REVIEW ARTICLE

Feasibility of Pediatric Non-Invasive Respiratory Support in Low- and Middle-Income Countries

KRISHNA MOHAN GULLA, SUSHIL KUMAR KABRA, RAKESH LODHA

From Division of Pediatric Pulmonology and Intensive Care, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi.

Correspondence to: Dr Rakesh Lodha, Professor, Division of Pediatric Pulmonology and Intensive Care, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, Ansari Nagar, New Delhi,110 029. rakesh_lodha@hotmail.com

Non-Invasive respiratory support can be viewed as mechanical respiratory support without endotracheal intubation and it includes continuous positive airway pressure, bi-level positive airway pressure, high flow nasal cannula, and non-invasive positive pressure ventilation. Over past few years, non-invasive respiratory support is getting more popular across pediatric intensive care units for acute respiratory failure as well as for long-term ventilation support at home. It reduces the need for invasive mechanical ventilation, decreases the risk of nosocomial pneumonia as well as mortality in selected pediatric and adult population. Unfortunately, majority of available studies on non-invasive respiratory support have been conducted in high-income countries, which are different from low- and middle-income countries (LMICs) in terms of resources, manpower, and the disease profile. Hence, we need to consider disease profile, severity at hospital presentation, availability of age-appropriate equipment, ability of healthcare professionals to manage patients on non-invasive respiratory support, and cost-benefit ratio. In view of the relatively high cost of equipment, there is a need to innovate to develop indigenous kits/ devices with available resources in LMICs to reduce the cost and potentially benefit health system. In this review, we highlight the role of non-invasive respiratory support in different clinical conditions, practical problems encountered in LMICs setting, and few indigenous techniques to provide non-invasive respiratory support.

Keywords: *Continuous positive airway pressure, High flow nasal cannula, Low- and middle-income countries, Non-invasive ventilation*.

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Non-invasive respiratory support (NRS) is defined as delivery of respiratory support without use of an invasive artificial airway such as endotracheal or tracheostomy tube. It can be delivered using negative pressure or positive pressure. In negative pressure ventilation, pressure surrounding the chest wall is lowered to decrease intra-pleural pressure and thus, tidal volume is delivered to patient. Iron lung, which was used in polio epidemic six decades ago is an example of negative pressure ventilation [1]. In positive pressure non-invasive respiratory support, pressure is applied at the mouth and/or nose in spontaneously breathing patients. Continuous positive pressure ventilation (CPAP), Non-invasive positive pressure ventilation (NIPPV) and High flow nasal cannula (HFNC) are examples of positive pressure non-invasive respiratory support [2]. These modalities work by stabilizing chest wall, unloading of diaphragm and accessory muscles of respiration, increasing tidal volume/minute ventilation, maintaining functional residual capacity (FRC) to prevent atelectasis and maintaining patency of upper as well as lower airways [3]. These may also help to avoid complications associated with invasive ventilation such as infection, ventilator-induced lung injury, and airway edema [3]. Apart from supporting respiratory system, non-invasive respiratory support also supports cardiovascular system [4]. Non-invasive respiratory support reduces the need for invasive mechanical ventilation, especially in mild to moderate cases of acute respiratory distress syndrome (ARDS) and acute lung injury [5-7]. In LMICs, cost-effective indigenously developed CPAP systems have been shown to reduce mortality and referral to tertiary care neonatal intensive care units (ICUs) in term and preterm babies with respiratory distress syndrome [8-10]. Though pediatric critical care is well developed in high-income countries, it still remains in its early stage in most LMICs due to lack of well-equipped intensive care units, trained staff, rapid access to necessary medications and supplies. Complications and mortality from high burden diseases like severe pneumonia, severe malaria and diarrhea can be reduced by training healthcare providers, selecting resource-appropriate effective indigenous equipment and co-operation from governing bodies and industry [11]. This review is aimed to address few issues relevant to the LMIC settings.

Are children from LMICs with specific respiratory problems likely to benefit from non-invasive respiratory support?

NRS can be safely used in clinical conditions such as pneumonia, bronchiolitis, asthma exacerbation, post-

extubation airway problems, acute respiratory failure in immuno-compromised children, post-operative respiratory failure (cardiac as well as non-cardiac), neuromuscular weakness, and obstructive sleep apnea [2] (**Box I**). Non-invasive respiratory support in pediatric acute respiratory failure is associated with improvement in physiological parameters such as heart rate, respiratory rate, saturation and decreased need for invasive mechanical ventilation [12]. HFNC was associated with higher ventilation free days at day 28 in children with acute hypoxemic respiratory failure [5]. Few chart reviews and proceedings from the Pediatric Acute Lung Injury Consensus Conference suggest that NRS can be safely used in children with mild to moderate- acute respiratory distress syndrome [13-15]. A recent systematic review on bubble CPAP (bCPAP) and HFNC therapy in children (day 1 to 12 years) with severe pneumonia and hypoxemia in developing countries concluded that bCPAP may be effective and the use of HFNC therapy is very limited in LMICs [16]. Non-invasive respiratory support is also commonly used in critically ill children with congenital or acquired heart disease with respiratory distress and was found to decrease both intubation re-intubation rates [17-19]. Non-invasive respiratory support is being used as first line therapy to correct hypoxemia/hypercarbia in immunocompromised children, especially those with mild to moderate ARDS and stable hemodynamic status [20-22]. In the recent past, there has been a trend towards NRS use even in obstructive lung diseases such as status asthmaticus in children [23-25].

Non-invasive respiratory support also has a role to support respiratory system in children with neuro-muscular disease (NMD). In a prospective study, where children with NMD (Duchenne muscular dystrophy, spinal muscular atrophy, limb girdle muscular dystrophy, congenital myopathy) and acute respiratory failure were treated with combination of NRS and mechanical in-exsufflator during hospital stay, physiologic indices such as PaO_2, PCO_2, pH, and PaO_2/FiO_2 improved in all patients without any mortality; this highlights the role of NRS in NMDs [26]. NRS is also commonly used in children to prevent re-intubation during post-extubation period in high-risk patients [27-30]. Summary of studies on utility of non-invasive respiratory support in pediatric respiratory failure is shown in **Web Table I**.

A recent systematic review on non-invasive ventilation in children and adults in LMICs, mostly from South Asia included 10 pediatric studies (*N*=1099). Pneumonia, malaria and dengue shock syndrome were the most common conditions requiring NRS. CPAP and bubble CPAP were commonly used NRS modes. Pooled risk for mortality was 9.5% (95% CI 4.6-14.5) and NRS failure was seen in 10.5% (4.6-16.5). Success rates of non-invasive respiratory support ranged from 57 to 96% and were higher in patients with acute asthma compared to pneumonia. Pooled risk of facial skin sores and pneumothorax were 2.4% (95% CI 0.8-3.9) and 1.9% (95% CI 0.1-3.9), respectively [31]. Apart from knowing the conditions where NRS can be successful, it is also equally essential to know the conditions where it is likely to fail and is contraindicated. Non invasive respiratory support is likely to fail in conditions when mean airway pressure (MAP) >11.5 cm of H_2O, FiO_2> 0.6, there is less or minimal decrease in heart rate/respiratory rate after 1-2 hours of initiation, presence of other organ dysfunction, or presence of severe disease (high PRISM/ Pediatric logistic organ dysfunction scores) [32-35]. Absolute contraindications are respiratory arrest, facial trauma/burns, upper airway obstruction, comatose patients, intolerance, intestinal obstruction and Gullian Barré syndrome (GBS) with absent gag reflex. From the above discussion, we can say that common diseases in our settings such as pneumonia, dengue, malaria are likely to benefit from non-invasive respiratory support, particularly in areas where ICU facilities are limited/ not available. Complications related to NRS are: *Barotrauma:* can lead to tension pneumothorax, pneumomediastinum, or massive subcutaneous emphysema especially when the child is very agitated; *Aspiration:* may occur due to gastric distension and vomiting; *Skin break down:* facial skin irritation and ulceration are seen with nasal or oronasal masks; *Nasal mucosal trauma:* use of nasal masks or nasal prongs obstruct nostrils and may lead to epistaxis in case of inadequate humidification; *Gastric distension:* when inspiratory pressures exceed lower

Box I Indications of Non-Invasive Ventilation

Clinical conditions with pulmonary shunt
Pneumonia
Acute lung injury
Inhalational injury
Pulmonary edema
Difficult intubation
Restrictive lung diseases
Scoliosis
Chest wall restriction
Interstitial lung diseases
Hypoventilation
Weaning from anesthesia
Neuromuscular disorders like spinal muscular atrophy and Gullian Barré syndrome
Upper airway obstruction
Obstructive sleep apnea
Altered mental status
Upper airway edema
Chronic lung disorders with increase/retained secretions
Cystic fibrosis
Primary ciliary dyskinesia
Palliation therapy for respiratory support

esophageal sphincter pressure (normally 10 mmHg) or when the patient swallows air (eg, during crying), it leads to gastric distension; *Eye irritation or injury:* ocular trauma, primarily corneal abrasion or ulceration, can occur if the edge of the mask is in contact with the eye surface. A flow chart on initiation and monitoring of NRS is shown in **Fig.1**.

Whether suitable indigenous equipment for providing non-invasive respiratory support are available? If not, is there a need to modify existing imported design of NRS machines for their use in LMICs?

Components required for NRS are interface, ventilator/ equipment and humidifier. Interfaces include nasal pillow, nasal cannula, oro-nasal mask, full-face mask, helmet (**Fig. 2**). In LMICs, availability and cost of interfaces are major hurdles to provide non-invasive respiratory support even in eligible children. Children with severe wasting usually have less buccal pad of fat, making fit of masks difficult. Another important equipment for non-invasive respiratory support is ventilator/specific equipment. Classical ICU ventilators or transport ventilators provide poor leak compensation and need separate air and oxygen source. Ventilators which are designed specifically for non-invasive ventilation are usually portable, do not need separate air source and compensate well for air leak. However, the machines available in the market deliver minimum tidal volume of 100-150 mL which is much higher than tidal volume of infants and small children. Another important issue to consider is the cost of equipment. In authors' experience, cost of portable ventilators used for home ventilation in infants and children is approximately INR 400 000- 500 000 (USD 5700-7200) apart from costs of the interface (e.g., mask), ventilator circuit tubing, humidifier, etc.; these costs may not be affordable by most families in a LMIC. Few BiPAP ventilator machines, which are designed for obstructive sleep apnea in adult population are available at somewhat lower costs, may be used in older children and adolescents. However, these machines have inherent problems like inability to titrate FiO_2, lack of adequate battery backup, high inspiratory time, ineffective humidification, etc. For a PICU in a LMIC offering invasive mechanical ventilation, it may be desirable to have non-invasive modes in the same mechanical ventilator. In addition, low cost HFNC and bubble CPAP equipment may

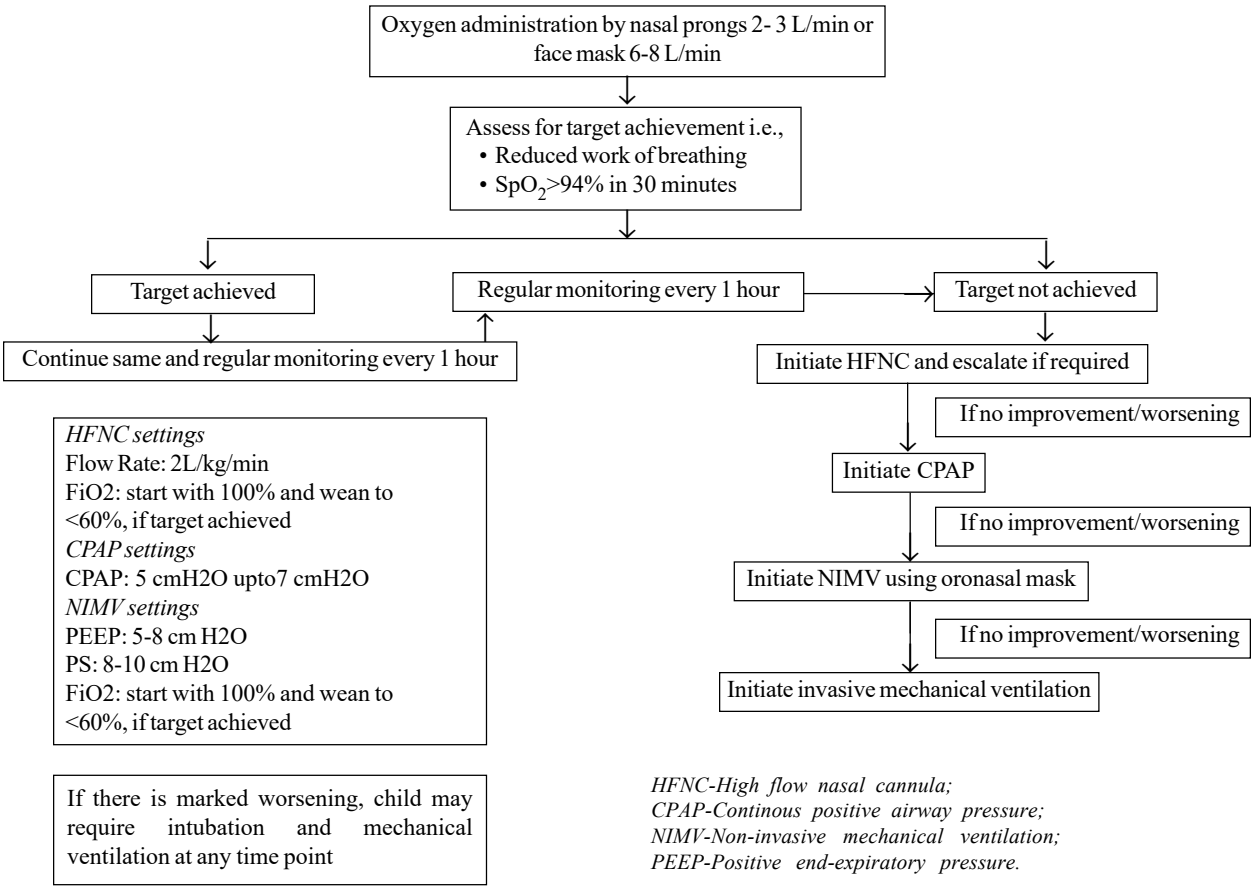

Fig.1 Flow chart of initiation and monitoring of non-invasive respiratory supprt.

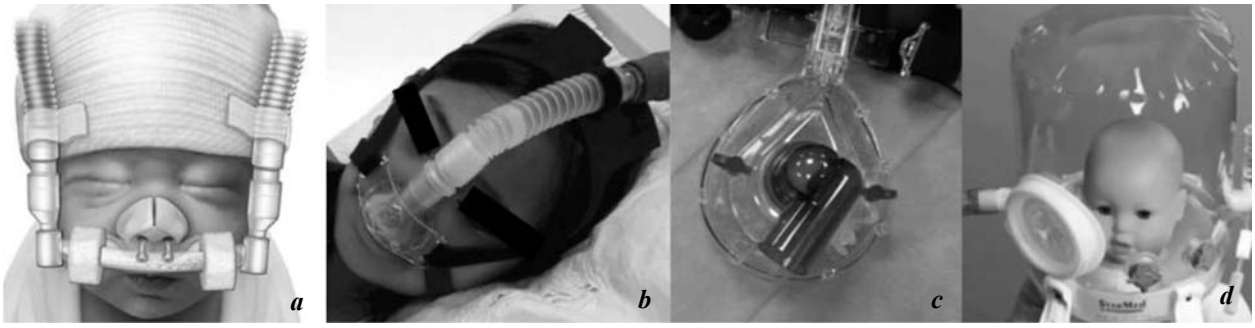

Fig. 2 Interfaces used for NIV (a-nasal cannula; b- nasal pillow; c- oronasal mask; d-helmet).

also be added. For units which do not have mechanical ventilators or inadequate numbers of ventilators, stand-alone low-cost HFNC and bubble CPAP equipment should be considered for installation.

Is there a need to have innovations in providing non-invasive respiratory support in LMICs?

In LMICs, in order to overcome the costs/availability issues, we may prepare indigenous equipment/devices to deliver NRS. Indigenously made CPAP equipment, bubble CPAP, have been used successfully in Indian PICUs. In a retrospective study from India, 60 children with acute hypoxic respiratory failure due to swine flu were treated with indigenous nasal bubble CPAP (NB-CPAP) (**Fig. 3**), which provided expiratory positive airway pressure of 5 cm H_2O and delivered FiO_2 of around 70%. All patients tolerated CPAP and none required endotracheal intubation [36].

In another study from India, indigenous CPAP was provided through flow inflating device-Jackson-Rees circuit (JR)/Bain circuit and using face mask as interface (**Fig. 4**). This study included 214 children and CPAP through flow inflating device was successful in 89.7% of cases, of which bronchiolitis accounted for 98.3%. A prolonged duration of CPAP support of >96 h was required in pneumonia. CPAP failure was noted in 10.3% of cases, the major risk factors being children <1 year and pneumonia with septic shock [37]. Jayashree, et al. [38] enrolled 330 children aged 1 month-12 years, with clinical pneumonia to bCPAP group (delivered via an underwater 'T' tube through nasal prongs) and nasal prongs group, and found that nasal CPAP is safe and effective. Indigenous HFNC circuit can also be prepared by using O_2/O_2-air mixture (blender) source, servo-control humidifier (heated wire humidifier), corrugated tubing and nasal prongs (**Fig. 5**). A blender can used to regulate FiO_2. One has to be innovative to assemble locally available equipment in their hospitals to prepare indigenous non-invasive ventilation equipment. However, one has to remember that quality of indigenous equipment for NRS needs to be assessed by treating physician.

Training healthcare professionals to provide non-invasive respiratory support

Training of health care personnel (doctors, nursing staff, technicians) is equally important for successful outcome of non-invasive ventilation in intensive care. An important aspect of training is to choose right patient at right time for initiation. Apart from initiation, other important aspect is to closely monitor and identify early failure within 1-2 hours of initiation and step up the respiratory support in a timely fashion to improve outcome. In LMICs, where the nursing staff to patient ratio is often inadequate, early identi-fication of failure poses an important challenge. The intensity/ frequency of monitoring may actually be greater for a child undergoing non-invasive ventilation than invasive

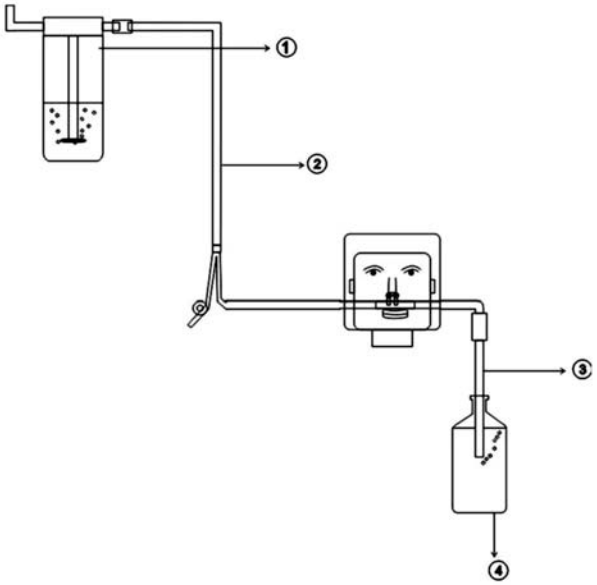

Fig. 3 Assembly of indigenous CPAP.
1- Oxygen supply through flow meter; 2- Nasal cannula; 3- Intravenous tubing cut and one end is attached to nasal cannula and other end is inserted in normal saline bottle to exert CPAP;4- Normal saline bottle showing bubbles during exhalation.

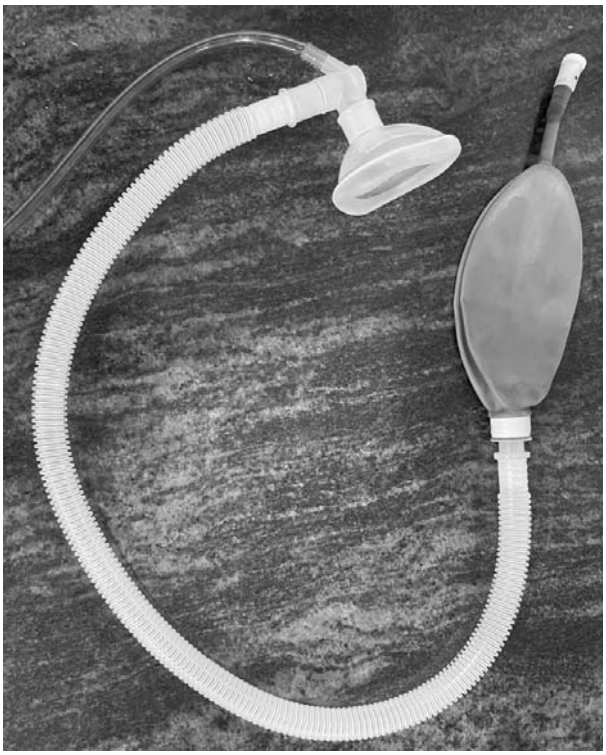

Fig. 4 Flow inflating bag used for providing continuous positive airway pressure.

ventilation. So, having adequately trained man-power is critical for safe application of non-invasive respiratory support in critically ill children.

Will non-invasive respiratory support be cost beneficial in these countries?

A study from India [9] evaluated the cost effectiveness of locally assembled low-cost CPAP system in neonates with respiratory distress, and found that neonatal mortality could be reduced using this CPAP system with cost of only 160 INR per one CPAP system.

In another study from Malawi [8], low-cost bubble CPAP system was used to treat neonatal respiratory distress and led to 27% absolute improvement in the survival when compared to standard care. A study on adults in India did cost-effective analysis of ward-based non-invasive respiratory support plus standard treatment with standard treatment alone in chronic obstructive pulmonary disease (COPD) with respiratory failure and found that ward-based NRS treatment increased the survival of patients with COPD respiratory failure, when ICU is not available, at a lesser cost [39]. Thus, non-invasive respiratory support in LMICs is not only cost-effective but also improves the outcome of patients requiring respiratory support.

Although India has now become a global market for many biomedical equipment and established itself as competitor for multinational counter parts, unfortunately hardly any of the NRS equipment or their parts are manufactured in India. So, there is an urgent need for establishing highly effective physician-engineer-industry collaborations for manufacturing cost effective, high quality non-invasive equipment as good as their multi-national counter parts. Often there are concerns about the quality of indigenous equipment; there has to be enough efforts put in by the manufacturers to ensure a certain level of quality of products, particularly for the safety features.

In developing countries, a child is likely to suffer around 0.3 episodes of pneumonia/year, and in developed countries it is 0.03 episodes per child/year [40]. Based on this, India is

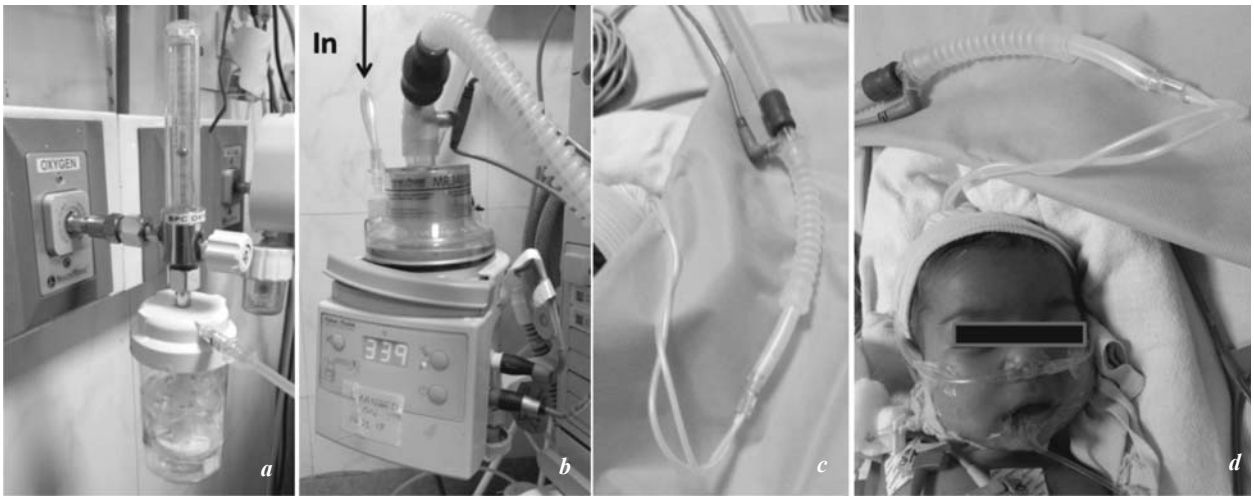

Fig. 5 Indigenous high flow nasal cannula; *a*) Oxygen source and flow meter; *b*) Servo humidifier; *c*) connection of nasal prongs to corrugated tubing from humidifier; *d*) Nasal prongs placed in nasal cavity and should be of appropriate size to allow leak.

predicted to have about 700 million episodes of acute respiratory tract infections and about 52 million episodes of pneumonia every year [41]. For example, Broor, et al. [42] had reported 43 episodes, 536 episodes, and 2387 episodes of severe acute lower respiratory infections, acute lower respiratory infections and acute upper respiratory infections, respectively per 1000 child years from northern India. This shows that majority of children with acute respiratory tract infection need home based care or isolation, few children may need hospital care and very few of them need either high dependency unit (HDU) care or ICU care. Hence, there is a need to invest more in development and procurement of devices providing simple oxygen therapy or non-invasive respiratory support as most children with acute lower respiratory tract infection can be managed with them if intervened early and invasive ventilation is needed only in few. A pyramid depicting burden of respiratory illness and requirement of respiratory support has been shown in **Fig. 5**. Hence, in contrast to the usual tendency of clinicians and hospital administrations for having more high-cost equipment for invasive mechanical ventilation, there is a need to invest in procuring more of non-invasive respiratory support systems for possibly a better cost-effective solution in LMICs.

Role of non-invasive respiratory support in COVID-19 pandemic

Children of any age can be infected with COVID-19, but the severity seems to be less than that in adult population. In a systematic review, children accounted for 1-5% of total diagnosed COVID-19 cases [43]. As of April 2, 2020, among the 1,49,760 laboratory-confirmed cases reported to the US CDC (United States Centers for Disease Control and Prevention), children of less than 18 years constituted only 1.7% (*N*=2572) [44]. Among these children, 147 (range 5.7%-20%) were reported to be hospitalized, with 15 (range 0.58%-2.0%) admitted to ICU.

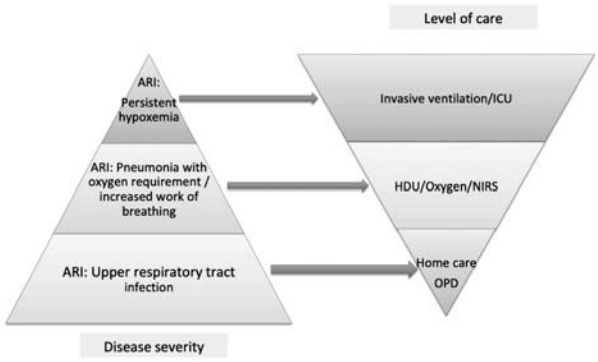

Fig. 4 Depiction of disease severity with level of care provided. *ARI-acute respiratory infection; HDU-High dependency unit*; *ICU-Intensive care unit; NRS-Non invasive respiratory support*.

In another report from China [45], out of 728 laboratory confirmed cases in children, 21 (2.9%) were either severe or critically ill. Children with severe/critical disease need respiratory support. When the respiratory status worsens in patients with non-COVID pneumonia, physicians use non-invasive ventilation without hesitation provided clinically appropriate. However, when noninvasive venti-lation is considered in patients with COVID pneumonia, there are concerns about aerosol generation, which may cause contamination of ICU environment and staff. There is an ongoing debate on whether to use HFNC/NIV in patients with COVID pneumonia [46]. Appropriately fitted interfaces in HFNC/NIV may restrict direct release of air during expiration into the environment. However, in our set-up, limited availability of appropriate-sized interfaces for children, lack of negative pressure isolation rooms in all health care facilities and limited availability of high quality personal protective equipment to health care workers make pediatric intensivists not to use HFNC/non-invasive respiratory support in this scenario. Despite the apprehension associated with use of these modalities, 137 out of 1287 ICU admitted patients (11% [95% CI, 9%-12%]), were treated with non-invasive ventilation in Italy [47]. In a report from China, 61 out of 84 patients with COVID-19 ARDS received non-invasive ventilation [48]. However, there are no data describing whether these modalities were successful at avoiding intubation. Hence, the decision to initiate HFNC or NIV in COVID-19 patients should be taken by balancing the risks and benefits to the patient, the risk of exposure to healthcare workers, and availability of resources.

Monitoring on HFNC/NIV: If HFNC or NIV is adminis-tered, vigilant monitoring with frequent clinical (respiratory rates, retractions, cyanosis, sensorium) and arterial blood gas evaluation every one to two hours is needed to ensure efficacy and safety. Some physicians try HFNC/NIV while the patient is in the prone position, though there is no evidence for the same.

Precautions: Airborne precautions should be undertaken. While using HFNC, additional surgical mask can be placed on the patient face and lowest effective flow rate should be used. When NIV is initiated, a full-face mask rather than a nasal or oronasal mask is preferred to minimize particle dispersion. The mask should have a good seal and should not have an exit valve. For older ch ildren, helmet can be used as an interface. Dual limb circuit with a viral filter on the expiratory limb on routine ICU ventilator is preferred compared to single limb circuit on portable BIPAP machines. It is preferable to titrate ventilator setting to lowest effective pressures (e.g., 5-10 cm H_2O). Innovations are also being tried using a constant flow canopy over the upper part of the patient bed, thus building a restricted area around the patient where non-invasive respiratory support can be safely used.

KEY MESSAGES

- Noninvasive respiratory support is feasible in LMICs
- Clinician-industry-government collaboration is needed to design indigenous devices
- Studies on comparing indigenous devices with standard non-invasive respiratory support machines/ devices with respect to clinical outcomes are needed
- High quality of indigenous devices needs to be ensured
- Close clinical monitoring is the key for success of non-invasive respiratory support

This canopy system consists of flexible plastic canopy that covers the upper part of the body, fan filtering unit (FFU) using high efficiency particulate air (HEPA) filters and an exhaust system creating negative pressure and transferring the filtered air out to the open atmosphere [48].

India has diverse health facilities and facilities should have its own guideline whether to provide NRS to patients with COVID-19 pneumonia depending on availability of appropriate interfaces, personal protective equipment, negative pressure rooms, adequate staffing, etc. We need to strike a balance between benefit to the patient and risk to health care workers while providing NRS.

CONCLUSION

Greater use of indigenous non-invasive respiratory support equipment, adequate training of healthcare providers to use and monitor and commitment from hospital administration are important steps to improve outcomes of children in LMICs. Though HFNC is a promising therapy, it has not been adequately studied in LMICs and requires further studies prior to its widespread use. Cost-effective evaluation including assessment of optimal professional staffing levels should be addressed in future studies of non-invasive respiratory therapies in LMICs. To fill up the existing huge demand supply gap of non-invasive ventilation equipment, there is a need to develop high quality, locally manufactured, affordable non-invasive respiratory support equipment by facilitating partnership between governing agencies and industry.

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