Recommendations on the use of non-invasive ventilation and high flow therapy with nasal cannulas in adult, paediatric and neonatal patients with severe acute respiratory failure. Consensus Document of the Spanish Scientific Societies (SEPAR, SEMICYUC, SEMES; SECIP, SENeo, SEDAR, SENP).

Keywords:

Non-invasive ventilation, recommendations, acute respiratory failure, high flow therapy with nasal cannulas, consensus

Relations with the industry and other conflicts.

The policy by the SEPAR/SEMICYUC Boards of Directors has been to sponsor the working meetings and position and consensus documents without commercial support, and all CC and WG members volunteered. Therefore, at the end of this document, all members of the CC and WG, as well as the reviewers, have revealed any potential conflicts of interest in detail and such conflicts have been addressed by the coordination of this document.

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Endorsements

Spanish Society of Pneumology and Thoracic Surgery [*SEPAR],* Spanish Society of Critical Care Medicine and Coronary Units [*SEMICYUC],* Spanish Society of Emergency Medicine [*SEMES];* Spanish Society of Paediatric Intensive Care [*SECIP]* the Spanish Society of Neonatology [*SENeo],* Spanish Society of Paediatric Pneumology [*SENP] and the* Spanish Society of Anaesthesiology and Resuscitation [*SEDAR]*

Society logos.

Spanish Society of **Pneumology and Thoracic Surgery** SEPAR

SEMICYUC THE PROFESSIONALS OF THE CRITICALLY ILL

Spanish Society of Urgency and Emergency Medicine

SECIP SPANISH SOCIETY AND FOUNDATION FOR PAEDIATRIC INTENSIVE CARE

SPANISH SOCIETY OF NEONATOLOGY SENeo

NEUMOPED Spanish Society of Paediatric Pneumology

SEDAR Spanish Society of Anaesthesiology, Resuscitation and Pain Management

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Summary

Non-invasive respiratory support (NIRS) comprises two treatment modalities, non-invasive mechanical ventilation (NIMV) and high-flow nasal cannula therapy (HFNCT), which are applied in adult, paediatric and neonatal patients with acute respiratory failure (ARF). However, the degree of agreement among the different specialties on the benefit of these techniques in different clinical settings is controversial. The aim of this consensus was to develop a set of good clinical practice recommendations for the application of non-invasive ventilation in patients with ARF, endorsed by all scientific societies involved in the management of adult and paediatric/neonatal patients with ARF.

To this end, the different societies involved were contacted, who, in turn, appointed some professionals with sufficient expertise in their application. A series of face-to-face meetings were held to try to reach consensus and, finally, a telematic vote was taken on each of the recommendations (a total of 71), which were based on a review of the literature and updating of the available evidence in relation to three categories; indications, monitoring and follow-up. For the classification of the level of agreement, an analogical classification system was chosen. The system is easy and intuitive to use and clearly states whether the procedure related to the NIRS should be done, could be done or should not be done.

Abstract

Non-invasive respiratory support (NIRS) comprises two treatment modalities, non-invasive mechanical ventilation (NIMV) and high-flow nasal cannula therapy (HFNCT) that are applied in adult, paediatric and neonatal patients with acute respiratory failure (ARF). However, the degree of agreement between the different specialties on the benefit of these techniques in different clinical settings is controversial. The objective of this consensus was to develop a series of good clinical practice recommendations for the application of non-invasive support in patients with ARF, endorsed by all the scientific societies involved in the management of adult and paediatric / neonatal patients with ARF.

The different societies involved were contacted, who appointed some professionals with sufficient expertise in its application. A series of face-to-face meetings were held to try to reach consensus and, finally, a telematic vote was organized for each of the recommendations (up to 71), which were based on a review of the literature and updating of the available evidence in relation to three categories; indications, monitoring and follow-up. For the classification of the level of agreement, an analogical classification system was chosen. The system is easy and intuitive to use and clearly states whether the procedure related to the NIRS should be done, could be done or should not be done.

1. Introduction

Non-invasive mechanical ventilation (NIMV) is a mode of respiratory support that involves the application of positive airway pressure to patients with respiratory failure of different aetiologies using an interface other than an orotracheal tube or tracheostomy. Nowadays, NIMV is a therapeutic strategy used in daily clinical practice in many clinical settings, especially for patients with ARF in hospitals [1]. Since the first pioneering studies in the late 1980s on the use of NIMV in patients with neuromuscular diseases, sleep apnoea or in Intensive Care Units (ICU) [2–4], an extensive corpus of clinical research exploring different applications, modalities, interfaces and comparisons with other therapies has been generated [4,5]. In general, the objectives of the application of NIMV in patients with ARF are: a) to avoid orotracheal intubation and its complications; b) to maintain the benefits of positive pressure ventilation and partial support for gas exchange and work of breathing.

The efficacy of NIMV has been evaluated in the context of common clinical conditions in the care of acute patients with acute respiratory failure (ARF), whether adult, paediatric or neonatal; these conditions include acute cardiogenic pulmonary oedema (ACPO) [6–9], ventilatory support for patients with respiratory failure and in the prevention of extubation failure [9–12].

However, although it is an extensively studied technique, some aspects remain controversial, such as its role in *de novo* hypoxaemic respiratory failure, the selection of interface and ventilatory modalities to optimise patient-ventilator interaction, comfort and side effects (e.g. leaks, asynchronies) [13–18]. In paediatrics, the most frequent indication for NIMV is infections, especially viral infections, causing bronchiolitis in paediatric patients under two years of age and severe bronchospasm crises in infants, school-aged children and adolescents. Infections pose a particularly important risk in paediatric patients with neuromuscular conditions, rib cage malformations and asthma [19]. In neonatology, its use has become widespread in all respiratory pathologies,

mainly during prematurity due to surfactant deficiency respiratory distress syndrome. In recent years, a new mode of non-invasive respiratory support, high-flow nasal cannula therapy (HFNCT), has also become widely used, providing a flow rate of up to 60 litres per minute of a humidified and thermally conditioned gas mixture [20].

2. Justification

This consensus document arises from the need to review and update the clinical practice on the use of non-invasive respiratory support (NIRS), NIMV and HFNCT in adult, paediatric and neonatal patients with ARF. To date, there is no document that compiles the clinical practice of the application of NIRS in the Spanish National Health System. It is therefore necessary to issue a set of recommendations on the application of NIMV and HFNCT by means of a consensus agreement and coordination between the main Spanish scientific societies involved in the management of patients with ARF in hospitals (Spanish Society of Pneumology and Thoracic Surgery [*SEPAR*], Spanish Society of Critical Intensive Care Medicine and Coronary Care Units [*SEMICYUC*], Spanish Society of Emergency Medicine [*SEMES*]; Spanish Society for Paediatric Intensive Care [*SECIP*] the Spanish Society of Neonatology [*SENeo*], Spanish Society of Paediatric Pneumology [*SENP*] and the Spanish Society of Anaesthesiology and Resuscitation [*SEDAR*]).

The aim of this document is to provide recommendations on the application of NIRS in ARF, both in adult and paediatric/neonatal patients, based on the best available evidence agreed by professionals.

3. Methods

A Coordinating Committee (CC) was formed by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) in December 2017. A Working Group (WG) was created, made up of representatives of most of the scientific societies involved in the care process for patients with acute respiratory failure requiring respiratory support (table 1), who supervised the quality and suitability of the processes and the consensus methodology, as well as the identification of the thematic framework of the contents to be validated (table 2). This working group of twenty-four experts, previously selected by their respective societies on the basis of their expertise in the subject, was responsible for drawing up the recommendations for good clinical practice after reviewing and compiling the best available evidence and formulating recommendations and suggestions for clinical practice structured in three phases of the care process: indications, monitoring and follow-up. In addition, a number of partners acted as external reviewers for the different societies.

Scientific society	Panel of partners
Spanish Society of Anaesthesiology, Resuscitation and Pain Management (SEDAR)	Javier García, Antonio Romero, Rafael Uña, Carlos Ferrando.
Spanish Society for Paediatrics/Paediatric Intensive Care (SECIP)	Alberto García-Salido, Mirella Gaboli, Julio Parrilla.
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Spanish Society of Neonatology (SENeo)	Ana Sánchez, Julio Moreno, Ana Concheiro.
Spanish Society of Pneumology and Thoracic Surgery (SEPAR)	Carlos Egea, Manel Luján, Miquel Ferrer, Sarah Heili, Eva Farrero, Juan F. Masa, Mónica González, Mª Angeles Sánchez, Mirella Gaboli.
Spanish Society of Paediatric Pneumology	Mirella Gaboli.
Methodological support	Iñaki Gutiérrez Ibarluzea.

Table 1. Scientific societies and representatives who have participated and certify the consensus document (in alphabetical order).

3.1. Definitions

ARF is characterised by a partial pressure of oxygen in arterial blood (PaO_2) of less than 60 mm Hg, when breathing ambient air at sea level (fraction of inspired oxygen (FiO_2) of 0.21) and of recent onset [21]. However, the concept of severe ARF is not well established. The most commonly used criteria in clinical studies in adults are a respiratory frequency (RF) over 20 or 25 breaths/min (it should be noted that in children and newborns, the physiological RF is closely linked to age and the above values may be perfectly physiological), clinical signs of respiratory effort (use of accessory muscles, respiratory pattern of chest-abdominal asynchrony, diaphoresis, cyanosis) or moderate-

to-severe hypoxaemia, commonly defined as a PaO_2/FiO_2 ratio of less than 200 mm Hg [22–24].

ARF in adults encompasses two distinct syndromic patterns. The first is *de novo* ARF which includes hypoxaemic patients without underlying chronic lung disease or cardiogenic pulmonary oedema, where hypercapnia is uncommon. The leading cause of *de novo* ARF is pneumonia, which accounts for approximately 75% of cases [20]. The second is acute hypercapnic respiratory failure, which includes patients with $PaCO_2$ exceeding 45 mm Hg at pH < 7.35 and occurs mainly in COPD patients during COPD exacerbation [22]. Pneumonias and respiratory infections with all their microbiological causes are the most frequent causes in paediatric patients, followed by exacerbations of pulmonary pathologies, with asthma being the most frequent. Other conditions such as sequelae of gastro-oesophageal reflux, rib cage malformations and sequelae of prematurity, among others, should also be highlighted.

3.2. Search strategy

A search was conducted in the databases PubMed/Medline, and Cochrane database of systematic Reviews and in the general Meta-search engine Google Scholar. The search strategy included original articles (experimental and quasi-experimental clinical trials, prospective observational studies), clinical practice guidelines, systematic reviews, expert consensus documents, excluding experimental studies, applied physiology studies, retrospective studies or case series published from January 1990 to April 2020. Conceptually, the search was divided into two branches: NIMV and HFNCT.

For the search of the NIMV branch, the following keywords were used: Non-invasive ventilation (Medical Subject Headings (MeSH)), Positive-pressure Respiration (MeSH), NIV (free text) and Acute Respiratory Failure (free text). The search for the HFNCT branch included: high flow nasal (free text), high flow nasal therapy (free text), high flow nasal oxygen (free text), high flow nasal cannula (free text), high-flow and Acute Respiratory Failure (free text). These terms were then combined using Boolean

operators to refine the search and filters specific to study types in the case of PubMed/Medline. Non-human studies, studies without abstracts and studies written in languages other than English or Spanish were excluded. Duplicate articles or those in the parallel branch were discarded. The initial reference list was refined by reading the title or abstract and having eligible articles independently reviewed by two people and dissensions resolved by a third. (Figure 1).

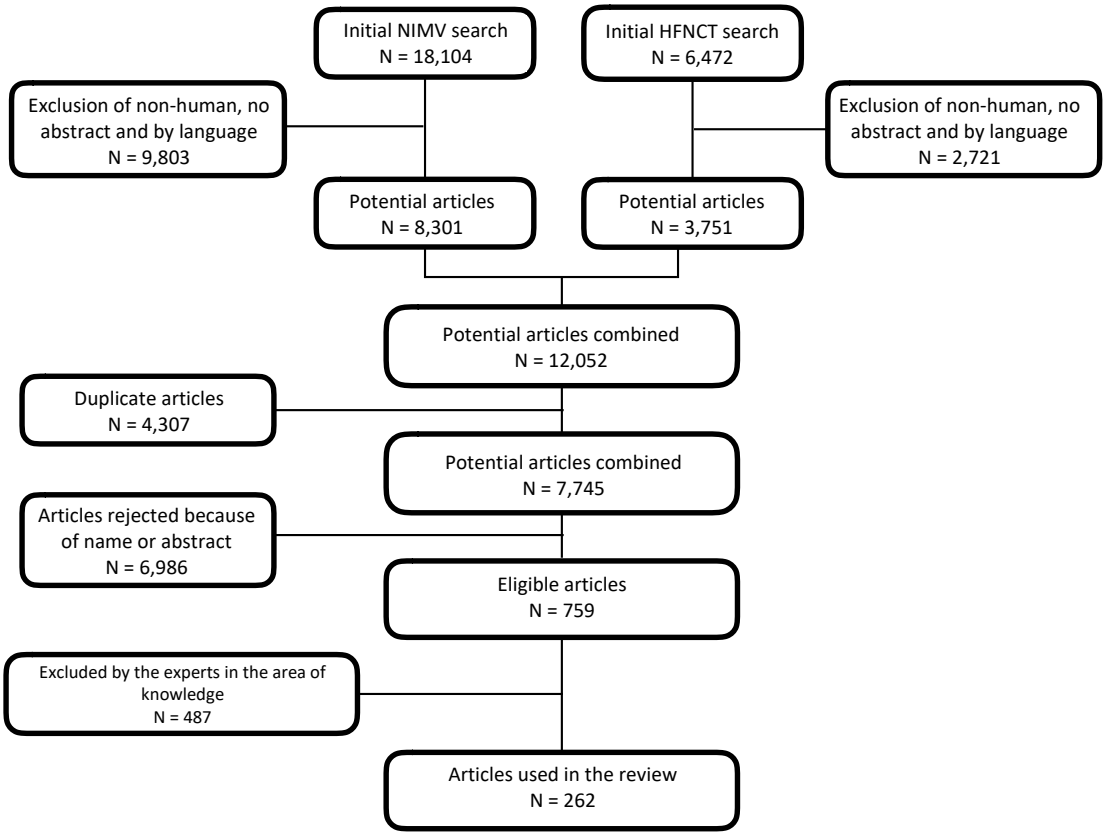


Figure 1. Literature review flow chart.

3.3. Agreement strategy

Within the framework of this multidisciplinary working group, three face-to-face meetings were held at the SEPAR and SEMICYUC headquarters (Madrid, 19 January 2018, 10 May 2018, 20 March 2019) in which both the CC and the WG participated. In

these meetings, the good clinical practice recommendations were assessed and discussed using a participatory and democratic methodology and a consensus system by qualified majority. Discrepancies among the WG members were resolved on the basis of the available literature, taking into account the highest quality evidence available for each recommendation selected; in the absence of information supported by quality evidence and where the participants considered the need to develop a good clinical practice recommendation, this was based on the majority consensus of the experts.

Subsequently, the document was reviewed and the recommendations and suggestions for good clinical practice formulated by the working group were differentiated into those related to adult patients and those related to paediatric/neonatal patients. For recommendations or suggestions, an analogue scale of "coloured symbols (lungs)" was used. The wide range of points to be agreed upon led the group to opt for this system instead of the traditional PICO question-based system, as used for example in the recent ERS/ATS guidelines.

The clinical practice suggestions were then submitted to a process of external validation (review), consisting of a committee of independent experts made up of two representatives from each participating scientific society, which showed the degree of agreement or disagreement with the panel of good clinical practice recommendations elaborated in the document by using the same analogue scale methodology. The drafting group responded to each of the suggestions received in a formal manner to arrive at the final document. In order to define the degree of agreement, a telematic vote was held once the key points had been defined. Voting groups were defined by patient age profile (adult, paediatric and neonatal), so that each specialist could only vote in the previously assigned group according to their experience. The tables in the document express the majority opinion, with a consensus of more than 50% of members being necessary to issue the corresponding recommendation or suggestion. In case of equality between two of the options (can or should be done) both have been reflected in the document.

Finally, the drafted report was subjected to a new round of validation by the CC and the WG, which reviewed both the text and the recommendations for good clinical practice formulated.

Where possible, consensus recommendations (clinical practice suggestions) were based on quality evidence, derived from available published data. Otherwise, tacit consensus was used where data were not available. However, due to feasibility, there was no systematic analysis of the quality of evidence using recognised sources of high quality and low bias rate as the most realistic approximation of quality and maximising practical utility based on our national health system, so that it could not be compromised. Therefore, a more user-friendly and intuitive analogue grading system was chosen that should allow healthcare professionals to easily contrast the current state of the best available evidence and subsequent guideline with the clinical practice suggestions issued in the document [25].

Therefore, and following the practices of the GRADE group (http://www.gradeworkinggroup.org), a green symbol denotes the consensus recommendation "should be done": indicated treatment or procedure that is based on at least one randomised trial, or is supported by strong observational evidence that it is beneficial and effective. A "yellow lung" indicates general agreement and/or scientific evidence in favour of a "can be done" for this statement or the usefulness/efficacy of a treatment or procedure. This is based on clinical trials conducted on a small number of patients or results that may not be broadly applicable to all patients with such characteristics. Finally, management strategies for which there is scientific evidence of potential harm or malpractice and which therefore should not be promoted ("should not be done") are indicated by a red lung (Table 2).

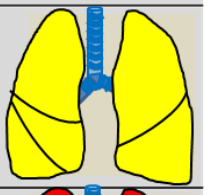
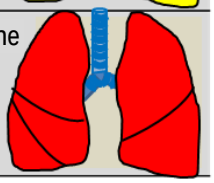
Definitions related to a treatment or procedure	Consensus statement instruction	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomised trial or is supported by strong observational evidence and consensus of authors (as indicated by an asterisk).	Should be done	
General agreement and/or scientific evidence favours the usefulness/efficacy of a treatment or procedure. May be supported by randomised trials based on small numbers of patients or not widely applicable.	Can be done	
Scientific evidence or general agreement not to use or recommend a treatment or procedure	Should NOT be done	

Table 2. Scientific reasoning for definitions based on "Coloured Lungs" for clinical practice suggestions.

This classification for our consensus document should not be considered literally similar to that used for the recommendations of other societies that apply a classification of levels of evidence (I-III) and a level of recommendation (A, B and C) or to the recommendations according to GRADE methodology [26], although they do agree with the practices of the latter on the practice of a complex and participatory consensus exercise, but they are intended to convey an operational clinical message that is easy to interpret for all professionals involved in the clinical management of adult or paediatric/neonatal patients with acute respiratory failure.

FIRST PART:

To whom should non-invasive respiratory support be administered?

4. Indications for NIMV

4.1. Adult patients in need of urgent support prior to obtaining a definite diagnosis

Both NIMV and HFNCT are NIRS measures used in the management of severe acute respiratory failure with the aim of avoiding endotracheal intubation. In certain situations, and in various settings, it is not always possible to obtain a definite diagnosis before NIRS is indicated.

In a patient with dyspnoea and signs of severe ARF of unknown cause, the use of respiratory support (mainly NIMV due to the lack of experience in HFNCT in this clinical context) may allow to gain the necessary time to gather essential information about the causal diagnosis, prognosis, baseline status of the patient or adequacy of the therapeutic effort.

This is a cohort of patients for which there is little experience in relevant literature. There is limited information on both the percentage of patients seen in this situation and the clinical features that lead to the indication of NIMV, especially considering that the results of complementary examinations are often not available and the decision is made on the basis of the "feeling of severity" of the symptoms.

There are no controlled studies comparing this practice with direct tracheal intubation, as these patients are not routinely represented in these studies. However, despite the lack of evidence, some authors suggest that NIMV would not worsen the prognosis of patients with severe ARF [24].

As a guideline, and taking into account the above, the criteria for the initiation of ventilatory support would be the following [22,27]:

- Clinical criteria:
    - Moderate-severe dyspnoea, with signs of respiratory effort, use of accessory muscles or paradoxical abdominal movement.
    - Tachypnoea.

- Blood gas assessment, if available:
    - Need for FiO_2 greater than 0.4 to achieve adequate oxygenation (88-92% in patients at risk of hypercapnia and greater than 92% in all other patients).
    - Acute ventilatory failure (pH < 7.35 with $PaCO_2$ >45 mm Hg).

In the presence of the above clinical criteria, NIMV can be initiated, provided there are no contraindications or indications for urgent intubation (Figure 2 and table 3). Subsequently and as quickly as possible, diagnostic evaluation should be continued to identify the diagnosis and prognosis of the disease causing ARF [28,29].

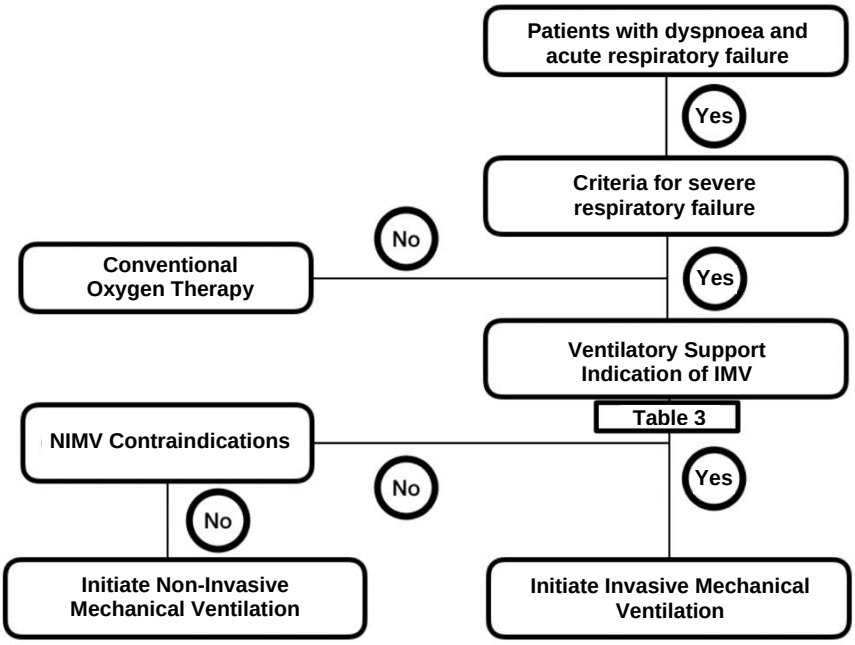


Figure 2. Decision algorithm for ventilatory support in a patient without a definite diagnosis.

Respiratory or cardiac paralysis
Breathing pauses or heart rate < 50 beats/min with loss of alertness or shortness of breath with signs of gasping
Uncontrollable agitation
Evidence of exhaustion, such as active contraction of accessory muscles with a paradoxical thoracic-abdominal movement
Massive aspiration or inability to adequately handle respiratory secretions
Haemodynamic instability unresponsive to fluids and vasoactive agents

Table 3. Indications for emergency invasive airway management.

4.2. Indication of NIMV in adult patients with a definite diagnosis

Once the necessary complementary examinations are available to make a diagnostic approach, the need to initiate NIMV will be assessed or a decision will be taken on its continuation if it has been initiated before diagnosis.

4.2.1. Acute chronic obstructive pulmonary disease (COPD)

When COPD is exacerbated, there is an increased mechanical strain due to high airflow resistance and dynamic hyperinflation, leading to muscle fatigue and respiratory acidosis. Positive pressure ventilation reduces the respiratory effort and increases alveolar ventilation, resulting in a decrease in both respiratory rate and air trapping. On the other hand, the increase in minute volume makes it possible to correct respiratory acidosis, and the application of external positive end-expiratory pressure (PEEP) compensates for the inspiratory effort required to overcome intrinsic PEEP [30].

The use of NIMV in patients with hypercapnic exacerbation of COPD became widespread in the 1990s after the publication of the first controlled studies. These

showed that the application of NIMV was associated with a reduction in intubation rate and mortality compared to conventional medical treatment [31–34].

In 2003, the first Cochrane systematic review was conducted, covering the high quality studies published up to then on the application of NIMV for patients with COPD exacerbation and respiratory acidosis compared to conventional medical treatment [35]. It concluded that the benefit was clear when selecting patients with respiratory acidosis, with a significant decrease in respiratory rate and improvement in hypercapnic acidosis after one hour of treatment, a reduction in the rate of intubations (relative risk 0.42) and a significant decrease in mortality (relative risk 0.41). Numerous studies and reviews carried out after 2000 have corroborated the clinical and prognostic improvement of these patients, provided that the application of NIMV is carried out under appropriate conditions, even outside intensive care units (hospital wards, emergency departments, etc.). Thus, the use of NIMV for COPD patients with pH below 7.35 and $PaCO_2$ > 45 mm Hg is reported to reduce the risk of intubation by 18-28%, the hospital stay by 2-5 days and mortality by 10-13% compared to standard medical treatment [36–39]. The benefit in the case of exacerbations without respiratory acidosis, on the other hand, has not been established [40,41].

There are few studies comparing the use of NIMV with intubation and invasive mechanical ventilation in patients showing severe exacerbations with criteria for immediate ventilatory support. Excluding patients in life-threatening conditions, the application of NIMV instead of invasive mechanical ventilation (IMV) can reduce the need for MV by more than 40%, although no impact on the prognosis of these patients has been demonstrated [42,43].

4.2.2. Acute cardiogenic pulmonary oedema (ACPO)

The application of positive airway pressure in patients with ACPO causes significant haemodynamic and respiratory effects, such as decreased right ventricular preload, decreased left ventricular afterload, increased cardiac contractility and cardiac

output, alveolar recruitment, reduced pulmonary shunt, increased pulmonary compliance and decreased respiratory effort. This leads to an improvement in dyspnoea, oxygenation and a decrease in respiratory rate within 30 minutes of initiation [30].

Multiple studies have demonstrated the superiority of continuous positive airway pressure (CPAP) and NIMV over conventional oxygen therapy in the treatment of ACPO, in terms of reducing the number of intubations (up to 22%) [44–46].

The first controlled studies evaluating the usefulness of non-invasive support in ACPO date back to the 1980s, and compared the efficacy of using CPAP versus conventional oxygen therapy (COT), demonstrating faster clinical improvement and a decrease in the number of intubations in the CPAP approach [45,47].

The first randomised controlled study evaluating the use of NIMV with pressure support obtained similar results [47], and several subsequent meta-analyses conclude that both techniques (CPAP and pressure support) reduce the rate of intubations and tend to reduce mortality with respect to COT (significant reduction with CPAP) [47,48].

However, in 2008 the 3-CPO study was published which included a large number of patients with acute pulmonary oedema and respiratory acidosis. The aim was to compare mortality between patients receiving CPAP, pressure support or COT. No significant differences in mortality were detected, although patients who received some form of respiratory support improved more rapidly [49]. There are design differences between the studies included in previous meta-analyses and 3-CPO that may account for these discrepancies. Even so, subsequent meta-analyses that include it continue to show that both techniques (CPAP and pressure support) reduce the rate of intubations, and that the application of CPAP in ACPO patients is also accompanied by a reduction in mortality [44].

Regarding the comparison of the two modalities, CPAP or NIMV, there are no data that support the superiority of one over the other in terms of evolution, although some clinical variables seem to improve more rapidly in patients treated with NIMV [50–52].

4.2.3. Respiratory decompensations in patients with Obesity-Hypoventilation Syndrome (OHS)

Patients with OHS often have exacerbations with hypercapnia and respiratory acidosis. The use of NIMV in these cases, analogous to COPD exacerbation, was associated with clinical and blood gas improvement [53]. However, the available evidence is still insufficient to make a firm and substantial recommendation and therefore the use of NIMV is only suggested in patients with OHS decompensation and the presence of respiratory acidosis.

4.2.4. NIMV in palliative care

The use of NIMV in palliative care must be differentiated from the use of NIMV as a therapeutic limit in those pathologies where its use is indicated (see section 4.2.7). In patients with ARF of different aetiologies, the use of NIMV can lead to symptomatic relief and/or prolong life for a few hours that may be essential for the patient and/or family [54]. It has been shown that using it improves dyspnoea and reduces morphine chloride requirements [55] and should be seen as an opportunity to improve dyspnoea while the rest of the palliative treatment is taking effect, defining short-term objectives and avoiding both generating expectations for the patient and family and prolonging the dying process [56,57]. The difficulty of generating high quality evidence in this field should be taken into account [41], perhaps experience in real life conditions could be an alternative, but the clinician should be aware that there is the possibility of administering NIMV as an adjuvant treatment for dyspnoea in palliative patients.

4.2.5. Severe exacerbation of asthma (SEA)

There is no good evidence regarding the prognostic improvement of the use of NIMV in patients with SEA [58]. However, a short NIMV test in such patients is possible on a case-by-case basis and under conditions of very close monitoring of the response (ideally in an ICU setting).

4.2.6. *De novo* hypoxaemic respiratory failure

The rate of intubation in patients with *de novo* hypoxaemic respiratory failure who receive NIMV is particularly high, ranging from 30-60%. It should be noted that 10-15% of patients with *de novo* acute respiratory failure receive NIMV and in a recent international observational study involving 2,813 patients with acute respiratory distress (ARDS), those initially treated with NIMV (15%) and severe hypoxaemia (PaO_2/FiO_2 < 150 mm Hg) had a higher mortality than those on invasive ventilation [61]. However, given that the condition may be due to several clinical entities, it warrants a separate analysis:

Pneumonia in non-immunosuppressed patients:

The use of NIMV in previously healthy patients with severe community-acquired pneumonia has a high failure rate and may delay the decision for orotracheal intubation and increase mortality [62]. The exception is COPD patients with exacerbation secondary to pneumonia, who have a better prognosis [63].

A recent prospective study involving 3,971 hospitalised patients diagnosed with pneumonia and treated with NIMV (27.9%) or invasive (IMV) showed an in-hospital mortality of 15.8%, 29.8% and 25.9% among patients treated with initial NIMV, initial IMV and failure of NIMV respectively [64]. It is noteworthy, however, that in the group

of patients initially treated with NIMV, previous cardiorespiratory comorbidity was more frequent and mortality was lower in NIMV-treated patients with such comorbidity.

In a retrospective study (2010-2011) of Medicare beneficiaries involving 2,757 patients over 64 years of age admitted for pneumonia who received mechanical ventilation, 19% received NIMV, with no difference in 30-day mortality compared to those who received IMV, and significantly lower medical expenditure [65].

In light of the studies, a NIMV test can be recommended for patients with cardiorespiratory comorbidity and pneumonia while it is not advisable for patients without such comorbidity, given the low quality and controversy of the evidence.

ARF in immunosuppressed patients

Although several studies supported the use of NIMV for the treatment of mild to moderate ARF in selected patients with immunosuppression of various aetiologies, the clinical benefits were not confirmed in a subsequent large clinical trial [66]. On the other hand, in a post hoc analysis of another cohort, which included 82 immunocompromised critically ill patients with hypoxaemic ARF, the two factors independently associated with endotracheal intubation and mortality were age and the use of NIMV as first-line therapy [67]. It is suggested, despite the lack of differences in the latest clinical trial [68], that HFNCT may be a better non-invasive strategy for these patients (see section on HFNCT), although NIMV remains a common strategy for these patients.

Looking ahead, studies are needed to assess the best strategy (NIMV sessions interspersed with COT-HFNCT or treatment with HFNCT alone). In a recent systematic review on the use of HFNCT in immunocompromised patients that included seven studies with 667 patients, the use of high flow was significantly associated with a reduction in mortality and intubation rate without increasing the length of ICU stay [69]. However, more randomised controlled trials are needed to allow confirmation of these findings and incorporation into clinical practice as a recommendation [70]. Therefore,

and in the absence of better-quality comparative studies with HFNCT, early NIMV may be an alternative to consider in patients with immunosuppression and ARF.

Acute hypoxaemic respiratory failure secondary to ARDS

Several studies and meta-analyses have shown a negative impact of the use of NIMV in patients with ARDS in the context of other organ failure, and it has not been shown to be superior to the use of HFNCT in these patients [20,71]. Only one pilot study in patients with mild ARDS (PaO_2/FiO_2> 200 and ≤300) showed decreased intubation and reduced cytokine levels with the use of NIMV, although these results could not be further confirmed [72]. There is also experience from a single-centre study that showed reduced intubation rates in patients with RDS when ventilated with a helmet-type interface [73]. Despite this, and due to the limited evidence, the use of NIMV cannot be recommended in severe hypoxaemic ARF secondary to ARDS. The only exception would be mild ARDS, as stated in the so-called "Berlin Definition" [74]

4.2.7. Patients with acute respiratory failure and do-not-intubate orders

The application of NIMV as a therapeutic limit for the treatment of ARF in patients with non-intubation orders has been extensively evaluated. A recent meta-analysis including 27 studies with a total of 2,020 patients with non-intubation orders [75]; in that study, survival after hospital discharge was 56% at one year in the NIMV branch and 32% in the conventional treatment branch, with no difference in the quality of life of survivors. In addition, these patients may benefit from early management in intensive or intermediate care units, with more experience in the management of the therapy [76]. In any case, the clinical issues related to quality of life in survivors, the degree of invasiveness or futility in non-survivors and the impact of NIMV in patients with orders for comfort measures alone do not seem to have been sufficiently evaluated yet. Therefore, the use of NIMV is suggested in patients with indication of therapeutic

limitation for intubation and invasive ventilation if they belong to any of the above groups in which NIMV efficacy is documented, provided that it also improves the feeling of dyspnoea during the procedure.

4.2.8. Neuromuscular diseases

It is the main cause of decompensation in such patients [77]. In the context of acute neuromuscular disease (myasthenic crisis, Guillain-Barré syndrome), especially with bulbar involvement, NIMV should be used with caution and with particularly close monitoring and evaluation of response to treatment [78]. In case of exacerbation of any cause (e.g., intercurrent infection) in patients with chronic respiratory failure secondary to neuromuscular and rib cage pathology, NIMV support is recommended to prevent and treat respiratory acidosis although the evidence of prognostic improvement is less than in COPD cases.

4.2.9. Thoracic trauma

In patients with thoracic trauma and hypoxaemia secondary to pulmonary contusion, NIMV can be used to prevent or treat hypoxaemic ARF once undrained pneumothorax or bronchopleural fistula have been ruled out [79]. According to the guidelines of the British Thoracic Society, the Canadian Critical Care Trials Group/Canadian Critical Care Society and more recently the joint guidelines of the European Respiratory Society and the American Thoracic Society, the indications and efficacy of NIMV in trauma-induced respiratory distress have so far been inconsistent and have simply received a low-grade recommendation [41,80,81]. The role that HFNCT may play in this indication is still unknown. In a clinical trial in adults with hypoxaemic ARF (PaO_2/FiO_2 < 200 mm Hg) with thoracic trauma, patients were randomised to receive treatment with either HFNCT or NIMV [82]. The study findings showed that the APACHE score was higher in the NIMV group. The study was stopped early due to a

significant difference in intubation rate (lower in the NIMV group). In the absence of higher quality studies, we suggest the use of NIMV in patients with ARF and thoracic trauma in the absence of undrained pneumothorax.

4.2.10. NIMV in weaning and extubation

Three different scenarios can be distinguished in this section, the application of NIMV to facilitate weaning and extubation, the treatment of ARF post-extubation, and finally the prophylactic application of NIMV post-extubation to prevent failure.

In the first scenario, a recent review conducted to assess whether the use of NIMV facilitates extubation included 16 trials of moderate to good quality, involving 994 participants, most of them with COPD [83]. Compared to controlled-modality switch-off, NIMV significantly reduced mortality, especially in trials that exclusively included participants with COPD (RR 0.36). However, this effect was not replicated in other, more heterogeneous types of patients. In addition, NIMV significantly reduced other secondary outcomes such as disconnection failure, length of ICU and hospital stay, but with a significant degree of heterogeneity. Subgroup analyses suggest that mortality benefits were significantly greater in trials that exclusively included participants with COPD compared to mixed groups.

On the other hand, it is important to differentiate the application of NIMV in mechanically ventilated patients as a weaning strategy between those patients who tolerated the spontaneous ventilation test (SVT) but have a risk factor for extubation failure (table 4), versus those patients in whom NIMV is applied as a weaning strategy and who have had an SVT failure. In this regard, the use of NIMV in patients in the weaning phase of mechanical ventilation, with SVT failure, did not show differences in patient evolution (lower mortality, duration of ventilatory support, reintubation or tracheostomy), compared to a conventional weaning strategy [84,85].

Age > 65 years
Heart failure as a cause of ARF
APACHE II > 12 at the time of extubation
COPD decompensation
Chronic pneumopathy with occurrence of hypercapnia during spontaneous breathing test
More than one of the following:
Failure of 2 consecutive spontaneous breathing tests
Chronic heart failure
$PaCO_2$ > 45 mmHg after extubation
Multiple comorbidities
Weak cough or stridor post-extubation

Table 4. Risk factors for extubation failure

In terms of preventive strategy in extubation failure, the literature suggests that prophylactic NIMV after extubation may be useful in preventing acute respiratory failure in selected patient groups [86–88]. The impact of prophylactic NIMV added to HFNCT has recently been evaluated in a multicentre randomised clinical trial involving 691 patients in the ICU at high risk of extubation failure. There was a decrease in the number of reintubations in the group of patients in which NIMV was applied immediately after extubation in addition to HFNCT, compared to the HFNCT-only group [89].

However, in the case of NIMV used to treat post-extubation acute respiratory failure, there is no clinical benefit [90] and it may even increase mortality by delaying reintubation [91], so its use is discouraged.

The exception to this rule is probably those patients who develop respiratory failure in the postoperative period following major elective abdominal surgery [92] or lung resection [93]. In a multicentre clinical trial [94] involving 293 patients who underwent elective or urgent abdominal surgery and developed hypoxaemic respiratory failure within the first postoperative week, the use of NIMV significantly reduced reintubation (33.1% in the NIMV group compared to 45.5% in the COT group) although

no significant difference in 90-day mortality was obtained (14.9% in the NIMV group compared to 21.5% in the standard oxygen therapy group). The application of NIMV was safe as there was no significant difference between the two groups in the incidence of serious adverse events, thus the application of NIMV compared to standard oxygen therapy is considered to significantly reduce the risk of reintubation, without producing adverse events. These findings support the use of NIMV in this setting [95].

In summary, in patients who tolerate an SVT and present risk factors for extubation failure, especially in patients with COPD exacerbation, a strategy of applying NIMV post-extubation reduces extubation failure (even in combination with HFNCT). However, in more heterogeneous groups, NIMV cannot be recommended as a strategy for weaning from mechanical ventilation [96]. For ARF post-extubation, IMV should generally be used as a rule of thumb.

4.2.11. NIMV in viral pandemic situations

The use of NIMV for severe acute respiratory syndrome (SARS) and other viral pandemics is controversial, with NIMV failure rates around 30% [97], but no evidence of viral spread to caregivers who took adequate precautions. More recently, NIMV has also been used in patients with ARF due to Influenza A H1N1, with failure rates ranging from 13% to 77% [98–100]. It has also been widely used in the recent SARS-Cov2 pandemic, however, the results of its application still need to be evaluated, although specific recommendations on its indications and mode of use have been made [101].

Despite the uncertainty of the evidence and the absence of randomised clinical trials, the positive data from most observational studies suggest that it can be considered for use in carefully selected patients in experienced centres and in a protected environment (negative pressure rooms).

4.2.12. Acute postoperative respiratory failure

Respiratory function is easily compromised in the postoperative period, with risk of atelectasis and diaphragmatic dysfunction. The main indication for NIMV in the

perioperative period is hypoventilation occurring during recovery from anaesthesia or from opioid drugs and sedatives. In addition, it may be worsened by upper airway obstructive phenomena due to hypotonia of the oropharyngeal muscles [102]. Patients with known pre-intervention sleep disordered breathing, OHS and neuromuscular disorders are particularly sensitive to these adverse events.

Both CPAP and NIMV improve respiratory function in the perioperative period by preventing acute respiratory failure. In a study of 830 patients undergoing planned cardiothoracic surgery at risk of respiratory failure, a randomised clinical trial comparing HFNCT versus NIMV after extubation showed that the use of HFNCT compared to NIMV was not associated with a higher rate of treatment failure or increased mortality [103].

A systematic review on safety of the technique including 2 studies and 269 patients indicates that the use of CPAP or NIMV are safe interventions in the short term in patients with upper abdominal surgery, although no differences in mortality and length of hospital stay were found. There were insufficient longer-term data on the potential relative adverse effects on complications associated with surgical anastomoses [95]. Other studies in patients during the perioperative period of bariatric surgery have also failed to demonstrate an increase in suture dehiscence due to the effect of positive pressure [104]. Similarly, no increased prevalence of tracheobronchial anastomotic leakage has been shown in 5 randomised studies, involving 292 patients undergoing thoracic surgery and receiving NIMV [105]. Therefore, as specified above, NIMV is suggested to be useful in postoperative ARF following abdominal and cardiothoracic surgery, without significant adverse effects at the level of surgical anastomoses.

4.3. Indications for NIMV in paediatric patients

4.3.1. General ARF (hypoxaemia with hypercapnia) and reintubation prevention

The use of NIMV in paediatric patients with general ARF has been shown to be effective in improving oxygenation, pH, lowering $PaCO_2$ and reducing the need for invasive mechanical ventilation [106]. Early use of NIMV in conjunction with a cough assistant is also recommended in patients with neuromuscular diseases (NMD), especially in paediatric patients with marked hypotonia [107] in order to avoid intubation. There is also experience in the same profile of patients in post-extubation situations, associated with a decrease in the rate of reintubation and shorter length of stay in Paediatric Intensive Care Units (PICU). Therefore, its use should be recommended for patients with NMD and high risk of post-extubation respiratory failure [108]. Similarly, this combination applied as preoperative training improves the postoperative respiratory outcome of paediatric patients scheduled for scoliosis surgery, reducing the time spent on mechanical ventilation and in the PICU [109]. Based on these observations, the use of NIMV can be suggested to avoid reintubation in any situation with a high risk of weaning failure (especially NMD) and in any paediatric patient with hypoxaemic and hypercapnic ARF, provided that there are no contraindications for NIMV [109,110].

4.3.2. Hypoxemic ARF without hypercapnia

NIMV has been used in paediatric patients with acute hypoxaemic respiratory failure without hypercapnia, with an oxygen saturation/inspired oxygen fraction ratio (SaO_2/FiO_2) between 160 and 270 (or PaO_2/FiO_2 between 175 and 300) and an absence of multi-organ failure [111,112]. In a study in paediatric patients with hypoxaemic ARF, the presence of respiratory distress was a predictor of early failure of NIMV [111], as was the number of organ failures [112].

In the case of ARF associated with primary or secondary immunodeficiency pathologies, NIMV has been used as first-line respiratory support to avoid endotracheal intubation, demonstrating a reduction in the risk of pneumonia associated with mechanical ventilation and an improved prognosis in extrapulmonary distress [113].

In a study focusing on NIMV in patients with pneumonia and hypoxaemic ARF, the rate of intubation in pneumonia was significantly lower than in patients with respiratory distress (17 vs 50%) [111]. The use of CPAP in paediatric patients with pneumonia and hypoxaemia has also been shown to reduce mortality in countries with limited economic resources [114,115].

The use of NIMV for moderate to severe ARF associated with viral infections, especially in acute viral bronchiolitis in young patients, has been shown to be useful in a very high percentage of cases. Its use improves hypoxaemia, improving gas exchange, stabilises the dynamic collapse of the airway and relieves muscle fatigue, making it possible to reduce the use of invasive mechanical ventilation, which is currently almost exclusively indicated in cases of respiratory distress associated with viral infection and high risk of contagion by secretions (severe epidemic outbreaks with particularly virulent micro-organisms). In recent years, HFNCT has been used as an alternative to NIMV in this pathology, but for the time being the efficacy of NIMV in acute bronchiolitis is still superior and more cost-effective [116–118].

In summary, NIMV is suggested for use in patients with moderate non-hypercapnic ARF, without respiratory distress and without associated organ failure. It has also proven useful in immunocompromised patients with ARF and in patients with moderate or severe ARF associated with viral infections (mainly viral bronchiolitis).

4.3.3. Paediatric patients with ARF in the context of severe asthma attacks

NIMV has been used to reduce muscle fatigue, improve gas exchange, counteract intrinsic PEEP, demonstrating efficacy in both clinical trials and observational studies [119–121] resulting in a low rate of intubation in these patients. In contrast, there is currently insufficient evidence to recommend high-flow therapy in paediatric patients with status asthmaticus [122].

4.3.4. Miscellaneous

These are rare clinical situations in which the use of NIMV has been documented, albeit without the support of observational studies with sufficiently large samples.

- Acute chest syndrome due to sickle cell disease: NIMV has been shown to improve alveolar oxygenation, decrease alveolar hypoventilation and decrease both the number of transfusions and exchange transfusions [123].
- Acute cardiogenic pulmonary oedema: NIMV has demonstrated efficacy and safety both before and after cardiac surgery, although its failure is often associated with pulmonary sequelae secondary to cardiac disease [124].
- Respiratory exacerbations in patients on MV at home: NIMV is indicated during transport to a hospital facility, preferably with a oronasal or full facial interface and with re-programming [78,125].
- Acute dynamic upper airway obstruction: Despite the scarcity of literature on the use of NIMV for acute upper airway stabilisation, its use is widespread in clinical practice and has been associated with a significant decrease in respiratory effort and improvement of gas exchange [126,127].
- Paediatric patients with dyspnoea and/or ARF in "end-of-life care" and without indication for invasive mechanical ventilation: as a comfort measure [128].

Thus, in summary, early use of NIMV is recommended in paediatric patients with diseases presenting with general ARF and as prevention of extubation failure, especially in patients with NMD. In situations of hypoxaemic ARF, a trial with NIMV (CPAP or pressure support) is recommended for one to two hours with close monitoring of the SaO_2/FiO_2 or PaO_2/FiO_2 ratio, taking into account the failure criteria described above. The same approach would be valid for patients with SEA. Finally, in ARF due to respiratory infection, especially in acute viral bronchiolitis in early-age patients, NIMV should be considered an appropriate supportive measure in any setting, from health transport to hospital services themselves.

4.4. Indications for NIMV in neonatology

In recent years, the use of NIMV has become widespread in all neonatal respiratory pathologies with mild-moderate respiratory failure in order to try to avoid endotracheal intubation and invasive mechanical ventilation [129].

The main situations in which experience exists are as follows:

4.4.1. Initial stabilisation after birth

Especially in situations of extreme prematurity, given that the greater the immaturity, the higher the incidence of apnoea and/or bradycardia after birth (< 32 weeks GA and/or < 1500 grams).

4.4.2. Respiratory Distress Syndrome (pathology of prematurity due to surfactant deficiency)

NIMV should be initiated prophylactically in all at-risk patients (< 30 weeks GA) who did not initially require intubation [130]. If FiO_2 requirements are higher than 30% in preterm infants, early treatment should be accompanied by intratracheal surfactant administration.

4.4.3. Preventing ARF after extubation

In preterm infants less than 30 weeks GA with Respiratory Distress Syndrome, the use of NIMV reduces the incidence of reintubation after weaning from conventional mechanical ventilation and extubation [131]. In the other gestational ages, it is carried out after individual assessment.

4.4.4. Other neonatal respiratory pathologies

NIMV has been used in apnoeas of prematurity, restrictive lung disease (bronchopulmonary dysplasia), meconium aspiration syndrome, pulmonary oedema, airway disorders (laryngomalacia, tracheomalacia), and diaphragmatic paralysis.

4.4.5. Extra-respiratory causes

NIMV has been used as a measure to reduce patent ductus arteriosus of prematurity and, in general, congenital heart diseases with pulmonary hyperflux [132]. It is also indicated for use in newborns with NMD or CNS disorders with hypoventilation.

5. Indications for high-flow nasal cannula therapy

5.1. Indications for HFNCT in adults

5.1.1. ARF in pneumonia and acute respiratory distress syndrome

Given the lack of evidence for the use of NIMV in these indications, according to the ERS/ATS clinical practice guidelines [41], COT remains the standard of care. HFNCT has been postulated as a treatment alternative, but studies analysing its use often include a case-mix of patients with various aetiologies as the cause of respiratory failure [20,133]. In addition, published protocols for the application of HFNCT vary widely, so again it is very difficult to analyse the results in aggregate. However, recent meta-analyses have found significant results through stratification of studies [134]. One of the main studies in hypoxaemic ARF [20] enrolled 310 patients in three groups, one with HFNCT, one with NIMV and one with conventional oxygen therapy. Although the outcome for the primary endpoint (intubation rate) was negative, mortality and the number of ventilator-free days were significantly lower in the group treated with HFNCT. In the subgroup study, the authors found a significant reduction in the intubation rate in patients with more severe hypoxaemia ($PaO_2/FiO_2 < 200$). It is important to note that this study excludes patients with other organ failures in addition to respiratory failure. Another study in the Emergency Department setting involving 303 patients[133] showed that the need for ventilatory support in the first 24 hours of respiratory failure was significantly lower with HFNCT.

Thus, HFNCT is recommended as the first respiratory support technique for patients with severe pneumonia and/or ARDS, as opposed to oxygen therapy and NIMV in patients without direct indication for orotracheal intubation.

5.1.2. ARF in immunosuppressed patients

The evidence for the use of HFNCT in this group of patients is limited. The only clinical trial analysing its use versus conventional oxygen therapy [135] applies HFNCT for very short periods of 2 hours, so the conclusions obtained on clinical objectives such as intubation or mortality must be interpreted with great caution. Even secondary objectives such as comfort do not obtain significant results. There are two studies of subgroup analyses of previous clinical trials: one in patients enrolled in a clinical trial randomising NIMV and conventional oxygen therapy, in which HFNCT is applied in both groups according to the decision of the attending clinician [66], which did not show favourable results for HFNCT. The second [67] analyses the immunosuppressed patients enrolled in the original FLORALI trial [20] and demonstrates, in the 82 patients included, that the best therapeutic option for these patients is HFNCT versus conventional oxygen therapy and NIMV, which has the highest mortality. An important limitation of these studies is that they include mixed groups with various causes of immunosuppression.

Therefore, and in the absence of further data on whether or not it is superior to COT, HFNCT can be used in patients with ARF and immunosuppression.

5.1.3. Preventing respiratory failure and reintubation after extubation

There are several studies that focused on the use of HFNCT for extubation failure with different designs. Of particular note are several studies comparing HFNCT with COT. In one study, a decreased risk of reintubation was observed with the use of HFNCT in patients with $PaO_2/FiO_2 \leq 300$ mm Hg [136], although it should be noted that reintubation was a secondary endpoint of the study. On the other hand, in another study [137], no conclusive results on reintubation rate were achieved when comparing HFNCT with COT in patients at high risk of reintubation and without hypercapnia, as the authors were unable to recruit the intended sample size. In patients at low risk of extubation failure, a controlled study documented a significant reduction in the reintubation rate

in the HFNCT group of patients compared to the COT group [138]. It is considered that although several meta-analyses have been published, there is no specific study on the risk of reintubation, so no definitive recommendations for HFNCT versus COT can be made.

Regarding the use of HFNCT after extubation, a controlled non-inferiority study [139] in non-hypercapnic high-risk failure patients confirmed the non-inferiority of HFNCT to NIMV in this heterogeneous group of patients, with a reduction in the rate of respiratory failure after extubation in the HFNCT approach, explained by the better tolerability of the technique that allowed strict application of the protocol. Finally, the recent results of the above-mentioned study in high-risk patients (especially in hypercapnia) support its use in combination with NIMV, which achieves the lowest reintubation rates [89]

Finally, in the group of patients extubated after surgery, the studies vary according to the surgery performed, the most studied being abdominal and cardiothoracic surgery. For instance, the OPERA trial [140] analyses the prevention of hypoxaemia with HFNCT in postoperative major abdominal surgery patients at moderate/high risk of postoperative respiratory complications, and found no benefit of HFNCT compared to COT.

In the case of cardiothoracic surgery, several studies have been published. The BiPOP trial [103] with a non-inferiority design using a 9% margin of HFNCT versus NIMV, and a combined primary endpoint, included 830 patients with postoperative respiratory failure or at high risk of reintubation, confirming the non-inferiority of HFNCT versus NIMV in this group of patients. Another controlled study [141] reported a lower need for therapeutic escalation with the use of HFNCT compared to COT, although again in low-risk patients and with a reintubation rate much lower than those reported in the other studies (0.6%), which limits the generalisability of the results.

In short, to sum up:

- The use of HFNCT after planned extubation may be considered in patients without hypercapnia and at low risk of reintubation.

- The routine and exclusive use of HFNCT to prevent reintubation in high-risk patients after extubation cannot be recommended. However, recent data supports its use in combination with NIMV.
- HFNCT may be considered as a therapeutic alternative to NIMV in postoperative cardiothoracic surgery patients with postoperative respiratory failure or at high risk of reintubation).

5.1.4 Pre-oxygenation prior to intubation

To date, three main pre-oxygenation options for orotracheal intubation have been analysed: HFNCT, NIMV and the combination of both. Unlike HFNCT, NIMV can only be applied in the initial phase of spontaneous ventilation, whereas HFNCT can be applied from the beginning, even in the phase prior to anaesthetic induction, and can be prolonged until the apnoea phase and even during intubation procedures. There have not been any comparative studies between NIMV and HFNCT during the pre-apnoea induction phase. The OPTINIV study in hypoxaemic patients mainly with pneumonia and respiratory distress showed that adding HFNCT to NIMV was associated with lower desaturation and higher mean SpO_2 during the apnoea phase [142]. This parameter has been shown to be critical in reducing pre-intubation oxygenation thresholds [143]. Only one controlled study has examined NIMV for this indication [144], and despite the positive results for its use, the design does not allow for a high-evidence recommendation in its favour. On the other hand, there are more studies analysing HFNCT for this same indication. In one of them, which included hypoxaemic patients at the time of intubation, no improvement in oxygenation was observed with respect to the use of COT, although the time to intubation was greater than 4 minutes in a large percentage of the patients analysed [145]. Nor was improvement with HFNCT found during the apnoea phase in another study of 150 patients [146]. Another study involving 40 patients with mild to moderate hypoxaemia [147] found no difference compared to COT. Key factors that seem to influence these results are the experience of the staff performing the technique, with differences disappearing when intubation times are

reduced, the type of study design, the degree of hypoxaemia prior to the intubation attempt and the pre-oxygenation technique used [148].

In summary, for hypoxaemic patients who are to be intubated on a scheduled basis, we suggest the use of pre-oxygenation techniques with NIMV and/or HFNCT rather than COT in order to reduce the risk of peri-intubation hypoxaemia. Mixed techniques of NIMV plus HFNCT should be reserved for severely hypoxaemic patients at high risk of early desaturation.

5.1.5 Miscellaneous

- ARF in bronchoscopy and other invasive techniques: Hypoxaemia is a common phenomenon during bronchoscopy that often limits its indication in patients with underlying ARF. Although there is experience and evidence on the use of NIMV as an alternative to conventional oxygenation in high-risk patients, studies with HFNCT are beginning to appear, mainly emphasising its safety, efficiency, comfort and tolerability [149].

- Acute Heart Failure (AHF) / Acute pulmonary oedema (APO): This is a field in which a high amount of evidence recommends the use of positive pressure (NIMV/CPAP). However, there are also studies in which the use of HFNCT in patients with moderate AHF improves dyspnoea at an early stage, reduces the respiratory rate and improves oxygenation compared to COT [150]. To date, there are no comparative studies between the use of CPAP and HFNCT in patients with APO. It is important to note that, in the recent recommendations of the European Society of Cardiology on the treatment of ARF secondary to AHF with non-invasive means, HFNCT appears as a therapeutic option in patients with moderate AHF who do not respond to COT or in those with an indication for and intolerance to NIMV [52].

- Hypercapnic respiratory failure in COPD: As in APO, the first line of treatment in exacerbation of COPD with respiratory acidosis remains NIMV. However, physiological and safety studies on the use of HFNCT in COPD patients with hypercapnia have recently been published [151,152], documenting a decrease in $PaCO_2$ values in the patients involved, which may allow its use in combination with NIV or as a method of weaning from NIV [152]. It remains to be determined in which patients it could serve as a viable alternative to NIMV.

- Patients in palliative care: HFNCT may be a therapeutic alternative for patients with a non-intubation order and ARF, especially in case of refractory dyspnoea or in patients unable to tolerate NIMV. The challenge for the future will be to identify patients in palliative or non-intubation status who could be treated with HFNCT from the outset in order to achieve greater comfort [153].

5.2. Indications for HFNCT in paediatric patients

In recent years, HFNCT has seen widespread application in the paediatric setting. This has led to its extensive use in cases of respiratory failure. This application, at present, is not always supported by consistent evidence and is still under development in many cases.

At the time of writing, it can only be stated, pending proof of cost-effectiveness [154], that HFNCT could have an intermediate place between COT and NIMV/CPAP treatment [118,155]. It should be made clear that this approach is a less effective therapy than CPAP and of course NIMV. At the same time, its indication should be individualised and should never delay the initiation of CPAP, NIMV or MV. This is of particular importance in situations of moderate and severe respiratory failure.

In the case of acute bronchiolitis, HFNCT cannot be recommended on-site as initial therapy for mild-moderate bronchiolitis. A systematic review including 9 randomised controlled studies suggests that HFNCT is safe as initial therapy in the respiratory

management of bronchiolitis but there is no evidence that it is beneficial compared to conventional oxygen therapy or CPAP [156,157]

In the ward setting, and as a post-COT approach, it could be useful in cases of mild hypoxaemia and preserved effort with the intention of avoiding therapeutic escalation (considering escalation as any additional therapeutic measure such as suctioning of respiratory secretions) although it has not been shown to decrease the likelihood of increased respiratory support, admission to PICU or intubation [158]. Should the use of HFNCT become widespread for the treatment of bronchiolitis on hospital wards, this therapeutic approach could lead to a disproportionate increase in costs [154,159]. There are no studies at present that have compared the use of CPAP with HFNCT in the paediatric inpatient ward setting, although the tolerability of HFNCT may be better with less nursing workload. In case of severe respiratory failure and admission to PICU, HFNCT should not delay the initiation of CPAP or NIMV [158,160].

Finally, there is also controversy about the potential usefulness of HFNCT in paediatric patients with asthma. The beneficial effects of humidified and heated oxygen do not seem to be sufficient to decrease the respiratory effort [122,161]. HFNCT has not been shown to be superior to COT in the management of asthma attacks in the paediatric emergency department [162]. At the same time, it does not appear that HFNCT alone can improve CO_2 elimination in paediatric patients [163]. Thus, its use in this group of patients can only be considered if there is a normal level of consciousness and should always involve very close monitoring. At the same time, and as indicated above, it should never delay the initiation of CPAP, NIMV or MV or the administration of bronchodilators.

5.3. Indications for HFNCT in neonatology

HFNCT is used in respiratory pathologies with mild-moderate respiratory failure [164]. There is evidence and consensus on CPAP weaning and ventilatory weaning to avoid reintubation in preterm patients > 28 weeks GA [165].

The determining factors that have led to its use have been its low reported side effects, improved patient and family comfort and the significant reduction of nasal lesions compared to NIMV.

6. Considerations specific to the use of NIMV in the pre-hospital environment

In adults receiving pre-hospital care, a clinical assessment is essential for the indication and initiation of NIMV. There is now sufficient evidence to support the safe use of NIMV, mainly in CPAP mode, in suspected acute pulmonary oedema, as it decreases the rate of orotracheal intubation and mortality [166–169]. However, in order to perform the technique safely, it is essential to strictly protocolise it by performing a thorough clinical assessment including the principles of section 4.1. [170] and rigorous pre-established criteria for endotracheal intubation, such as those shown in table 3, and provided there is no therapeutic limit in this regard [169].

There is little evidence for pathologies other than acute pulmonary oedema. For patients with COPD exacerbation, it is suggested that NIMV could be used safely.

In cases of ARF in paediatric patients without altered level of consciousness, NIMV in the pre-hospital setting can stabilise the patient and improve their condition during transport. In particular, ARF in the context of bronchiolitis, asthma attacks or acute laryngitis often benefit most from early use of NIMV, and NIMV has been shown to reduce the need for intubation. In many of these situations, the use of CPAP, which is easier to use in the pre-hospital setting, has been shown to be sufficient and not inferior to NIMV at two pressure levels. In contrast, there is insufficient evidence to recommend the use of high-flow therapy in the same conditions [171–173]. Finally, patients with NMD and home NIMV in case of ARF should be transferred with at least the same level of assistance they regularly receive at home.

7. Contraindications to non-invasive respiratory support

There is no clear consensus on absolute and relative contraindications for the use of NIMV in adults. Contraindications are based on two points: on the one hand, that NIMV would be technically impossible to use and, on the other hand, that the results of NIMV would not be adequate for the pathology. There are a number of situations that preclude the application of NIMV and in which the assessment of orotracheal intubation (OTI) is mandatory (Table 5).

The contraindications for NIMV in paediatric patients are not very different from those described for adults. It is worth highlighting the situations in which the use of NIMV could worsen the patient's prognosis by delaying endotracheal intubation and conventional mechanical ventilation [174,175], such as cardiorespiratory arrest, the need for airway protection, as during coma or active gastrointestinal haemorrhage, severe respiratory failure with absence of respiratory effort or with risk of imminent respiratory exhaustion/respiratory arrest, haemodynamic instability, undrained pneumothorax, malformations hindering interface placement, abundant secretions and finally cases of hypoxaemic respiratory failure with SaO_2/FiO_2 ratio less than 160 or PaO_2/FiO_2 less than 175 for the worst documented prognosis.

Similarly, in newborns, the existence of certain facial or nasal malformations (such as choanal atresia) would make NIMV technically unfeasible. In case of risk of intestinal perforation (immediate abdominal postoperative period), it is advisable to delay the start of surgery or to do so with minimal support to avoid abdominal distension. Similarly, it would be contraindicated in case of congenital diaphragmatic hernia before corrective surgery.

As HFNCT is a comfortable and better tolerated therapy than NIMV, there seems to be a lower rate of rejection due to lack of patient cooperation. Being a recent technique, there are not yet many studies on its contraindications.

Absolutes • Cardiorespiratory arrest or apnoea with indication for endotracheal intubation • Need for immediate airway isolation • Inability to adapt any type of interface to the patient's face, due to facial trauma, or atypical facial phenotype. • High suspicion of upper airway obstruction • Lack of control of airway secretions (abundant or ineffective coughing) • Shock that cannot be stabilised with volume or inotropes • Threatening haemoptysis or haematemesis • Coma (except in hypercapnic encephalopathy) • High suspicion of undrained pneumothorax (Priority drainage of pneumothorax)
Relative: • Uncontrollable vomiting or epistaxis • Recent upper airway or upper digestive tract surgery. Although it has traditionally been considered a relative contraindication, there are no studies to support this. • Pregnancy: there is no experience in the literature in this area. • Lack of adequate equipment or technical training.

Table 5. Contraindications to NIMV in adults.

SECOND PART:

HOW TO PERFORM NON-INVASIVE RESPIRATORY SUPPORT?

8. Risk stratification

Cases in which the use of NIMV/HFNCT may be considered, but which have a high failure rate and therefore merit greater dedication and resources, should be assessed from the outset by a specialist who has access to an environment with adequate monitoring and immediate availability to initiate advanced life support measures (Table 6). Similarly, cases initiated outside the above areas that do not improve within a reasonable time (1 to 3 hours as a guideline) or where NIMV is expected to be required for a prolonged period of time should be treated in the abovementioned environment.

Low risk of NIMV failure Treatment with NIMV / HFNCT	High risk of NIMV failure Treatment with NIMV / HFNCT
In ER / monitoring areas	In intensive care units (ICUs)
• COPD exacerbation. • Hypoventilation associated with obesity. • Restrictive / neuromuscular diseases. • Acute cardiogenic pulmonary oedema. • Hypoxaemic ARF with limitation of treatment with invasive mechanical ventilation.	• Failure of NIMV / HFNCT without limitation of treatment with invasive mechanical ventilation. • Pneumonia with severity criteria in immunocompetent / immunocompromised patients. • Thoracic trauma. • Acute respiratory distress syndrome (ARDS).

Table 6. Recommendations for risk stratification of NIMV in patients with acute respiratory failure in the hospital

In paediatrics, severity can be determined with the help of some prognostic indices that allow determining the severity of ARF, such as the "pulmonary score" or its modified version in the case of asthma that includes the assessment of oxygen saturation when breathing room air [176], the Taussig scale, used to assess stridor associated with upper airway obstruction [177] or the Wood-Downes Ferrés scale for bronchiolitis [178]. Thus, if there is no improvement in the indices used in the initial assessment after one or two hours of NIMV in an emergency room, the risk of NIMV failure should be considered high and the patient should be transferred to a PICU for further treatment in a more appropriate setting. In the case of hypoxaemic ARF, risk factors for failure [111,179–181] are mainly age (higher risk at younger age), baseline and 2-hour respiratory and heart rate, generic severity scales (such as PELOD, PRISMIII, PIM1, PIM2), hypercapnia, respiratory acidosis and, especially, severity of hypoxaemia (need for FiO_2 greater than 0.6 within 2 hours of starting NIMV, PaO_2/FiO_2 and/or SpO_2/FiO_2 that do not improve after 2 hours of NIMV, especially if they remain below 170 and 160 respectively).

Finally, stratification of patients in neonatology does not apply, since all neonatal patients with non-invasive respiratory support are admitted to neonatal units under strict monitoring and medical and nursing care specific to these units.

9. Physical environment and staffing

9.1. Particularities of application in a pre-hospital environment

In general, a more difficult patient adaptation to NIMV is to be expected. In addition to the difficulties inherent to the technique, extreme care must be taken to monitor gas reserves, consumption and leaks, both of oxygen and medical air, especially in Air Medical Transport (AMT) and in prolonged ground transfers. Mechanical breakdowns of the means of transport as well as weather conditions can increase transport times and therefore gas consumption and the occurrence of complications.

In addition, and especially in AMT, anxiety increases and therefore the appearance of complications such as rejection of the procedure. Finally, the expansion of gases in flight at high altitudes can lead to increased gastric distension.

9.2. Hospital units for adult patients

Regardless of its physical location, the minimum characteristics that a unit offering NIRS as a treatment should have are specified in table 7.

In terms of human resources, the training, experience and involvement of the professionals is almost more important than the location where NIRS is performed; an adequate doctor-patient ratio (no more than 1:6), nurse-patient ratio (no more than 1:4) with a minimum essential monitoring of 24 h including night time can be an independent factor for the success of the therapy, no matter where it is performed [182,183].

Mandatory	Recommended
- 24-hour presence of trained and experienced medical and nursing staff. - Rapid access to orotracheal intubation (OTI). - Continuous oximetry (SpO_2). - Protocolised monitoring of respiratory frequency (RF), heart rate (HR), blood pressure (BP) and temperature. - Availability of specific ventilators for NIMV with autonomy for transport within the hospital environment, adaptable to different consumables and with monitoring of ventilatory parameters and provision of alarms. Ideally, they should have monitoring by means of flow / time and pressure / time graphs. - A minimum of two different types of masks for the option of interface rotation. - At least one aerosol therapy system adapted to the consumable. - At least one active humidification system.	- Control via telemetry. - -Non-invasive transcutaneous CO_2 monitoring ($ptCO_2$). - Nurse/patient ratio 1:3 - 1:4. - Possibility of on-site arterial blood gas monitoring. - Access to bronchoscopy. - Access to ultrasound. - Access to respiratory physiotherapy.

Table 7. Characteristics of an adult unit for implementation of NIRS

9.3. Paediatric units

NIRS should be performed in a safe environment and by experienced personnel, preferably PICU, with material, equipment and tubing appropriate to the patient's weight and age. Warm humidification is recommended to avoid accumulation of secretions. The presence of parents or caregivers is also recommended.

In terms of monitoring needs, access to venous blood gases and continuous monitoring of level of consciousness, pulse oximetry, respiratory rate and heart rate should be ensured. Patients should be closely monitored to avoid ulcers, gastric distension (present at inspiratory pressures above 25 cmH_20), barotrauma and conjunctivitis. Care algorithms developed and applied by experienced NIMV nurses are useful for this purpose [184].

9.4. Neonatal units

In addition to the monitoring requirements specified above for paediatric patients, the following are desirable: transcutaneous gas monitoring, access to chest radiology and ultrasound. In terms of staffing, a neonatal specialist or, in the absence of such, a paediatric specialist with expertise in neonatal NIMV and in the management of neonatal respiratory pathology, and neonatal nurses with experience in NIMV. The recommended nurse to patient ratio is 1:2.

10. Material and technology requirements

10.1. Ventilators

10.1.1. Desirable features of ventilators used for NIMV in adult patients

- The ventilators used should be NIMV-specific and easy to operate, as most of the time they have to be used by staff with a high turnover rate. On the other hand, critical patient ventilators, although most of them already have specific algorithms for NIMV, are mostly designed to work with leak-free circuits and double tubing. The use of home ventilators in acute patients is not recommended, except in cases of patients with home ventilation and who present good initial evolution with their ventilator during the acute phase.

- Light in weight or, failing that, easily transportable (trolley with wheels).

- Self-contained (with internal battery if possible).

- Efficient leakage compensation.

- Availability of internal port/mixer for oxygen (capable of providing 100% FiO_2) or other medical gases or possibility to connect to the high-pressure system of the hospital gas supply.

- Versatility in terms of the most frequently used ventilatory modes in NIMV, with continuous positive airway pressure (CPAP), dual level pressure or pressure support (PSV), and pressure control ventilation (PCV) being the indispensable modes.

- Possibility of invasive ventilation or alternatively optional software, especially for eventualities during transport or the need for urgent intubation.

- Parameterisation: it should be possible to regulate pressure levels, to have a sensitive inspiratory trigger, primarily flow or electronic, a programmable ramp or rise time and an expiratory cycle that can be pre-set or programmable.

- Monitoring of tidal volume, leakage and ideally pressure and time flow curves in real time.

- Sufficient and programmable alarms (tidal volume, minute volume, leak, ventilation rate, apnoea, low pressure).

- Versatility, for use of different types of consumables (tubing, interface, expiratory valve) without loss of ventilator efficiency.

- Be prepared for the possibility of using active humidification and aerosol therapy without interfering with the quality of ventilation.

10.1.2. Devices for paediatric NIMV application

Usually the lack of specific ventilators for paediatric patients leads to the use of other equipment initially designed for adults, but which are easily adaptable to the paediatric patients [17]. Both NIMV ventilators and conventional ventilators with non-invasive modules are used (those without such a module are not considered suitable). Wherever possible, equipment that is approved to accommodate patients weighing up to 5 kg should be used. Underweight infants may also have adaptation and synchronisation problems requiring inspiratory sensitivity systems other than the flow systems conventionally used, such as the one used in the NAVA® (neurally adjusted

ventilatory assist) model, based on the capture of the electrical activity of the diaphragm [185,186].

10.1.3. Devices for neonatal NIMV application

In neonatology, ventilatory devices are classified into variable flow generators, which are specifically designed for NIMV and usually offer more stable pressure levels and less respiratory effort, and continuous flow generators, which also include bubble CPAP and T-piece resuscitators, allowing for continuous or intermittent pressure delivery. The initial recommendation would be to use variable flow generators rather than continuous flow generators.

10.2. Expendable equipment

10.2.1. Tubing and expiratory valve systems

Most NIMV ventilators use single-branch circuits where there must be (if not included in the mask) an expiratory port attached as close to the patient's face as possible, which is necessary to avoid the phenomenon of CO_2 re-inhalation, and which by definition generates an intentional leak. Some single-branch circuits also incorporate a proximal pressure line for pressure monitoring close to the patient, which also contributes to the correct estimation of leakage and tidal volume.

Other single-branch circuits incorporate an active pneumatic expiratory valve, similar to those used in ventilators for critically ill patients. In these cases, leak ports should not be used in conjunction.

Some ventilators also offer the possibility to work with dual branch circuits, where inspiration and expiration are separated, thus avoiding the phenomenon of CO_2 re-breathing, as well as contributing to the accurate monitoring of exhaled tidal volume.

Finally, the use of an antibacterial filter at the outlet of the respirator is recommended. Likewise, in the case of communicable diseases, such as SARS-CoV2, it is especially important to avoid dispersal of the virus into the atmosphere for the safety of the healthcare personnel, so it is recommended to place a second bacterial viral filter between the interface and the intentional leak, which should not be in the mask but in the tubing [101].

The ventilators used in paediatrics usually have double branch tubing connected by a "Y" piece to the interface, and are therefore leak-free. For all other ventilators, the considerations made above with regard to valves and expiratory ports apply.

In neonatology, ventilatory circuits are usually double tubing in continuous flow generators or specifically designed tubing in variable flow. Both circuits share two elements, the gas mixer (air/O_2) to guarantee the adjustment of the administered FiO_2, and the gas heating and humidification system (see corresponding section).

10.2.2 Interfaces

This is the connecting device that facilitates the physical but also functional relationship between two independent elements: ventilator and patient. It is an indispensable element in NIMV, conveying positive pressure to the patient without any artificial component introduced into the airway.

Its correct selection (size, morphology according to the patient's features) is fundamental for the correct development of the procedure, as it is the element that most frequently causes a lack of comfort and in a high percentage is the cause of rejection of the NIMV.

<u>Generic characteristics of an interface suitable for NIMV for adult patients</u>

- Rigid, transparent, lightweight frame with at least one multifunctional accessory port (pressure measurement, gas addition, etc.). The expiratory port may sometimes be incorporated as holes in the structure.

- Cushioning that provides a stable and comfortable seal.
- With anti-suffocation safety valve and little instrumental dead space if possible, to avoid re-breathing.
- With a lightweight, breathable, non-deformable fastening system (harness) made of non-allergenic material, with an easy-to-remove fastening system in case of emergency.
- Models available in a variety of sizes.

Table 8 describes the types and differential characteristics of the main interfaces, of which the nasobuccal and total face interface are the preferred choice for the acute patient, although in the recent SARS-CoV2 pandemic, positive experiences have been reported with the helmet [187]. HFNCT nasal cannulas have also been included in the table as they are considered a specific type of interface (see section 12.2.6)

Type	Advantages	Disadvantages
Nasal	Greater comfort. Less dead space.	Oral leakage leading to reduced efficiency. Not recommended in ARF except for intolerances or weaning/interfacial rotation.
Oronasal	Most commonly used in ARF and in emergency situations in general. Reasonable dead space (180 - 200 cc). They can provide an expiratory port and must provide a safety valve. Wide variety of models and sizes.	Claustrophobia. Possible aspiration due to vomiting and secretions. Skin or eye damage due to leakage.

Full facial	Minimal peri-mask leakage. Reduced feeling of claustrophobia. Greater tolerability.	Greatest dead space. Possible aspiration due to vomiting and secretions. Possible eye irritation. Possible condensation in active humidification if the surface is large. Difficulty in administering nebulised drugs due to conjunctival effects.
Helmet	Possible in case of facial deformity. Ability to speak, cough and eat. Reduced feeling of claustrophobia. Good tolerability.	High dead space (up to 10 litres). High cost. Increased noise.
High-flow nasal tubing	Good tolerability Various diameters	Particulate aerosolisation (to be considered in pandemics).
Other	Nasal pillow system. Nasobuccal with olives.	Used in home-based NIMV, less experience in acute settings.

Table 8. Types of interfaces

Interface fitting procedure:

- Communication with the patient and their cooperation as far as possible is essential.
- Never insert the interface before the ventilator is already programmed and ready to start the procedure.
- Ensure that the anti-suffocation valve is working properly.
- Protect pressure areas, including the neck and armpits if a helmet-type interface is used (if dressings are used, they should be changed once a day, especially in

the elderly). The skin on the patient's face should be moisturised at breaks regardless of the interface and protection method used.

- Do not exert too much pressure when fastening the harness (allow 2 fingers to pass through after fastening).
- Check for unintentional peri-mask leaks.
- When using full face or helmet type interfaces, try to keep the conjunctivae moisturised.
- Semi-sitting position, with head at 45°. It should be noted that in a SARS-CoV2 pandemic situation, the combination of NIMV or HFNCT and prone position has been successfully tested [188].

As for paediatric interfaces, despite technical advances in recent years, there are still few specific interface models for paediatric patients, and the variability in size, face and head shape observed in the paediatric age range, especially up to the age of 6-8 years, is very high. The same type of interface described for adults is usually used, but in paediatric size, and it should have the generic characteristics described above. When positioning the interface, after protection of the support points, the possibility of collaboration of the paediatric patient and the patient's communication skills must be taken into account.

It is advisable to have several alternatives ready, especially for those patients whose physical characteristics (facial profile, presence of pressure ulcers), type of illness (insufficient strength to activate inspiratory sensitivity) or possibility of collaboration (refusal of the technique due to inability to understand the situation) do not adequately adapt to the one initially chosen as theoretically ideal.

The choice of interface and fixation system adapted to newborns is crucial for the success of NIMV. The size of the interface is especially important, it must minimise leakage and not cause decubitus injuries. Devices that tolerate a higher level of area leakage and allow a laxer fixation, together with the use of hydrocolloid protectors and rotation of interfaces avoid this type of injury. The main interfaces used in neonatology are the following (figure 3):

- Short binasal cannulas have the highest degree of evidence and their use is associated with lower resistance and reintubation rate compared to other interfaces.

- Nasal mask, as an alternative rotation system with binasal cannulas. The main drawback with both interfaces is leakage through the mouth with losses of up to 2-3 cm H_20 of pressure.

- Mono-nasopharyngeal tube. This is a cut endotracheal tube inserted up to the nasopharynx, mainly used in the context of transport.

- Other interfaces: RAM cannulas, face mask (in term NB), nasobuccal mask (in delivery room) [186].

Figure 3. Main types of intubation used in neonatal NIMV: short binasal cannulas, nasal masks, nasopharyngeal tube, RAM and high flow cannulas.

Table 9 shows different options for interface selection in paediatric and neonatal patients according to age.

Age	First choice	Alternative
Newborns	Short binasal prosthesis Nasal mask	Mono-nasopharyngeal tube RAM cannula Full facial mask
Infants	Full facial	Short binasal prosthesis Helmet Nasal mask
2 to 6 years	Full facial	Nasal or nasobuccal mask
Over 6 years old	Full facial	Nasal or nasobuccal mask

Table 9. Technical options for interface selection in paediatric and neonatal patients.

10.2.3. Humidification and aerosol therapy. Devices and indications

NIMV recommends the use of active humidification systems, which optimise the gas at physiological temperature and humidity (31-33 °C), with active humidification greater than 30 mg H_2O/L regardless of ventilatory parameters, leakage and ambient conditions. Active humidification shall not add resistance or dead space to the system.

Active humidification (with hot water vapour) can reduce upper airway resistance and improve comfort in case of major leaks [189]. In several short-term studies, active humidification decreased upper airway dryness, which may improve tolerance and facilitate secretion clearance [190,191].

This recommendation is especially important in younger paediatric patients, where the high flow rates used cause airway dryness and may hinder body temperature

control. Also regarding newborns, gas conditioning has been associated with increased patient comfort and improved respiratory mechanics. If a mask is used as an interface, the temperature may be poorly tolerated or cause excessive condensation and require additional adjustment.

10.2.4. Aerosol therapy

Aerosol therapy with bronchodilators is a common treatment in many of the patients for whom NIMV is indicated. The primary objectives would be to apply aerosol therapy without discontinuing NIMV (except in the use of interfaces that include the eyes, although experience in paediatrics shows that there are no problems when beta2 adrenergics or anticholinergics are administered), and to try to achieve the highest drug deposition in the distal airway with the least side effects. When using a nebuliser, it should ideally be placed between the non-leaking mask and the tubing if the intentional leak is in the tubing. Conversely, if the intentional leak is in the mask, the nebuliser can be placed in the area closest to the ventilator [192].

Different devices are available to perform aerosol therapy during NIMV:

- Ultrasonic and jet nebulisers: suitable for larger volumes of solution, where the drug is delivered through T-tubes adapted to the main tubing.

- Vibrating mesh nebulisers; these are lightweight devices, capable of homogeneous aerosolisation of solutions and suspensions and in some models can be directly coupled to the interface.

- Pressurised cartridge with adapter; requires spacer chambers of at least 100 ml, and manual activation must coincide with the inspiratory phase of the ventilator. They should be attached as close to the patient as possible, between the distal end of the tubing and the mask.

In paediatrics, aerosol therapy is applied in a similar way to that used in adult patients, although the drug to be administered is sometimes different. The indication of not suspending NIMV for administration is also maintained. Even taking into account that there may be more loss of medication in the circuit, the possibility of more distal deposition of the drug in the airway prevails. No significant or unusual side effects have been demonstrated when aerosolised bronchodilators are applied to children ventilated with a full facial mask. The only exception to consider would be when the interface is a helmet, because the medication is not applied directly to the patient, but accumulates ineffectively in the gas that distends the helmet.

10.2.5. CPAP devices

A conventional ventilator can be used in CPAP mode or a non-mechanical CPAP device can be used. The latter are easy to use, low-cost systems and have the advantage of not depending on battery or electrical current, facilitating their application in any environment, including out-of-hospital settings. This device consists of an oronasal mask, the valve that generates the positive pressure and the connection tube to the gas-oxygen source. The device contains four micro channels in its wall that accelerate the flow, and converge in the virtual valve generating turbulence that gives rise to pressure. The level of pressure generated depends on the flow of oxygen administered and the ventilatory mechanics of the patient, so for a flow of 30 L/min it could generate a CPAP of approximately 5 - 7 cm H_2O in the absence of leaks [193].

Moreover, its non-airtight operating system allows the passage of a tube through it to assist the patient (aspiration, etc.) or to perform therapeutic procedures such as bronchoscopy [194].

Although it is possible to use these devices in paediatrics, most of them are not approved for young children and appropriate controls and flow and pressure measurements must be carried out, in addition to strict and continuous cardiorespiratory monitoring. Special mention should be made of bubble CPAP, a non-invasive ventilation strategy for infants and young children with respiratory distress syndrome secondary to infectious conditions. In this method, mixed and humidified oxygen is administered through short binasal cannulas or a nasal mask and the pressure in the circuit is maintained by immersing the distal end of the expiratory tube in water. The depth to which the tube is submerged under water determines the pressure generated in the airway. As the gas flows through the system, it "bubbles" and prevents the build-up of excessive pressures. The results in the treatment of pneumonia in young children in countries with scarce health and economic resources are particularly important [114,115]

12.2.6. HFNCT devices

It is a system that incorporates a comfortable nasal cannula as an interface with a design capable of providing flow rates of up to 60 litres/minute, sized for adult, paediatric and neonatal patients. In paediatric patients, the calibre of the cannula is adapted to the size of the nostril, occupying approximately 50% of it, to allow leakage and avoid the phenomenon of overpressure generated by the flow, if there is no leakage. In neonate patients, the peri-cannula leakage should be 20-40% of the diameter of the choana. In all cases, the interface is coupled to a connecting socket with an internal metal filament resistor to prevent temperature variations and possible condensation inside the socket. In general, it is recommended to use deionised water or simple rinsing water as the humidification source. Gas regulation is carried out by means of calibrated high-flow rotameters, capable of supplying gas flows up to 70 litres/minute. A system with two rotameters can be used (one for the O_2 source and one for the air source) or a single O_2 rotameter adapted to a turbine system that provides the air flow in a similar way to a fan. In addition, it incorporates an active humidification-heating system which must always be operative and which is capable of conditioning the

gas to physiological conditions, i.e. 100% relative humidity and a temperature of 37 °C [195].

11. Device programming

11.1. A brief reminder of the ventilatory modes

11.1.1. Ventilatory mode classification variables

The primary variable that determines the mode of ventilation is the control or limiting variable, which is the one controlled by the ventilator and which remains constant despite changes in ventilatory mechanics. The two variables commonly controlled by ventilators are pressure and volume so that mechanical ventilation is primarily classified into volumetric or volume-controlled ventilation and barometric or pressure-controlled ventilation [196].

In volumetric ventilation, the programmed volume remains constant and is the independent variable while the pressure depends on airway resistance and thoracopulmonary compliance. In barometric ventilation, the programmed inspiratory pressure is constant and is set as the independent variable, while the volume varies according to the set pressure level and changes in the mechanics of the respiratory system (table 10).

In acute-phase NIMV, pressure-controlled ventilation is mainly used because of its ability to compensate for leaks and to easily synchronise with the patient [80,196].

	VOLUME-LIMITED VENTILATION	PRESSURE-LIMITED VENTILATION
INDEPENDENT VARIABLE	VOLUME	PRESSURE
DEPENDENT VARIABLE	PRESSURE	VOLUME
LEAK COMPENSATION	NO	YES
MODES	Assisted-controlled (A/C) Controlled (C)	Spontaneous (S) Spontaneous-timed with backup rate (S/T) Assisted-controlled (A/C) Controlled (C)

Table 10. Ventilatory modes.

In recent years, hybrid modes (AVAPS/iVAPS®) have emerged that combine the advantages of pressure-limited ventilation with the goal of maintaining an assured tidal volume. The ventilator adjusts inspiratory pressure between limits (maximum and minimum) to maintain the pre-set volume. The inspiratory pressure level will not exceed the programmed maximum pressure, even if the pre-set volume is not reached. There is insufficient data in the literature to support the benefits of this hybrid mode compared to the pressure-limited mode [197].

11.1.2. Ventilation modes and parameters to be programmed for pressure-controlled ventilation

As shown in table 11, the main parameters to be programmed are **inspiratory and expiratory** pressure levels (IPAP/EPAP). The difference between the two pressures is known as the **pressure support (PS)**. It should be noted that some ventilators are programmed on the basis of the latter value (PS + EPAP or PEEP in some models) instead of programming the IPAP. PEEP can be titrated at the bedside using ultrasound if there is a need to ventilate collapsed dependent regions [198]. The same technique can be used to determine Auto-PEEP compensation [199,200].

PARAMETERS TO BE SET FOR PRESSURE-LIMITED VENTILATION	
INSPIRATORY PRESSURE (IPAP)	Inspiratory pressure (cm H_2O)
EXPIRATORY PRESSURE (EPAP)	Expiratory pressure (cm H_2O)
PRESSURE SUPPORT (PS)	Pressure differential (IPAP-EPAP) (cm H_2O)
RESPIRATORY FREQUENCY	Breaths per minute
ACTIVATION SENSITIVITY (Inspiratory trigger)	Numerical value or ordinal scale (L/min)
CYCLE SENSITIVITY (Expiratory trigger)	% peak flow decline, numerical value or ordinal scale (l/min)
RAMP OR RISE TIME	Milliseconds or numerical scale
MAXIMUM INSPIRATORY TIME	Seconds
MINIMUM EXPIRATORY TIME	Seconds

Table 11. Summary of parameters to be set in pressure-limited ventilation.

In addition, a number of secondary parameters have to be programmed:

- ***Ramp or rise time****:* This is the time between the start of the inspiratory cycle and the point at which the set inspiratory pressure is reached. The greater the patient's demand for flow, the faster the need to pressurise the airway. It should be noted that this variable directly influences the expiratory trigger or cycling sensitivity by modifying cycling times according to whether peak inspiratory flow is reached earlier or later.

- ***Respiratory frequency***: number of controlled breaths delivered by the ventilator in one minute in the absence of patient effort. It is usually set slightly below the patient's RF.
- ***Minimum and maximum inspiratory time***: some ventilators have a maximum time limit safety mechanism for inspiratory duration to cope with very long inspiratory times in case of severe leaks. There is also the possibility of minimum time limitation to avoid very short cycles.

- ***Inspiratory trigger or activation threshold***: indicates the level of patient effort required to initiate a ventilator-assisted breath. It is usually set on a numerical (1-9) or nominal scale (Trigger - sensitive: 1-3 / medium 4-6 and not very sensitive > 6 bpm).

- ***Expiratory trigger or cycle sensitivity:*** indicates the flow level at which the change from inspiration to expiration occurs. It may be set as a percentage of the peak flow achieved (e.g., at 25% of peak inspiratory flow), or at predetermined values of peak flow set on a numerical [1-9] or nominal scale (sensitive, medium, not very sensitive). Notably, some ventilators have an automatic triggering and cycling mechanism (Auto-Trak Sensitivity™ Respironics) that continuously senses the patient's breathing patterns and automatically adjusts the sensitivity and cycling thresholds.

In view of the above, pressure ventilators can be operated in spontaneous (S) mode, where the respiratory rate is the patient's spontaneous rate (there is no safety rate); spontaneous/timed (or assisted/controlled), where, in addition to patient-initiated breaths, additional ventilator-initiated breaths are delivered if the patient's respiratory rate falls below the set backup rate, or controlled, where the ventilator initiates breath cycles at a set respiratory rate and cycling occurs at a fixed inspiratory time. Therefore, it is a time-activated, pressure-limiting and time-cycled ventilation mode. If pressure control is used, a variety is the assisted/controlled mode where cycling always occurs by time, regardless of whether the cycles are spontaneous or ventilator cycles (table 12).

	ACTIVATION	CYCLE
MODES	PATIENT	PATIENT
MODE S/T	PATIENT OR VENTILATOR (Backup RF)	PATIENT
MODE A/C	PATIENT OR VENTILATOR (Backup RF)	VENTILATOR (adjustment of inspiratory time)
MODE C	VENTILATOR (adjustment of RF)	VENTILATOR (adjustment of inspiratory time)

Table 12. Activation and cycles in the different ventilatory modes (S: assisted; S/T: assisted with a safe respiratory frequency; A/C: assisted-controlled, C: controlled)

In clinical practice, pressure ventilation in spontaneous mode is the mode of choice in acute hypercapnic respiratory failure. It is important to know the characteristics and nomenclature of the equipment to optimise parameter settings. In paediatrics, spontaneous mode ventilation is also the mode of choice in acute general, type II respiratory failure and the rescue mode in type I respiratory failure that cannot be improved with CPAP.

11.1.3. Other respiratory support systems: CPAP and HFNCT

They are not considered as ventilation systems per se as they do not provide inspiratory support.

CPAP (Continuous Positive Airway Pressure)

A continuous positive pressure modality delivered throughout the respiratory cycle and applied over the patient's spontaneous breathing. Therefore, only one level of positive pressure must be programmed, which generates beneficial respiratory and haemodynamic effects [201,202].

High-flow nasal cannula therapy (HFNCT)

The HFNCT system delivers an oxygen-air mixture that can meet or exceed the spontaneous inspiratory demand of patients [203], allowing for an FiO_2 of 21-100%, generating flow rates of up to 60 bpm. Although it is not a ventilation system per se, its ability to achieve better oxygen concentrations with greater patient comfort has led to its widespread use in both paediatric [204] and adult patients in the treatment of acute hypoxemic non-APO respiratory failure [205].

Three HFNCT action mechanisms are postulated: a washout effect in the nasopharyngeal dead space, a reduction of upper airway resistance, with a consequent decrease in respiratory effort [206] and a certain level of PEEP [207]. Moreover, the beneficial effect on mucociliary transport should not be forgotten [208].

11.2. Programming of the devices

11.2.1. NIMV in adult patients

Generic procedure / approximation

If a pressure mode is used, an initial inspiratory pressure of around 10-12 cm H_2O and an expiratory pressure of around 5-6 cm H_2O can be programmed, with a FiO_2 required to achieve the desired oxygenation level. It would even be possible, if the clinical situation permits, to start treatment for a few minutes with CPAP and then switch to pressure support as soon as clinical tolerance is confirmed.

From this point on, changes will be made according to changes in RF, tidal volume (TV), blood gas and respiratory mechanics parameters. The targets would be a TV greater than 300 ml (or 5 ml per kilo of ideal weight) and a RF less than 25 rpm. If hypoxaemia is severe, expiratory pressure (EPAP or PEEP) can be slowly increased to try to achieve an SpO_2 of 90% with a FiO_2 of less than 60%. In any case, correction should be progressive and the appearance of blood gas deterioration in the first check-ups should lead to reconsideration of treatment.

Specific procedure for each of the parameters:

- **Target support pressure levels (IPAP/PS):**
  - As PS increases, inspiratory effort decreases. However, excessive pressure support [209] may lead to patient intolerance and desynchronisation with the ventilator.

- **Expiratory pressure level (EPAP/PEEP):**
  - The objectives of the chosen EPAP/PEEP should be, first of all, to counteract Auto-PEEP when it exists, especially in COPD patients [210], to increase the functional residual capacity, with the consequent improvement of the ventilation-perfusion ratio (characteristic in APO), prevention of re-inhalation (a minimum EPAP of 4 cm H_2O is usually

sufficient) in case a single branch circuit is used [211] and prevention of upper airway collapse in patients with obstructive sleep apnoea [212].

- Thus, one can start with a minimum PEEP/EPAP of 4 cm H_20 and gradually increase it, seeking to counteract Auto-PEEP and in case of loss of aeration in the dependent zones, thoracic ultrasound can be useful in titration if one has experience. Finally, in case of periodic decreases in flow, apnoea or hypopnoea should be suspected and PEEP/CPAP should be titrated until they are eliminated.

- **Secondary parameters:**

  - **Trigger or threshold**. Ventilator activation thresholds can be either pressure or flow. Flow threshold selection is generally considered to be better than pressure threshold selection, but their difference in clinical efficacy or ventilator adaptation is not determined [213]. At very sensitive thresholds, the so-called "auto trigger", or activation of the ventilator without inspiratory drive from the patient, may occur. It occurs mainly in situations of high leakage, very low respiratory rates and low ventilatory drive. At the opposite extreme is the so-called "failed cycle" (ineffective effort), where the patient generates an inspiratory effort that does not reach the flow threshold, a situation that frequently occurs in cases of dynamic hyperinflation or if the inspiratory trigger is excessively demanding. Both asynchronies have important clinical and pathophysiological consequences because they increase respiratory effort and may lead to NIMV failure.

  - **Pressurisation ramp.** In one study, intermediate ramps showed the best results in terms of tolerance. In contrast, excessively slow ramps resulted in decreased tidal volume and increased respiratory effort and frequency [214]. Therefore, there is no fixed rule for determining which ramp time is best, but it seems that both excessively long and excessively short ramp times are associated with asynchrony [215]. It seems advisable to

individualise the ramp, starting with medium pressurisation ramps and gradually adjusting it in order to achieve the lowest respiratory rate, the highest TV and optimal respiratory mechanics, also considering the patient's comfort.

- **Inspiratory time / Expiratory cycling.** Under normal conditions, inspiratory time should be shortened in cases of obstructed flow to avoid air trapping. Conversely, increases in inspiratory time, not exceeding a ratio of 1:1, may be necessary in cases requiring greater ventilatory efficiency. In case of leaks, the use of the "maximal inspiratory time" should also be considered if the ventilator incorporates this parameter (set to a physiological time of 0.8 to 1.2 seconds). Failure to adjust the inspiratory time provided by the ventilator [216] may be another source of asynchronies (see monitoring section).

11.2.2. Ventilation programming in paediatrics

Although pressure modes are more commonly used, it can also be used in volumetric mode, by first programming the tidal volume (TV), which should be higher than that used in invasive ventilation (up to twice as high), to compensate for dead space and interface leakage. PEEP can be started at 4 cmH_2O and increased to 8-10 depending on hypoxaemia and atelectasis.

In pressure modes, the PS level should be around 4-5 cm H_2O above PEEP. Once tolerance is achieved, it can be increased in 2 cm H_2O intervals of inspiratory pressure until the respiratory effort is reduced (typically 12-18 cm H_2O). The safety RF in case of PS is usually set to values between 15-20 respirations per minute. The I:E ratio and inspiratory time should be as close to the patient's as possible (in ARF typically short inspiratory times and in young paediatric patients even very short (0.3-0.5 seconds). The

inspiratory trigger is usually a flow trigger, but sometimes the patient may fail to activate the ventilator (common in paediatric patients under three months of age). In this situation, an increase in rescue RF very close to that of the child is required (the ventilator "controls the child"). The use of the NAVA® modality, referred to above as a possibility to improve synchrony, is not universally available. Its use in paediatric and neonatal NIMV started in 2010 and is very promising, with patient-ventilator synchrony being its main advantage. Its main disadvantage is the cost and the learning curve of the technique. In expert hands the results are optimal for all ages [184–186]. In terms of pressurisation ramps and expiratory cycling, the considerations indicated above are valid for the adult population, but always bearing in mind that the physiological inspiratory time in paediatric patients is lower than in adults and varies with age in inverse proportion to the RF. In case of hypoxaemia, FiO_2 shall be programmed or supplemental oxygen shall be provided in the inspiratory line. The expiratory pressure shall be increased slowly until a SaO_2 greater than or equal to 93% is achieved with the lowest FiO_2.

When non-NIMV specific ventilators are used, the use of spontaneous-timed modalities is recommended. This will be of greater interest the younger the patient given the high baseline respiratory rate. In these cases the considerations made above for adult modalities apply.

11.2.3. Protocol for initiation of neonatal NIMV

Starting parameters are usually set according to modality, weight and/or gestational age and respiratory pathology. FiO_2 should be adjusted according to SpO_2 targets as specified in table 13. In pressure modalities the inspiratory pressure is usually set to higher pressure values about 2-4 points above the PEEP level, which may vary depending on the required alveolar recruitment and haemodynamic tolerance. The initial PEEP is usually 5-6 cm H_20 rising to 7-8 cm H_20.

Gestational age	Target Hb saturation (%)	Alarms min/max %*
≤32 weeks	90-94%	89-95%

>32 weeks **	92-97%	91-98%

Table 5. Relationship between SpO_2 and gestational age in the newborn.

11.2.4. HFNCT-specific programming

In adults, HFNCT can be started with a minimum FiO_2 to maintain SpO_2 around 93-94% - in cases of associated chronic lung disease SpO_2 between 88-89% -, and a temperature of 37 °C. The therapeutic flow target for the adult patient is considered to be from 45-50 l/m [217]. This fact, together with the hypothetical need for high FiO_2 and the less secure fixation of the nasal cannula (risk of accidental removal) make the monitoring environment particularly important in this type of therapy.

Roca et al [218] described a simple way to analyse the risk of intubation at 12 h in patients with pneumonia treated with HFNCT with the so-called ROX index (SpO_2/FiO_2:RF). A value ≥ 4.88 is associated with a higher probability of successful treatment of the patient.

In paediatric patients, the initial scheduling of HFNCT is not yet well defined. As a general rule, in infants under one year of age, flows should always be greater than 2 l/min and should be adjusted to body weight under the formula of 2 l/kg/min up to 8-10 kg body weight. In older paediatric patients, flows should always be higher than 6 l/min and can be used up to 20 or 30 l/min, close to what would be 1 l/kg/min. FiO_2 should be set for a target peripheral oxygen saturation between 92 and 97%. The default temperature is set to around 37 °C for optimal humidification. To avoid condensation phenomena, the tubing can be insulated if the room temperature is low. In exceptional cases, the temperature of the socket can be lowered to 34 °C [175]. In very young children, a dummy can be used to reduce mouth leakage and maintain the PEEP effect of HFNCT.

In neonatology, the main indication for HFNCT remains post withdrawal support of other NIMV modalities, but it is increasingly used as an initial support modality, with

an initial range of 4-8 l/min flow. When clinical and blood gas targets are reached, tapering can be initiated to 2 l/min, at which point it can be withdrawn.

One of the challenges for the future would be to establish and protocolise in treatment guidelines the actual indications and protocols for initiation and withdrawal for HFNCT [219].

THIRD PART: FOLLOW-UP AND MONITORING

12. Procedure for monitoring and controls of NIMV/HFNCT in adults

Monitoring the management of acute respiratory failure during NIRS should allow early detection of complications and signs of therapeutic failure, avoiding delay of orotracheal intubation (OTI) and initiation of invasive mechanical ventilation (IMV) in indicated cases [220,221]. The monitoring strategy should be individualised for each patient and depends on the clinical severity and the setting. It is based on the following points:

12.1. Physiological parameters

- Patient's level of consciousness: the persistence of a low level of consciousness with no other cause suggests therapeutic failure.

- Respiratory frequency: a decrease in RF in the first hours of treatment is a sign of a good response. Bradypnoea (<10 rpm), however, may indicate failure.

- Respiratory effort: the use of accessory respiratory muscles decreases with a good response to treatment, as does paradoxical breathing. Gasping breathing indicates the need for immediate OTI in indicated cases.

- Heart rate and rhythm: tachycardia is a physiological response to hypoxaemia, so it usually subsides or improves with adequate ventilatory support and treatment of the underlying disease. Bradycardia should alert to possible cardio-respiratory arrest and the need for OTI.

- Blood pressure: hypertension may appear as an acute phase parameter and its persistence may be related to intolerance to ventilatory therapy. The application of intrathoracic positive pressure leads to changes in preload and afterload, and in patients with a dysfunctional left ventricle, may lead to deterioration, hypotension with low output and the need for OTI.

12.2. Gas exchange and electrocardiogram parameters

- Oxyhaemoglobin saturation by pulse oximetry (SpO_2): should be used in continuous monitoring, especially during the first hours. May be unreliable in the presence of carboxyhaemoglobin and methaemoglobin and especially in states of low peripheral perfusion or use of vasoactive drugs.

- Arterial blood gases: A first check-up should be performed at the time of onset of NIMV. If the evolution is favourable, subsequent monitoring should be at the discretion of the clinician. Some authors postulate the possibility of performing such controls with venous blood gases, at least in some groups of patients, such as cardiogenic APO without shock and without chronic obstructive respiratory pathology [222].

- Transcutaneous monitoring of PaO_2 and $PaCO_2$: non-invasive method with good correlation to arterial gases making it optimal for continuous monitoring, especially of $PaCO_2$.

- Electrocardiogram: monitoring is advisable and important in patients with a heart rate higher than 120 beats per minute or in case of arrhythmia or cardiomyopathy [223].

12.3. Ventilator parameters

Many ventilators allow real-time monitoring of flow and pressure curves. Visual analysis of the morphology of these curves can help to identify pathological patient-ventilator interactions.

Depending on the equipment, an estimate of leakage, tidal volume, respiratory rate and the presence of spontaneous or controlled cycles is also available. Leakage monitoring is important, as unintentional leakage due to poor interface settings can lead to asynchrony, discomfort and ventilation failure. Tidal volume monitoring in pressure mode is also important to detect and treat both hypoventilation and high tidal volumes that may induce asynchronies or worsen ventilator-induced lung injury, even when using NIMV [224]. Its normal value is approximately 5-10 ml/kg ideal weight [225] and significant variations in this may suggest the presence of leakage or upper airway (UA) obstruction. The most frequent asynchronies in pressure mode are summarised together with the mechanisms and their correction in table 14 [19,226–229]. Figure 4 also shows the hierarchical assessment sequence of the asynchronies.

Type	Phase in which it occurs	Asynchrony	Cause	Solution
Extrinsic		Leak	• Poor mask fit • Bad circuit connection	• Fitting of mask and harnesses • Change of mask • Correct connection of circuit parts
		Closure of UA	• Obstructive events • Glottis closure	• Increase EPAP (PEEP) • Decrease PS
Intrinsic	Inspiratory effort	Ineffective effort	• Insensitive inspiratory trigger • Auto-PEEP: due to obstructive pathology or excessive support • Prolonged cycles	• Increase inspiratory trigger sensitivity • Increase EPAP or decrease PS (depending on cause)
		Auto trigger	• Leaks • Very sensitive inspiratory trigger • Excessive EPAP • Problems with the tube fittings • Hiccups • Heart rate interference	• Check for leaks • Harder inspiratory trigger • Decrease EPAP • Fix problems with the tube fittings • Treat hiccups if necessary • Check heart rate and rhythm and, if necessary, initiate corrective measures
		Double trigger	• Unmet ventilatory demand	• Increase Tinsp and/or support
	Pressurisation	Flow requirement	• Excessively slow pressurisation time	• Increase pressurisation rate • Increase PS
		Overshooting	• Excessively fast pressurisation time	• Decrease pressurisation rate ("ramp")
	Cycle	Short cycle	• Tinsp of the ventilator lower than that demanded by the patient	• Increase Tinsp (increase maximum Tinsp or change cycling criteria) • Increase PS
		Long cycle	• Ventilator inspiratory time longer than demanded by patient	• Fix leaks • Decrease Tinsp (decrease maximum Tinsp or change cycling criteria) • Decrease IPAP

Table 14. Asynchronies: causes and solutions.

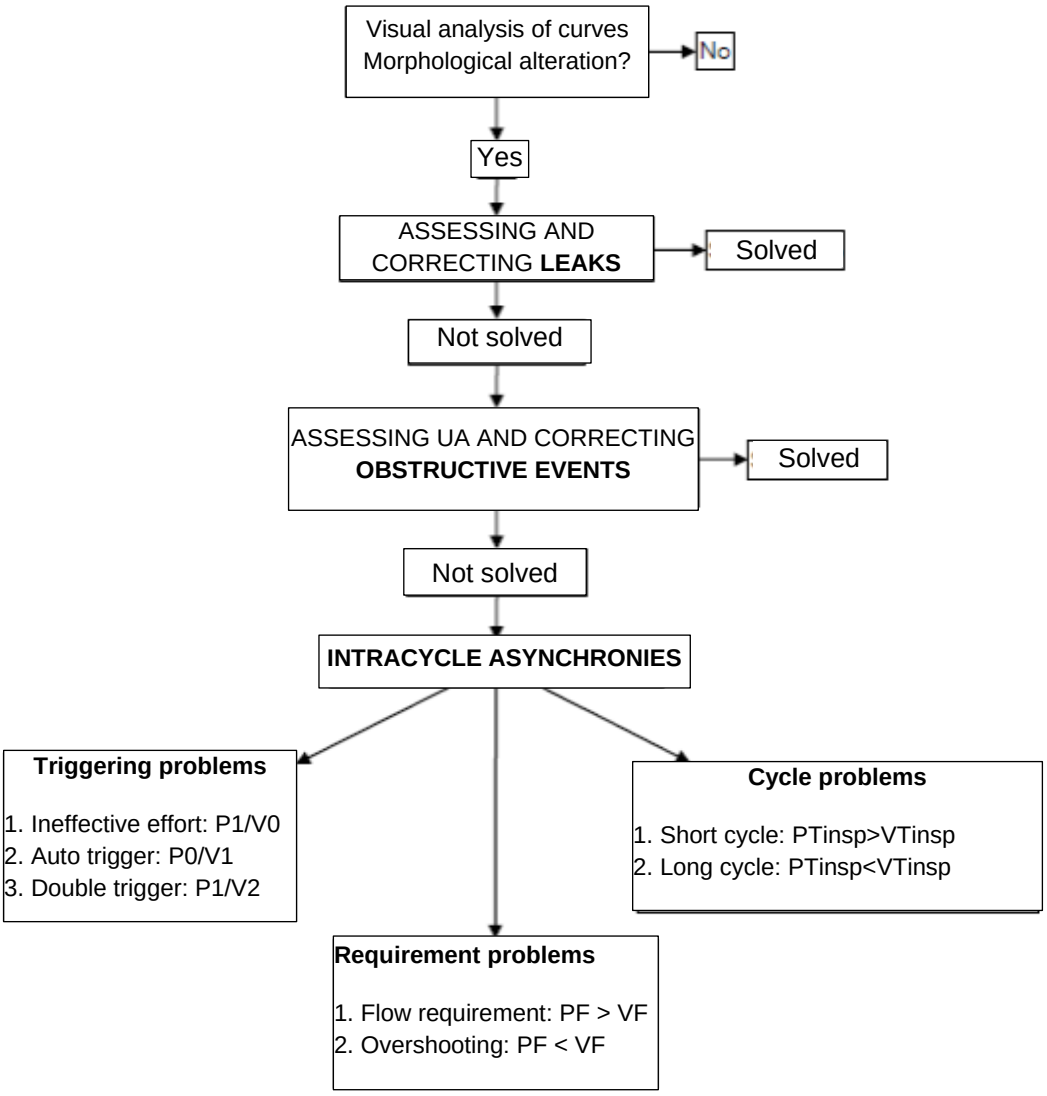


Figure 4. Schematic assessment of asynchronies.

UA= upper airway. P: patient. V: ventilator. 0,1,2 = number of cycles demanded by P or assisted by V. F= flow. PF> VF= the patient requires more flow than that provided by the ventilator. PF< VF= the ventilator delivers more flow than the patient requires. PTinsp> VTinsp= the Patient's inspiratory time is greater than the inspiratory time provided by the Ventilator. PTinsp< VTinsp= the patient's inspiratory time is less than that provided by the Ventilator.

13. Criteria for failure. Therapeutic actions in case of failure

13.1. NIMV failure

Increased in-hospital mortality among patients with NIMV failure who have required endotracheal intubation [230,231], especially if delayed [62], makes early detection of NIMV failure imperative [34].

13.1.1. NIMV failure criteria

Discontinuation of NIMV for failure should be performed if, after correction of ventilatory parameters and mask titration, there is no satisfactory clinical or blood gas response or a worsening of these parameters on assessment within one hour (or earlier if clinical worsening is suspected) of NIMV initiation [232,233].

The clinical and blood gas criteria indicative of NIMV failure are summarised as follows [234].

(1) Deterioration of the patient's condition or failure to improve symptoms:
   a. Persistence of dyspnoea and increased respiratory effort with intercostal and supraclavicular pull.
   b. Persistently elevated respiratory rate. An increase in respiratory rate within one hour of initiating the technique may be predictive of failure of NIMV [235], whereas a decrease in respiratory rate may be predictive of success [236].
   c. Impaired level of consciousness (encephalopathy or agitation).

(2) Intolerance to the technique with patient's desire to withdraw NIMV treatment.

(3) Inability to synchronise with the ventilator.

(4) No improvement or deterioration of arterial blood gases during the first hours of NIMV. It can be assessed after one hour of treatment and is fairly indicative at 6 hours [232]. It is important to note, however, that blood gases alone are not a criterion for intubation. The parameter for assessing the efficacy of NIMV will differ depending on the initial blood gas disturbance:

   a. Hypercapnic respiratory failure: in non-COPD patients with hypercapnic ARF, persistent respiratory acidosis with elevated $PaCO_2$ levels after one hour of NIMV is predictive of failure [230].
   b. Acute hypoxaemic respiratory failure: the presence of $PaO_2/FiO_2 \leq 146$ mm Hg after one hour of NIMV, or a $PaO_2/FiO_2 \leq 175$ mm Hg in patients with acute respiratory distress syndrome (ARDS) has been independently associated with failure of the technique [232,233]. There are no precise recommendations for determining failure of NIMV in hypoxaemic respiratory failure as it may result from different clinical entities [232].

(5) Significant bronchorrhoea that the patient is unable to expectorate.

(6) Haemodynamic instability, acute myocardial ischaemia, potentially lethal ventricular arrhythmias.

(7) Need for immediate endotracheal intubation.

13.1.2. Failure according to the type of underlying pathology

The pathology leading to acute respiratory failure is a predictor of success of NIMV, with exacerbation of COPD and acute pulmonary oedema of cardiogenic cause being the causes with the best response to this technique [237]. Both are pathologies of rapid resolution when compared to other causes with a higher failure rate of NIMV such as pneumonia [235,238] or ARDS [233].

13.1.3. Time-dependent failure of NIMV

Three types of failure are described, depending on the time elapsed since the start of the NIMV [239].

Immediate failure: occurs within the first hour of onset of NIMV. It is usually due to inability to manage secretions, intolerance of the technique (e.g. due to claustrophobia), poor synchrony with the ventilator [240] and encephalopathy with confusion, agitation or coma.

Premature failure: occurs within 1-48 hours of initiation of NIMV and is the most common type of failure. In hypoxaemic ARF it has been associated with higher initial severity rates, and is characterised by the inability to achieve PaO_2/FiO_2 > 150 mm Hg, persistent tachypnoea (>30 breaths/minute) or worsening chest radiographic infiltrates. Hypercapnic respiratory failure is characterised by the failure to achieve pH > 7.25, increased tachypnoea, low level of consciousness, and may be associated with laboratory signs of active infection, poor nutritional status or high severity indices.

Late failure: failure occurs after the first 48 h. These are patients with a good initial response to NIMV who show a late deterioration. This is associated with the development of nosocomial infection [241], delirium or sleep disturbances [242].

13.4. Therapeutic actions in NIMV failure

Lack of response or clinical or gastric worsening in patients with NIMV should be followed by an early change of therapeutic strategy in order not to delay endotracheal intubation if indicated. Indeed, the clinician should be aware that any unnecessary delay

of intubation may increase mortality. That said, the actions that can be taken to try to treat failure without resorting to OTI are, first of all, to review the medical treatment administered, as well as to rule out the presence of any complications such as pneumothorax, bronchial aspiration or the development of heart failure. There are different therapeutic actions that can be considered before determining definite failure of the technique [232,243]:

Choice of ventilator: the choice of ventilator can be an important factor in the success of NIMV, specific ventilators for NIMV have been shown to achieve better synchrony between patient and ventilator [236].

Leak assessment and choice of interface: the tolerance of the interface used is crucial for the success of the technique. The seal of the interface must be checked and excess leakage assessed. Most studies in patients with acute respiratory failure use oronasal masks, although face masks or helmets have also been used with success [244,245]. Changing the interface can be an effective remedy to an initial NIMV failure [246].

Changes in ventilatory parameters or ventilatory mode:

In patients with respiratory acidosis and increased respiratory effort, if $PaCO_2$ cannot be reduced, the programmed parameters should be modified by increasing the inspiratory pressure to values close to 20 cm H_2O. In the event of persistently high $PaCO_2$, the circuit connections should be checked and the correct position of the expiratory valve verified to avoid re-breathing of exhaled air. In the absence of NIMV response with assisted modalities in patients with hypercapnic encephalopathy, a switch to an assisted/controlled mixed modality with variable rescue rate can be made. Careful increase of the programmed minimum respiratory rate may improve outcomes in these cases [247].

In patients with refractory hypoxaemic respiratory failure, the PEEP (or EPAP) value may be increased. In this type of patient, if the initial modality applied is CPAP, a

change to an inspiratory assist modality to reduce the respiratory effort may be considered [248].

Controlled sedoanalgesia: in patients with poor adaptation to NIMV (due to claustrophobia, agitation, disorientation or discomfort), and after failure of the above-mentioned non-pharmacological measures, the use of closely monitored sedoanalgesia may be used to improve tolerance to the technique [249,250]. Some authors, based on the recent experience of the SARS-CoV2 pandemic, propose the use of opioids to decrease the respiratory drive, although there is insufficient evidence to make a recommendation [251].

Respiratory physiotherapy: in initial acute respiratory failure, respiratory physiotherapy is not recommended, especially if associated with bronchospasm. Patients with bronchorrhoea without the ability to expectorate effectively should not be maintained on NIMV. Depending on the patient's clinical situation, physiotherapy techniques to promote expectoration should be considered.

Switching to other non-invasive respiratory support: there are no studies demonstrating that oxygen therapy by HFNCT in hypoxaemic ARF can be a rescue treatment for NIMV. It is also important to remember that the use of HFNCT is preferred in hypoxaemic patients and when the cause is acute respiratory distress, but if the respiratory rate is not below 30 rpm within one hour, intubation should not be delayed [20,252].

Endotracheal intubation: the decision to intubate is primarily governed by clinical rather than blood gas criteria. Any of the major criteria listed in table 3 should lead to

intubation. In addition, the presence of two of the following minor criteria during the first hour of treatment should also prompt consideration of endotracheal intubation:

(1) Respiratory rate > 35 rpm or higher than its initial value.

(2) pH < 7.30 or lower than baseline, or $PaCO_2$ > 20% of baseline.

(3) PaO_2/FiO_2 < 150 mm Hg.

(4) Worsening of hypercapnic encephalopathy.

14. Criteria for withdrawal of NIMV/HFNCT after control of acute respiratory failure

14.1. Withdrawal of NIMV

14.1.1. In exacerbated COPD

Normalisation of pH and $PaCO_2$ <50 mm Hg are commonly used parameters for discontinuation of NIMV, although restoring respiratory centre function requires more time to normalise $PaCO_2$ than to correct acidosis.

The optimal duration of NIMV in the initial period and the most effective way to withdraw it as the patient improves has been the subject of debate. As respiratory effort decreases and dynamic pulmonary hyperinflation reverses with medical treatment of the exacerbation, spontaneous ventilation tends to normalise. The greater the relevance of infection as a precipitating cause of acute hypercapnia, the more likely the complete reversal of the process, but in some patients it is not possible to normalise $PaCO_2$, especially in those with evidence of chronic hypercapnia on admission.

In most studies, the aim is usually to treat with NIMV for most of the time during the first 24 h. However, the actual time patients spend on NIMV is often shorter than planned, ranging from a median of 20 h in one study [34] to 7 h in another [253]. The usual clinical practice is to gradually reduce NIMV time, with increasing periods of spontaneous breathing during the day, while continuing NIMV at night. $PaCO_2$ monitoring with and without NIMV is a useful measure in deciding how quickly to withdraw NIMV. A gradual reduction of ventilator pressures, attempting to adjust ventilator conditions to improve patient comfort is important and is a reflection of patient recovery. In those patients with a less obvious infectious cause of exacerbation and/or evidence of chronic hypercapnia, other causative factors such as associated

heart failure, obstructive sleep apnoea or obesity-associated hypoventilation should be evaluated. In these cases, it may be beneficial to use NIMV for longer periods of time than standard [254].

Two recent studies have shown, however, that prolongation of nocturnal NIMV after recovery from an episode of hypercapnic exacerbation is not effective in preventing subsequent relapses of acute hypercapnic respiratory failure, hospital readmission or mortality in patients with exacerbated COPD without prior indication for home ventilation [255,256], and results in a longer stay in intermediate care. These studies suggest that in these patients, NIMV can be withdrawn directly when the acute episode resolves, pH normalises and both $PaCO_2$ and overall clinical condition improve, with tolerance of spontaneous breathing without ventilatory support [257].

14.1.2. In neuromuscular and ribcage diseases

Recovery is generally later than in acute COPD, so withdrawal of NIMV should be slower, and NIMV should be continued overnight. The higher the HCO_3 concentration on admission, the longer the period of ventilatory support required to reduce the degree of compensatory metabolic alkalosis. It is recommended to aim for $PaCO_2$ around 45-50 mm Hg on spontaneous breathing. After resolution of the episode, most patients with neuromuscular or rib cage diseases will require home NIMV. This should be continued overnight until the patient is linked to a chronic home ventilation service.

14.1.3. In Obesity-Hypoventilation Syndrome

Although there is no evidence for this type of patients, withdrawal of NIMV during wakefulness should be done as in acute COPD, although in this case it is advisable to continue NIMV during the night. After an episode of hypercapnic chronic ARF, the possible indication for long-term nocturnal home ventilation, either non-invasive ventilation or CPAP, should always be evaluated. In addition, the possible indication for

bariatric surgery and optimal home ventilatory settings should be considered as part of the management of these patients.

14.2. Withdrawal of HFNCT

It is difficult to establish guidelines for weaning from HFNCT and replacing it with a conventional oxygen therapy system. However, it would seem reasonable to first decrease FiO_2 and then flow. Randomised clinical studies use as criteria for weaning from HFNCT the improvement of signs of respiratory distress (RF < 25 rpm) and severity of hypoxaemia based on PaO_2/FiO_2 [67,70].

15. Criteria for continuing long-term home ventilation

The number of patients who, after receiving NIMV in an acute situation, are subsequently treated with home mechanical ventilation (HMV), has increased progressively and significantly in recent years.

Acute ventilation is often the final stage of very prevalent pathologies that remain underdiagnosed in the general population (OHS, sleep apnoea-hypopnoea syndrome -SAHS-...) and/or pathologies with previous HMV criteria (neuromuscular diseases, restrictive diseases...) [258], which for various reasons have an acute onset.

In this regard, when deciding on a referral to an HMV unit, it should be considered whether the acutely established NIMV belongs to the group of patients in whom previous HMV criteria already existed, or whether it is the acute process and its subsequent evolution that motivates the indication for HMV.

The following is a summary of the most prevalent situations that may require HMV after acute NIMV.

15.1. COPD with hypercapnia after withdrawal of NIMV

Persistent hypercapnia after hospital discharge in COPD patients who have required acute NIMV is associated with a high risk of readmission and increased mortality [259,260]. However, the indication for HMV in these patients remains controversial at present and requires further studies to confirm it. Two recent publications support the indication for HMV once the acute episode is over [261,262] with positive results in terms of reduced mortality, hospital readmissions and improved quality of life. In contrast, the RESCUE trial [263] found no positive results in the HMV group. One of the studies [261] supports the indication for HMV in patients who are in

stable stage IV GOLD. In contrast, a more recent study [262] establishes the indications for HMV after severe exacerbation in patients who remain hypercapnic (> 56 mm Hg) 2-4 weeks after hospital discharge, which would be the same recommendation as recently published clinical guidelines [264].

The positive results of these studies are probably influenced by the different selection of patients (higher level of hypercapnia and severity in those who benefit) and, pending further evidence, these data are key to identifying potential candidates for HMV: advanced-stage COPD patients with severe hypercapnia after withdrawal of NIMV. The time to decide on HMV does not necessarily have to be during hospitalisation, so post-discharge follow-up is essential to detect the group of patients who may benefit from HMV.

The existence of other comorbidities, such as obesity, adds a component of hypoventilation to the situation of permanent diaphragmatic fatigue in which these patients find themselves. In addition, the co-existence of COPD and SAHS may be present [265], and in both situations, referral to a Sleep Unit should be made once clinical stability has been restored.

15.2. SAHS vs OHS

Often patients without COPD are carriers of OHS and/or SAHS with no previous diagnosis or treatment who debut with acute respiratory failure precipitated by different situations: respiratory infections, surgical procedures, ingestion of CNS depressant medication, etc. Once the acute situation is resolved, the need for HMV or CPAP should be considered according to the sleep study and evolution [266]. Similarly, patients previously treated with CPAP may require a change to NIMV during an acute process and should be referred to a sleep and/or ventilation unit to assess the need of HMV.

15.3. Restrictive diseases (rib cage disorders, diaphragmatic pathology, slowly or rapidly progressive neuromuscular diseases, etc.)

Restrictive diseases, whatever their aetiology, often progress to a situation of hypoventilation requiring treatment with HMV [258].

Patients with restrictive pathologies such as kyphoscoliosis or with neuromuscular diseases such as Amyotrophic Lateral Sclerosis, Steinert's Myotonic Dystrophy or Duchenne disease, among others, lead to a rapidly or slowly progressive failure that may start or worsen suddenly, manifesting as ARF requiring NIMV and later HMV.

In this group of patients, referral and subsequent monitoring of ventilatory support and other respiratory aids if required (cough assistant etc.) is essential.

15.2. NIMV in palliative care

Chronic respiratory pathology in terminal phase, as well as diseases of different aetiologies in palliative phase may require NIMV in acute situations [54,267]. Once this has been overcome, HMV may be a valid option to improve dyspnoea and quality of life as suggested in the recent ERS/ATS guideline [41]. The decision to maintain ventilation must be individualised for each patient and agreed between the parties involved (patient, family and healthcare professionals), assuming that, although it will not modify the final evolution of the disease, it may offer an increase in the patient's expected survival.

16. Paediatric-specific follow-up

16.1. Evaluation of the effectiveness of the NIMV

The objectives do not differ considerably from those of adult patients, and continuous clinical and functional monitoring of the patient should be established, especially during the first 4-6 hours, and admission to the unit with continuous monitoring is recommended until improvement and progressive stability of the patient is observed. In addition to comfort, respiratory effort, respiratory dynamics, thoracic excursion, respiratory frequency (RF), and heart rate (HR) should be monitored, according to the attached tables 15 and 16, as well as monitoring of the level of consciousness with the modified Glasgow scale for infants (table 17). Discontinuous monitoring of certain parameters such as blood pressure (BP), cardiorespiratory auscultation or chest radiology should also be performed. As for interpretation, there are a number of nuances to be taken into account [174,175]:

- It is especially important to monitor the level of consciousness, as a decrease in consciousness in the context of ARF is almost always an indication for OTI.
- Spontaneous RF should decrease if NIRS is effective, bearing in mind that normal RF changes with age and that bradypnoea in the context of ARF is almost always an indication for OTI.
- Both respiratory effort and HR (physiological response to hypoxaemia) should decrease with adequate support.
- ECG monitoring is essential in the presence of cardiomyopathy and recommended in all acute circumstances in order to detect arrhythmias promptly.

Age	Respiratory frequency (rpm)
0 - 6 months	30 – 50
6 months – 1 year	20 – 40
1 – 2 years	20 – 30
2 – 6 years	15 – 25
6 – 10 years	15 – 20
More than 10 years	13 - 15

Table 15. Table of respiratory frequency by age.

Age	Heart rate (bpm)
Newborn	110 – 160
1 – 2 years	100 – 150
2 – 5 years	95 – 140
5 – 12 years	80 – 120
More than 12 years	60 – 100

Table 66. Heart rate by age.

Opening of the eyes	Verbal response	Motor response	Points
		Spontaneous movements	6
	Babbling	Withdrawal on touch	5
Spontaneous	Irritable Crying Consolable	Withdrawal in pain	4
To voice	Crying in pain	Abnormal bending	3
To pain	Complaints to pain	Abnormal extension	2
None	Absence	None	1

Table 7. Modified GCS for infants.

Mild Glasgow between13-15; moderate Glasgow between 9-12; severe Glasgow less than 9

- Blood gas parameters.

    - *Oxygenation*: When applying a NIRS technique in children, continuous monitoring of SpO_2 should be maintained, as serial arterial blood gas analyses are not usually performed, unless a cannulated artery is available. In practice, continuous monitoring of haemoglobin oxygen saturation ($SatO_2$) in arterial blood by pulse oximetry and calculation of the $SatO_2$/inspired oxygen fraction index is used to monitor oxygenation. Arterial blood gases would only be indicated if the ratio does not improve with NIRS and especially in the presence of ARDS. Continuous, non-invasive transcutaneous oxygen pressure measurement is reliable only if

haemodynamic stability is present and could complement $SatO_2$ for hypoxaemia control.

- *Ventilation*: In practice, intermittent measurement of venous or capillary partial pressure of carbon dioxide (PCO_2) or continuous monitoring of transcutaneous PCO_2 or exhaled carbon dioxide ($EtCO_2$) is used to monitor ventilation, taking into account the limitations of this technique when using NIMV systems with built-in leakage. Recently, transcutaneous PaO_2 and $PaCO_2$ monitoring offers interesting non-invasive alternatives to clinical practice.

Taking into account the above, the clinical criteria for improvement will be a decrease in HR, RF, respiratory effort (dyspnoea) and accessory respiratory muscle activity, in approximately 1-2 hours from the onset of NIMV. A number of respiratory distress scales (Pulmonary Score, Wood-Dowes, Tussing, etc) are also used to assess evolution. Regarding blood gas criteria, a decrease in $PaCO_2$ in hypercapnic ARF and a decrease in FiO_2 requirements in hypoxaemic ARF should be detected within 2 hours of initiating NIMV.

As in adult patients, it may be useful to monitor ventilator charts in order to detect and correct asynchronies. This also includes leakage monitoring. It should be noted that TV estimates are often more inaccurate than in adults because the measurements are at the lower limit of the equipment's measurement capabilities. As a guideline, if leaks are less than 7 bpm, the mask is probably too tight and pressure injuries may occur. If leakage is too high, conjunctivitis and dryness may occur. An adequate leak is generally less than 30 bpm (intentional + unintentional) although this may vary depending on the ventilator and interface.

Finally, it is also important to control possible adverse effects, such as clinical surveillance of the support areas of the mask (especially on the nasal bridge), protection

wit hydrocolloid dressings, massaging the support area during breaks, rotating the interfaces, using protective oils or similar, and control of gastric distension, with the use of a nasogastric decompression tube, especially in the youngest patients. The main complications are listed in table 18.

Problem	Solution
Irritant dermatitis in the nasolabial fold area	Occasional use of colloid creams to alleviate discomfort
Most frequent skin necrosis in the area of the bridge of the nose	Mask rotation, pressure relief with hourly frequency for 1 minute, preventive use of hyper-oxygenated fatty acid spray, use of hydrocolloid
Irritant conjunctivitis	More frequent in children with lagophthalmos, minimise leakage and use shields to seal the eyelids.
Interface or airway obstruction	Small nasopharyngeal tubes obstructed by secretions
Claustrophobia	May be due to a too tight mask or lack of vision
Gastric distention	Inspiratory pressures greater than 25 cm H_2O Nasogastric tube placement
Food aspiration	Use transpyloric tube feeding
Pneumothorax (rare)	If it occurs, assess placement of drainage tube and continue with the technique
Airway obstruction by secretions	Humidification defect

Table 8. Complications that may compromise the efficacy of NIMV in paediatric patients.

16.2. Analysis of the NIMV failure

The most important predictors of failure of NIMV in paediatric patients are the severity of hypoxaemia, patient age and respiratory effort. Persistent hypoxaemia and/or respiratory distress without significant change after two hours of adequate technique are factors that predict the need to intubate the patient, with transition to conventional mechanical ventilation. Related to the underlying pathology, the best response to NIMV is found in patients with acute bronchiolitis and respiratory infections in neuromuscular patients without ARDS criteria.

Therefore, the key factors to consider, especially in the first 4-6 hours of NIMV in paediatric patients, are as follows:

- Failure to improve symptoms or deterioration of the patient. Thus, HR and RF should be, according to the patient's age, lower than when the technique was initiated, in the absence of pain or fever. A persistence of RF above 2 standard deviations from normal for the patient's age would be a sign of poor prognosis, as well as persistence of tachycardia that cannot be explained by another cause (fever, pain, etc.).
- Presence of haemodynamic instability.
- Increased oxygen requirement resulting in a decrease in the SpO_2/FiO_2 ratio [111,174,179].
- Asynchrony with the ventilator.
- Persistence of blood gas disturbances (pH and pCO_2).
- Development of unmanageable complications in NIMV (abundant secretions, severe hypoxaemia, decreased level of consciousness, haemodynamic disturbances).
- Refusal of treatment or wish to discontinue treatment by parents or guardians.

Failure of NIMV in an episode of ARF usually leads to intubation of the patient, unless intubation has been previously ruled out. In such patients, the ineffectiveness of NIMV

in alleviating dyspnoea should lead to other treatments [174,268]. In this regard, it should be noted that in paediatrics, HFNCT has not been shown to be superior to NIMV, considering all possible scenarios. However, CPAP has been shown to be useful as a rescue treatment for failure of HFNCT in acute bronchiolitis [269,270]. Only in isolated circumstances, e.g. in patients intolerant to NIMV, can HFNCT be used to improve patient comfort [122,271,272].

16.3. Discontinuation

The optimal duration of NIMV in ARF associated with acute bronchiolitis or severe asthma attacks will depend on the evolution of the infectious process in the first case and the response to bronchodilator treatment in the second. Thus, viral infections with a favourable evolution (without ARDS) usually resolve in 10-15 days, with the first 5-7 days being the most likely to require NIRS, which can be progressively withdrawn. In the absence of underlying pathology, it is not necessary to maintain NIMV during sleep. In asthma attacks without concomitant infection and with good response to systemic corticosteroids, NIMV is usually maintained for 48-72 hours and withdrawal may be more rapid.

In patients with neuromuscular pathology or with restrictive alterations of the rib cage, it is very common for the episode of ARF to reveal the need for prolonged ventilation in the context of more or less compensated chronic respiratory failure (CRF) in the absence of infections. Withdrawal of NIMV is usually done more slowly, with the aim of maintaining normal daytime ventilation, without supplemental oxygen, and maintaining it in sleep for several weeks, until completion of baseline respiratory function studies. For progressive weaning, e.g. in neuromuscular patients, respiratory support is progressively reduced to a pressure support of 4-6 cmH_2O on EPAP, which in turn is maintained at 5-7 cmH_2O. It is important that the FiO_2 required for normal saturations is 21% and, in any case, no higher than the patient had before the ARF episode. Once clinical stability and the absence of intercurrent processes that could interfere with the success of weaning is verified, weaning is continued for longer and longer periods,

keeping the NIMV in sleep until it is established whether the patient should continue with home NIMV.

In the case of patients who do not require progressive withdrawal, for example, patients with acute viral bronchiolitis or in the case of hypoxaemic respiratory failure, the resolution and/or control of the infection, the absence of systemic involvement by the infection, the absence of complications and the need for minimal respiratory support should be verified: CPAP with FiO_2 below 30% or NIMV with EPAP of 5-6 cm H_2O and IPAP around 8-10 cm H_2O, and FiO_2 of 25-30%. In this situation, support can be withdrawn directly [19].

16.4. Referral to a chronic ventilation unit

In paediatrics, most NIMV in acute patients is performed in the PICU. Patients with known chronic respiratory failure (CRF) or a pathology at risk of CRF, prior to the acute episode that led them to receive NIMV, should be evaluated in a pulmonology clinic with knowledge of long-term NIMV application and management of NIMV at home. Likewise, if no progress is made during weaning from NIMV and the episode of respiratory failure appears to be prolonged over time, the team performing chronic NIMV in paediatrics should assess the patient before discharge from the PICU in order to transfer them to ventilator support that can be used on hospital wards or at home, and progressively define the type of support that the patient will maintain, depending on the clinical situation, the underlying pathology, the patient's age, the hours of the day during which support is required, the availability of equipment and the experience of the centre.

17. Neonatology-specific follow-up

17.1. Monitoring the efficacy of NIMV in newborns

The main goal of NIMV and/or CPAP is to achieve adequate lung recruitment with improved ventilation/perfusion ratios. The most important parameters in the follow-up are the following:

- Oxygenation: CPAP/NIMV titration should allow SpO_2 control with FiO_2 requirements typically below 0.4 [273,274]. The patient's oxygen saturation should be within the limits corresponding to their gestational age (table 13).

- Ventilation: controls are usually performed with pCO_2 measurement in venous or capillary blood, although transcutaneous pCO_2 monitoring is possible. Permissive hypercapnia values can sometimes be tolerated, even with NIMV, up to pCO_2 values of 60-65mm Hg, with pH >7.25 [273].

- Clinical check-up: there are scales for assessing respiratory distress, such as the Silverman score, which are based on physical examination data such as respiratory rate, the presence of sub/intercostal and sternal tugging, etc. In this context, increased respiratory effort or poor clinical control of respiratory effort is often associated with inadequate lung recruitment.

- Radiological screening: chest radiology can help to assess the degree of lung recruitment, thus avoiding pressures that contribute to overdistension. It can also be useful to check for the absence of atelectasis and/or condensation, and, if clinically suspected, to rule out the presence of ectopic air [273]. Similarly, lung ultrasound may also have a role in the management of newborns with CPAP/NIMV, although it requires specific training and experience of staff for its correct interpretation [275].

17.2. Failure of CPAP/NIMV in neonatology

When CPAP/NIMV failure is suspected, in addition to checking the correct functioning of all components of the system used, it is especially important to position the patient with proper airway alignment (especially in preterm infants).

The criteria that are considered indicative of CPAP/NIMV failure in newborns are the following:

- Clinical criteria:
    - Need for FiO_2 > 0.4-0.5 to achieve target oxygen saturation (depending on gestational age and underlying pathology).
    - Respiratory distress that is progressive or not improving from baseline.
    - Apnoeic pauses requiring vigorous pacing with need for bag and mask ventilation, especially if > 3 episodes occur in one hour with desaturation and/or bradycardia.

- Blood gas criteria:
    - Respiratory acidosis with pH < 7.25 with pCO_2 > 60 mm Hg.

17.3. Therapeutic options in case of failure

- NIMV optimisation:
    - Increase in PEEP up to 7-8 cm H_2O and in inspiratory pressure.
    - Assessing the transition from CPAP to NIMV.

- Assess the increase in controlled breaths per minute at NIMV to a maximum of 40 rpm.

- Intubation and initiation of MV if all of the above fail [273,276].

17.4. Procedure for maintenance, complications and discontinuation or withdrawal of NIMV

17.4.1. Maintenance

The newborn with CPAP/NIMV requires specific and comprehensive nursing care, which is the basis for the success of this mode of respiratory support. Patient positioning should favour thoracic expansion and airway alignment, facilitating the passage of airflow. Placement of an open orogastric tube is necessary to avoid gastric overdistension and frequent aspiration of the tube is sometimes necessary to evacuate accumulated air. The patient does not necessarily have to remain on an absolute diet; it is recommended to start feeding preferably through an orogastric tube.

It is crucial to select the most appropriate size of interface for each patient, making frequent changes of nasal interfaces (binasal-nasal mask) to alternate pressure points. It is also useful to place nasal shields at identified pressure points to minimise skin injury. Frequent nasal lavage with physiological saline is recommended, avoiding direct suctioning of the nostrils with a nasal probe to avoid causing further damage to the nasal mucosa [277,278].

17.4.2. Complications.

- Obstruction to the flow path, due to poor positioning of the interface and/or accumulation of secretions, which can destabilise the patient.

- Nasal septum and philtrum lesions related to the pressure exerted by the interface, which can be of varying severity: mild (skin reddening), moderate (erosion) or severe, leading to tissue necrosis of the affected area.

- Sinking of the nasal root and upper jaw secondary to the pressure of the fixation systems, generating deformities of the facial mass.

- Deformity of the nares: dilatation and anteversion of the nares, with asymmetry in the case of the use of mono-nasal interfaces.

- Air trapping and inadvertent PEEP: alveolar overdistension may worsen hypoxaemia and hypercapnia.

- Presence of ectopic air: pneumothorax, pneumomediastinum, pulmonary interstitial emphysema.

- Overdistension of intestinal loops and decreased gastrointestinal blood flow, although CPAP/NIMV has not been linked to gastric perforations or as a trigger for necrotising enterocolitis.

17.4.3. Discontinuation/withdrawal

There is no strict protocol for withdrawal of NIMV. It is advised that oxygen requirements be below 0.4 to maintain adequate oxygenation, no apnoea and/or bradycardia, and absence of respiratory effort [273].

- Withdrawal of NIMV: progressive decrease in inspiratory pressure to 15 cm H_2O, and safety breathing rate to 10-15 cycles per minute. If this situation is well tolerated, a switch to nasal CPAP can be considered.

- Withdrawal of CPAP: in general, CPAP pressure is gradually decreased to 5 cm H_2O and FiO_2 less than 0.3. Once this situation is reached, CPAP is withdrawn and the patient is switched to COT or HFNCT depending on their clinical situation.

There is no clinical evidence to support that the method of periodic CPAP disconnections or pressure decrease from 5 cm H_2O to 2 cm H_2O or less is superior to that of abrupt CPAP withdrawal [276,278].

- Withdrawal of HFNCT: there are no specific guidelines for weaning from HFNCT and replacing it with a COT system. However, it seems reasonable to first decrease FiO_2 and then flow. An acceptable recommendation could be to maintain the flow rate until correct oxygenation is achieved with a FiO_2 of less than 0.3. The reduction in flow should be slow (1 l/min every 6-8h). Finally, when the patient presents a correct oxygenation with 2 l/min or less and with a FiO_2 less than 0.3, the replacement of HFNCT by a conventional oxygen therapy system can be considered.

18. Complications associated with NIRS

The most common complications of NIMV, together with their corresponding methods of resolution, are summarised in table 19 [277,279–283]

Complication	Action
Dryness/irritation of the respiratory mucosa	• Use of an active humidifier. • Adjusting pressures and FiO_2
Pressure ulcer	• Appropriate choice of interface • Use of cushioning and hydrocolloid pads • Oils with hyper-oxygenated fatty acids • Skin hydration • Short NIMV breaks • Adequate nutritional level
Gastric distention	• Lower pressures if possible • Sitting position • Nasogastric tube
Otitis and sinusitis	• Adequate secretion clearance, active humidification • Valsalva manoeuvres
Conjunctivitis	• Leakage control
Chest pain	• Analgesia
Accumulation of secretions	• Treatment of underlying disease • Active humidification • Promote voluntary cough • Provoke cough reflex (tracheal pressure in suprasternal recess) • Cough assistants
Agitation and intolerance to NIMV	• Ensure proper ventilator operation • Secure connections, tubing and interface • Ensure correct patient position (seated) • Check for leaks and asynchrony • If anxious: reassure patient and assess mild sedation
Barotrauma	• Avoid excessive pressure • If it occurs, consider placement of intercostal drainage and whether or not to continue with NIMV.

Complication	Action
Pneumonia and broncho-aspiration	• Proper secretion management • Interfaces for quick disconnection in case of vomiting • Monitor level of consciousness
Haemodynamic alterations	• Increased volemia: use of crystalloids or colloids • Decreased ventilatory support: pressures and respiratory rate • Use of vasoactive drugs

Table 19. Complications during NIMV and how to resolve them [277,279,283–286].

As far as HFNCT is concerned, complications are so far scarce and barely reported in the literature, the most frequent ones being the following:

- Self-limiting chest pain at the start of the technique.
- Headache.
- Heat intolerance: modern devices allow temperature regulation to values of 31-34-37 °C.
- Epistaxis.
- Intolerance to noise, especially in older devices.
- Sinusitis: as with epistaxis, adequate hydration of the nasal mucosa in physical contact with the cannulas is advisable.
- Pneumothorax: described in neonatology.
- Pressure ulcers in contact areas due to prolonged use of the technique, mainly in the subnasal sulcus and cheekbones, the preventive strategy being the same as for NIMV.
- Aspiration of condensation liquid from the socket and burns caused by it, related to poor quality consumables.

Table 20 reflects the side effects attributable to HFNCT reflected in a recent treatment study in 44 patients with acute chronic heart failure with dyspnoea and/or hypoxaemia to conventional oxygen therapy [150].

- Heat intolerance (most common). - Lack of acoustic comfort. - Self-limiting retrosternal chest pain. - Headache. - Paradoxical sensation of dryness in nasal and pharyngeal mucosa. - Intolerance to flow. - Condensation in the tubing. - Intolerance to cannulas. - Malar erythema.

Table 90. Most common complications of HFNCT.

19. Conclusions

Clinical practice recommendations, summarised in tables 21 to 27, have been developed regarding the current use of NIMV/HFNCT for acute respiratory failure in adult, paediatric and neonatal patients.

In summary, the clinical management of acute respiratory failure in adult and paediatric-neonatal patients must take into account the heterogeneity of clinical scenarios with respect to indications, stratification and follow-up for the use of non-invasive ventilation and high-flow nasal cannula therapy. The recommendations contained in this document reflect for the first time the degree of agreement between the main scientific societies and provide an updated working tool for all physicians in charge of the management of adult and paediatric-neonatal patients with acute respiratory failure that allows to reduce the clinical variability in the care of these patients.

It is highly likely that some of these recommendations will change over time with the generation or consolidation of scientific knowledge in this field, especially regarding the role of NIMV and HFNCT versus other emerging technologies such as extracorporeal CO_2 oxygenation and extraction. A systematic, dynamic and holistic approach is therefore needed to improve the management of this prevalent problem and thus reduce the significant burden of medical care in the hospital setting to improve patient outcomes.

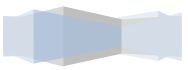


Table 21. Consensus recommendations for indications for NIRS (NIMV) in adult patients

Clinical context	Recommendation	% majority option
Trial of NIMV in patients with clinical signs of severe ARF without established clinical causal diagnosis, provided that the need for continuation or withdrawal of NIMV is reassessed once the necessary diagnostic data are available.		66 %
Treatment with NIMV in patients with chronic ARF and respiratory acidosis (pH<7.35) secondary to COPD exacerbation.		100%
NIMV (either CPAP or pressure support) in patients with cardiogenic APO.		100%
NIMV in OHS and respiratory acidosis.		66%
NIMV in severe exacerbation of asthma.		93%
NIMV in pneumonia and hypoxaemic ARF in patients without co-morbidity.		73%
NIMV in viral pandemics.		73%
NIMV in pneumonia and hypoxaemic ARF in patients with cardiorespiratory co-morbidity.		93%
NIMV in immunosuppressed pneumonia and hypoxemic ARF.		66%
NIMV in adult respiratory distress and mild hypoxaemic ARF.		60%
NIMV in adult respiratory distress and moderate-severe hypoxaemic ARF.		86%
NIMV in patients with non-intubation orders in groups where efficacy has been documented.		53%
NIMV as an adjuvant treatment for dyspnoea in palliative patients.		73%
NIMV in restrictive or neuromuscular pathology with exacerbation of any cause, especially infectious, in order to prevent the occurrence of respiratory acidosis.		50/50%
NIMV in patients with chest trauma and secondary ARF.		66%
NIMV as a weaning technique in patients with hypercapnic respiratory failure and intolerance to the spontaneous breathing test.		53%
NIMV post-extubation in patients with failure risk criteria.		71%
NIMV in post-extubation ARF.		71%
NIMV in postoperative ARF in abdominal and cardiothoracic surgery.		50/50%
NIMV (CPAP) in pre-hospital care for suspected APO.		73%
Pre-hospital NIMV in suspected exacerbation of COPD.		53%

Table 22. Consensus recommendations for indications for NIRS (NIMV) in adult patients

Clinical context	Recommendation	% majority option
HFNCT as the first ventilatory support technique versus oxygen therapy and NIMV in ARF secondary to pneumonia or distress.		60%
HFNCT in ARF in immunocompromised patients against NIMV.		66%
HFNCT after planned extubation in patients without hypercapnia and at low risk of reintubation.		61%
HFNCT combined with NIMV to prevent reintubation in patients at high risk of reintubation.		53%
HFNCT as a therapeutic alternative to NIMV in postoperative cardiothoracic surgery patients with postoperative respiratory failure or at high risk of reintubation.		60%
HFNCT in hypoxaemic patients or patients at high risk of hypoxaemia who are to be intubated on a scheduled basis.		50/50%
HFNCT in endoscopic techniques.		73%
HFNCT as a palliative approach to treating ARF.		60%

Table 23. Consensus recommendations for indications for NIRS in paediatric patients.

Clinical context	Recommendation	% majority option
NIMV in general ARF without contraindications (hypoxaemia + hypercapnia) provided there are no contraindications.		84%
NIMV in paediatric patients with neuromuscular pathology, weaning from IMV to avoid reintubation.		94%
NIMV in paediatric patients in any situation with high risk of IMV weaning failure to avoid reintubation.		77%
NIMV in paediatric patients with moderate hypoxaemic ARF (PaO_2 40-60 mm Hg; saturation 75-90%; PaO_2/FiO_2 200-300), without hypercapnia, without associated organ failure.		50%/50%
NIMV in immunocompromised paediatric patients with moderate hypoxaemic ARF due to pneumonia without haemodynamic failure to avoid intubation.		69%
NIMV in paediatric patients with moderate to severe ARF associated with viral infections, primarily viral bronchiolitis.		77%
NIMV in paediatric patients with ARF in the setting of moderate-severe asthma or status asthmaticus, to avoid intubation.		82%
NIMV in paediatric patients with acute pulmonary oedema of cardiogenic origin.		87%
NIMV in paediatric patients with dynamic upper airway obstruction.		82%
NIMV in paediatric patients with intention to improve comfort in the context of a palliative approach and orotracheal intubation not indicated.		87 %
High-Flow Nasal Cannula Therapy (HFNCT) as initial therapy for mild-moderate bronchiolitis on the inpatient ward.		50%
HFNCT in the paediatric ward with the intention of avoiding therapeutic escalation in mild-moderate bronchiolitis.		50%
HFNCT in paediatric intensive care in patients with acute bronchiolitis.		72 %
HFNCT in paediatric intensive care in patients with bronchospasm.		72 %

Table 24. Consensus recommendations for indications for NIRS in neonatal patients.

Clinical context	Recommendation	% majority option
Preventive NIMV in all preterm patients (< 30 weeks GA) with respiratory distress.		100 %
NIMV after extubation and to prevent reintubation in preterm infants < 30 weeks GA.		100%
NIMV in stabilisation after birth at < 32 weeks GA and/or < 1500 grams birth weight.		100%
HFNCT in newborns with mild-moderate respiratory failure.		100 %
HFNCT after extubation and to prevent reintubation in the preterm patient > 28 weeks GA.		100%
HFNCT on weaning from nasal CPAP.		100%

Table 25. Consensus recommendations for the procedure and follow-up of NIRS in adult patients

Clinical context	Recommendation	% majority option
Stratification of patients who are candidates for NIRS. Prioritisation of high-risk patients for admission to intensive care.		93%
Use of specific acute NIMV ventilators or critical patient ventilators with NIMV module.		80%
The interfaces of choice in the acute adult patient are nasobuccal and full facial masks.		87%
Pressure ventilation in spontaneous mode is the mode of choice in acute respiratory failure.		93%
Continuous monitoring of physiological parameters during the procedure (RF, HR, SpO_2).		93%
Monitoring with the help of the analysis of the flow and pressure curves provided by the ventilator.		67%
Use of active humidification during NIMV.		53%
Assessment of the efficacy of NIMV within one hour of initiation, with assessment at 4-6 h being a good indicator of success/failure of the technique.		93%
If no response to NIMV is obtained, early discontinuation of the technique should be considered and endotracheal intubation and invasive ventilation should be considered.		100%
Direct withdrawal of NIMV in patients with COPD exacerbation after normalisation of pH and improvement of overall clinical condition.		53%
Assessment of the continuity of NIMV in acute OHS after resolution of the acute episode, as many patients have underlying sleep disturbances.		73%
Assessment of post-acute chronic home ventilation requiring NIMV in patients with restrictive lung disease, neuromuscular disorders and COPD in which PCO_2> 56 mm Hg persists at discharge.		80%
In the application of HFNCT, use flows between 40-50 bpm in patients with moderate hypoxaemic ARF with minimal FiO_2 to maintain SpO_2 around 93-94% with humidification and temperature as previously noted.		100%

Table 26. Consensus recommendations for NIRS procedure and follow-up in paediatric patients.

Procedure	Recommendation	% majority option
In paediatric patients, the clinical criteria for improvement should be assessed 1-2 hours after starting the technique: decrease in HR, RF, which should be in accordance with the patient's age, improvement in respiratory effort (dyspnoea) and decrease in the activity of accessory respiratory muscles.		97 %
PaO_2 / FiO_2 or SaO_2 / FiO_2 should be monitored in the paediatric patient.		97 %
Pressure ventilation in spontaneous mode is the initial mode of choice in general acute respiratory failure (hypoxaemia + hypercapnia).		74 %
CPAP mode is the initial mode of choice in type I ARF, hypoxaemic without hypercapnia, with preserved respiratory effort.		74 %
Use of active humidification in the paediatric patient		94 %
During non-invasive respiratory support, it is necessary to maintain good positioning of the patient and placement of a nasogastric tube.		64 %
In acute-phase NIMV in paediatric patients, the PS level should be around 4-5 cm H2O above the expiratory pressure level (PEEP or EPAP). Once patient tolerance is achieved, the PS level can be increased in 2 cm H2O intervals until the respiratory effort is reduced.		94 %
The withdrawal of NIMV in the paediatric patient depends on the pathology for which the indication is given: the shorter the time of evolution, the faster the withdrawal.		69 %
In paediatric neuromuscular patients, chronic non-invasive home support may be required.		97 %

Table 27. Consensus recommendations for NIRS procedure and follow-up in neonatal patients.

Clinical context	Recommendation	% majority option
Use of active humidification in neonatal patients.		100%
The interfaces of choice in neonatology are short binasal cannulas or nasal masks.		100%
The ventilators of choice for neonatal NIMV are variable flow generators as opposed to continuous flow.		100%
FiO_2 according to $SatO_2$ for GA.		100%
Maintain good patient positioning and orogastric tube placement.		100%
Consideration of the need for a FiO_2 of 0.4-0.5 to achieve target saturation according to gestational age, progressive dyspnoea and apnoea pauses, and persistent respiratory acidosis as criteria for failure.		100%
Initiate withdrawal of NIMV when FiO_2<0.4, no apnoeas and/or bradycardias, and no clinical signs of respiratory distress.		100%

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21. Abbreviations

ACPO	Acute cardiogenic pulmonary oedema
AHF	Acute heart failure
AMT	Air Medical Transport
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
CC	Coordinating committee
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COT	Conventional oxygen therapy
CPAP	Continuous positive airway pressure
CRF	Chronic respiratory failure
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
GA	Gestational age
HFNCT	High-flow nasal cannula therapy
HMV	Home mechanical ventilation
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressure
Kg	Kilogram
L	Litres
lpm	Litres per minute
min	Minute
MV	Mechanical ventilation
NAVA	Neurally adjusted ventilatory assist
NIMV	Non-invasive mechanical ventilation
NIRS	Non-invasive respiratory support
NMD	Neuromuscular diseases
OHS	Obesity-hypoventilation syndrome
$PaCO_2$	Partial pressure of CO_2 in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PaO_2/FiO_2	Ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen
PCV	Pressure controlled ventilation
PEEP	Positive end-expiratory pressure
PICU	Paediatric intensive care units

PS	Pressure support
PSV	Pressure support ventilation
RF	Respiratory frequency
rpm	Respirations per minute
RR	Relative risk
S	Spontaneous mode
S/T	Spontaneous-timed mode with backup-respiratory rate
SAHS	Sleep apnoea-hypopnoea syndrome
SaO_2	Arterial oxyhaemoglobin saturation
SaO_2/FiO_2	Arterial oxygen saturation to inspired oxygen fraction ratio
SARS	Severe acute respiratory syndrome
SEA	Severe exacerbation of asthma
SECIP	Spanish Society for Paediatric Intensive Care
SEDAR	Spanish Society of Anaesthesiology and Resuscitation
SEMES	Spanish Society of Emergency Medicine
SEMICYUC	Spanish Society of Critical Intensive Care Medicine and Coronary Care Units
SENP	Spanish Society of Paediatric Pneumology
SEPAR	Spanish Society of Pneumology and Thoracic Surgery
SpO_2	Oxyhaemoglobin saturation measured by pulse oximetry
SpO_2/FiO_2	Ratio between arterial saturation by pulse oximetry and inspired oxygen fraction
SVT	Spontaneous ventilation test
TV	Tidal volume
UA	Upper airway
WG	Working group