High Flow Nasal Cannula Therapy in the Emergency Department: Main Benefits in Adults, Pediatric Population and against COVID-19: A Narrative Review

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ABSTRACT

This review aims to summarize the literature's main results about high flow nasal cannula therapy (HFNC) HFNC benefits in the Emergency Department (ED) in adults and pediatrics, including new Coronavirus Disease (COVID-19). HFNC has recently been established as the usual treatment in the ED to provide oxygen support. Its use has been generalized due to its advantages over traditional oxygen therapy devices, including decreased nasopharyngeal resistance, washing out of the nasopharyngeal dead space, generation of positive pressure, increasing alveolar recruitment, easy adaptation due to the humidification of the airways, increased fraction of inspired oxygen and improved mucociliary clearance. A wide range of pathologies has been studied to evaluate the potential benefits of HFNC; some examples are heart failure, pneumonia, chronic pulmonary obstructive disease, asthma, and bronchiolitis. The regular use of this oxygen treatment is not established yet due to the literature's controversial results. However, several authors suggest that it could be useful in several pathologies that generate acute respiratory failure. Consequently, the COVID-19 irruption has generated the question of HFNC as a safety and effective treatment.

Our results suggested that HFNC seems to be a useful tool in the ED, especially in patients affected by acute hypoxemic respiratory failure, acute heart failure, pneumonia, bronchiolitis, asthma and acute respiratory distress syndrome in patients affected by COVID-19. Its benefits in hypercapnic respiratory failure are more discussed, being only observed benefits in patients with mild-moderate disease. These results are based in clinical as well as cost-effectiveness outcomes. Future studies with largest populations are required to confirm these results as well as establish a practical guideline to use this device.

KEYWORDS

emergency; oxygen; respiratory diseases; high flow nasal cannula; pediatrics; COVID-19

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INTRODUCTION

Respiratory support is applied in the Emergency Department (ED) in several situations to provide adequate oxygenation and alveolar ventilation. Oxygen therapy (OT) consists of administering oxygen at a higher concentration than atmospheric. These concentration values are directly proportional to the altitude. Its indications include both acute and chronic pathologies in children and adults. The main objectives of oxygen therapy are: a) to treat and/or prevent hypoxemia; b) decrease myocardial demand; c) decrease respiratory effort, and d) treating pulmonary hypertension (1, 2). Historically, these situations have been treated with conventional oxygen therapy (COT), which flow is limited to less than 15 L/min. Besides, this system has other limitations, including poor precision of exact oxygen delivery, insufficient heating and humidifying, and poor tolerance (3).

Several authors have demonstrated the adverse effects of breathing dry air in a clinical and physiopathological way. In these situations, the nasal mucosa generates excessive water reducing the nasal mucociliary clearance (4). Cold air is also known to induce bronchoconstriction in patients with asthma and increased airway resistance in the upper airway to protect the lungs (5, 6). Also, it is observed that poor humidified gas cause acute damage and inflammation in epithelial cells (7). Finally, unwarmed oxygen support is associated with mask discomfort, nasal and oral dryness, eye irritation, nasal and eye trauma, and gastric distention (8). However, these subjective clinical effects are not apparent, being discussed by several authors recently (9, 10).

High flow nasal cannula therapy (HFNC) was created to avoid all the COT limitations in respiratory failure treatment. This system may provide a gas flow up to 60 L/min, allowing a precise FiO_2 (11). This system consists of the administration of high oxygen flows through nasal cannulas and increased use in recent years due to its excellent tolerance and ease of use (12). The air is administered humidified (humidity between 95–100%) and warm (34–40 °C). This system's benefits are due to the gas's humidification and temperature, which reduces metabolic expenditure, improves compliance and lung elasticity and facilitates tolerance and comfort. Furthermore, other advantages of these systems are decreasing the nasopharyngeal dead space, lowering the inspiratory resistance, and providing a certain degree of pulmonary distension pressure (CPAP). Which is neither measurable nor adjustable, but has numerous benefits (decreases atelectasis, improves the ventilation/pulmonary perfusion (V/Q) ratio, and, in premature patients, reduces apnea) (2, 13). Table 1 summarizes the advantages, disadvantages, indications and contraindications of HFNC.

Tab. 1 Advantages, disadvantages, indications and contraindications of high flow nasal cannula therapy.

Advantages	Humidification and heat of the administered gas – Improves ciliary movement and clearance of secretions – Improves lung compliance and elasticity – Reduces metabolic work – Improves patient tolerance and comfort – Prevents dryness and damage to the nasal mucosa – Prevents reflex bronchoconstriction Nasopharyngeal dead space lavage – Displaces expired air from the naso and oropharynx • Reservoir for inspiration • Anatomical oxygen reservoirs – The total volume that the patient must move is less, reducing the work of breathing – Better control of (FiO_2 set = FiO_2 delivered) Decreases inspiratory resistance, thus decreasing the work of breathing Provides some degree of lung distending pressure (alveolar recruitment) – Variable, unpredictable, not adjustable – Reduces atelectasis – Improves ventilation/perfusion ratio – Reduces apneas in premature babies
Disadvantages	Side effects – Mild: runny nose, facial erosions, condensation of nasal prongs with low flows, meteorism and abdominal distention (assess nasogastric tube) – Severe: barotrauma (uncommon) if very high flows are generated or nostrils are obstructed by cannulae (special care in neonates and preterm newborns), nosocomial infection (system contamination)
Indications	Hypoxemic respiratory failure Mild-moderate hypercapnic respiratory failure Respiratory failure in immunocompromised Acute heart failure Asthma, bronchiolitis, pneumonia Withdrawal of invasive and non-invasive mechanical ventilation Preoxygenation and passive oxygenation in orotracheal intubation Patients in palliative situation
Contraindications	Uncooperative patient Agitated patient Recent nasal surgery or trauma Need to preserve airway

According to age, the flow rate of high-flow oxygen therapy differs, varying from 2–8 L/min in infants and range up to 60 L/min in adolescents and adults. This system's indications have increased in recent years, being accepted generically in moderate acute respiratory failure cases or in cases of hypoxemia that do not respond to conventional oxygen treatment (2, 14).

This review aims to summarize the primary uses of HFNC in both the pediatric and adult populations. The manuscript will be divided into the main pathologies where this system has been studied.

ACUTE HEART FAILURE

Acute heart failure (AHF) is a prevalent and life-threatening medical condition requiring hospital admission and adequate oxygen therapy (15). In the United States, one million ED admissions are due to this pathology every year (16). It has been found that 90% of these patients suffer dyspnea (17), observing in almost 50% hypoxemia, hypercapnia, acidosis, or a combination of these (18). In different AHF syndromes, respiratory failure is most frequently seen in acute cardiogenic pulmonary edema (CPO), in cardiogenic shock, and cases associated to other lung alterations, including respiratory infections, bronchial hyperresponsiveness, and exacerbation of chronic obstructive pulmonary disease (COPD) (19). The potential benefits of this technique in this entity are based in two mechanisms: a) due to the low level of positive end-expiratory pressure (PEEP) provided (<5 cmH_2O), which improves alveolar recruitment and tidal volume, contributing to alveoli clearance and to $PaCO_2$ decrease. However, this effect depends on airflow as well as on a closed mouth, being the last one often difficult to maintain in severe respiratory failure (20); and b) the capacity of HFNC to provide continuous washout of dead space in the upper airways, preventing the rebreathing of CO_2. Therefore, it is obtained a functional reduction in dead space and reducing minute ventilation by slowing down the breathing frequency and reducing work of breathing (21).

The benefits of HFNC in AHF in the ED have been studied, especially in the recent years. A preliminary study revealed that this oxygen device system reduces dyspnea and refractory hypoxemia compared to COT in patients affected by AHF due to CPO after 24 hours of treatment (22). This data was confirmed in a similar situation by the same authors after 1, 2, and 24 hours, revealing an improvement in pH without significant increases in $PaCO_2$. Increased tolerance and fewer side effects were also observed (23). Similarly, Ko et al. observed an a significant improvement after 30 of the respiratory rate, lactate clearance, and arterial blood gas parameters, in comparison with conventional oxygen therapy (24). However, these results do not agree with recent studies, where COT showed similar effects to HFNC after 72 h attending to N-terminal pro-brain-type natriuretic peptide variations, dyspnoea by visual analog scale, peak expiratory flow, and clinical outcomes up to 30 days following hospital discharge (25).

It is well known that non-invasive ventilation reduces the rate of intubation and mortality in patients with acute heart failure (26). However, recent studies studied the potential benefits of HFNC in these patients. It has been observed that 30-day mortality is not increased in patients treated with HFNC compared to CPAP in CPO in the ED (27). However, these authors observed a non-significant increase in treatment failure secondary to respiratory worsening due to the less control of PEEP, reducing the effects over compliance, alveolar recruitment, decrease of left ventricular afterload and right ventricular preload. These results agree with a recent study performed by Marjanovic et al. (28), observing a similar effect in $PaCO_2$ levels after treatment for 1 h as well as pH, breathing frequency and signs of work of breathing.

HFNC has also been compared with invasive ventilation (IV). A study performed by Kang et al. (29) divided refractory patients to COT in the in two groups: HFNC and intubation treatment groups. The study showed that the first group had a similar result of improved oxygen saturation and in-hospital clinical outcomes than the intubation group in AHF. Mean arterial pressure, heart rate, and pulse oxygen saturation during the first 6 hours were evaluated. In addition, 86.8% of the patients were successfully recovered from progressive hypoxemia without endotracheal intubation.

As a result, the European Society of Cardiology included the HFNC as a therapeutic option in patients with moderate AHF. They do not respond to conventional oxygenation or in those with an indication for non-invasive ventilation (NIV) and intolerance (30).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD affects 15–20% of the adult population, being the fourth leading cause of death in the United States (31). This pathology is characterized by airflow limitation leading to dyspnea, cough, and sputum production. Exacerbations can be defined as a worsening of chronic respiratory symptoms and acute respiratory failure. Most of them are produced due to respiratory tract infections, being necessary COT or different oxygen therapy support systems if respiratory acidosis is observed (32). Classically, patients with refractory results in COT treatment or respiratory acidosis are treated with NIV or IV. However, in recent years, HFNC has been introduced in daily practice. The clinical and physiological support is based on: 1) The heated and humidified air diminish injuries to ciliary motion, reduces the inflammatory response and epithelial cell cilia damage, and decrease the airway water loss; 2) HFNC determines a washout from CO_2 from the dead pharyngeal space; The PEEP effect generated, and 4) The more stable FiO_2 provided compared to COT (33).

The literature has been observed in several manuscripts recently about the potential benefits of HFNC in COPD exacerbations. Preliminary studies compared HFNC and COT in COPD exacerbations (34). The authors observed a decrease of $PaCO_2$ in HFNC treated patients compared to COT treatments. However, non-significant differences have been observed in PaO_2 and respiratory rate. This study agrees with Bräunlich and Wirtz (35), where authors observed that $PaCO_2$ and pH levels were significantly improved after HFNC moderate acidotic and non-acidotic hypercapnic COPD exacerbations. However, the limitation of this study was the non-comparison with a control group. These studies were performed in exacerbated COPD patients during the admission, providing the possibility to apply this technique in the ED.

High-flow therapy has also been compared with NIV, one of the main treatments in acidotic hypercapnic COPD exacerbations. Cortegiani et al. (36) observed that HFNC was no inferior to NIV in COPD patients affected by mild-moderate hypercapnic respiratory failure in the ED. Besides, this treatment was more comfortable. NIV was applied with a PEEP of 3–5 cmH_2O, and results were assessed 2 and 6 hours after the beginning of the treatment. A similar study was performed by Sun et al. (37) in the Intensive Care Unit (ICU), found that the mortality rates after 28 days did not differ from NIV treated patients. In addition, HFNC was observed to generate fewer complications, including a significant decrease in the number of nursing airway care interventions and a minor skin breakdown. Similar results have been observed by Cong et al. (38) in the Respiratory Department, observing that HFNC and NIV treated patients showed improved blood gas parameters, revealing better comfort, fewer complications, and increased nursing satisfaction in the HFNC group. All these studies were performed in exacerbated patients, including in the ED, suggesting the potential benefits of this technique in the ED.

Avoid IV treatment is also a central objective of the treatment of COPD exacerbations. HFNC has been observed to do not increase the intubation rate and 30-day mortality compared to NIV treatment (39).

Bronchiectasis, a common comorbidity in patients affected by chronic airway diseases (40), causes the severe phenotype of asthma (41) as well as COPD (42). A single-arm study observed that HFNC effectively improved dyspnoea, decreased respiratory rate, improved gas exchange, and increased mucus production in patients with acute exacerbation of COPD and coexisting bronchiectasis. However, due to the characteristics of the study's design, these results may not be extrapolated (43).

ASTHMA

Asthma is a common obstructive airway disorder in children and adults. This disease is characterized by cough, paroxysmal wheezing, and chest tightness. Approximately 300 million patients suffer from this illness around the world (44). The mortality rate is 0.16–0.21 death per 100,000 habitants, with a rate of intubation in asthma attacks of 0.04% (45, 46).

There are few research studies about the benefits of HFNC in adults in asthma attacks in adults. Moreover, all the studies have been compared with COT. It has been observed that forced expiratory volume in one second (FEV1), dyspnoea, PaO_2, and O_2 saturation improved significantly in asthma exacerbations after 24 h of treatment in a study performed in the ED. However, these results were similar to COT (47). These results have been confirmed in severe bronchial asthma patients complicated with respiratory failure in the ED (48). HFNC and COT treated patients presented a significant improvement at 2, 8, 24, and 48 h after admission in terms of PaO_2 and $PaCO_2$ levels, heart rate, and respiratory rate. There were no significant differences in both groups. However, a higher improvement trend was observed in the HFNC treated group, considering the authors a promising treatment for this type of patient.

As an adult population, the benefits of HFNC in the pediatric population are still unclear, with few literature reports. Compared to NIV, HFNC has been observed to do not increase the length of stay in a Pediatric Intensive Care Unit (PICU) (49). However, 40% of patients treated with HFNC required an escalation to NIV, increasing the length of stay 3-fold longer in this subgroup. Consequently, the authors conclude that HFNC may delay NIV support and potentially cause more extended respiratory support and longer length of stay.

Whereas the benefits of HFNC compared to NIV are controversial, it is suggested that this treatment could be better than COT in severe asthma (50). The authors observed that heart rate, respiratory rate, blood gas results, and acidosis are increased in HFNC treated via nasal compared to COT. However, the length of stay was higher, being suggested to be due to the nasal high flow group's increased complexity. These results agree with recent studies performed in the ED, observing benefits after 2 hours of treatment (attending to Pulmonary Score). In addition, no adverse effects were founded (51). González Martínez et al. (52) obtained similar results in a pediatric hospital ward population, founding that child with higher Pulmonary Score values and a more significant number of previous admissions required HFNC more frequently. However, some studies suggest that HFNC did not have any beneficial effects compared to COT, observing not clinical benefits as well as a diminished time of stay (53). Due to that, future studies should be focused on selecting a better population to apply this treatment.

PNEUMONIA

The evidence of HFNC in both adult and pediatric age is short. Pneumonia is the leading cause of death in children between one month and six years old (54). There is only a study developed in children (55). The authors compared COT, HFNC, and bubble continuous positive airway pressure (bCPAP). Until the clinical trial stop due to the worse results observed in COT treated patients, HFNC did not have statistical differences compared to bCPAP. However, these results may not be generalized due to the early end of the study.

In the adult population, there are not reports explicitly about HFNC and pneumonia. It has been observed that HFNC is associated with less dyspnea and mouth dryness, and was more comfortable compared to the face mask. It is also observed to improve PaO_2 levels with a lower respiratory rate (56). Previous observation states that HFNC does not show an increased risk of tracheal intubation than NIV and COT. It is observed a decreased mortality-ratio after 90 days (57). Potential benefits of HFNC in acute respiratory failure in patients affected by pneumonia have also been observed in the ED, observing an improvement of oxygenation compared to COT (58). These results agree with a previous study where HFNC was not compared with a different treatment. The authors observed an improvement in respiratory rate, breath per minute, oxygen saturation, and increased PaO_2 levels (59).

To select patients who may be most benefited from HFNC treatment, some authors have suggested an index denominated ROX (Respiratory rate-OXygenation). This easy-to-use index is defined as the ratio of $SatO_2/FiO_2$ (60).

BRONCHIOLITIS

Acute bronchiolitis is the most common cause of hospitalization in infants younger than 12 months of age. Between 50 and 82,000 infants diagnosed with acute bronchiolitis are admitted in United States hospitals each year, mainly due to respiratory syncytial virus (RSV). Likewise, between 10 and 16% require admission to the (PICU). This illness's management represents a significant economic impact between 365 and 585 million dollars per year (61, 62).

Traditionally, these patients' respiratory support has been performed with NIV, demonstrating an essential improvement of the clinical severity scales and decreased respiratory rate and difficulty. However, this treatment is poorly tolerated by infants (63).

In the literature exists little evidence about HFNC benefits in bronchiolitis. The first study reported concluded that HFNC therapy achieved a significant improvement in heart rate, respiratory rate, and scale of severity in patients with bronchiolitis in a pediatric ward. It was observed a few adverse effects. Finally, a decrease in the use of resources due to the decrease in length of stay and PICU admissions (64). These promising results were not confirmed in a study including 1,937 patients, where HFNC used on the general pediatric wards did not provide a significant change in total hospital length of stay, PICU length of stay and transfer rate, intubation rate, or 30-day readmission for patients with bronchiolitis (65).

The benefits of HFNC compared to COT in bronchiolitis still unclear. It is observed that HFNC had significantly lower rates of escalation of care due to treatment failure than those in the group that received standard. Patients who suffered treatment failure with COT were benefited from HFNC rescue therapy. However, these promising results did not reflect significant differences in the duration of hospital stay or oxygen therapy (66). It is also suggested that HFNC may also reduce respiratory rate (67). A rescue therapy's role in reducing the proportion of children requiring high-cost intensive care has been observed previously. As previously showed in the ED, the authors did not find a modification in the underlying disease process and length of oxygen therapy (68). Whereas these studies were developed in the pediatric ward and the ED, Ergul et al. (69) performed a randomized controlled study in ICU. Authors observed that HFNC use decreased the treatment failure rate and the duration of both oxygen therapy and ICU treatment COT provided by diffuser mask, suggesting that HFNC should be the first choice for treating patients admitted to the ICU with severe bronchiolitis.

Comparing HFNC with NIV in bronchiolitis treatment, it is observed that the first one is increasing its use in the clinical practice (70). However, the benefits of this treatment still not clear. It is suggested that HFNC treatment is non-inferior to NIV attending to respiratory rate, pCO_2, or Modified Woods Clinical Asthma Score (M-WCAS). It could also be more comfortable due to the fewer score in the Neonatal Infant Pain Score (NIPS). Finally, attending to the length of stay, it was not observed statically significant differences, concluding the authors that these results must be confirmed in large multicenter studies (71).

ACUTE RESPIRATORY FAILURE SECONDARY TO CORONAVIRUS DISEASE (COVID-19)

COVID-19 has quickly spread and has now become a global public health problem. As of May 9, 2021, globally, 157,362,408 cases and 3,277,834 deaths have been reported (72). Clinical manifestations include respiratory failure, pneumonia, and acute respiratory distress syndrome (ARDS), which may be observed in 25–34% of cases (73). Oxygen support is required in all these cases; it is necessary to know which treatment is better in each moment to avoid the delay of invasive treatments (74). Consequently, HFNC has been considered a potential treatment of these patients due to the possibility of providing high flow concentration of oxygen with a short effect of PEEP. However, the usage of HFNC is much controversial due to concerns about the benefits and risks of aerosol-dispersion (75).

There are few studies about HFNC benefits in COVID-19 respiratory symptoms. Favorable results were observed by Geng et al. in an 8 case series attending to PaO_2/FiO_2 results. After 24 h of treatment, this value increased from 259.88 ± 58.15 mmHg to 280–450 mmHg, being all discharged without NIV requirements during the admission (76). It is suggested that beneficial results of HFNC are increased if the PaO_2/FiO_2 ratio is higher than 200 mmHg, observing significant differences compared to those where this value is lower. In these patients, NIV could be considered as a rescue therapy showing promising results (77). It has been associated that HFNC decreases in the intubation rate. It also showed a decrease in mortality due to less hospital-associated/ventilator-associated pneumonia in the HFO group than in the intubation group (78). These results agree with recent studies with large number of patients, observing that the ROX index after 6h initiating HFNC had good predictive capacity for HFNC outcomes (79). In addition, this index as well as SOFA has been observed to help to identify patients with higher likelihood of intubation (80).

It is well known that COVID-19 infection affected especially to elderly population. Due to the difficulty of accept these patients with several comorbidities in ICU, HFNC has been purposed to be an effective treatment reducing mortality rate (81).

However, these promising results attending to mortality has been not observed in other result; where HFNC significantly reduces intubation and subsequent invasive mechanical ventilation but does not affect case fatality (82–84). Authors suggest that these results may be generated due to the complexity and no typical features of ARDS developed by COVID-19 patients (85, 86).

Prone position (PP), which improves the mismatch of ventilation-perfusion and opens the atelectatic lungs by adequate sputum drainage, has been established as therapeutic management of COVID-19 patients in ICU (87). It is observed that in severe patients affected by COVID-19, early PP with HFNC therapy improves the PaO_2/FiO_2 ratio. In addition, in the ten patients used, the demand for medical staff was reduced, being safe for patients and professionals (88), like previously reported (89). Similar results were observed in a 9 cases series with severe ARDS with PaO_2/FiO_2 lower than 150 mmHg. The mean blood oxygen saturation and the mean blood oxygen partial pressure increased significantly, whereas the mean partial pressure of carbon dioxide decreased significantly. Only two patients required invasive mechanical ventilation (90). These results have also been observed in other case series, showing that the efficacy of early PP combined with HFNC is higher than those who received COT (91). In addition, it is also noted that dexmedetomidine, a potent anti-inflammatory proposed as a novel therapeutic strategy to attenuate multi-organ dysfunction of COVID-19 patients (92), may be useful with HFNC facilitating the acceptance of long periods of awake PP (93).

According to this data, it could be considered HFNC as a promising treatment in ARDS due to COVID-19. However, these results must be confirmed, focusing on which type of patients will benefit more from HFNC. There are some cases reports in the literature where, after improvement with NIV, begin the HFNC generated a sharp decrease of PaO_2/FiO_2, requiring invasive treatment (94).

CONCLUSIONS

HFNC seems to be a useful tool in the ED, especially in patients affected by acute hypoxemic respiratory failure, acute heart failure, pneumonia, bronchiolitis, asthma and ARDS in patients affected by COVID-19. Its benefits in hypercapnic respiratory failure are more discussed, being only observed benefits in patients with mild-moderate disease. If we analyze these results attending to the population age, these theories have a strongest evidence in pediatric patients affected by bronchiolitis. Attending the adult population, the strongest evidence could be observed in acute hypoxemic respiratory failure secondary to acute heart failure. It is necessary to remark than all the studies are performed in small number of populations, and mainly in ICU as well as ward patients, requiring in the future large clinical trials to confirm these results, especially in the ED. However, due to the severity as well as type of patients (patients with acute exacerbation of a chronic pathology, including COPD or health failure), it could be proposed that this device could be an important treatment in the ED.

The positive results of this therapy are based in the capacity to provide high flow rates, as well as the heating and humidification of gas. Due to that, it has been found to be more tolerable and comfortable than other devices, including COT and NIV, avoiding the risk of skin lesions in the last device. In addition, HFNC promote a PEEP effect (<5 cmH_2O), which improves alveolar recruitment and tidal volume, contributing to alveoli clearance and to $PaCO_2$ decrease.

It is necessary to develop clinical practice guidelines regarding how and when initiate HFNC, protocols for titration and weaning, type and frequency of serial clinical assessment, and clear definitions as to what constitutes treatment failure and the need to escalate to NIV or IV. In the literature has been suggested a potential delay on escalation in adults' patients treated with HFNC, leading to worsening outcomes [95]. Similar results have been observed in children, observing a difference between failure time in HFNC (7–14 hours) compared to NIV (less than 2 hours), remarking the need for continual monitoring beyond the ED [96].

Finally, it is important to evaluate the cost-effectiveness outcomes of HFNC compared to COT and NIV. In the United Kingdom, is estimated to save £469 (USD $608) per patient compared to standard oxygen therapy and £611 (USD $793) per patient compared to NIV [97]. A similar study has been developed in Finland, observing that the treatment cost of an episode of acute bronchiolitis is between €1,312–2,644 (USD $1,786–3,600) if HFNC is applied, compared to €1,598–3,764 (USD $2,175–5,125) if the patient is treated with COT [98]. These results are related with a decreased number of patients admitted in the PICU, remarking the need to develop clinical practice guidelines about the application of this treatment.

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