Twagirumugabe *et al. Critical Care* (2025) 29:492
https://doi.org/10.1186/s13054-025-05688-x

Critical Care

REVIEW Open Access

Advanced non-invasive respiratory support in resource-constrained settings: a narrative review

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Abstract

Advanced non-invasive respiratory support techniques include high flow oxygen, continuous positive airway pressure, and non-invasive ventilation. Given their relative simplicity and lower resource intensity as compared with invasive mechanical ventilation, these mechanisms of respiratory support represent an attractive opportunity for use in patients with acute respiratory failure in resource-constrained settings. High flow oxygen in particular has the potential to provide high levels of respiratory support with relatively low levels of human and other resources to a wide variety of patients with respiratory failure, including those with delirium or obtundation. Even after the COVID-19 pandemic, during which utilization of these techniques increased in high-income countries, low and lower-middle income countries still have little access to advanced non-invasive respiratory support. Evidence from high-income countries and limited evidence from low-income countries suggest that these respiratory support methods may be particularly beneficial in resource-constrained settings; however, the evidence also suggests that the populations chosen and particularly the attention and resources invested in implementation are critical in ensuring the safety and effectiveness of non-invasive support. While non-invasive respiratory support does not require the complex training and monitoring needed for invasive support (e.g. specific risks associated with the endotracheal tube, sequelae of sedation, complex ventilator modes), it nonetheless requires resources in order to be applied effectively. Particular domains that need careful consideration are: clinical systems of care; oxygen consumption and connector compatibilities; human resources and training; location within the hospital; acceptability; cost; and device characteristics. In addition, ongoing research is needed that includes randomized controlled trials with attention to context, so that clinicians in resource-constrained settings can apply relevant evidence for non-invasive respiratory support for patients in their settings.

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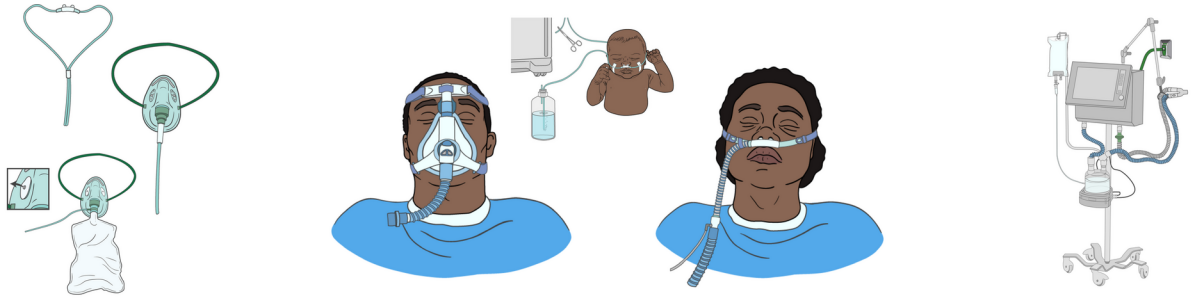

Standard flow oxygen
- Nasal cannula
- Facemask
- Non-rebreather facemask

Advanced non-invasive respiratory support
- **CPAP / bubble CPAP / NIV**
- **High flow oxygen**

Invasive mechanical ventilation

Key considerations for the implementation of advanced non-invasive respiratory support in resource-constrained settings:
- clinical systems of care
- oxygen consumption and connector compatibilities
- human resources and training
- location within the hospital
- acceptability
- cost
- device characteristics

Fig. 1 Methods of respiratory support, with a focus on advanced non-invasive respiratory support in resource-constrained settings. Images by OpenCriticalCare.org, Creative Commons SA-NC

Introduction

Patients with acute respiratory insufficiency can be supported with measures along a continuum of options including standard flow oxygen (SFO) via nasal cannula, facemask, or non-rebreather facemask; advanced non-invasive respiratory support; and invasive mechanical ventilation (IMV) (Fig. 1). Systems of advanced non-invasive respiratory support, which include high flow oxygen (HFO), continuous positive airway pressure (CPAP), and non-invasive ventilation (NIV), have been extensively studied for their impact on clinical outcomes in a wide variety of disease states, scenarios, and subpopulations including Chronic Obstructive Pulmonary Disease (COPD) exacerbation, asthma exacerbation, acute cardiogenic pulmonary edema, acute hypoxemic respiratory failure of any cause, acute hypoxemic respiratory failure from COVID-19, pre-intubation oxygenation, post-extubation support, pre-hospital transport, immunocompromised patients, and both adults and children [1–17]. Almost all of these investigations, particularly for adults, have occurred in high-income or upper-middle income countries. The use of advanced non-invasive respiratory support has increased over time in high-income countries, with particular increases observed during the COVID-19 pandemic [18, 19].

Because they require fewer human and technical resources than IMV, advanced non-invasive respiratory support techniques have the potential to be a particularly good fit for the needs of patients with respiratory failure in resource-constrained settings. HFO, with its less-intensive monitoring needs and better tolerance profile as compared with NIV, appears to be a particularly promising modality. However, in our experience and in the literature, non-invasive support is not widely employed in resource-constrained settings.

We discuss here what is known about the epidemiology of advanced non-invasive respiratory support in resource-constrained settings, evidence regarding its effectiveness from high-income country (HIC) studies, evidence regarding its effectiveness from low and lower-middle-income country (LMIC) studies, and important challenges and considerations for its implementation in resource-constrained settings.

Epidemiology of advanced non-invasive respiratory support in resource-constrained settings

Utilization before, during, and after the COVID-19 pandemic

The little published data on the "epidemiology" of advanced respiratory support suggests that IMV is sparsely available in LMICs, but that NIV and HFO are even less utilized.

Before the COVID-19 pandemic, the LUNG SAFE study, a prospective observational study of patients with Acute Respiratory Distress Syndrome (ARDS) in 50 countries (though no low-income countries), reported that 436 (15.5%) of the 2,813 patients with ARDS in the study were managed with NIV in the first two days after meeting diagnostic criteria [20]. When we studied

ARDS in a single tertiary center in Rwanda in 2016, not one patient with ARDS received NIV or HFO, while 31% received IMV [21]. In a survey of all four central hospitals and a random sample of 9 of the 24 public sector district hospitals in Malawi, administered just before the pandemic in 2020, none of the nine district hospitals had available NIV [22, 23].

During the COVID-19 pandemic, advanced non-invasive respiratory support was used very commonly in HICs and less so in LMICs. The International Severe Acute Respiratory and Emerging Infection (ISARIC) – World Health Organization (WHO) Clinical Characterisation Protocol for Severe Emerging Infections studied a global cohort of patients hospitalized with COVID-19, including a subgroup of patients who were on HFO, NIV, or IMV within the first 24 h of admission [24]. This cohort consisted of 66,565 patients, with 82.6% from HICs and17.4% from LMICs. In HICs, 48.0% of patients were on HFO in the first 24 h; 38.6% on NIV; and 13.4% on IMV; in stark contrast, in LMICs, only 16.1% were on HFO; 24.9% on NIV; and 59.1% on IMV. In a survey of patients with COVID-19-associated ARDS in 13 Ugandan hospitals (including government, private for-profit, and private faith-based hospitals), HFO was the highest level of respiratory support in 47/499 (9.4%); NIV including CPAP in 96/499 (19.2%); and IMV in 180/499 (36.1%) [25].

After the pandemic, it appears this relative underutilization of NIV and HFO in LMICs persists. In our observational study of hypoxemia and oxygen delivery in five tertiary academic hospitals in Kenya, Malawi, and Rwanda in 2022-23, we found that only 2 of the 1739 (0.1%) consecutively admitted hypoxemic patients were receiving NIV at the time of screening, and only 1 (0.1%) HFO; this is in the context of 100 patients (5.8%) being intubated on IMV [26].

Why the low utilization of advanced non-invasive respiratory support in resource-constrained settings?

We speculate that one reason for the lower utilization of NIV and HFO compared to IMV in resource-constrained settings is simply that they represent relatively "newer" technologies, and new technologies often spread first in resource-rich settings. IMV began its rise via tracheostomy in the 1950s with the polio epidemic in Denmark, and was very commonly used via endotracheal tube in HICs by the 1970s; NIV's use in hospitals was not common in HICs until the late 1980s–90s [27]. HFO is even newer: it was first used in neonates in 2001, and rapidly spread in pediatric use; [28] its use in adults grew after a 2015 randomized controlled trial (RCT) found a mortality benefit from HFO over SFO or NIV for acute hypoxemic respiratory failure in adults [7].

International donors during the COVID-19 pandemic heavily favored donations of IMV devices over devices capable of NIV or HFO. We know that there was concern among international donors around the amount of oxygen used with the non-invasive support modalities. This is a valid concern, though there is also evidence that HFO used wisely can actually decrease the total amount of oxygen used [14]. We will discuss this further later.

Since most donated ventilators did not have the capacity to be used for NIV or HFO, nor were mask or high flow nasal cannula consumables usually provided, clinicians in LMICs have not had the opportunity to use these modalities regularly or to develop systems for their use. This lack of availability and familiarity contribute to the ongoing relative low usage in hospitals in LMICs.

The evidence for effectiveness of advanced non-invasive respiratory support in resource-constrained settings that emanates from HICs

Some known physiology-based advantages of non-invasive support apply to resource-constrained and resource-rich settings alike. NIV can provide oxygen, positive pressure, and ventilatory support without the potential airway complications, ventilator-associated infections, and sedation complications that can occur with IMV. HFO provides washout of anatomic dead space, heating and humidification of inhaled gas, minimal positive end expiratory pressure (2–4 cm H_2O), reduced respiratory rate and inspiratory effort, and reduced transpulmonary driving pressures [29]. HFO is likely better than NIV for most indications, given its lower-profile nasal cannula, better-tolerated gas delivery, safety even in patients who are delirious or at high risk of aspiration, likely lower risk for pressure-induced lung injury, and compatibility with eating and proning [30, 31]. As noted above, many clinical trials have demonstrated efficacy or effectiveness of HFO, CPAP, and NIV in HIC and upper-middle-income-country trials for various indications [1–17].

While the physiologic advantages are universally applicable and the trial results may also be generalizable at least in part, the potential to provide advanced respiratory support with fewer resources holds particular promise for resource-constrained settings.

The evidence from HICs for NIV and HFO suggests a possible mortality benefit with NIV, and a decrease in need for intubation with both NIV and HFO [1, 3]. Imagine a patient in a resource-constrained setting without HFO or NIV available who requires escalation of respiratory support after being on SFO for acute hypoxemic respiratory failure; if a ventilator is not available, or the ventilation is unsafe due to low numbers of staff or inadequately trained staff, that patient will die. If this is a patient who could be supported through his or her respiratory failure with NIV or HFO (i.e., "reduced need

for intubation"), the presence of those modalities could result in survival. Thus, the finding of a decreased need for intubation with NIV or HFO could mean increased survival in settings where safe ventilation is less available.

A study during the COVID-19 pandemic modelled outcomes under various pandemic-induced constrained conditions using HFO in addition to IMV in the United States; it found that the use of HFO resulted in fewer deaths and greater ventilator availability in a scenario of ventilator scarcity [32]. This finding aligns with our clinical suspicion that the availability of advanced non-invasive respiratory support has the potential not only to improve patient outcomes, but also to use resources more efficiently.

The evidence for effectiveness of advanced non-invasive respiratory support in resource-constrained settings that emanates from LMICs

As noted above, the evidence for the use of NIV and HFO in various patient populations in resource-rich settings is quite well developed [1–13]. In resource-constrained settings, the evidence is extremely sparse. While the physiologic rationale for the use of advanced non-invasive forms of respiratory support is the same, differences in epidemiology, time to presentation, and availability of other therapeutic resources may mean that the effectiveness of advanced non-invasive respiratory support is different in resource-constrained as compared with resource-rich settings [33, 34]. Resuscitation in sepsis is a classic example: liberal fluid resuscitation in adults with sepsis was initially thought to be beneficial, then found to be neutral as compared with conservative fluids in high income countries; liberal fluid resuscitation was found to be definitively harmful in adults and children with sepsis in African sites [35–37].

An observational study in South Africa prospectively enrolled 293 patients on HFO at two tertiary hospitals during the COVID-19 pandemic to determine the feasibility and utility of HFO in a relatively resource-constrained setting [31]. The patients were severely hypoxemic, with a median arterial oxygen partial pressure to fraction inspired oxygen ratio (P_aO2/F_iO2) of 68; despite this, 47% of patients successfully weaned from HFO and survived, without requiring IMV. Bubble CPAP, an even less technologically intensive form of advanced respiratory support for younger children, has demonstrated feasibility and utility in resource-constrained settings for two decades [38, 39].

A meta-analysis of the impact of NIV in LMICs was published in 2018 [40]. The meta-analysis included both adults and children, observational (37 studies) and trial (17 studies) data, acute respiratory failure and peri-extubation period, with the majority of the data stemming from South Asia and urban settings, and little data from the lowest income countries or rural hospitals. It did not explicitly include HFO in its search; the authors note only one study they found included HFO, and they note that HFO was emerging as a popular modality in HICs at the time, with promise for LMICs. The meta-analysis found that NIV appeared to be safe and effective in LMICs, though its finding were limited by the reliance on observational data, high risk of bias in data, and statistical heterogeneity.

Trials of CPAP and HFO in children

Two meta-analyses of CPAP in children in 2020 and 2022 found three trials that examined the impact of CPAP on children under age 5 in resource-constrained settings [16, 17, 41–43]. Both meta-analyses found the data to be conflicting, of low certainty, and with too much heterogeneity to draw conclusions on mortality impact. The initial randomized controlled trial (RCT) published in 2015 included 225 children under five years old with very severe pneumonia and hypoxemia in a single center in Bangladesh comparing bubble CPAP, SFO, and HFO [17]. It was stopped early due to a higher observed mortality in the SFO arm as compared with the bubble CPAP arm; the authors acknowledged that early cessation of the trial reduced the certainty of the findings. In 2017, a cluster crossover trial was performed in two non-tertiary hospitals in Ghana, in children ages 1 month to 5 years with signs of respiratory distress including tachypnea and use of accessory muscles or nasal flaring [43]. This study enrolled 2200 children; it found no difference in unadjusted 2-week mortality, but did find a significant 2-week survival advantage for children one year old and younger, after adjusting for study site, time, and clinically important variables. Then in 2019, a randomized controlled trial of bubble CPAP versus SFO in children ages 1 month to 59 months with severe pneumonia and at least one additional high-risk comorbidity in Malawi was published [16]. It was stopped early, at 644 of the intended 900 enrolled, due to futility, with a signal for higher in-hospital mortality in the CPAP arm. The investigators postulated likely underlying sources of harm being related to implementation factors and supporting resources.

Most recently in 2024 (after the above meta-analyses), a team in Ethiopia published a pragmatic cluster-randomized controlled trial comparing a locally made bubble CPAP with SFO in 12 general hospitals in Ethiopia, in children ages 1 month to 5 years with severe pneumonia and hypoxemia [15]. All children were treated in general wards, in a dedicated corner near the nursing station, had a nurse-to-patient ratio of 6 to1, and physician to patient ratio of 18 to 1, and had access to oxygen and medications. The study enrolled 1240 children, and found a

reduction both in the primary outcome of treatment failure (a composite variable), and in-hospital mortality.

This most recent study seems to confirm the conclusions of the meta-analyses above, as well as a meta-analysis of contextual factors: [44] contexts and systems, including careful selection of populations most likely to benefit, adequate numbers and training of staff, close monitoring and clear escalation pathways, daily physician supervision, appropriate equipment, and ongoing monitoring of outcomes and quality of care, are critical to the safe administration of CPAP in children in LMICs.

Finally, one study has examined HFO as an intervention in children in resource-constrained settings [14]. The COAST study was an open-label fractional factorial design examining children between ages 28 days and 12 years with pneumonia and either severe hypoxemia (SpO2 < 80%) or hypoxemia (SpO2 80–91%) in 2 hospitals in Kenya and 4 hospitals in Uganda. It compared 48-hour mortality outcomes with permissive hypoxemia, SFO, and HFO. While it was stopped early for feasibility in the setting of protests in Uganda around the ethics of the permissive hypoxemia arm, it nonetheless enrolled 1,852 children, and demonstrated a trend toward 48-hour mortality benefit with HFO as compared with SFO (48-hour mortality 9.3% vs. 13.4% respectively in the severe hypoxemia stratum, n = 388; 1.1% vs. 2.5% respectively in the hypoxemia stratum, n = 1454). Importantly, it also found that the total oxygen used was *lower* in the HFO arm, even in the severe hypoxemia stratum. This seemed to be due at least in part to the number of children in the HFO arm who were supported with air only, without need for blended oxygen.

Trials of NIV and HFO in adults

Trials in adults in LMICs are even more sparse. A study during the COVID-19 pandemic in three hospitals in Columbia randomized a total of 220 adults with COVID-19 and compared HFO and SFO; it found that HFO significantly reduced need for IMV, and significantly reduced time to clinical recovery [11]. Colombia is an upper middle-income country, but since most trials are performed in high-income countries, it nonetheless may speak more to LMIC contexts than other trials.

Likewise, the Brazilian BRICNet Research Network has provided a considerable amount of evidence around respiratory support modalities, most recently in the RENOVATE randomized trial, which compared NIV and HFO in patients with acute respiratory failure in five categories (non-immunocompromised, immunocompromised, chronic obstructive pulmonary disease (COPD) exacerbation, acute cardiogenic pulmonary edema, and COVID-19) with a noninferiority primary outcome and Bayesian approach with dynamic borrowing [10]. BRICNet's body of work is providing evidence for respiratory support that emanates from outside of the usual North American, European, and Australian contexts. However, Brazil is also an upper middle-income country, so likely still reflects results that are relevant to significantly higher levels of resources than most settings in LMICs.

Finally, a single-center randomized controlled trial of HFO versus non-rebreather facemask in COVID-19 patients in India, an LMIC, enrolled 120 patients in 3 months in 2021. It found a statistically significant difference in escalation of oxygen therapy, but no difference in survival [45].

Two studies in adults in LMICs are currently ongoing. The ARISE trial in Uganda is a stepped wedge trial of CPAP, HFO, and SFO for adults with acute hypoxemic respiratory failure in multiple hospitals in Uganda; it has completed enrollment [46]. The BREATHE trial is an implementation-effectiveness randomized controlled trial of HFO versus SFO in adults with acute hypoxemia in five hospitals in Kenya, Malawi, and Rwanda; it is currently enrolling [47].

Clinical challenges and considerations for resource-constrained settings

While advanced non-invasive respiratory support has the potential to be even more beneficial in resource-constrained settings than it is in resource-rich settings based on current evidence as above, its use nonetheless raises multiple important challenges and considerations (Fig. 1).

The 2019 randomized controlled trial of bubble CPAP in children ages 1–59 months with severe pneumonia and one other high-risk comorbidity in a general pediatric ward in a Malawi hospital noted above is an excellent example of the need to rigorously consider implementation and context. This study unambiguously demonstrated the very real risks involved with advanced non-invasive respiratory support in resource-constrained settings, and the critical need to ensure that infrastructure, staffing, and systems support safe administration [16]. The study was stopped for futility, with a signal for harm in the bubble CPAP arm. This was an unexpected result given widespread clinical experience with bubble CPAP in young children; the investigators postulated likely underlying sources of harm being aspiration, oxygen toxicity, equipment contamination, and lack of physician oversight. This study appropriately sought to understand the impact of bubble CPAP in a real world setting, and found that even this most feasible version of advanced respiratory support could actually cause harm without adequate systems in place.

Particular issues that need careful consideration are: clinical systems of care; oxygen consumption and connector compatibilities; human resources and training;

location within the hospital; acceptability; cost; and device characteristics (Fig. 1).

Clinical systems of care

A multicenter retrospective analysis of the uptake of pulse oximetry in children at hospitals that were part of a Clinical Information Network (CIN) in Kenya is a sobering demonstration of how difficult it can be to implement the systematic use of pulse oximetry, let alone the more complex requirements of advanced respiratory support [48]. Eighteen hospitals in Kenya were purposefully selected to join the CIN, which was designed to improve the quality of routine pediatric hospital data for quality improvement activities and research, and included quarterly clinical audits and feedback reports for hospitals on the quality of their care. Pulse oximetry use did improve in the seven years of the study, from ≤ 25% to 81.5%; however, in 87% of cases where oxygen was prescribed, children either had no pulse oximetry measured, or had SpO2 ≥ 90%, above the recommended threshold for oxygen. There was large variability in pulse oximetry use across the hospitals, suggesting the influence of differences in equipment supply and maintenance, local leadership, training, and other factors impacting health service delivery [49].

Implementation science offers a variety of helpful frameworks and examples for LMIC hospitals hoping to expand their respiratory support to include NIV or HFO.

A multidisciplinary team examined hospitals in Kenya and Tanzania during the COVID-19 pandemic and noted that while resources were scarce as determined by readiness scales, "higher scores on resource readiness scales were often misleading, as resources were often insufficient or not functional in all the clinical areas they are needed" [50]. The team followed patients' journeys through interviews and group discussions, and thereby discovered important gaps in care, particularly around transitions of care. They noted that, "Efforts to improve care for the critically ill patients, which is a complex process, must include a whole system and whole facility view spanning all areas of patients' care and their transitions …".

A recent realist review of contextual factors influencing implementation of bubble CPAP in LMICs included a systematic literature review and iterative rounds of expert surveys and focus groups to identify 18 context-mechanism-outcome configurations (CMOCs), and then synthesized the information into a final theory of implementation with five levels: (1) the bubble CPAP device (appropriateness and sustainability in the context), (2) local partnerships and infrastructure, (3) clinical and technical teams, (4) caregivers and the community, and (5) institutional practices [51]. This provides a detailed framework for initiating a new form of respiratory support into a hospital.

Another paper from Peru, an upper middle income country, describes a team's successful implementation process of HFO in a pediatric ICU in detail [52]. They noted the critical need for engaged key stakeholders, identification of the unique challenges of the local environment, recruitment of local champions, and ongoing communication with providers.

After a study in an ICU in a tertiary hospital in Bangladesh demonstrated positive impact of bubble CPAP for children with pneumonia [17], researchers sought to understand the feasibility of bubble CPAP in non-tertiary district hospitals in Bangladesh [53]. The study found fundamental barriers to implementation including inadequate number of pulse oximeters, lack of power generator backup, high patient load with an inadequate number of hospital staff, and inadequate and non-functioning oxygen flow meters.

Oxygen consumption and the oxygen ecosystem

In addition to clinical care systems, oxygen production and delivery systems are also critical to the safe use of advanced non-invasive respiratory support in resource-constrained settings. One concern that arose multiple times during the COVID-19 pandemic was the potential for non-invasive forms of respiratory support to use large amounts of oxygen, with oxygen itself being a scarce resource. Due to the continuous nature of its oxygen flow, HFO set at 60 L per minute and 100% FiO2 can use five times the amount of oxygen as IMV set at 100% FiO2; due to leakage around the mask, NIV can use almost twice the amount of oxygen as IMV [54]. A retrospective observational study conducted in three intensive care units (ICUs) in the Netherlands and Spain found that actual oxygen consumptions was 4.9 higher in patients who started with HFO as compared with those who started with IMV [55]. However, in a pre-COVID-19 clinical trial comparing HFO to SFO in children with acute pneumonia in East Africa, the amount of oxygen consumed was *lower* with HFO compared to SFO, as almost half of children in the HFO arm achieved target oxygenation with flow of only ambient air without additional oxygen [14]. The capability to monitor oxygen consumption, plan for increased demand, and preempt shortages is critical. Some newer oxygen plants can provide real time data on oxygen use; an oxygen calculator available on opencriticalcare.org allows for manual tracking, which is more time-intensive but can provide accurate oxygen use data [54, 56].

In addition to monitoring the quantity of oxygen used, an understanding of the interconnected pieces of the oxygen ecosystem is important. In its training on the *clinical* management of COVID-19 with non-invasive

support (emphasis added), the World Health Organization (WHO) detailed the need to understand high versus low pressure sources of both medical oxygen and medical air (oxygen plants, cylinders, concentrators), as well as the pressure or flow regulator between the gas source and the respiratory support device [57]. This highlights the necessity of a functioning and integrated oxygen ecosystem in order to administer NIV and HFO safely.

A specific example of this was noted by a team in a Kenyan hospital that was piloting the use of HFO in children; they found that flowmeters at >15 LPM could not be connected to the oxygen wall ports in their high dependency unit, requiring use of cylinders that could function with flow meters with higher flow rates [58]. Our own experience with launching a study of HFO in five hospitals in Kenya, Malawi, and Rwanda demonstrated the need for no fewer than six different connectors for the high flow device to the piped wall oxygen; and this was in the relatively homogenous case of all sites having on-site oxygen plants with piped oxygen [47]. We also found variability in the purity of oxygen being supplied; lower purity obviously impacts the effectiveness of any mode of oxygen delivery. We also found that one hospital had its pressures set at a level too low to support HFO; when we investigated the cause, we learned that this was an oxygen conservation measure due to high rates of oxygen leaks at the wall ports. Moving forward with HFO at that hospital required infrastructural improvements to decrease leaks at wall ports, so that higher pressures could be maintained.

Hospitals must have functioning oxygen ecosystems, including reliable sources of oxygen with adequate purity, methods to monitor oxygen consumption, and interfaces to connect with non-invasive oxygen support.

Human resources and training

While NIV and HFO may offer a less human resource-intensive form of respiratory support for some patients, they both still require expertise; if this need for specialized clinical care is not recognized or available, NIV and HFO may not be a useful or safe alternative to IMV.

One critical consideration in human resources for advanced non-invasive respiratory support is the sheer number of skilled staff members, and in particular nurses. It is both intuitive and supported by evidence that increasing nurse-to-patient ratios leads to better patient outcomes [59]. This is problematic given the inequities in numbers of nurses globally: as of 2021, HICs had 9.8 nurses and midwives per 1,000 population, while low-income countries (LICs) had 1.0 per 1000 population [60].

Turnover is also a significant challenge, requiring ongoing training not only to refresh staff, but also to train new staff on a regular basis; this is a consideration that applies to both resource-constrained and resource-rich settings [30, 53, 58, 61].

Protocols can be effective tools in training and adherence to quality care [61]. One implementation study in the United States for HFO in the wards found the need not only for protocols for set up and use, but also for weaning and preventing skin breakdown [30].

An observational study in an academic hospital in Italy demonstrated that even short (3-hour) on-the-job training for nurses can be effective in a setting like the COVID-19 pandemic where many patients were receiving NIV [62]. Short courses can have substantial impact on patterns of care in emergency care, as demonstrated by documented changes in clinical care process after two short courses in a hospital in rural Liberia [63]. Seven hospitals in Nepal introduced a Clinical Practice Guideline (CPG) developed and rolled out by ICU nurses; they found that the guideline did not substantially increase use of HFO in patients eligible for its use, but HFO was found to be highly acceptable, appropriate, and feasible based on post-implementation surveys [64].

A review and international consensus process examining education and training on NIV in 2019 found scarce evidence of structured education on NIV in LMICs, and provided detailed recommendations for training to improve safety and effectiveness of use [65]. A Delphi process on Essential and Emergency Critical Care (EECC) surveying 269 experts with clinical expertise in different acute medical specialties from 59 countries and all resource settings rightly emphasized the need for respiratory support care training to be fully integrated into training for other essential clinical processes [66].

In the literature and in our experience training staff for a randomized controlled trial of HFO versus SFO [47, 67, 68], we found that training is needed for a vast array of inter-related topics: recognizing appropriate candidates; use of the device itself including troubleshooting; monitoring and titrating to a target SpO2 range with a simultaneous priority on oxygen conservation [69]; patient device interaction and how to help patients tolerate the support; transport practices in the setting of an advanced device; liberating from the device; recognizing the need for escalation to IMV; airway management expertise to allow escalation to IMV; and end of life and goals of care discussions.

An example of the importance of training not only on device operation, but also other topics, is the needed proficiency in patient selection. NIV is not appropriate for all patients who otherwise would get IMV. An overcorrection and over-use of NIV as a replacement rather than partial alternative to IMV could cause harm, in patients with decreased consciousness, for instance. In a prospective study of adult patients in the medical and surgical wards of a large academic Zambian hospital over

five months, 48.5% of the participants met criteria for delirium [70]. In our research group's recent study of all adults admitted with hypoxemia over four months in five African hospitals, over one-third of patients had altered mental status on admission [26]. Given the severity of illness of patients with respiratory failure in these settings, delirium and loss of consciousness are common, and NIV will not be appropriate for many of these patients.

Where to use advanced non-invasive respiratory support

In an international study including 51 countries (with only six lower-middle-income countries and no low-income countries), 66% of respondents reported using NIV in the wards [71]. One study described the implementation of HFO on the floors in the United States (US), including protocols, widespread training, respiratory therapist monitoring at least every four hours, and meticulous tracking of patient safety and adverse events [30]. More than half of patients in this study avoided the ICU; HFO outside the ICU was deemed safe and efficacious.

An observational study during the COVID-19 pandemic in two relatively resource-constrained referral hospitals in South Africa demonstrated the feasibility of delivering HFO in medical wards [31]. An analysis of all four central hospitals in Malawi found that, while all had NIV and IMV available in their ICUs, none had NIV available in their high-dependency units (HDUs) or wards [22, 23]. However, a study of 13 hospitals in Uganda during the COVID-19 pandemic found that NIV and HFO were used almost exclusively in the wards, as ICU beds were reserved for patients needing IMV [25]. There seems to be a high degree of variability in whether advanced non-invasive respiratory support is used exclusively in an ICU or HDU, or expanded to the ward setting.

Using advanced respiratory support in wards is likely to be critically important to its feasibility in LMICs; a recent study of point prevalence critical illness in 22 countries in Africa found that 69% of critically ill patients were cared for in wards [72]. While HICs have between 5 and 30 ICU beds per 100,000 population, limited data suggests only 0.1 to 2.5 ICU beds per 100,000 population in LMICs [73]. In a recent study conducted in a Rwandan referral hospital, only 17.6% of patients who met criteria for ICU admission were able to be transferred to the ICU within 24 h of meeting criteria, and only 27.2% were ever admitted to the ICU; among this population of ICU-eligible patients, mortality was 44.8% [74].

However, an international prospective study of 40,440 patients with severe COVID-19 in 43 countries (only 6.2% from lower-middle income countries and none from low-income countries) adjusted for multiple demographic and severity-of-illness variables, and found that patients cared for outside an ICU had a higher 28-day mortality than those cared for in an ICU [75]. This signal for higher mortality with advanced respiratory support performed outside an ICU is reason for pause; however, the context of overwhelmed health systems during the pandemic has to be taken into consideration. It is easy to imagine that ICU staffing and resources remained relatively resource-rich in the pandemic surges, as compared with ward staffing and resources in the same hospitals. This extreme stretching of resources during the pandemic is not generalizable to other time periods without the burden of the pandemic; however, resource-constrained settings are chronically in a "stretched" situation, so this finding suggests the need for caution in providing NIV and HFO outside the more-resourced setting of the ICU in LMICs. In our own experience in highly resourced clinical settings in the US, the stated reason for confining NIV and HFO to the ICUs is the critical importance of recognizing the need for escalation to IMV when it occurs, and the ability to escalate quickly. A patient on HFO in particular can "look good" while on maximum HFO support, with clinicians not recognizing that he or she is on the cusp of needing IMV. Using regular required monitoring intervals including quantitative triggers such as the imputed PaO2/Fio2 ratios or ROX index (ratio of oxygen saturation as measured by pulse oximetry/Fio2 to respiratory rate) [67] to ensure recognition of need for escalation may be critical for the safety of NIV and HFO in the wards.

Acceptability

The acceptability of "new" devices is a critical feature of adoption of advanced non-invasive respiratory support. An important study in a district hospital in Malawi included eight focus group discussions with mothers whose children were in a trial of bubble CPAP versus SFO [76]. One participant stated that "oxygen kills babies". Mothers acknowledged delaying treatment for their children to avoid oxygen, and removing oxygen. Interestingly, after treatment, in both arms, mothers were supportive and said they would recommend oxygen therapy.

Cost

Two older studies of cost effectiveness of NIV in COPD have been published. One was a theoretical model based in ICUs [77], and the other was based on a small ward-based randomized controlled trial in the United Kingdom [78]; both demonstrated cost effectiveness of NIV.

The decision to invest in new devices and the accompanying needed clinical systems requires an understanding of both expected outcomes, as well as relative cost compared to alternatives.

Devices

We have found that the most critical characteristics of devices are those that are needed for sustainability: the existence of reliable maintenance contracts for ongoing biomedical support from the manufacturer, and harmonized purchasing of multiple of the same devices to support training, biomedical support, and purchasing of consumables. The government of Kenya launched a Managed Equipment Services (MES) public private collaboration in 2015, designed to integrate the supply, installation, testing, maintenance, and replacement of medical equipment including ventilators, monitors, syringe and infusion pumps, ECG machines, defibrillators, and resuscitation trolleys over a seven year contractual period [79]. We have seen first-hand the value of having the same ventilator make and model across ICUs in Kenya, with service contracts and the same supply chain for consumables, making critical care accessible for more people. We have also seen first-hand the difficulties that arise with training, maintenance, and consumables procurement when multiple devices without ongoing service contracts are used.

Specific aspects of HFO devices that are important for meeting the needs of resource-constrained settings include the following [47, 68]:

- humidification chambers that can be filled automatically, or at least infrequently, as the filling can be a burden for already over-burdened nurses; [58, 80].
- battery capability both for periods of interrupted electrical supply, as well as for transport within the hospital;
- the ability to use ambient air rather than requiring medical air;
- temperature regulation of high flow gas, even in clinical environments that experience wide swings in temperature;
- the ability to connect with multiple forms of oxygen supply;
- the capacity for a given device to be used for IMV, NIV, and HFO;
- consumables for NIV and HFO that are affordable, reusable, and with reliable supply chain;
- filters that can withstand environments that are open to outside air, including dust; and.
- devices that conserve oxygen to the extent possible.

Mekontso Dessap et al. have described the need for a "frugal innovation" approach to respiratory devices [81]. They note that "Having a universal access to oxygen and respiratory support, irrespective of the context and constraints, necessitates: i) developing cost-effective, energy-efficient, and maintenance-free oxygen generation devices; ii) improving the design of non-invasive respiratory devices (for example, with oxygen saving properties); iii) conceiving fully frugal ventilators and universal monitoring systems; iv) broadening ventilation expertise by developing end-user training programs in ventilator assistance. The frugal innovation approach may give rise to a more resilient and inclusive critical care system. This paradigm shift is essential for the current and future challenges."

We are aware of several instances of "frugal innovation" in the non-invasive respiratory support space. The Boussignac CPAP valve (Vygon, Ecouen, France) is a non-invasive positive pressure system that does not require electricity and can be connected to any NIV mask; pressure is generated by gas flow passing through microcapillaries, creating a "virtual valve" [46]. This device was further refined with the addition of an antimicrobial filter between the mask and valve to avoid viral aerosol dispersion during the COVID-19 pandemic [82]. Its ability to provide positive end expiratory pressure (PEEP) without requiring electricity, and its flexibility in connecting with various masks, make it a potentially useful version of CPAP for resource-constrained settings. It has been used clinically, including in pre-hospital settings [83].

Another example of a non-invasive device designed to meet specific challenges of resource-constrained settings is the Oxygen-Efficient Respiratory Aid (OxERA), which provides PEEP, but with a lower oxygen consumption than standard CPAP [84]. Developed in South Africa, it was used during the COVID-19 pandemic. Another example of an innovation designed to conserve oxygen was described in 2023: a recirculation circuit tested with a simulated helmet CPAP; oxygen-enriched gas escaping from the PEEP valve has carbon dioxide removed, and then is entrained by the Venturi flow generator and redirected to the helmet [85]. This has not been used clinically. A final example of a device fit for purpose during the COVID-19 pandemic was the UCL-Ventura device for delivering CPAP [86]. It is a simple, purely mechanical non-invasive respiratory support device that delivers CPAP; it was simplified from an earlier device so that it could be connected to piped oxygen; it was then further modified to conserve oxygen. While the development and regulatory process in the UK was remarkably rapid in the early days of the COVID-19 pandemic, with 10,000 devices being produced within a month of the initial brainstorming session, the designers nonetheless found it very hard to get regulatory approvals for sale or donation, and in LMICs especially [87]. The device was used in Peru, and an observational feasibility study in 45 patients with COVID-19 at three hospitals found the device to be overall feasible and acceptable for use [88].

Conclusion

NIV and HFO appear to be relatively under-utilized in LMICs, as compared with HICs. The COVID-19 pandemic saw increases in utilization worldwide, but less markedly in LMICs. HFO in particular is likely to be a better option than NIV in many cases, given that it is tolerated better and is simpler to implement; however, HFO is currently even less utilized than NIV in resource-constrained settings. This is likely because it is a newer technology and carries particular concerns around the quantity of oxygen required. Current evidence from HICs and sparse evidence from LMICs for the effectiveness of advanced non-invasive respiratory support suggest that these modalities may be particularly beneficial in resource-constrained settings. However, the evidence also suggests that key implementation factors are crucial in determining whether these modalities will be beneficial, neutral, or harmful. Considerations that must be addressed when making decisions to use NIV, CPAP, or HFO in resource-constrained settings include: clinical systems of care; oxygen consumption and connector compatibilities; human resources and training; location within the hospital; acceptability; cost; and device characteristics. More and better evidence that emanates from resource-constrained environments, and that describes context in detail, is critical for understanding how to best apply advanced non-invasive respiratory support in resource-constrained settings.

Acknowledgements.

Acknowledgements
We thank Dr. Cornelius Sendagire and Dr. Tiara Calhoun for insights and references they provided for this work.

Author contributions
TT and ER conceived the manuscript and revised it in accordance with reviewers' comments. All authors participated in writing the manuscript, reviewed it, and approved its final version.

Funding
Authors did not receive any funding for this particular writing.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
All authors allow the publication as Open Access source.

Competing interests
The authors declare no competing interests.

Received: 10 January 2025 / Accepted: 27 September 2025
Published online: 14 November 2025

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