SPECIAL ARTICLE

Novel Coronavirus 2019 (2019-nCoV) Infection: Part II - Respiratory Support in the Pediatric Intensive Care Unit in Resource-limited Settings

MANU SUNDARAM[1], NAMITA RAVIKUMAR[2], ARUN BANSAL[2], KARTHI NALLASAMY[2], BASAVARAJA GV[3], RAKESH LODHA[4], DHIREN GUPTA[5], MARTI PONS ODENA[6], ASHWATH RAM RN[7], MURALIDHARAN JAYASHREE[2] FOR THE INTENSIVE CARE CHAPTER OF INDIAN ACADEMY OF PEDIATRICS

From [1]Division of Critical Care Medicine, Sidra Medicine, Doha, Qatar;[2]Division of Pediatric Critical Care, Department of Paediatrics, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India [3]Pediatric Intensive Care Unit, Indira Gandhi Institute of Child Health, Bangalore, Karnataka, India; [4]Department of Pediatrics, All India Institute of Medical Sciences, Delhi, India; [5]Pediatric Intensive Care Unit, Sir Ganga Ram Hospital, Delhi, India;[6] Department of Pediatric Intensive Care, Sant Joan de Due Hospital, Barcelona, Spain; and[7]Department of Pediatric Intensive Care, Manipal Hospital, Bangalore, India.

Correspondence to:Dr Arun Bansal, Professor, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. drarunbansal@gmail.com

Received: March 26, 2020; Initial review: March 28, 2020; Accepted: March 31, 2020.

The 2019-novel coronavirus predominantly affects the respiratory system with manifestations ranging from upper respiratory symptoms to full blown acute respiratory distress syndrome (ARDS). It is important to recognize the risk factors, categorize severity and provide early treatment. Use of high flow devices and non-invasive ventilation has been discouraged due to high chances of aerosol generation. Early intubation and mechanical ventilation areessential to prevent complications and worsening, especially in resource-limited settings with very few centers having expertise to manage critical cases. Hydrophobic viral filter in the ventilator circuit minimizes chances of transmission of virus. Strategies to manage ARDS in COVID-19 include low tidal volume ventilation with liberal sedation-analgesia. At the same time, prevention of transmission of the virus to healthcare workers is extremely important in the intensive care setting dealing with severe cases and requiring procedures generating aerosol. We, herein, provide guidance on non-invasive respiratory support, intubation and management of ARDS in a child with COVID-19.

Keywords: *2019- nCoV, Aerosol generation, ARDS, Management, Pandemic, SARI.*

Published online: **March 29, 2020;** ***PII:*** **S097475591600152**

Novel coronavirus 2019 (2019-nCoV) infection has been declared a pandemic by the World Health Organization (WHO). We elaborated the epidemiology, preparedness of intensive care units, clinical course, intensive care needs and complication of patients with Coronavirus disease (COVID-19) in a previous article [1]. In this write-up, we will focus on the respiratory manifestations, progression and intensive care management of respiratory complications of COVID-19. As we learn more about the 2019-nCoV (novel coronavirus) and the impact this has had on the patients and health care workers (HCW) globally, the focus has shifted to safety of the HCW so that the patients can be treated appropriately and kept safe. This is based on the lessons learned from previous epidemics and mitigating steps to reduce risks to HCW. Most of the following suggestions are based on expert opinionon providing safe care in these challenging times.

RESPIRATORY DISEASE DUE TO 2019 NCOV INFECTION

Clinical Course

The most common presentation is short history of prodrome with myalgias, malaise, cough and low-grade fever. As per the case series from China, only 40-70% of the pediatric patients have fever as an initial presentation [2-4]. During the second week of illness, progression of the disease gradually leads to difficulty in breathing. Reports from China have suggested that it takes an average of 8 days for the development of dyspnea and 9 days for the onset of pneumonia/pneumonitis [5].

Investigations

CDC does not currently recommend chest radiography (CXR) or computed tomography (CT) to diagnose COVID-19 [6]. Viral testing remains the only specific method of diagnosis and has been discussed in detail in part-I [1]. Confirmation with the viral test is required, even if radiologic findings are suggestive of COVID-19 on CXR or CT scan [7].

Differential Diagnosis

The clinical presentation and findings on chest imaging in COVID-19 are not specific.The clinical presentation of COVID-19 overlaps with other infections like influenza, respiratory syncytial virus (RSV), adenovirus, human meta-pneumovirus, non COVID-19 coronavirus, atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine laboratory tests. In the context of pandemic and local transmission setting in, the travel history will become irrelevant. There are some radiological and hematological findings that may help indicate COVID-19, even though they are not very specific [1].

Classification of Severity

Severity of illness is based on the presenting symptoms and has been discussed previously [1]. Patients can shed RNA from 1-4 weeks after symptom resolution, but it is unknown if the presence of RNA equals presence of infectious virus. As per current guidelines, COVID-19 patients are "cleared" of isolation once they have 2 consecutive negative RNA tests collected >24 hours apart. This practice may not be clinically possible in our setting due to various constraints. Therefore, keeping them in isolation for longer duration is the key.

MANAGEMENT OF HYPOXEMIC RESPIRATORY FAILURE

One of the key considerations during management is mitigating risk to health care workers. Hypoxemia can be present due to impaired respiratory functions in COVID-19. Oxygen supplementation treatment can correct hypoxemia and relieve secondary organ damage caused by hypoxemia[8]. The management of children with Severe acute respiratory illness (SARI) in COVID is similar to any other viral pneumonia with ARDS but with strict precautions to reduce risk of transmission[9].

Protection From Aerosol

All aerosol generating procedures/events require donning of personal protective equipment which includes N95 mask, goggles or face shield, cap, full sleeve gown and shoe cover (***Table* I**) [10]. Where possible, a nebulizer may be replaced with an MDI and spacer for administration of bronchodilators. NIV generates droplets >10 μm in size and most fall on local surfaces within 1-meter distance. Learning from droplet dispersion studies, HCWs who are providing NIV, chest physiotherapy or working within 1 meter of an infected patient should have a high level of respiratory protection [11-13].

Oxygen Therapy

Oxygen therapy is necessary for patients with oxygen saturation (SpO_2) less than 90% and/or with signs of respiratory distress. It has been noted that many elderly patients with severe hypoxemia may not have obvious symptoms of respiratory distress [14]. It is pertinent that the evaluation of all children with respiratory symptoms should include pulse oximetry. Low flow oxygen devices are recommended as high flow devices have the potential for risk of spread through aerosol generation. Nasal cannula at flows of 2-4 L/min is a good choice for milder forms of SARI. A triple layer mask should be used to cover the mouth and nose of the patient over the nasal cannula, especially during transport, unless the child does not tolerate [15].

Heated Humidified High Flow Nasal Cannula (HHHFNC/HFNC)

HFNC therapy can be useful in special situations for hypoxia. A flow of 2-3 mL/kg with FiO_2 targeted to SpO_2 is used. However, it is necessary that when patient is on HFNC interface, HCW are wearing optimal airborne PPE and child is managed in negative pressure rooms,if available [16]. In infants, while HFNC is being given they can be placed in an oxygen hood to minimize dispersion. Surviving Sepsis Guidelines recommend HFNC in milder cases of adult SARI [17]. However, no such guidelines are there for children. HFNC should be tried for a maximum of 1-2 hours. Signs of improvement are decrease in heart rate and respiratory rate by 10-20%, decrease in FiO_2 requirement to less than 50% and improvement in oxygen saturations.

Patients with worsening hypercapnia, acidemia, respiratory fatigue, hemodynamic instability or those with altered mental status should be considered for early invasive mechanical ventilation.

Non-invasive Ventilation

Over the last two decades, the use of non-invasive ventilation (NIV) is increasing in children with viral illness and the rates of intubation are reducing. At the same time there is paucity of literature regarding the use of NIV in respiratory pandemics.

Table I Aerosol Generating Events and Procedures in the Intensive Care Unit

Aerosol generating events	*Procedures vulnerable to aerosol generation*
Inadequate seal during	Laryngoscopy
NIV or HFNC	Intubation
Nebulization	Front of neck access
Endotracheal suction	Laryngoscopy
CPR prior to intubation	Bronchoscopy
Extubation	
Coughing/sneezing	

NIV-non-invasive ventilation; HFNC – High flow nasal cannula.

In a Chinese observational study in adults of the SARS outbreak, it was shown that NIV was effective in preventing the use of endotracheal intubation in 70% of patients because of early initiation of NIV. In this study, none of the HCW acquired SARS from the patients. This was attributed to NIV being applied in a negative-pressure environment with strict PPE regime and close monitoring of the HCW involved [18]. In another study from Toronto during SARS, the use of NIV was discouraged after clinicians contracted the disease when a patient was intubated following NIV failure [19]. Therefore, some clinicians consider NIV is contra-indicated for acute respiratory failure due to airborne respiratory diseases unless it is used in a negative-pressure isolation room and strict precautions are taken [19].

After the two viral pandemics, most of the professional societies including the European Respiratory Society, European Society of Intensive Care Medicine, and American Association for Respiratory Care have recommended against NIV use to treat acute respiratory failure due to H1N1 influenza, particularly in severely ill patients. Thus, NIV is accepted as a high-risk procedure that should be used cautiously because of possible spread of infection [20-23].

Routine use of NIV is not recommended in COVID-19. It should be used only in selected patients with hypoxemic respiratory failure. Ideally, negative pressure single rooms are preferable for patients on NIV. However, in an outbreak of such a magnitude, some professional societies recommend keeping a distance of at least two meters between two beds. Due to the high percentage of failure with NIV and the rapid progression of the hypoxemic failure due to COVID-19, all patients receiving NIV need a clear plan for treatment failure.

Selection of interface is the key for success and protection of the HCWs. Preferred interfaces are helmet, total face mask and oro-nasal non-vented masks.Risks of NIV include delayed intubation, large tidal volumes and injurious trans-pulmonary pressures. Limited data suggest a high failure rate in patients with other similar viral infections such as MERS-CoV [24].

$PaO_2/FiO_2$is a sensitive and accurate indicator of oxygenation function on NIV and can be used to define the severity of ARDS once the patient has been on a PEEP of 5 cm for a minimum of 30 minutes. Invasive ventilation must be considered if PaO_2/FiO_2 ratio is below 300. In the absence of an ability to do an arterial blood gas, the SpO_2/FiO_2 can also be used to identify oxygenation failure as long as the FiO_2 has been titrated to get saturations between 92%- 97%.

The most recent World Health Organization (WHO) interim guidance on management of the novel-CoV has also recommended the use of NIV for mild cases of ARDS without hemodynamic instability [8].

Conventional ventilators with NIV option having double lumen tubing is a safer option than NIV ventilator with single lumen tubing requiring exhalation port to washout the CO_2. Antiviral/Antibacterial filters should be attached to the exhalation limb of the circuit to reduce environmental contamination. Alternatively, when these options are not available, home ventilators with built-in oxygen blender or transport ventilators can provide adequate mechanical ventilation.

Bubble CPAP

In situations where both non-invasive and invasive mechanical ventilation are not available, bubble nasal CPAP (commercial or indigenous) may be used for newborns and children with severe hypoxemia as these are readily available alternative in resource-limited settings.To minimize environmental contamination the infant could be placed in an oxygen hood to reduce droplets.

These patients should be on continuous monitoring and cared for by experienced personnel capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 2 hours).

Patients with known contraindications for NIV like moderate/severe ARDS with PaO_2/FiO_2 ratio below 200, hemodynamic instability, multi-organ failure, or abnormal mental status should receive invasive ventilation from the very beginning.

Intubation

During the previous SARS epidemics in China and Singapore, infection rates were higher in doctors and nurses carrying out endotracheal intubation [relative risk (95% CI)-13.3 (2.99–54.04)] [20]. In an observational study of influenza-A and influenza-B in exhaled breath, viral RNA was seen in one-third of infected patients and 99% of particles had a diameter of <5 µm when sampled during tidal breathing [25]. Studies have demonstrated that particles <10 µm in diameter are more likely to cause infection in the lower respiratory tract [9,10]. Coronavirus virions (or 'particles') are spherical particles with diameters of approximately 125 nm (0.125 µm) [26].

Tracheal intubation should be performed as early as possible for patients with aPaO_2/FiO_2 ratio <300, worsening trend of the SpO_2/FiO_2 ratio <200, worsening respiratory distress, high concentration (>60%) of oxygen on HFNC or multiple organ dysfunction.

Preparation : Prepare the plan, ready the equipment and set-up the ventilator prior to intubation (***Table* II**). At least three personnel are needednamely, airway operator, airway assist and a nurse for medication. The most experienced person should intubate to ensure minimum number of attempts to decrease aerosol generation. Wherever possible, usedisposable equipment. Video laryngoscopy is ideal to protect the intubating HCW from operating too close to the airway (***Fig*.2**). If equipment or expertise isnot available, take measures to reduce droplets during the procedure using a plastic sheet (***Fig*. 1**).

Pre-medication: Use benzodiazepine (midazolam 0.1-0.2 mg/kg) with opioid (fentanyl 2-3 µg/kg) combination for sedation and analgesia. Short acting neuromuscular blockers like rocuronium is preferred (if unavailable, use a higher dose of vecuronium or atracurium as per availability).

Pre-oxygenation: After a quick assessment for anatomically difficult airway, pre-oxygenation is carried out with non-rebreathing mask (NRM) or tight-fitting face mask attached to a self-inflating ambu-bag with 100% oxygen for 5 minutes. A hydrophobic viral filter between the mask and ambu-bag is recommended and some units cover the head, neck and chest with transparent plastic apron/sheet to prevent aerosol contamination (***Fig*.1**). Avoid bag and mask ventilation (BMV) to limit aerosol and if needed, use low tidal volume with lesser breaths.

Intubation: Cuffed endotracheal tubes (ETT) must be used in all ages and cuff needs to be inflated immediately following intubation. Disposable ventilator circuit with a viral filter attached at the expiratory limb (between circuit and machine) is used. Heat moisture exchanger (HME) is preferred for humidification. Ventilator should be in 'stand-by' mode and only to be turned on after connected to the patient. Prior to connecting to ventilator, the ETT can be clamped or attached to a viral filter. Closed suction (inline suction catheters) is preferred to prevent aerosol generation. If not available, open suction may be performed with aerosol precautions and after administering a dose of short acting neuromuscular blocking agent.

Invasive Mechanical Ventilation

Lung protective mechanical ventilation (MV) is recommended strategy for management of acute hypoxemic respiratory failure. SSC guidelines in adults recommend low tidal volume strategy (4-8mL/kg), limiting plateau pressures to <30 cmH_2O and using higher PEEP (>10 mm Hg) [17]. Permissive hypercapnia is well tolerated and may reduce volu-trauma. Viral filters should be utilized, and circuits should be maintained for as long as allowable (as opposed to routine changes) (***Table* III**).

Prone Ventilation

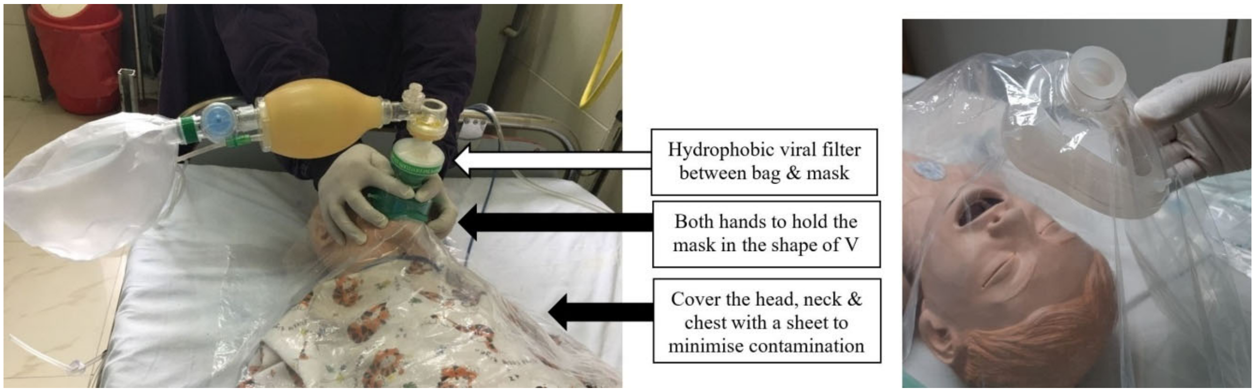
Prone ventilation is a recommended strategy in adults with PaO_2/FiO_2 <150 to improve lung mechanics and oxygenation.Patient is usually kept prone for12-16 hours. Prone ventilation can be ceased once $PaO_2/FiO_2$is > 150 for more than 4 hours in the supine position. However, in children and resource-limited setting, due to limited availability of HCWs and PPEs, it may not be possible to prone the child and may unnecessarily increase the risk of infection to the healthcare workers.

Fluid Management

To reduce pulmonary exudation and improve oxygenation, the fluid balance should be strictly controlled while ensuring adequate end-organ perfusion. Fluid restriction to 70-80% maintenance is necessary to prevent fluid overload.

Table II Intubation Trolley and Tray and Modifications for Use in COVID-19 Patients

Equipment (size appropriate)	*Specific for COVID-19 patients*
Laryngoscope with blade	Video laryngoscope is preferred to increase the distance between the health worker and patient
Endotracheal tube	Micro-cuffed and cuffed tubes to minimize aerosol as well as leak in acute respiratory distress syndrome (ARDS)
Suction catheter	Closed suction to minimize contact with secretion, aerosol release & de-recruitment
Hydrophobic viral filter	Used between the ambu bag and mask as well as in the ventilator circuitat the expiratory end
Oxygen & ventilation delivery devices	For pre-oxygenation, use non-rebreathing mask or a flow inflating device (Jackson Rees) Ensure adequate mask seal Avoid bagging if using self-inflating bag
Drugs – Sedo-analgesia & neuromuscular blockade	Use liberal sedation &neuromuscular blockade to avoid coughing and ultra-rapid sequence intubation
Adjuncts	Stylet, Bougie and second-generation laryngeal mask airway (LMA) devices readily available if initial plan fails



(*a*) (*b*)

Fig. 1 *(a) The assembly of bag, viral filter and mask along with plastic sheet to minimize aerosol; (b) Preparing the sheet with an opening for the mask.*

Fig 2A Fig 2B

Fig. 2 *(a) Video-laryngoscope assisted intubation; (b) shows a sheet covering the face and chest during intubation.*

Strategies to Prevent Ventilator-Associated Pneumonia (VAP)

VAP bundled strategies should be strictly implemented as per recommendations [27].

Weaning and Extubation

Once the patient's PaO_2/FiO_2 is more than 300 the neuromuscular blockade and sedatives must be weaned and discontinued. Extubation should be performed if the patient is considered ready for extubating to nasal O2 as post-extubation NIV is avoided where possible.Aerosol precautions are essential during extubation. Few units practice extubating using a plastic bag over the face with a tight seal after inflating with oxygen (***Fig.* 4**) or some units use a transparent large plastic sheet over the face and chest to capture droplets from coughing and suctioning. Post-extubation, the need for HFNC or NIV can be assessed while reducing monitoring.

Various professional bodies have given their recommendations for respiratory support in pediatrics and adult [8,15,17,28] and these are summarized in ***Table* IV**.

Table III Strategies in the Management of Acute Respiratory Distress Syndrome in COVID-19

Management similar to any ARDS	*Specific with respect to COVID*
Lung protective ventilation	Early invasive ventilation – avoid HFNC and NIV
Tidal volume 4-6 mL/kg	Avoid steroids – may prolong viral shedding
Limit Plateau pressure <28 cm H2O	Use liberal neuromuscular blockadeto prevent coughing
PEEP start with 7-10 and titrate to 15 cm H_2O	Proning involves risk of exposure to HCW and best avoided
Limit FiO_2<60% with permissive hypoxemia	Avoid nebulization
Avoid fluid overload (FO) - target FO <5%	
Sedo-analgesia titrated to sedation scores	
Early enteral nutrition – initiate within 24 hours and achieve full feeds by 48 hours	
Transfusion trigger hemoglobin<7 g/dL if stable hemodynamics and oxygenation	
Target hemoglobin 10g/dL in refractory hypoxemia or unstable shock	

NIV – non-invasive ventilation; HFNC – high flow nasal cannula; HCW-healthcare worker; PEEP – peak end-expiratory pressure.

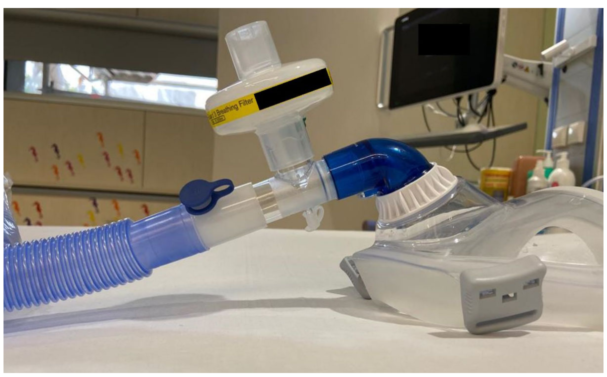


Fig. 3 *Use of expiratory filter in single limb NIV tubing (use a non-vented mask).*

Fig. 4 *Covering the face with a plastic bag or a sheet, to prevent aerosol spread during extubation.*

CONCLUSION

SARI is the most common presentation of COVID-19 and requires intensive care support. Low flow oxygen devices are preferred to high flow devices to prevent aerosol generation. Early intubation and mechanical ventilation are recommended to delay progression and need for emergent intubation, which poses significantly higher risk of transmission of infection to HCW. Use of HFNC and NIV is to be avoided routinely and if necessary, a full PPE with aerosol precautions is a must. Management of ARDS includes lung protective ventilation with liberal sedation-analgesia and avoidance of steroids.

Contributors: MS, NR, AB, KN: substantial contribution to the conception and design of the work, anddrafting the work; GVB, RL, DG, MPO, ARRN, MJ: substantial contributions to the acquisition and interpretation of data for the work,and revising it critically for important intellectual content.All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding: None; *Competing interest*: None stated.

Table IV Summary of Respiratory Support Guidelines for COVID-19 Patients

	WHO [7]	*SCCM [16]*	*PICS UK [27]*	*ANZICS [14]*
HFNO with precautions	+/–	+	+	+
NIV with precautions	+/–	+/–	+	–
Invasive ventilation	+	+	+	+

WHO – World health organization, SCCM – Surviving sepsis campaign, PICS UK – Pediatric intensive care society UK, ANZICS – Australian and New Zealand Intensive Care Society.

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