REVIEW ARTICLE

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

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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

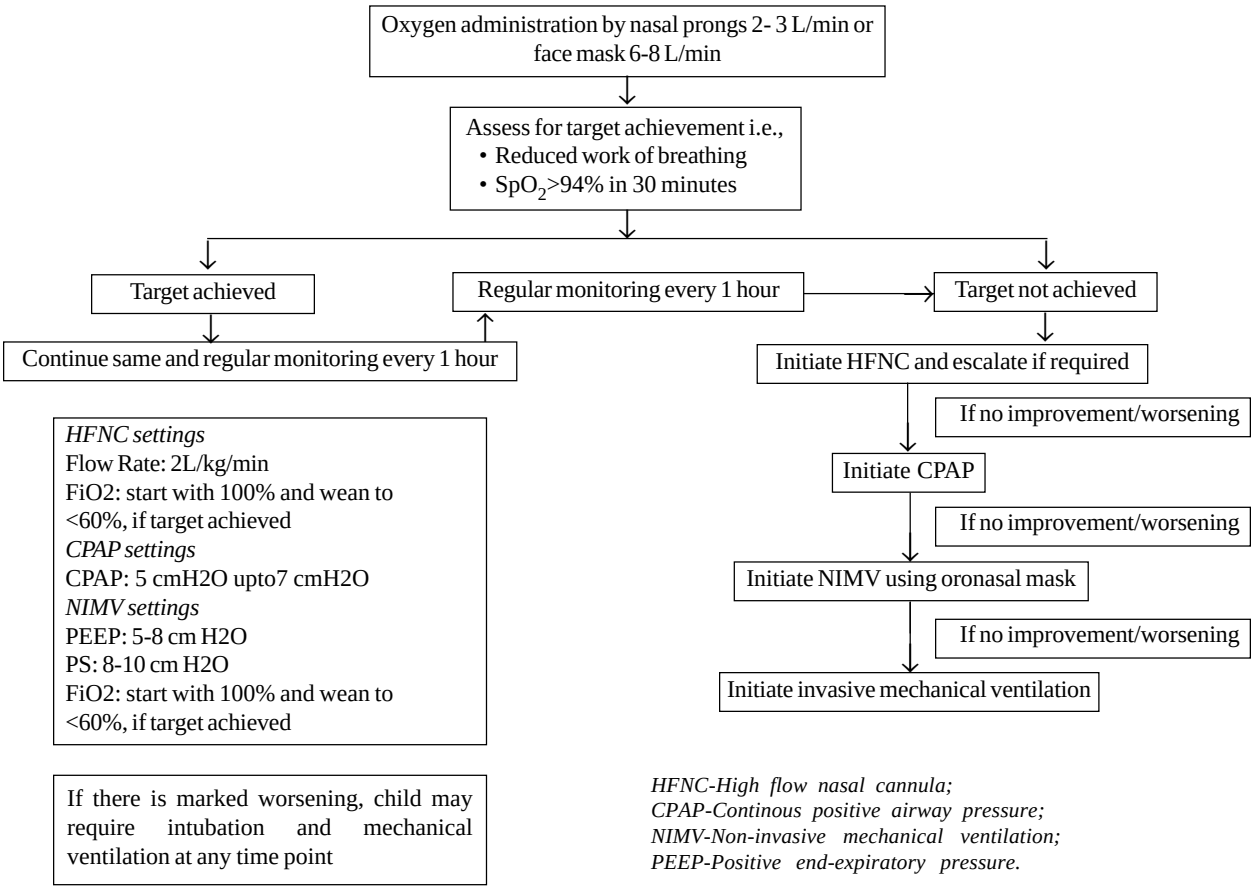

Fig.1 Flow chart of initiation and monitoring of non-invasive respiratory supprt.

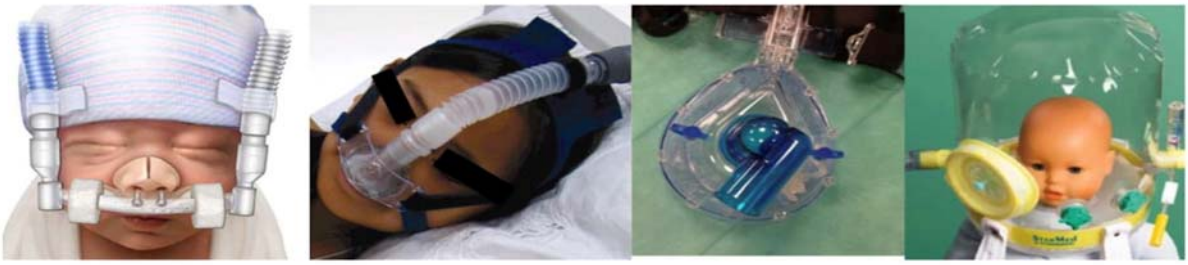

Fig. 2 Interfaces used for NIV (a-nasal cannula; b- nasal pillow; c- oronasal mask; d-helmet).

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

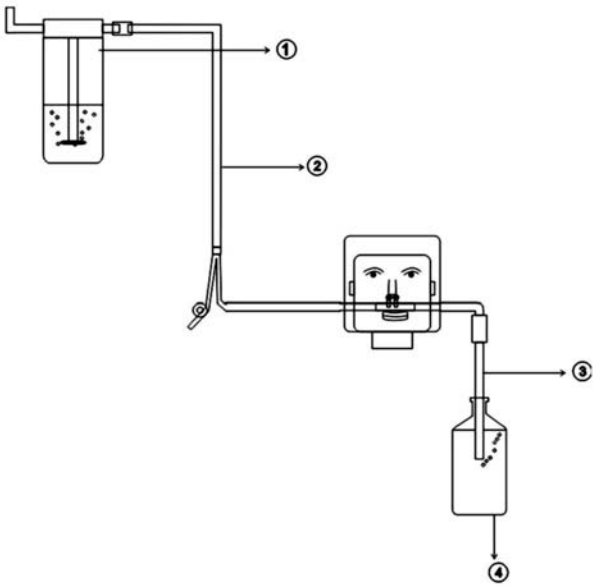

Fig. 3 Assembly of indigenous CPAP.
1- Oxygen supply through flow meter; 2- Nasal cannula; 3- Intravenous tubing cut and one end is attached to nasal cannula and other end is inserted in normal saline bottle to exert CPAP;4- Normal saline bottle showing bubbles during exhalation.

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

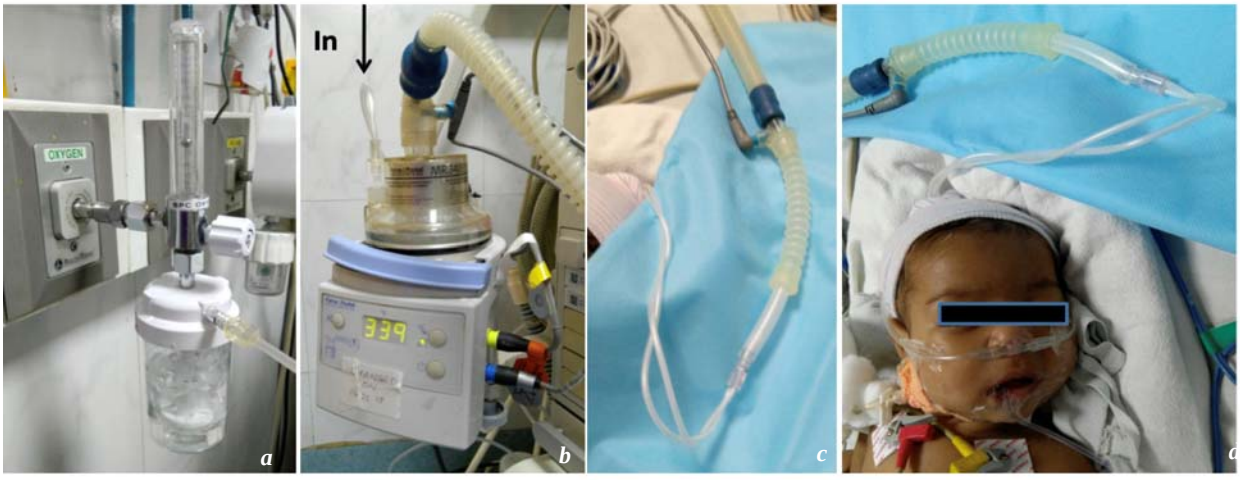

Fig. 5 Indigenous high flow nasal cannula; *a*) Oxygen source and flow meter; *b*) Servo humidifier; *c*) connection of nasal prongs to corrugated tubing from humidifier; *d*) Nasal prongs placed in nasal cavity and should be of appropriate size to allow leak.

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.

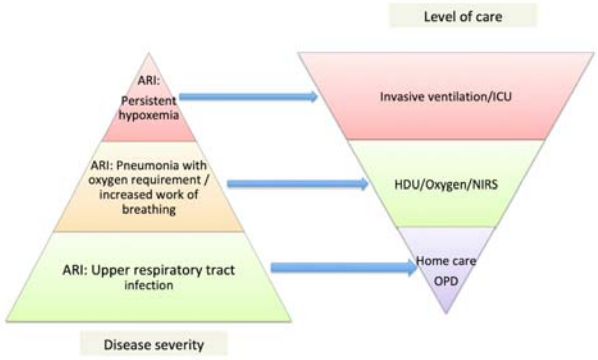

Fig. 4 Depiction of disease severity with level of care provided. *ARI-acute respiratory infection; HDU-High dependency unit; ICU-Intensive care unit; NRS-Non invasive respiratory support.*

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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Web Table I Summary of Various Studies on Use of Non Invasive Respiratory Support in Children

Author, year	Population	Methodology	Intervention	Objectives/Outcome variables	Results	Conclusion
Yanez et al., 2008 (12) (N=50)	1month -15 years Children with respiratory failure based on FiO2 requirement >50% to maintain SPO2 >94%, with moderate to severe respiratory distress	RCT Study group (N=25): NIV plus standard therapy Control group(N=25): Standard therapy	Study group received inspiratory pressure:12-18 cm H2O expiratory positive airway pressure 6- 12 cm H2O Control group: mask oxygen at FIO2 >50% to keep saturation at >94%	Primary outcome: Need to intubate, Secondary outcome: improvement in vital signs and gas exchange for 48 hrs	Intubation rate was significantly lower in study group (28% vs 60%,p=0.045) Heart rate and respiratory rate were significantly lower after 1 hr of treatment compared with admission in study group.	NIV improves hypoxemia, signs and symptoms of acute respiratory failure and also prevents endotracheal intubation
Fortenberry et al, 1995 (13) (N=28)	Children <18 years with signs of respiratory distress who are likely to get intubated or re-intubated	Retrospective	All children received BiPAP through nasal mask		Respiratory rate decreased significantly with BiPAP(45±18 breaths per minute to 33±11, p<0.001). PaO2 improved (71±13 mm Hg to 115±55), PaCO2, pulse oximetry saturation, and pH all improved significantly (p<0.01) Only 3 of 28 patients required intubation or re-intubation.	Non-invasive nasal positive pressure mask ventilation can be safely and effectively used in pediatric patients to improve oxygenation in mild to moderate hypoxemic respiratory insufficiency and it also avoids reintubation.
Essouri et al.,2006 (14) (N=114)	Children treated by Non invasive positive pressure ventilation(NPPV) over five consecutive years in PICU	Retrospective	Nasal or facial masks were used with dual limb circuit Mode used: Pressure support with positive end expiratory pressure	Failure of NPPV defined by the necessity of endotracheal intubation during the PICU stay	77% were successfully treated by NPPV without intubation The success rate of NPPV was significantly lower (22%) in patients with acute respiratory distress syndrome (p< 0.05) high PRISM II and PELODS at admission were associated with unsuccessful NPPV 9.6% who received NPPV died	NPPV could be proposed as a first-line treatment in children with acute respiratory distress, except in those with a diagnosis of acute respiratory distress syndrome.
Essouri et al., 2015 (15)	Children(1month – 18 years) with acute respiratory distress syndrome(ARDS)	Systematic review on non invasive ventilation in children with ARDS			NPPV can improve gas exchange and potentially prevent intubation and mechanical ventilation in some children with mild pARDS NPPV is not indicated in severe pARDS An oronasal interface provides superior support, The efficacy of high-flow nasal cannula compared with noninvasive positive pressure ventilation is unknown	NPPV can be beneficial in children with pediatric acute respiratory distress syndrome, particularly in those with milder disease.

Gupta P et al., 2012 (17)	Children between the ages 1 day and 18 years with acute respiratory failure who required NIV in a cardiovascular intensive care unit (CVICU)	Retrospective	Prophylactic group: NIV was given directly after extubation Non- prophylactic group: NIV was given after signs and symptoms of respiratory failure developed. Modes of NIV used were CPAP and BiPAP. CPAP or EPAP was initiated with 4–5 cm H2O for all and maximum of 10–12 cm H2O IPAP was initiated at 6–8 cm H2O and maximum of 18–20cm H2O was given	To identify the predictors of NIV success in preventing extubation failure in critically ill children with heart disease. To assess the efficacy of prophylactic NIV therapy To determine the characteristics, outcomes, and complications associated with NIV therapy in pediatric cardiac patients	221 events were included 172 responders (77.8 %) and 49 non-responders (22.2 %) were noted 201 events received CPAP with 156(78%) responders, 20 events received BiPAP with 16(80%) responders 58 events (26.3 %) were assigned to the prophylactic group and 163 events (73.7 %) to the nonprophylactic group. The prophylactic group experienced significantly shorter CVICU stay (median, 49 vs 88 days; p = 0.03) and hospital stay (median, 60 vs 103 days; p = 0.05)	NIV can be safely and successfully applied in critically ill children with cardiac disease to prevent extubation failure
Fernandez, et al.,2016 (18) (N=200)	Children 3days – 16 years age requiring NIV after heart surgery in a PICU over 12 years	Retrospective observational study comparing the first 6 years of the study with the last 6 years.	Physician driven use of NIV (CPAP/BiPAP)		Duration of NIV was 3 days (median) Mortality rate was 3.9%. The use of NIV was increased from 13.2% in first 6 years to 29.2% in the second 6 years (p <0.001). CPAP was the most common modality of NIV (65.5%). The use of BiPAP increased from 15% in first 6 years 42.9% in the second 6 years period (p < 0.001) NIV failed in 15% of patients. The mortality rate did not change between the two periods	NIV is increasingly being used in the postoperative period of heart surgery It is associated with a lesser need for invasive mechanical ventilation CPAP was the most common modality and in the in the latter years, the use of BIPAP has increased significantly
Kovacikova L et al, 2013 (19) (N=82)	Children 1day – 18 years age with congenital heart disease (post operative)	Prospective observational study	NPPV with pressure support and/or pressure control mode was applied Median PEEP used 10 cm H2O (4–12) Median maximum IPAP used was 21 cm H2O (10–28) Interfaces used were Naso-pharyngeal tube, Oro-nasal mask, or helmet	NPPV was used (1) in patients with hypoxemic or hypercarbic respiratory failure or those who were likely to require intubation based on clinical signs; (2) as a preventive measure in patients with high risk for extubation failure	Within the first hour of NPPV, partial pressure PaO2/FiO2 was increased, and pCO2, RRwere decreased. In 59.8 % of cases, NPPV prevented tracheal intubation The Aristotle Basic Complexity score, presence of infection, residual cardiac defect, and pH <7.36 in the first hour were independent predictors of NPPV failure	NPPV improved oxy-genation and decreased respiratory effort in pediatric cardiac patients, A high-complexity surgical score, presence of infection, residual cardiac defect, and pH <7.36 in the first hour are predictors of NPPV failure
Pancera CF et al. 2008 (20) (N =239)	Immunocompromised children with acute respiratory failure	Retrospective Two groups 1.NIVgroup(N=120), defined as children who received NPPV as the first choice for at least 24 hours 2. Invasive	The NIV mode used was pressure support with positive end-expiratory pressure. Nasal mask was used Decision to initiate NIV was by the	To evaluate the feasibility of NPPV in PICU To assess the clinical efficacy of NPPV To identify predictive factors	1/4thof the patients from the NIV group subsequently required intubation. Independent predictive factors for intubation were solid tumors cardiovascular dysfunction and	NIV can be used as first- line treatment in children with malignancies who develop acute respiratory failure, except those with severe hemodynamic compromise

		ventilation group(N=119) defined as children who received conventional MV as the first choice	physician	for endotracheal intubation	therapeutic intervention scoring system score (TISS) >40 points	
Piastra et al., 2009 (22) (N=23)	Immunocompromised children with acute respiratory distress syndrome (ARDS)	Retrospective	Mode: pressure support mode or pressure controlled Interface: face mask/helmet	To evaluate the feasibility of non-invasive ventilation (NIV) in immunocompromised children with ARDS	Early and sustained improvement in P/F ratio were observed in 82 and 74% of cases, respectively. 13 out of 23 (54.5%) avoided intubation and were discharged from the PICU PICU and intra-hospital mortality was higher for NIV-non responders (p <0.001) PICU stay was shorter for NIV responders (p = 0.03).	NIV administration is feasible and well tolerated in immunocompromised children with ARDS. A short NIV trial can be used to verify the usefulness of the technique.
Basnet et al., 2012, (23) (N=20)	Children age 1-18 years admitted to PICU with status asthmaticus with a clinical asthma score 3-8 after receiving one dose of methylprednisolone, 1 hr of continuous albuterol (SABA), and three doses of ipratropium bromide	RCT NPPV plus standard treatment versus standard treatment alone	BiPAP mode with face mask/nasal mask was used Inspiratory positive airway pressure was gradually increased to 8 cm H2O to achieve a tidal volume of 6–9 mL/kg and end-expiratory positive airway pressure to 5 cm H2O	Improvement in the clinical asthma scores	Improvement in clinical asthma score was significantly greater in non invasive positive pressure ventilation group compared to standard group at 2 hrs, 4–8 hrs, 12–16 hrs, and 24 hrs after initiation of interventions (p<0.01). There were no major adverse events related to NPPV. 9 out of 10 patients tolerated NPPV through the duration of the study	Early initiation of non invasive positive pressure ventilation, along with short acting β-agonists and systemic steroids, can be safe, well-tolerated, and effective in the management of children with status asthmaticus
Thill et al., 2004 (24) (N=20)	Children admitted to the pediatric intensive care unit with acute lower airway obstruction	RCT, cross over	Group 1: 2 hrs of NIV followed by crossover to 2 hrs of standard therapy Group 2: 2 hrs of standard therapy followed by 2 hrs of NIV BiPAP was used using nasal mask IPAP of 10 cm H2O and an EPAP 5 cm H2O, were used	Improvement in clinical asthma severity (CAS) score	Non invasive ventilation decreased signs of work of breathing compared with standard therapy There was no serious morbidity associated with noninvasive ventilation.	Non invasive ventilation can be an effective treatment for children with acute lower airway obstruction
Pilar et al., 2017 (25) (N=42)	Children (1.5 – 14 years) with acute severe asthma admitted to PICU	Retrospective Patients were given high flow nasal cannula (HFNC) or non invasive ventilation (NIV) as per physician discretion	For NIV, BiPAP mode was used with full face masks or oronasal masks as interface IPAP of 8 cmH2 O and EPAP of 4 cmH2O were used to achieve a tidal volume of 6-9 ml/kg. IPAP and EPAP were titrated based on tidal volume, saturation and clinical signs For HFNC, flow rates: 2 L/kg/min for the first 10 kg plus 0.5 L/kg/min for each kg above that (maximum	Primary outcome measure was failure of initial respiratory support (need to escalate from HFNC to NIV or from NIV to invasive ventilation). Secondary outcome measures were the duration of respiratory support and PICU length of stay (LOS)	22 received NIV 20 received HFNC The mean EPAP was 5cmH2O (4-7) and the mean IPAP was 12cmH2O (8-17) No treatment failure in NIV group 8 children (40%) in the HFNC group required escalation to NIV. The PICU length of stay was similar in both the groups. HFNC failure subgroup had longer respiratory support duration and longer PICU stay compared to HFNC success subgroup.	Early initiation of NIV is a safe and feasible initial alternative for the treatment of severe asthma exacerbation. HFNC could potentially delay the initiation of NIV in severe cases and result in longer PICU stay, and the consequent morbidity and cost

			flow 50 L/min)			
Fioretto et al., 2015 (27) (N=108)	Children aged 1month to 3 years who were intubated and mechanically ventilated for 48 hours	RCT	NIV group(N=55): NIV was provided using conventional ventilator with PC-SIMC-PS mode. Initial PEEP of 5 cm H2O, IPAP of 15 cm H2O, PS of 10 cm H2O, and FiO2 of 50% Maximum PEEP of 10cmH2O Maximum IPAP of 20cmH2O and maximum PS of 15cm H2O were used A nasal or facial mask was used as interface. Standard group (N=53): Oxygen by nasal cannula		Reintubation rates in NIV group was 9.1% and in standard group was 11.3%(p=>0.05) No difference in length of PICU stay or hospital stay	No differences were seen between groups. The number of excluded patients was high
Juan P. Bonora et al., 2018 (29) (N=255)	Children aged 1 month to 18 years old who required post extubation NIV	Retrospective multicenter Rescue NIV (N=112): implementation of NIV within 48 hours of extubation due to respiratory failure Elective NIV (N=143): implementation of NIV prophylactically after extubation	NIV modes included pressure support ventilation, pressure-assist/control ventilation, bi-level pressure support, continuous positive airway pressure	To determine the rate of post-extubation NIV success and the factors associated with failure or success	The rates of success in rescue and elective NIV were 68.8% and 72.7%, respectively Mortality was higher among patients in whom rescue NIV failed	The use of post-extubation NIV may be a useful to prevent re-intubation
Mayordomo-Colunga J et al., 2010 (30)	Children admitted to PICU who had invasive ventilation for at least 12 hours and then extubated	Prospective observational study Types of NIV elective NIV: when the patient was extubated directly to NIV rescue NIV: when the child developed respiratory failure within 48 hours ofextubation	BiPAP was used Nasal mask, facial mask/helmet were used as interface In elective NIV, EPAP was set at 1-2 cmH2O higher than previous PEEP during invasive ventilation. In rescue NIV, initial EPAP was 4-5 cmH2O IPAP was started at 6-8 cmH2O in both	To determine post-extubationNIVcharacteristics and to identify risk factors of postextubation NIV failure.	rescue and elective NIV had success rate of 50% 81% respectively(p = 0.037).	Post-extubation NIV seems to be useful in avoiding reintubation when applied immediately after extubation