory end of the ventilator limb to reduce secondhand aerosol exposure
5. Proper personal protective equipment must be worn during the aerosol generating procedure in an Airborne Infection Isolation Room (AIIR).

Recommendation 19: The use of nebulization for the delivery of B2 agonists among children having bronchospasm should only be used for limited specific situations under strict aerosol generating procedure protective measures and must be avoided as much as possible.
(Strong recommendation for practice, Very low grade evidence)

3.1.3. The Limited Use of Nebulizers Among Covid-19 Children

The Limited Indications of Nebulization Include [50]

1. Severe life-threatening respiratory distress,
2. Patients with compromised ventilation,
3. Uncooperative patients
4. Children with poor response to pMDI

If nebulization is indicated, this should be done under controlled conditions with the respirator therapist in appropriate personal Protective Equipment (PPE). Single patient device and rigorous application of infection control protocols must be observed.[50]

When Performing Aerosol Generating Procedures (AGPs) which includes aerosolized treatment delivery by nebulization, CDC recommends that a health care professional (HCP) should wear an N95 or higher-level respirator such as disposable filtering facepiece respirators, and elastomeric respirators, eye protection, gloves and a gown[8].

- The number of HCP present during the procedure should be limited to only those essential for patient care and procedure support. Visitors should not be present for the procedure.
- AGP's should ideally take place in an Airborne Infection Isolation Room(AIIR)
- Clean and disinfect procedure room surfaces promptly as described in the section on environmental infection control.

As per several expert recommendations it would be ideal to use inline closed-system nebulizers like the mesh nebulizers, and not the conventional jet nebulizers when nebulization is used among COVID-19 patients. Then again we cannot overemphasize that it is still best to minimize aerosol treatment among COVID-19 patients and for the subset of children needing aerosol therapy, the pMDI is still the most feasible approach especially in the local setting.

3.2 Pressurized metered dose inhaler (pMDI) and Administration Techniques

A. Salbutamol Dose for Pressurized Metered Dose Inhaler (pMDI) for Non-intubated and Intubated Children

Recommendation 20: It is strongly recommended that for suspected or confirmed COVID-19 children presenting with bronchospasm initial dose of salbutamol 2 puffs for children ≤ 5yo; 4 puffs children 6-11 yo and adolescent (100mcg/actuation) delivered is strongly recommended.

If symptoms persist after initial bronchodilator: a further 2–6 puffs of salbutamol for <5 yo 4-10 puffs (>6 yo) should be repeated every 20 minutes until good clinical response is achieved.

(Strong, recommendation, Low-grade evidence)[7 51]

Remarks:

There is no direct evidence on the dosage of salbutamol in treating bronchospasm specific for children with COVID-19. Based on evidences extrapolated from studies and current guidelines for asthma, administration of four puffs (0.4mg) of salbutamol may be explored as a means of bronchodilation for pediatric COVID-19 who are not intubated and presenting with bronchospasm.

The optimal dose for pMDI is not well established. However, most studies used nominal dosage ratios between pMDI and nebulizer from 1:1 to 1:13 to determine the dose needed by pMDI to achieve effectiveness comparable to the standard nebulizer doses.[38] A double blind, randomized, placebo-controlled trial by Colacone and colleagues found out that 0.4mg albuterol pMDI achieved similar bronchodilation to that of 2.5mg albuterol by nebulization (1:6 ratio). In another study by Schuh and co-workers, done in children with mild acute asthma comparing initial albuterol treatment with low dose pMDI (2 puffs), high dose pMDI (6-10 puffs), and via nebulizer (0.15mg/kg), showed that there was no significant difference in terms of improvement of FEV1 (p=0.12), clinical score,

respiratory rate, or O2 saturation. Neither the low dose nor the high dose MDI groups had any side effects. [59]

The Global Initiative for Asthma 2020 recommends a dose of 2-6 puffs for children ≤ five (5) years old and 4-10 puffs for children ≥ six (6) years old.[51]Doses may be repeated every 20 minutes until good clinical response is achieved based on the GINA guidelines.[51] This is based on several experimental trials using repeated treatments at short intervals (4 puffs every 10-15 minutes). The number of treatments required was adjusted depending on each of the patient's response as there are uncertainty of aerosol delivery from different devices.[38]The drug delivery with pMDI per actuation is only 10–20% of the total dose of drug prescribed. Hence, proper technique of administration is crucial to ensure optimal drug delivery to the lungs.

There is no direct evidence on the dosage of salbutamol in treating bronchospasm specific for intubated children with COVID-19. Evidences were extrapolated from infants with bronchopulmonary dysplasia, adults with COPD, in vitro, and in vivo animal studies. Infants' pattern of breathing with high respiratory rate and low tidal volume decreases the time available for aerosol deposition thereby reducing drug delivery into the lungs. Hence, for ventilator-supported infants, administration of one or two puffs of albuterol pMDI with chamber is sufficient for routine therapy. In certain situations, such as severe airway obstruction or when administration technique is not optimal, increasing the dose to achieve clinical response may be needed. Titrating the dose, as opposed to using a standard dose, may be used as an alternative to achieve maximal bronchodilatation.[66.67]

B. Pressurized metered dose inhaler (pMDI) Administration Techniques

B.1 Non – Intubated Children

Steps on how to use pMDI in non-intubated children:

1. Remove the mouthpiece cover and shake the inhaler thoroughly.
2. Prime the pMDI into the air if it is new or has not been used for several days. *
3. Assemble the apparatus and check for foreign objects.
4. Keep the canister in a vertical position.
5. Sit up straight or stand up.
6. Breathe all the way out.
7. Follow the instructions below based on the type of device interface used:

With the mouthpiece:

a. Place the mouthpiece of the spacer between their teeth and seal their lips. Make sure that their tongue is flat under the mouthpiece and does not block the pMDI.
b. Actuate the pMDI as they begin to breathe in slowly. Also make sure to inhale slowly if the device produces a "whistle" indicating that inspiration is too rapid.
c. Move the mouthpiece away from the mouth and hold their breath for 10 seconds. If they cannot hold their breath for 10 seconds, then hold for as long as possible.

With the mask:

a. Place the mask completely over the nose and mouth and make sure it fits firmly against the face.

b. Hold the mask in place and actuate the pMDI as they begin to breathe in slowly. Also make sure to inhale slowly if the device produces a “whistle” indicating that inspiration is too rapid.
c. Hold the mask in place while the child takes six normal breaths (including inhalation and exhalation), then remove the mask from the child’s face.
d. Wait 15–30 seconds if another puff of medicine is needed.
e. Repeat steps above until the dosage prescribed by the patient’s physician is reached.
f. If taking a corticosteroid, rinse the mouth after the last puff of medicine, spit out the water, and do not swallow it.
g. Replace the mouthpiece cover on the pMDI after each use.

* For Salbutamol HFA, prime with 2 puffs when it is new and when not used for 14 days.

Note. Reprinted from Pulmonary disease aerosol delivery devices: a guide physicians, nurses, pharmacists, and other health care professional, 3rd ed. (p.36), by K. Gregory, L. Wilken, & M. Hart, 2017. Copyright [2017] by the American Association for Respiratory Care. Permission requested.

B.2 Intubated Children

Steps on how to use pMDI in ventilator-supported children:

1. Position patient in a semi-recumbent position (Head of bed elevated to 20-30°).
2. Suction ETT and airway secretions using a closed suction catheter.
3. Shake pMDI and warm to hand temperature.
4. Place pMDI in the bidirectional in-line adapter connected to the inspiratory limb of the ventilator circuit about 15cm from the ETT.
5. Remove the heat and moisture exchanger (HME), if used. Do not disconnect humidifier.
6. Ensure that there is no leak in the circuit.
7. Actuate pMDI at the beginning of inspiration.
8. Wait for at least 15 seconds between actuations; deliver total dose.
9. Observe the response.

Note. Adapted from “How should aerosols be delivered during invasive mechanical ventilation,” by R. Dhand, 2017, Respiratory care, 62(10):1343–1367. Adapted with permission.

Rationale:

The efficiency of drug delivered through pMDI varies widely. Thus, the importance of proper administration technique to ensure optimal drug delivery to the lungs. Studies have shown that aerosol deposition is influenced by size of the endotracheal tube (ETT), heat and humidity, ventilator mode and settings, patient position, and location of the pMDI in the ventilator circuit.

The efficiency of aerosol deposition is lower with narrow ETT (<6mm) due to impaction. A 40% to 60% reduction in drug delivery was observed when internal diameter of the ETT was reduced from 6 to 4 mm.[70] Drug losses within the ETT may be minimized by placing the aerosol generator at a distance from the ETT rather than attaching it directly.[71]

When the aerosol is exposed to humidity, the particle size increases thus a greater amount of aerosol is lost, reducing drug delivery by 40% to 50%. A pediatric model of mechanical ventilation showed that when humidity was changed from 54% to 100%, the mass median aerodynamic diameter of an hydrofluoroalkane formulation increased from 1.2um to 2.8um.[70] However, removing the humidifier is not routinely recommended as more time would be added to each treatment because it requires disconnection of the ventilator circuit and allowing it to dry. Moreover, even with a humidified circuit, a significant effect was noted with as few as 4 puffs.[9]

Shaking of pMDI prior to administration was found to be important. The failure to shake a pMDI canister that has been standing overnight may decrease total emitted and respirable dose by as much as 25% and 35%, respectively.[72]

Ventilator mode and settings may have an influence on drug delivery. Studies have shown that higher tidal volume, longer inspiratory time, and slower inspiratory flow rate improve aerosol delivery.[63, 73] Moreover, drug delivery is improved when a pMDI is synchronized with a simulated spontaneous breath compared with a controlled ventilator breath of similar tidal volume. Significant results were also obtained when pMDI actuation is synchronized at the beginning of inspiration. Failure to synchronize would result in the reduction of inhaled drug mass by 35%.[74]

For ventilator-supported patients who are unable to sit upright during aerosol administration, several studies showed significant bronchodilator response when pMDI is administered in a semi recumbent position with head of the bed elevated to 20° to 30°. [9, 65, 75]

Different Types of Chamber/Adapters Used To Connect The Metered Dose Inhaler (MDI) Canister To The Ventilator Circuit

Recommendation 21: In ventilator-supported children, clinicians can consider using bidirectional in-line adapter when administering pMDI. This should be connected to the inspiratory limb of the ventilator tubing before the Y-piece. Unidirectional in-line and elbow adapters may be used as alternatives but are less effective.
(Weak recommendation, Low-grade evidence)[1,9,18]

Remarks:
Actuator devices are adapters used to connect the pMDI canister to the ventilator circuit. The use of these devices can be considered to enable more efficient delivery of pMDI in intubated children. Several types are commercially available including chamber adapters (cylindrical and reservoir) and non-chamber adapters (inline and elbow) [Fig. 15].

Chamber adapter requires removal of the adapter after delivery of the drug. Hence not recommended for intubated COVID-19 patient. This procedure will lead to aerosol transmission of the virus.

Non chamber adapters are recommended in the delivery of pMDI in intubated COVID-19 patients. As with bidirectional in-line adapter, it had a higher delivery efficiency when compared with unidirectional in-line adapter and was comparable with chamber spacers in performance.[1] The advantage of bidirectional in-line adapter over chamber adapters is that it is small hence dead space volume is expected to be minimal. This device can stay in-line, thereby avoiding disruption of the ventilator circuit prior to aerosol therapy. Because of the aforementioned advantages, clinicians should consider using bidirectional in-line adapter to deliver pMDI for ventilator-supported patients to minimize the risk of aerosol transmission of the virus.

Connecting the pMDI and chamber in the inspiratory limb of the ventilator circuit before the Y-piece increases aerosol deposition with improved potential for clinical response. This was demonstrated in an in-vitro adult model of mechanical ventilation wherein they quantified the emitted dose of albuterol delivered distally to an ETT from three different positions. pMDI and chamber placed in the inspiratory limb 15 cm from the Y-piece (17.0±1.0%) showed the highest aerosol deposition when compared to placing the pMDI between ETT and Y-piece (7.6±1.3%) , and 15 cm from the ventilator before the inlet of the humidifier (2.5±0.8%).[69]

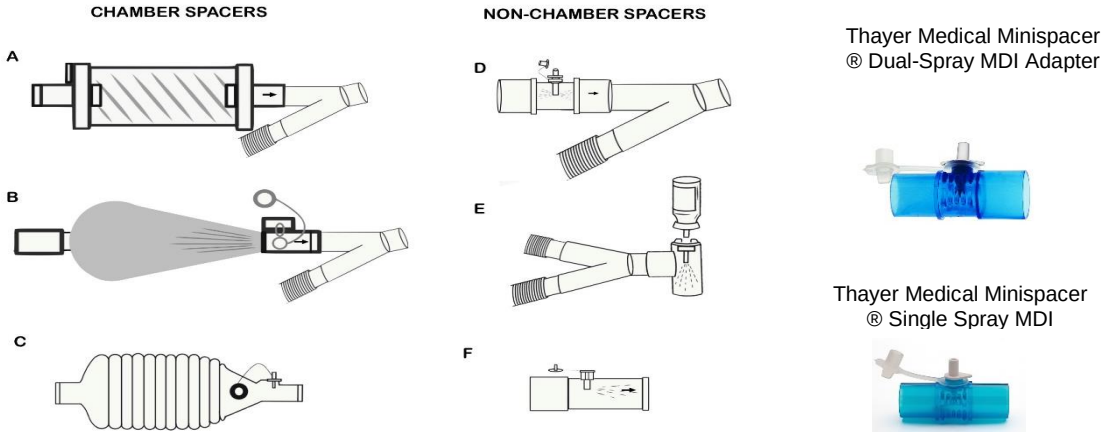


Fig. 15. Different types of chamber/adapters used to connect the metered dose inhaler (MDI) canister to the ventilator circuit. **A**, non-collapsible cylindrical chamber; **B**, aerosol cloud enhancer (ACE) spacer, with which the MDI flume is directed away from the patient; **C**, collapsible cylindrical chamber; **D**, bidirectional in-line adapter; **E**, elbow adapter; **F**, unidirectional in-line adapter. Modified from "Bronchodilator therapy in mechanically ventilated patients," by J.B. Fink, M.J. Tobin, & R, Dhand, 1999, *Respiratory care,* 44(1):53– 69. Modified with permission.

3.3 Airway Clearance

AIRWAY CLEARANCE /RESPIRATORY PHYSIOTHERAPIES RATIONALE FOR USE FOR

Recommendation 22: For airway clearance procedures, we strongly recommend the following strategies among pediatric COVID-19 patients: Ensuring adequate oxygenation, appropriate inhalation therapy, keeping the respiratory tract unobstructed, appropriate reassessment of airway patency and non-invasive/invasive respiratory support and mechanical ventilation, and judicious use of fluids and vasoactive medications.
(strong recommendation, moderate grade evidence).

COVID-19

Rationale for Use of Airway Clearance Procedures / Respiratory Physiotherapy for Covid-19

The main objective of airway clearance is to facilitate clearance of respiratory secretions, inflammatory exudates, or aspirated material in infants and children.[78,79]

Airway clearance or respiratory physiotherapy may be beneficial in the respiratory treatment and physical rehabilitation of patients with COVID-19, although a productive cough is a less common symptom, physiotherapy may be indicated if patients with COVID-19 present with airway secretions that they are unable to independently clear.

Thomas, et.al. highlighted key concepts in the principles of physiotherapy among patients with confirmed or suspected COVID-19. Respiratory physiotherapy management should be evaluated on a case-to-case basis based on the patient's medical indications. Patients who may benefit from physiotherapy include COVID-19:

a) Patients with copious airway secretions which they not be able to clear on their own,
b) High-risk patients with neuromuscular disorders and other co-morbid illnesses which result in increased mucus production or weak cough,
c) Mechanically ventilated patients with inadequate airway clearance.
d) Severe symptoms of pneumonia or with chest imaging findings showing consolidation.[76]

Respiratory Physiotherapy techniques:

a) Positioning
b) Active cycle of breathing
c) Manual and/or ventilator hyperinflation
d) Percussion and vibrations
e) Positive expiratory pressure therapy
f) Cough maneuvers
g) Airway suctioning

These are some examples of respiratory physiotherapy techniques that may be useful in aiding airway clearance for Covid-19 patients. However, the authors emphasized that because of aerosolization and exposure risks, these interventions should only be provided when clinically indicated.[57] Airway clearance procedures may be done only when needed and are not frequently required in COVID-19 patients.[77]

Because of risk of aerosolization while performing respiratory physiotherapy procedures for COVID-19 patients, the risks versus benefits should be carefully measured before proceeding with these interventions on a case-to-case basis. Examples of potentially aerosol-generating respiratory physiotherapy procedures include the following: cough-generating procedures, techniques for gravity-assisted drainage or techniques and manual procedures such as expiratory vibrations, percussion or manually-assisted cough and use of positive-pressure breathing devices. Open suctioning, nasopharyngeal or

oropharyngeal suctioning, manual hyperinflation, sputum induction and mobilization techniques which result in coughing of the patient likewise pose risks of aerosolization.[57]

It is recommended that airborne precautions should be observed for health care workers performing aerosol-generating interventions among patients with COVID-19, this include use of the following personal protective equipment (PPE): N95/P2 mask, long-sleeved, fluid-resistant gown, face shield or goggles, gloves, hair cover and liquid-impermeable shoes. Furthermore, for personnel caring for critically ill patients with COVID19, it should be emphasized that they are adequately trained in proper use and donning and doffing of PPE.[57]

Chapter 4

4. PULMONARY CARE IN SPECIAL SITUATIONS OF PEDIATRIC COVID-19

4.1 ASTHMA IN CHILDREN DURING THE COVID-19 PANDEMIC

4.1.1 USE OF INHALED CORTICOSTEROIDS AS CONTROLLER MEDICATION USE

Recommendation 23: The administration of existing medications for asthma controller medications should be continued for pediatric patients with asthma during the COVID-19 pandemic.
(Strong recommendations, Low-quality evidence)

- The administration of existing medications for asthma control should be continued for pediatric patients with asthma during the COVID-19 pandemic.
- The usual guidelines for prompt initiation of systemic glucocorticoids for asthma exacerbations be still followed.
- Inhalers for asthma medications are preferred over nebulizers for patients with asthma and COVID-19 to prevent aerosolization of the virus and thereby enhancing disease spread.

Remarks:

In the rapidly evolving data among COVID-19 confirmed children, there are relatively few data at this time to demonstrate a specific increased risk for COVID-19 among asthmatics. Reports of pediatric patients from China[88,89] Korea,[90] Italy[91] and Brazil[92] did not describe asthma as a noted risk for acquiring COVID-19 as of data collection for this report.

Although among American children who tested positive for Sars-Cov2 However, a growing number of reported pediatric COVID confirmed cases from the United States , 345 pediatric cases with information on underlying conditions, 80 (23%) had at least one underlying condition was found. The most common underlying conditions were chronic lung disease (including asthma). [3]

Guideline based managements of the use of Inhaled steroids help to minimize risk of an asthma control and exacerbation are not affected when one is infected with the Sars-COv2 virus. [49,51,93] Stopping them may worsen asthma control and thereby increase the risk for complications of COVID-19 leading to associated need for interaction with the health care system, if acquired. Beyond the direct risk of the infection itself, there is also a risk of experiencing an asthma exacerbation triggered by coronavirus infection.[93] It is worthwhile to note that viral infections are primary causes of wheezing in children less than 5yo[51] and among older individuals as overwhelming evidence demonstrate the association of asthma exacerbations with viral infections in the community.[94]

4.1.2. USE OF SYSTEMIC CORTICOSTEROIDS DURING ACUTE EXACERBATIONS

Patients with COVID-19 infection and a concomitant acute exacerbation of asthma and COPD should receive prompt treatment with short term systemic glucocorticoids as indicated by usual guidelines. Delaying therapy can increase the risk of a life threatening exacerbation.

There is currently no evidence to suggest that short-term use of systemic corticosteroids to treat asthma exacerbations increases the risk of developing severe COVID-19, Overall, the known benefits of systemic glucocorticoids for acute exacerbations of asthma and COPD outweigh the potential harm in COVID-19[93]

The GINA 2020 Report recommends the provision of a written Asthma Action Plan for each child with asthma. This helps patients to recognize and respond appropriately to worsening asthma. It should include specific instructions for the patient about changes to reliever and controller medications, how to use oral corticosteroids (OCS) if needed and when and how to access medical care. [51]

The short course of oral corticosteroids (OCS) dose include: (GINA Report 2020)

Children less than 5year old

a. A dose of OCS equivalent to prednisolone 1–2 mg/kg/day, with a maximum of 20 mg/day for children under 2 years of age and 30 mg/day for children aged 2–5 years,
b. A course of 3–5 days being sufficient in most children of this age, and can be stopped without tapering but the child must be reviewed after discharge from the emergency room department

Children 6yo- 11yo

a. For children 6–11 years, the recommended dose of OCS is 1–2 mg/kg/day to a maximum of 40 mg/day usually for 3–5 days. Patients should contact their doctor if they start taking OCS
b. Dose of 40–50 mg/day usually for 5–7 days for patients who:
   - Fail to respond to an increase in reliever and controller medication for 2–3 days
   - Deteriorate rapidly or who have a PEF or FEV1 <60% of theirpersonal best or predicted value
   - Have a history of sudden severe exacerbations.

When indicated inhaled medications during exacerbations or bronchospasms, the preferred mode of aerosol therapy will be the use of pressurized metered dose inhalers (pMDIs) over nebulizer use to limit transmission of potentially viable COVID-19 aerosolized droplets to susceptible bystander hosts.

Chapter 5

5. DISCHARGE and ENDING ISOLATION OF PEDIATRIC COVID-19 PATIENTS

Recommendation 24: We strongly recommend that based on the latest DOH updated guidelines, symptomatic patients COVID-19 Patients (suspect/ probable/ confirmed) who have fulfilled completion of 14 days isolation, clinically recovered and no longer symptomatic can be discharged and tagged as recovered without RT-PCR or antibody testing and provided that there is a clearance from licensed physician.

(Strong recommendation, low-grade evidence).

Remarks:

Based on the latest Department of Health of the Philippines guidelines released last May 29, 2020 in the Memorandum No. 2020-0258 on Expanded Testing for COVID-19, Symptomatic COVID-19 Patients (suspect/ probable/ confirmed) who have fulfilled completion of 14 days isolation, clinically recovered and are no longer symptomatic can be discharged and tagged as recovered without RT-PCR or antibody testing and provided that there is a clearance from licensed physician.[141]

The guidelines specify that for symptomatic patients, if there is no available RT-PCR rapid antibody tests (RATs) may be used, however, “regardless of results symptomatic patients must still be isolated for 14 days or until asymptomatic, whichever is longer.” [141]

- If the symptomatic patient tested IgM negative on RAT, SARS-CoV-2 RT-PCR testing must be obtained, and if the result of the RT-PCR is negative, the patient still has to complete the 14-day quarantine period; however, if the RT-

PCR turns out to be positive, the patient is a confirmed COVID-19 and must be treated and isolated as such. In settings where RT-PCR testing is unavailable, the recommendation is to isolate the patient for 14 days until asymptomatic, whichever is longer.[141]

- On the other hand, if the patient is symptomatic and IgM positive (probable COVID-19), RT-PCR testing must be done, and if positive, the patient is treated and isolated as COVID-19. In case the RT-PCR is negative, the patient still has to complete the 14 day quarantine, or until asymptomatic, whichever is longer, and repeat RAT once without symptoms. [141]
-
- In cases wherein RT-PCR is not available, the patient must be isolated for 14 days or once without symptoms, whichever is longer, and repeat RATs is recommended once the patient is asymptomatic or at 14 days of quarantine, whichever is longer.
    - If on RAT, the patient is IgG positive, the patient can be free from quarantine, while is the result is IgM positive and IgG negative, the quarantine can be extended by 7-day increments and repeat testing.
    - In case the patient still remains to be IgM positive but IgG positive for two consecutive repeat tests after the 14-day period, the patient may have a potential false positive result, and the patient may be referred to an infectious disease specialist for further evaluation and management [141]

Among Asymptomatic COVID-19 patients , they may be released from quarantine after 14 days if patients remains asymptomatic for the whole 14-day quarantine period, even without RT-PCR/antibody testing and furthermore, there is no need to do repeat RT-PCR testing before discharge and tagging as recovery.[14]

Recommendation 25 : We strongly recommend, that home isolation should be discontinued based on the guidance for Symptom based-strategy with the following conditions: patient has completed 14 days quarantine OR patient has at least 3 days (72 hours) have passed since recovery (based on resolution of fever without use of antipyretics and improvement of respiratory symptoms) and has at least 10 days have passed since symptoms first appeared ,whichever is longer.

(Strong-recommendation, low-grade evidence)

Based on the latest DOH guideline as specified in the earlier recommendation, symptomatic COVID-19 patients who have recovered and are no longer symptomatic, completed 14 days of isolation can be discharged and labelled as recovered upon clearance by a medical doctor. [141] For asymptomatic patients, COVID-19 patients without symptoms can end quarantine after 14 days if patients remains asymptomatic for the complete duration of this period (14 days).[141]

- The discharged patient should self-isolate at home or in a safe place until the resolution of fever for at least three days and clinical improvement of other symptoms
- Follow-up visits or monitoring via phone or telemedicine can be considered

- Patients discharged to a closed-population environment should be placed in a single room until ten days after the onset of symptoms have passed and the resolution of fever for at least three days and clinical improvement of other symptoms
- Discharged immunocompromised patients must self-isolate until all of the following are fulfilled: at least 14 days after onset of symptoms have passed and resolution of fever for at least three days and clinical improvement of other symptoms.

Family members and other contacts of COVID-19 patients

- shall self-quarantine for 14 days after the last contact with the infected patient
- should stay at home isolation for ten days should they develop symptoms, until the resolution of fever for at least three days and clinical improvement of other symptoms

For COVID-19 patients under isolation, based on the CDC guidelines, the decision to end home isolation should be based in consideration of local circumstances. Based on the CDC guidance on ending home isolation updated as of May 3, 2020, for the *symptom-based strategy* (formerly termed non-test based strategy), the home isolation period is extended from 7 to 10 days after symptoms first appeared in COVID-19 patients who have symptoms. Thus, for COVID-19 patients who have symptoms, isolation may be discontinued based on the following conditions: at least 3 days (72 hours) have passed since recovery (based on resolution of fever without use of antipyretics and improvement of respiratory symptoms) and at least 10 days have passed since symptoms first appeared. [98] Furthermore, the *time-based strategy* in asymptomatic laboratory-confirmed COVID-19 patients, the home isolation period was also extended from 7 to 10 days based on the said guideline. The CDC states that the rationale for thesaid update are recent evidences of longer time duration of viral shedding, they also specified that this will be revised as additional evidences will be available.[98]

Current guidelines on discharge and isolation are evolving based on the recent available scientific evidence, knowledge and understanding of the disease, hence these recommendations may also change over time.

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PAPP RAPID ADVISE on PULMONARY CARE IN PEDIATRIC COVID19 ALGORITHMS (*June 2020 version*)

Classification and Respiratory Management of Symptomatic Pediatric Confirmed COVID-19

I. IDENTIFY

CLINICAL PRESENTATION

(+/-) Fever & /or cough & /or GI sx
w/or w/o other Sx

→ Evaluate exposure → **Covid-19 Suspect**

II. CONFIRM

RT-PCR for SARS CoV 2 NP /OP SWAB

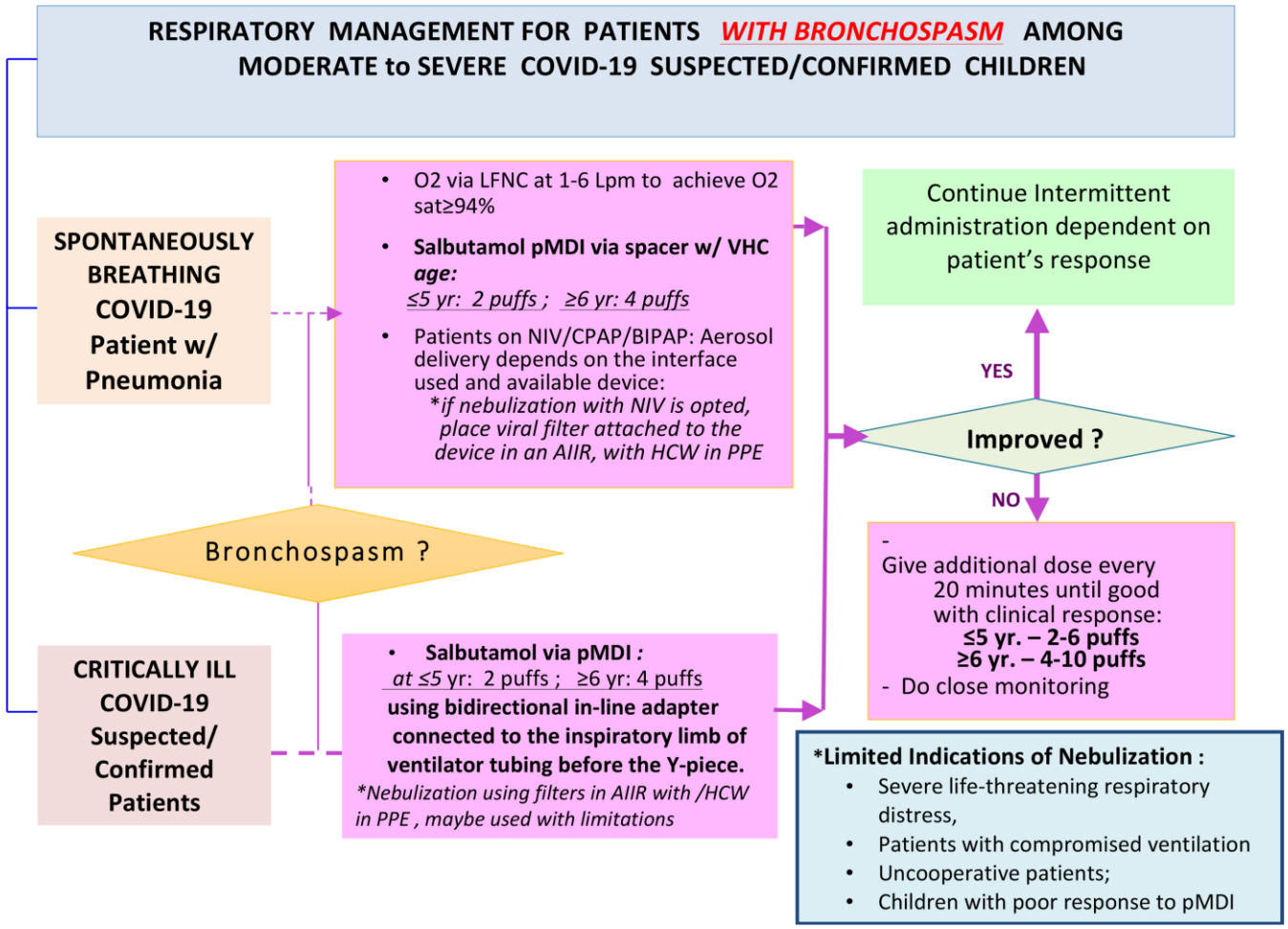
→ **(-) Probable COVID 19**

→ **+ Laboratory Confirmed COVID 19**

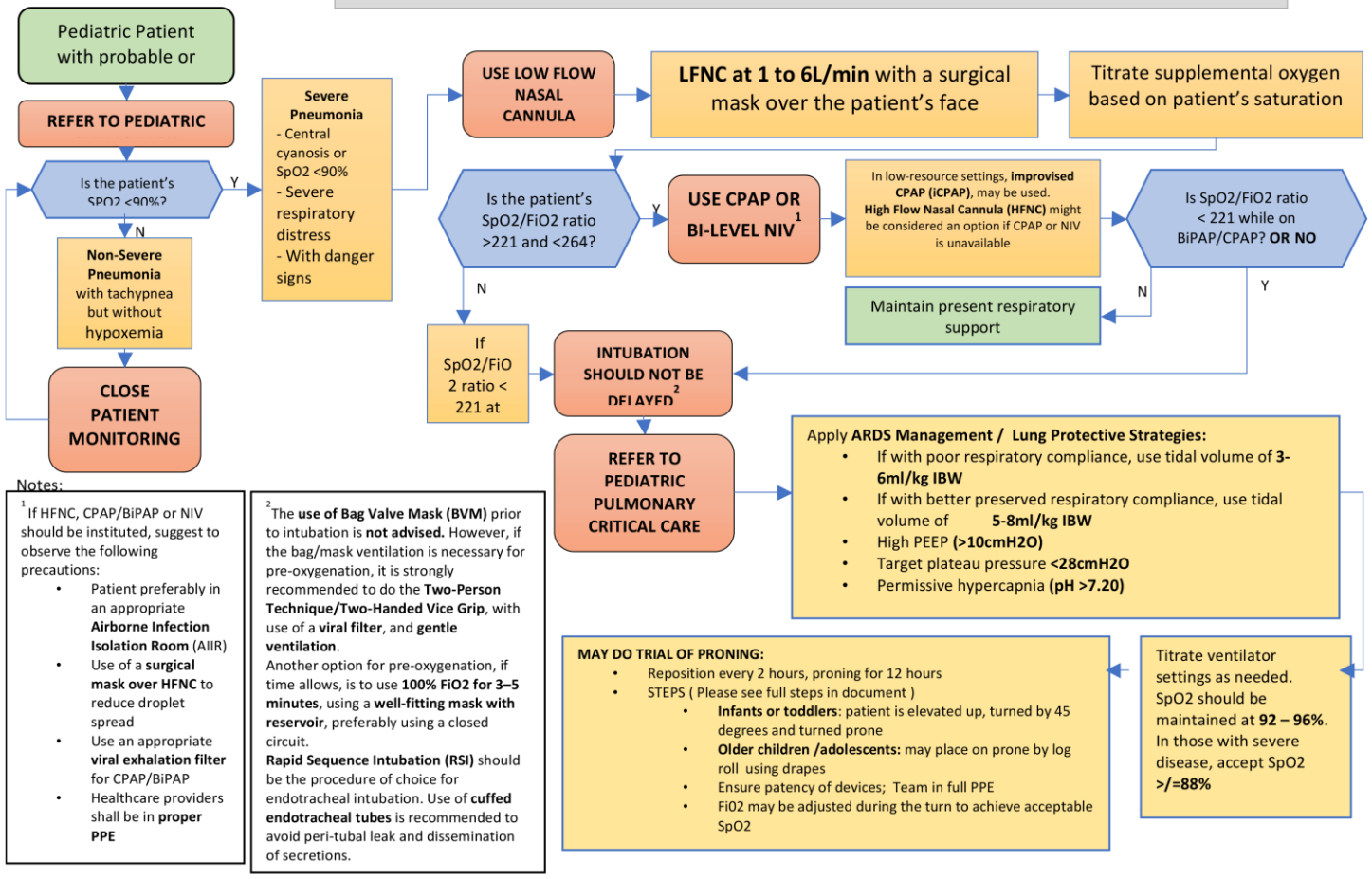
III. CLASSIFY CASES

Symptomatic			
MILD	**Moderate**	**Severe**	**Critical**
		PNEUMONIA	
	NON SEVERE	**SEVERE**	**ARDS**
Acute URTI Fever, cough, Flu like +/- fever or only GI sx ie nausea, vomiting, abdominal pain and diarrhea rash Congested pharynx no auscultatory abnormalities	**Pneumonia** fast breathing: < 2 months: ≥ 60 2–11 months: ≥ 50 1–5 years: ≥ 40 +/- wheezing No hypoxemia	**Pneumonia with Early severe respiratory distress** Fever, +/- cough, +/- GI Sx Dyspnea, + central cyanosis Grunting, chest indrawing O_2 sat < 90% at room air	**Respiratory failure,** +/- shock MODS Encephalopathy, Myocardial injury or heart failure, Acute kidney injury Liver Injury Coagulation dysfunction
	Chest Xray CT scan CBC CRP ESR Procalcitonin	Chest Xray CT scan ALT AST PT PTT LDH Creatinine, BUN serum electrolytes CK-MB D Dimer Arterial Blood gases Serum Ferritin	Chest Xray CT scan ALT AST PT PTT LDH Creatinine, BUN serum electrolytes CK-MB D Dimer Arterial Blood gases Serum Ferritin

2


RESPIRATORY MANAGEMENT FOR PATIENTS WITH BRONCHOSPASM AMONG MODERATE to SEVERE COVID-19 SUSPECTED/CONFIRMED CHILDREN
SPONTANEOUSLY BREATHING COVID-19 Patient w/ Pneumonia
O2 via LFNC at 1-6 Lpm to achieve O2 sat≥94%
Salbutamol pMDI via spacer w/ VHC age:
≤5 yr: 2 puffs ; ≥6 yr: 4 puffs
Patients on NIV/CPAP/BIPAP: Aerosol delivery depends on the interface used and available device:
*if nebulization with NIV is opted, place viral filter attached to the device in an AIIR, with HCW in PPE
Continue Intermittent administration dependent on patient's response
YES
Improved ?
NO
Bronchospasm ?
Give additional dose every 20 minutes until good with clinical response:
≤5 yr. – 2-6 puffs
≥6 yr. – 4-10 puffs
- Do close monitoring
CRITICALLY ILL COVID-19 Suspected/ Confirmed Patients
Salbutamol via pMDI :
at ≤5 yr: 2 puffs ; ≥6 yr: 4 puffs
using bidirectional in-line adapter connected to the inspiratory limb of ventilator tubing before the Y-piece.
*Nebulization using filters in AIIR with /HCW in PPE , maybe used with limitations
*Limited Indications of Nebulization :
Severe life-threatening respiratory distress,
Patients with compromised ventilation
Uncooperative patients;
Children with poor response to pMDI

Respiratory Management of Pediatric Patient with Probable or Confirmed COVID-19 Pneumonia



Notes:

[1] If HFNC, CPAP/BiPAP or NIV should be instituted, suggest to observe the following precautions:

- Patient preferably in an appropriate **Airborne Infection Isolation Room** (AIIR)
- Use of a **surgical mask over HFNC** to reduce droplet spread
- Use an appropriate **viral exhalation filter** for CPAP/BiPAP
- Healthcare providers shall be in **proper PPE**

[2] The **use of Bag Valve Mask (BVM)** prior to intubation is **not advised.** However, if the bag/mask ventilation is necessary for pre-oxygenation, it is strongly recommended to do the **Two-Person Technique/Two-Handed Vice Grip**, with use of a **viral filter**, and **gentle ventilation**.
Another option for pre-oxygenation, if time allows, is to use **100% FiO2 for 3–5 minutes**, using a **well-fitting mask with reservoir**, preferably using a closed circuit.
Rapid Sequence Intubation (RSI) should be the procedure of choice for endotracheal intubation. Use of **cuffed endotracheal tubes** is recommended to avoid peri-tubal leak and dissemination of secretions.