*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*
*e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 1 Ser.11 (January. 2020), PP 15-21*
*www.iosrjournals.org*

# Efficacy on the Use of High Flow Nasal Cannula in De Novo Acute Hypoxemic Respiratory Failure

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***Abstract:*** *Acute hypoxemic respiratory failure (AHRF) is one of the leading cause of morbidity and mortality among patients presenting to the Emergency Department. AHRF increases hospital and ICU admissions. There has been conflicting evidence regarding the use of Non Invasive Ventilation (NIV) in the management of patients with acute hypoxemic respiratory failure. More recent data is now available, encouraging the use of high-flow nasal cannula as a useful alternative to conventional oxygen therapy in management of patients with AHRF. Despite its use in pediatric patients as a first-line treatment for respiratory distress syndrome and apnea of prematurity, its clinical application in adults is still limited as there are no established clinical benefits which would encourage its use. Therefore, this review provides more recent evidence on the clinical benefits of high-flow nasal cannula in adult patients with de novo acute hypoxemic respiratory failure including mechanism of clinical benefits.*

***Methods:*** *This is a narrative review; we searched articles on Google Scholar and PubMed using the following keywords: efficacy, high flow nasal cannula, high flow oxygen nasal therapy, de novo acute hypoxemic respiratory failure, and acute hypoxemic respiratory failure.*

***Results:*** *HFNC offers several clinical benefits in patients with de novo acute hypoxemic respiratory failure includingdecreased mortality and intubation rate, improved oxygenation and comfort, and increased treatment success rate.*

***Conclusion:*** *HFNC is a well-tolerated treatment method and offers several advantages in patients with de novo AHRF hence may be used as a first line treatment method in these kind of patients.*

***Keywords:*** *Efficacy, high flow nasal cannula, high flow oxygen nasal therapy, de novo acute hypoxemic respiratory failure, and acute hypoxemic respiratory failure.*

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Date of Submission: 06-01-2020 Date of Acceptance: 21-01-2020

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## I. Introduction

De novo acute hypoxemic respiratory failure (AHRF) can be referred to as a respiratory failure occurring in patients without chronic cardiopulmonary disease or prior chronic respiratory disease [1]. AHRF is a common presentation that contributes to significant hospital admissions in many parts of the world, and it is associated with a significant increase of endotracheal intubation with high mortality [2]. De novo AHRF is characterized by hypoxemic respiratory failure, defined as significant hypoxemia (arterial oxygen tension/inspiratory oxygen fraction ratio ($PaO_2/FiO_2$) $\leqslant 200$), tachypnea (respiratory rate >30–35 breaths/min) and most patients experience pneumonia or acute respiratory distress syndrome (ARDS) [1]. The management of this condition is still challenging due to the high rate of endotracheal intubation with an associated in-hospital mortality rate of 20.6% [3].

The primary supportive treatment in hypoxemic respiratory failure has been conventional oxygen therapy (COT), which is delivered using nasal prongs or masks [4]. The maximal flow rates that can be produced by these devices are limited (up to 15 L/min) because the heat and humidity of administered gas are insufficient; it therefore dries and injures the mucosa [5]. Oxygen flow delivered using conventional nasal prongs or masks, is far lower than the inspiratory flow of a patient with acute respiratory failure (ARF) hence the room air dilutes the supplemental oxygen, resulting in a significant decrease in the fraction of the inspired oxygen ($FiO_2$) that finally reaches the alveoli [6].

Several articles have been published on noninvasive ventilation since the 1980's, but some aspects remain unresolved .e.g. its use in de-novo hypoxemic respiratory failure [7]. The use of non-invasive ventilation as a treatment modality for de novo AHRF has been associated with a high failure rate, and therefore it is not recommended in the management of patients with de novo AHRF [1, 8].

It has been demonstrated that low expired tidal volume is almost impossible to achieve in the majority of patients receiving non-invasive ventilation for de novo acute hypoxemic respiratory failure because of too high tidal volume (TV) delivered by the ventilator [9] and this is one of the reasons associated with noninvasive ventilation failure and increased mortality in this kind of patients.

Consequently, these high tidal volumes result in ventilator-induced lung injury, prolonged ICU stays, and increased mortality, among other complications [9]. The use of a continuous positive airway pressure alone as high as 10 cm H2O improved oxygenation but failed to decrease the patient's respiratory effort significantly. Also, the presence of leaks around the mask increases with the airway pressure during NIV and may generate specific patient-ventilator asynchronies [10].

Recent evidence suggests the use of High Flow Nasal Cannula (HFNC), which has emerged as a non-invasive strategy in the management of patients with de novo AHRF. HFNC is a non-invasive respiratory supportive therapy that can deliver up to 60 L/min of a heated (about 37oC), humidified air (100% relative humidity), and oxygen through a wide bore and soft nasal prong [11]. They include air oxygen blender, active humidifier, heated inspiratory circuit and nasal cannula. Through HFNC, the fraction of inspired oxygen can be titrated to 100%, and the mean airway pressure increases with increasing gas flow rates [12].

This device is made of four major parts as shown in figure 1.

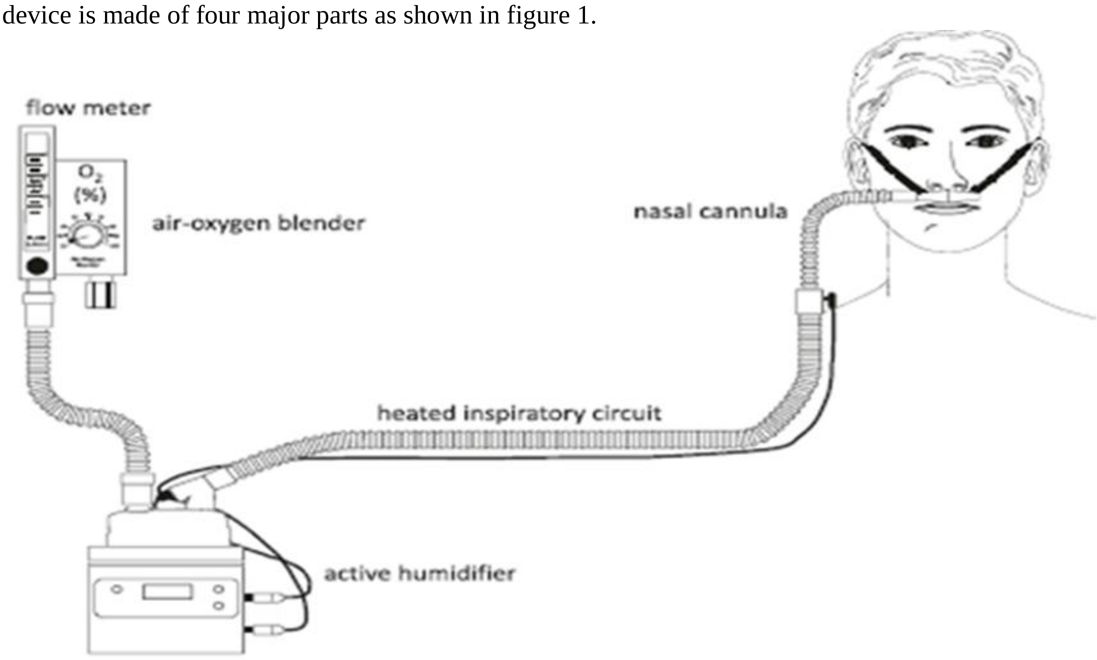


Figure 1. A typical set up of high-flow nasal cannula therapy devices. An oxygen gas blender allows $FiO_2$ from 0.21 to 1.0 to generate and release about 60 L/min flow rate. An $O_2$ is heated and humidified in an active humidifier chamber and then goes to the tubing system of the heated and humidified inspiratory circuit. This inspiratory circuit connects to the nasal cannula that is attached to the patient's nose. Then, a patient is able to breathe heated and humidified $O_2$ that will alleviate the symptoms of respiratory failure (1).

HFNC provides adequate oxygenation due to its ability to keep up with the high inspiratory flows in dyspneic, hypoxemic patients, and reducing entrainment of room air that dilutes FiO2 with standard oxygen systems. Besides, HFNC flushes the nasal and oropharyngeal dead space; therefore, the initial bolus of air at the start of inspiration is freshly oxygenated gas rather than oxygen-depleted gas that has just been exhaled [13].

HFNC is a relatively safe method, simple to use, and can be applied even at the emergency department settings. It is also a well-tolerated option, and a practical treatment approach in patients with de novo AHRF in the absence of criteria for immediate intubation, including patients with PaO2/FiO2 less than 300, and bilateral infiltrates [14].

The use of HFNC would bridge the treatment gap between COT, NIV, and invasive ventilation hence overcoming the challenges associated with the management of patients with AHRF. Moreover, in resource-limited countries, the use of HFNC will reduce the need for an increased number for health care providers as intubation, and mechanical ventilation needs one on one care.

## II. Material and Methods

**Study Design:**This is a narrative review; we searched articles on Google Scholar and PubMed using the following keywords: efficacy, high flow nasal cannula, high flow oxygen nasal therapy, de novo acute hypoxemic respiratory failure, and acute hypoxemic respiratory failure.

**Inclusion criteria:**
1. We included observational studies, clinical trials, retrospective and prospective studies, systematic reviews and meta-analyses, and other narrative reviews.
2. Articles on the use of High flow nasal cannula in the management of patients with de novo acute hypoxemic respiratory failure.
3. A total of 39 articles were included in this review.

**Exclusion criteria:**
1. We excluded articles and abstracts, not in English.
2. Articles with negative results on the use of High flow nasal cannula in patients with de novo acute hypoxemic respiratory failure.
3. Articles on the use of High flow nasal cannula in patients with acute hypoxemic respiratory failure secondary to chronic cardiopulmonary disease such as COPD, heart failure.
4. Articles on de novo acute hypoxemic respiratory failure not treated with High flow nasal cannula

## II. Result

This review focuses on current evidence on the clinical benefits of the use of high flow nasal cannula in the management of patients with acute hypoxemic respiratory failure.

**Clinical Benefits Of Hfnc Therapy**

Several studies highlight how HFNC could offer advantages over COT or NIV in de novo ARF [15, 16]. These clinical benefits include decreased mortality and intubation rate, improved oxygenation and comfort, and increased treatment success rate as summarized in table 1.

**Table 1**: Summary of current evidence on the clinical application and benefits of HFNC in treatment of patients with AHRF

| Author | Study design | Sample size (n) | Conclusion |
|---|---|---|---|
| Coudroy, R. et al. (2) | observational cohort study | 115 patients | HFNC, when compared to NIV in the treatment of patients with AHRF, Intubation and mortality rates, was lower in patients treated with HFNC alone than NIV. |
| Frat, J. P.et al (3) | prospective observational study | 28 subjects | When compared to standard oxygen therapy, HFNC was better tolerated than NIV and allowed for significant improvement in oxygenation and tachypnea in patients with AHRF. |
| Frat, J. P.(4) | a multicenter, open-label trial | 310 patients | There is a significant difference in 90-day mortality in patients with AHRF treated with HFNC as compared to COT or NIV. |
| Huang, H. B.et al(5) | review and meta-analysis | 7studies involving 667 patients | HFNC therapy significantly improve the clinical outcomes of immunocompromised patients with AHRF |
| Kang, Y. S.et al(6) | Retrospective study | 91 patient | In immunocompromised patients with AHRF, HNFC therapy improves SF ratio 48 hr. post-treatment and 28-day mortality |
| Lee, C. C.et al(7) | systematic review | 12 studies | HFNC may be an alternative therapy to COT and NIV in the treatment of patients with AHRF as it improves oxygenation, patient comfort, and work of breathing. |
| Mace, J.et al(8) | prospective before-after study | 102 patients | Patients with AHRF treated with HFNC had better oxygenation, less breathlessness and were more likely to show improved respiratory failure 1hr post-therapy as compared to COT. |
| Mauri, T.et al(9) | prospective randomised cross-over study | 17 patients | Progressive increase in HFNC flow rate decreases inspiratory effort and improve lung aeration, dynamic compliance and oxygenation. |
| Mauri, T.et al(10) | prospective, randomised, cross-over study | 40 patients | HFNC therapy may improve comfort in a patient with severe hypoxemia |

| | | | |
|---|---|---|---|
| Mauri, T.et al(11) | a prospective randomised crossover study | 15 patients | HFNC exerts various physiologic effects such as less inspiratory effort and improved lung volume and compliance in patients with AHRF. |
| Messika, J.et al(12) | Observational study. | 607 subjects | In the treatment of patients with AHRF, HFNC may be considered as first-line therapy |
| Nagata, K.et al(13) | a retrospective single-centre cohort study | 782 pre-HFNC and 930 post-HFNC | For AHRF subjects with NIV intolerance, HFNC might be an alternative treatment option |
| Ni, Y. N.et al (14) | systematic review and meta-analysis | Eight trials with 1084 patients | Compared both with the COT and NIPPV HFNC can improve the prognosis of patients with AHRF when used before MV. |
| Ni, Y. N.et al(15) | Systematic Review and Meta-analysis | 18 trials with 3,881 patients | In patients with ARF, HFNC is a more reliable alternative therapy than NIPPV or COT in reducing the rate of endotracheal intubation |
| Rochwerg, B.et al (16) | systematic review and meta-analysis | 9 RCTs (n = 2093 patients). | HFNC may reduce the need for tracheal intubation in patients with AHRF without impacting mortality. |
| Xu, Z.et al(17) | systematic review and meta-analysis | 18 RCTs (n = 4251 patients) | When used as a primary support strategy, HFNC was found to be more effective than COT and NIV in reducing treatment failure, rates of extubation failure and reintubation when used after extubation. |
| Zhao, H.et al(18) | systematic review and meta-analysis | 11 studies that enrolled 3459 patients(HFNC, n = 1681 | HFNC reduced the rate of intubation, mechanical ventilation and the escalation of respiratory support compared to COT, but showed no better outcomes when compared to NIV |
| Zhu, Y.et al(19) | systematic review and meta-analysis, | Four studies that involved 703 patients | In the subgroup analysis, HFNC therapy showed to decrease the rate of escalation of respiratory support and the intubation rate when ARF patients were treated with HFNC for >/=24 h compared with COT. |

**Intubation rate**

Studies are now available evidencing how HFNC use can offer benefits on the intubation rate in patients with AHRF. HFNC is a more reliable alternative than noninvasive positive pressure ventilation (NIPPV) and COT in reducing the rate of endotracheal intubation [16] in adult patients with ARF in comparison to NIPPV and COT. It was also demonstrated that HFNC therapy might decrease the frequency of escalation of respiratory support and the intubation rate when patients with ARF were treated with HFNC for >/=24 h compared with COT [17]. Similar results were obtained in another study that compared HFNC to COT, HFNC reduced the rate of intubation, mechanical ventilation, and the escalation of respiratory support [18].

In a meta-analysis done to evaluate the effect of high-flow nasal cannula oxygen therapy compared with other oxygen techniques in immunocompromised patients, it was found that HFNC was associated with a reduction in short term mortality (28 days) and intubation rate [19]. Another study concluded that HFNC might decrease the need for tracheal intubation in patients with acute hypoxemic respiratory failure [20].

**Mortality rate**

Several studies highlight how HFNC use can offer mortality benefit in patients with AHRF. Research done on patients with non-hypercapnic acute hypoxemic respiratory failure, who were treated with high-flow oxygen, standard oxygen, or non-invasive ventilation, found that there was a significant difference in 90-day mortality reduction for the group treated with HFNC [21]. Similar results were obtained in a study of immunocompromised patients with acute respiratory failure, where HFNC treatment was associated with a reduction in 28-day mortality [22]. In another study done on this subset patient with acute respiratory failure admitted to the intensive care unit, the results suggested that intubation and mortality rates could be lower in patients treated with HFNC alone than with NIV[23].

**Improved oxygenation and comfort**

Different studies have documented that the use of HFNC is associated with improved oxygenation and comfort. HFNC use exerts multiple physiologic effects, which include less inspiratory effort, lower respiratory rates, improved lung volume, and compliance, also reduced minute ventilation, dead space washout, and improved oxygenation [24]. Compared with standard oxygen therapy and NIV in subjects with AHRF, HFNC was better tolerated and allowed for significant improvement in oxygenation and tachypnea [25, 26].

**Success rate**

HFNC use has proved to be successful in the treatment of patients with AHRF. One observational study concluded that HFNC might be considered as first-line therapy in ARF, including patients with ARDS, as

HFNC showed a high success rate during treatment [27]. A comparative study done on patients before and after the introduction of the HFNC (pre- and post-HFNC periods) revealed that in the post-HFNC period, significantly fewer subjects required mechanical ventilation (NIV or invasive ventilation), had fewer ventilator days and more ventilator-free days [28]. A systematic review and meta-analysis demonstrated that HFNC could improve the prognosis of patients compared both with the COT and NIV when used before MV [29]. Another systematic review and meta-analysis concluded that HFNC was superior to COT in reducing treatment failure when used as a primary support strategy and in reducing rates of extubation failure and reintubation when used after extubation [30].

**Mechanisms Of Clinical Benefit Of Hfnc Therapy**

The clinical benefits associated with the use of HFNC are brought by several mechanisms which include heating and humidification, positive end expiratory effect, washout of nasopharyngeal dead space and high nasal flow rate. These mechanisms are summarized in table 2.

**Table 2**: Mechanisms of HFNC and its clinical benefits

| Mechanism | Physiologic and clinical benefit |
|---|---|
| Small, pliable nasal prongs | • Enhanced patient comfort |
| Heat and humidification | • Facilitates removal of airway secretions.<br>• Avoids airway desiccation and epithelial injury<br>• Decreased work of breathing<br>• Enhances patient comfort |
| Washout of nasopharyngeal dead space | • Improved ventilation and oxygen delivery |
| Positive end-expiratory (PEEP)effect | • Remove auto-PEEP(when present)<br>• Reduce the work of breathing<br>• Enhance oxygenation |
| High nasal flow rate | • Reliable delivery of fraction of inspired oxygen($FiO_2$)<br>• Improved breathing pattern(e.g., increased tidal volume, decreased respiratory rate) |

**Heating and humidification**

The warmth and absolute humidity of oxygen provided by HFNC results in increased water content in mucous which improve secretion clearance, decrease airway inflammation, and also decrease the work of breathing and avoid airway desiccation and epithelial injury, decrease energy expenditure especially in the setting of acute hypoxemic respiratory failure which subsequently leads to improved compliance and better comfort even at lower temperature [31, 32].

**High nasal flow rate**

The delivery of very high flow rates of gas is one of the benefits that could be obtained from the use of a high-flow nasal cannula. There is a progressive decrease in inspiratory effort and improved lung aeration, dynamic compliance, and oxygenation with increasing HFNC flow rate [33]. High flow rates generated by HFNC can match or even exceed the patient’s inspiratory flow demand, thus reducing entrainment of room air and dilution of administered oxygen [34]. Patients with acute hypoxemic respiratory failure presents with tachypnea, and their peak inspiratory flows (PIF), which may generally be 30 L/min - 60 L/min at rest, can reach upwards to 60 - 120 L/min keeping these patients on a 15 L/min may not provide adequate support, therefore matching their peak inspiratory flow demands with the use of a high-flow device will improve a patient's work of breathing [35].

**Continuous positive airway pressure (CPAP) effect**

Several studies show that HFNC increases nasopharyngeal airway pressure that peaks at the end of expiration (i.e., “PEEP effect’’). As the flow increases, nasopharyngeal pressure increases (i.e., a dose-effect). The CPAP effect is most significant, with the mouth closed [36]. Estimates are 0.7- 1 cm H20 of PEEP for every 10 L/min of flow delivered with closed mouth breathing but this may vary from patient to patient due to factors such as the patient’s size (obese, adult, child), the litre flow rate being delivered (L/min), and mouth open versus closed breathing (pressure may escape when a patient's mouth is open) [37], can all affect the amount of PEEP being delivered.

**Small pliable nasal prongs**

The tight-fitting mask of non-invasive continuous or bi-level positive pressure ventilation (CPAP or BPAP) can be uncomfortable for some patients. Oxygen delivery through soft and pliable nasal prongs (which is lighter) has proved to be a well-tolerated and comfortable alternative to NIV or COT in AHRF patients. This will lead to higher compliance with HFNC hence, improvement in the patient's oxygenation and work of breathing [38].

**Washout of Dead-space**

It has been demonstrated that during normal respiration, we rebreathe a third of our previously expired gas, so instead of breathing 21% (room air) and negligible amounts of carbon dioxide, we may rebreathe about 15 - 16% oxygen and 5 - 6% carbon dioxide. This is because the previously exhaled breath (low in oxygen and containing carbon dioxide) is not fully emitted and remains in the upper airway, hence not all of that gas will enter the alveoli during inspiration. The inspired gas will be a mixture of the new atmospheric gas (21% $FiO_2$, negligible $CO_2$) and their previously exhaled gas (< 21% oxygen with a more significant amount of $CO_2$) that enters the alveoli for gas exchange. The percentage of gas rebreathed increases in patients with acute respiratory failure, resulting in more substantial amounts of carbon dioxide rebreathed as we inspire from a mixed reservoir in the upper airway. High-flow rates of the HFNC provides a continuous flow of fresh gas by washing out carbon dioxide and replacing with oxygen-rich gas hence washing out the patient's pharyngeal dead-space (the old gas low in oxygen and high in $CO_2$), thus improving breathing efficiency [35, 39].

## III. Discussion

HFNC is a useful and practical treatment approach in the management of patients with de novo AHRF and relatively safe method that can be easily applied in different settings. In the absence of criteria for immediate intubation, patients with de novo AHRF should be placed on HFNC, even in the situation of severe pneumonia. However, other researchers have noted that the treatment of patients with de novo AHRF with HFNC made no difference to the clinical outcome as compared with conventional oxygen therapy and non-invasive ventilation.

In most of the studies that have been done, HFNC was used after initiation of COT or MV; hence, the efficacy of HFNC could not be fully explored as a patient has already been subjected to the damaging effects of COT or MV. To fully explore the benefits of HFNC and improve the prognosis of patients compared both with the COT and MV, HFNC should be initiated before COT or MV.

Moreover, randomized control studies should be done to prove the efficacy of HFNC when started early enough in patients with AHRF instead of COT or NIV.

Never the less there should be personalized bedside titration of HFNC settings to improve tolerance and physiologic benefits. There should also be Institutional guidelines with a set of indicators for early improvement and failure of HFNC. However, upon patient deterioration and meets the criteria for intubation, the patient should be intubated immediately, and further delays should be avoided to prevent the detrimental effects of delayed intubation.

## IV. Conclusion

HFNC offers several clinical benefits in patients with de novo AHRF hence may be used as a first line treatment method in these kind of patients.

## Acknowledgement

My sincere gratitude to everyone who contributed to the critic, the whole organization of the manuscript and for the moral and social support during preparation of this manuscript.

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Chiku Badru Mwimbo, et.al. "Efficacy on the Use of High Flow Nasal Cannula in De Novo Acute Hypoxemic Respiratory Failure". *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(1), 2020, pp. 15-21.