



Submitted on: 10/15/2020
Approved on: 12/10/2020

ORIGINAL PAPER

High Flow Nasal Cannula in pediatrics: when, how, and why?

Samara Damin¹, Camila de Souza Espindola¹, Adriana Koliski¹, Marcelo Rodrigues¹, Valéria Cabral Neves¹, Debora Carla Chong Silva¹, José Eduardo Carreiro¹

Keywords:

Pediatrics,
Oxygen therapy,
Acute respiratory failure,
Cannula.

Abstract

Objectives: to carry out a non-systematized bibliographic review and propose a flowchart for the use of HFNC in pediatrics. **Methodology:** this is a non-systematic review, where studies published in the last five years were selected with the aim of proposing a flowchart to guide the use of HFNC in pediatrics. **Results:** we found 34 papers, fifteen were excluded because they only addressed the neonatal population, five because they did not address the topic, one because it did not have the full text and one because it was a study protocol. In addition to the twelve papers in the initial search, we included eleven more papers considered relevant to the objective of this review, selected from the reference lists. From the data obtained in the selected papers, we report on the definition of therapy, components of the device, parameters to be adjusted, mechanisms of action, indications and contraindications, benefits and possible complications of its use, resulting in a flowchart for using this treatment modality. **Conclusion:** studies suggest that high flow is a safe, well-tolerated and easy-to-apply method. In addition, it can avoid the need for non-invasive and invasive mechanical ventilation. A flowchart to optimize its use in pediatrics can be advantageous for the success of therapy.

¹ University Hospital - FEDERAL UNIVERSITY OF PARANA, Intensive Care Unit - Curitiba - PR - Brazil

Correspondence to:

Samara Damin.

Hospital de Clínicas. R. Gen. Carneiro, 181 - Alto da Glória, Curitiba - PR, 80060-900. E-mail: samaradamin@gmail.com

INTRODUCTION

Approximately 75% of children admitted to Intensive Care Units (ICU) need some type of ventilatory support, regardless of the reason for admission¹. Children with significant respiratory effort may need invasive ventilation, which can cause ventilation-induced lung injury, need for prolonged sedation, and ventilation-associated respiratory infections. Thus, whenever possible, the use of non-invasive ventilation (NIV) should be prioritized, such as high-flow nasal cannula therapy (HFNC), which during the last decade has emerged as a new method to provide ventilatory support in patients with respiratory failure¹.

The HFNC aims to increase the volume of air and oxygen, heated and humidified, through the airways, using flows above 6 L/min. The high and continuous flow creates a degree of pressure in the airways, generating a certain level of positive end-expiratory pressure (PEEP), in addition to washing the dead space of the upper airways². The results are reduced work of breathing and improved gas exchange, in addition to a reduction in the need for orotracheal intubation³. In addition, due to the fact that the air is heated and humidified, this method tends to be better tolerated by children³.

Due to its physiological effects, HFNC is able to reduce respiratory rate, heart rate and carbon dioxide pressure, in addition to increasing oxygen saturation within the first hour of use⁴. HFNC is also capable of reducing the energy expenditure of the respiratory muscles, being important, especially in younger children, as their muscles are poor in oxidative fibers, which increases vulnerability to muscle fatigue when exposed to significant respiratory effort⁵.

Its installation is simple and fast, the parameters to be adjusted are the temperature, the air flow (in L/min), and the fraction of inspired oxygen. The device consists of a nasal prong coupled to a circuit that supplies hot and humid air, mixing oxygen with compressed air through a blender, and this allows precise control of the oxygen concentration and the inspiratory flow that reach the patient through the nasal cannula. In addition, it has a powerful humidifier, which allows oxygen to enter the lungs in a very similar way to what would occur physiologically under normal conditions⁶.

Knowing the benefits of HFNC therapy, the objective of this study was to carry out a current review of the literature on the use of high-flow nasal cannula in pediatrics, aiming to propose a flowchart for the use of high-flow nasal cannula in a pediatric service.

METHODS

A non-systematic literature review was carried out on high-flow nasal catheters in the pediatric population (28 days of life to 14 years of age), excluding studies carried out in neonatology. The keywords “high-flow nasal cannula” and “children” were used, and their equivalents in Portuguese.

The databases consulted were PubMed, Cochrane Library, Liliacs and Scielo. Reference lists of initially selected studies were consulted to identify additional relevant publications. Filters were added to select studies published in the last 5 years and that corresponded to meta-analyses, systematic reviews, and prospective, randomized clinical trials. There was no language restriction in the search.

LITERATURE REVISION

Non-systematized literature review carried out according to the following flowchart:

From the data obtained in the selected papers, we reported on the definition of therapy, device components, parameters to be adjusted, mechanisms of action, indications and contraindications, benefits and possible complications of its use.

High Flow Nasal Cannula

The correct name for the high-flow nasal cannula (HFNC) is oxygen therapy with humidified and heated HFNC^{7,8}. It is a relatively new non-invasive respiratory support method used in cases of respiratory distress^{8,9}.

This method consists of a system where oxygen (O₂) is heated, humidified, titrated and delivered via nasal cannula to provide a gaseous mixture at different flow rates, where high concentrations of oxygen and pressure are continuous in the airways¹⁰.

Currently, to be considered “high flow”, the gas flow must be greater than 6 liters per minute (L/min), and rates of up to 30 liters per minute can be used in children^{8,10}.

The HFNC equipment consists of a closed system, which generally comprises an oxygen mixer which regulates the flow of pressurized air; a water reservoir; a heater and humidifier; an insulated heated circuit that checks and protects the temperature and humidity the conditioned gas delivered to the patient; and a special nasal cannula. The parameters, which must be defined before starting therapy, include: temperature, gas flow (in liters per minute) and oxygen concentration in the gas mixture⁶.

The use of HFNC requires minimal technical skills and training can be provided within a short period of time to those who are less familiar with the therapy¹¹.

There is no consensus regarding the ideal flow in pediatric patients. Commonly, the flow rates are regulated according to body weight. While some recommend the use of 1 L/kg/min, others suggest 2 to 3 L/kg/min^{6,7,12}. According to the literature, it is recommended to start with a flow of 4-6L/min, and progress up to the target flow according to the patient's weight⁹.

The equipment allows the FiO₂ to be adjusted between 0.21 and 1.0^{2,7,9}. Initially, it is suggested to be 0.4, which can be increased according to pulse oximetry, seeking oxygen saturation (SpO₂) greater than 92%⁹.

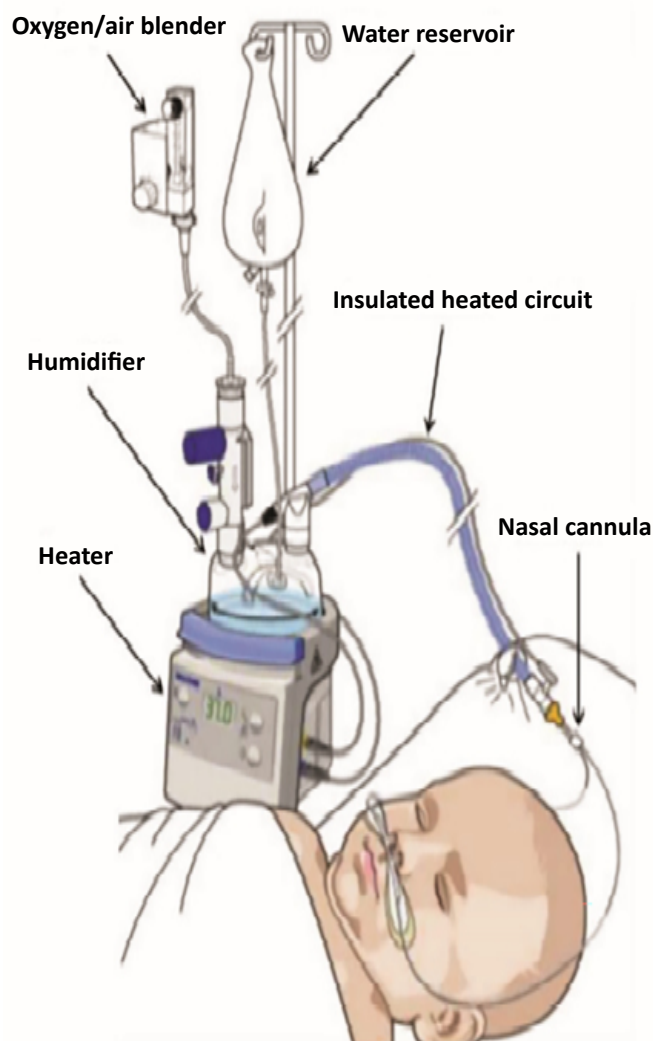


Figure 1. Components of the high-flow device: oxygen-air blender, a water reservoir, humidifier, heater, heated circuit, and nasal cannula¹³.

The gas temperature is usually kept constant, about 1 to 2 °C below body temperature⁹. Therefore, the recommended temperature for children ranges from 34 to 37°C. To obtain the ideal humidity, close to 100%, values close to 37 °C are more beneficial^{6,7}.

Cannula size varies by age and body weight, but manufacturers recommend that the cannula cross-sectional area not exceed 50% of the nostril orifice area, due to the risk of air trapping, unexpected elevations in pressure of the airways and consequent risk of pneumothorax^{2,7}. At the same time, the nasal tips must fit comfortably in the nostrils and prevent the entry of ambient air around the cannula, a problem that occurs with standard nasal cannulas². Manufacturers offer a variety of cannula sizes, from the smallest for premature newborns, as well as children of various ages, to adult-sized cannulae. Each manufacturer has a maximum flow rate for each cannula size².

Table 1. Adapted from Kwon, 2020, showing the flow adjustment according to the child's weight and age.

AGE	WEIGHT (KG)	FLOW (L/MIN)
< 1 MONTH	<4	5-8
1 MONTH - 1 YEAR	4-10	8-20
1-6 YEARS	10-20	12-25
6-12 YEARS	20-40	20-30
12-18 YEARS	>40	25-50

Regarding the HFNC mechanism of action, the main benefits of the therapy are: “washing” of the airways, the generation of positive end-expiratory pressure (PEEP), the increase in the fraction of inhaled oxygen, the improvement of respiratory mechanics and better adaptation of patients when compared to other methods of ventilatory support.

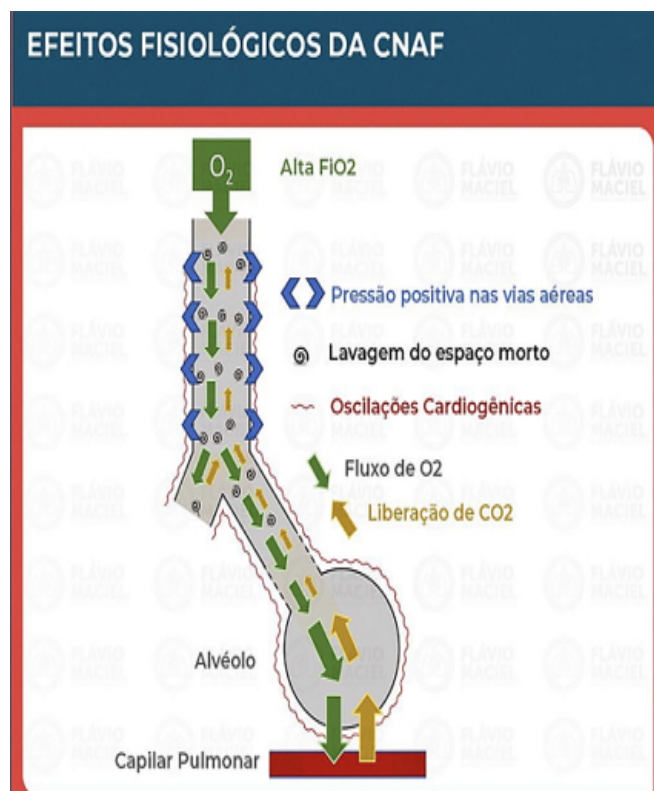


Figure 2. Physiological effects of HFNC on the airways¹².

Legend:

Alta FiO₂: High FiO₂

Pressão positiva nas vias aéreas: positive pressure in the airways

Lavagem do espaço morto: dead space washing

Oscilações cardíacas: cardiogenic oscillations

Fluxo de O₂: O₂ flow

Liberação de CO₂: CO₂ release

Alvéolo: alveolus

Capilar pulmonar: Pulmonary capillar

The nasopharyngeal dead space washing theory explains the effects observed in HFNC. The air present in the nasopharynx and trachea has a high proportion of CO₂ at the end of expiration during normal breathing. This air is incorporated into the oxygenated air in the next respiratory cycle, which reduces the efficiency of gas exchange⁹. In patients receiving HFNC therapy, the fresh gas rich in oxygen rapidly covers the nasal cavity, pharynx and trachea, while the gas rich in CO₂ is washed from dead spaces through the flow generated by the device, improving alveolar ventilation and reducing the effects of rebreathing. Thus, CO₂ is excreted and ventilation-perfusion balance is restored^{11,13}.

It is noteworthy that the extra thoracic dead space per kilogram of body weight decreases exponentially with increasing age. In young children, it is up to three times higher compared to adults. This suggests that the effect of dead space washing is especially important in younger children^{9,11}.

The provision of PEEP is critical to all non-invasive ventilation techniques. HFNC generates positive airway pressure, triggering alveolar recruitment of collapsed areas and an increase in functional residual capacity^{7,11}.

There is some debate about the level of PEEP provided by high-flow devices. The exact values may vary from patient to patient, as factors such as the size of the child, the size of the cannula, the flow rate of liters being delivered, and open mouth versus closed mouth breathing (pressure can escape when the mouth is open) directly affect these values². The best estimates are 1 cmH₂O of PEEP for every 10 L/min of flow administered with the mouth closed. This positive end-expiratory pressure can be between 2 and 6 cmH₂O^{2,14}.

HFNC reduces the intake of ambient air, thus minimizing the dilution of the desired gas composition and improving oxygenation when compared to low-flow devices^{7,10,11}.

A significant amount of energy is expended by children to heat and humidify gases during normal breathing. In addition, the nostrils and nasal passages have a large surface area and cause high airway resistance^{9,11}. The use of HFNC provides a flow equal to or greater than the patient's peak inspiratory pressure, neutralizing the area where there is greater resistance in the respiratory tract. Thus, it prevents nasopharyngeal collapse that normally occurs during spontaneous breathing^{9,11}.

The heated and humidified oxygen delivered by HFNC can also improve mucociliary clearance, decrease airway inflammation, not induce bronchoconstriction (as it occurs with cold gas) and decrease energy expenditure in the setting of acute respiratory failure^{2,7,14}. In addition, heated and humidified air does not irritate the respiratory mucosa, leading to greater comfort and less dryness of the mucous membranes^{2,11}.

Another highlight is that nasal cannula contact occurs mainly in the nostrils and cheeks, reducing the risk of skin lesions on the face, compared to interfaces used in other NIV modes, where the tight mask can be uncomfortable for many patients^{2,11}.

Indications for High Flow Nasal Cannula

HFNC was first introduced to treat premature infants as an alternative to CPAP, but recently a marked increase in the use of HFNC has been observed in the care of infants and young children hospitalized with bronchiolitis⁸.

Despite the need for further studies, there is growing evidence of its use in other diseases such as pneumonia, sepsis, croup, asthma and respiratory syndrome caused by COVID-19. It can be useful as a bridge to intubation and post-extubation support, recurrent apneas, post-operative respiratory support, heart failure and upper airway obstruction^{2,7,9,11}.

HFNC was shown to be superior to conventional oxygen therapy to reduce respiratory distress in children with asthma, aged 1 to 14 years, who had moderate to severe asthma exacerbations¹⁵.

As for use after extubation, a prospective randomized study showed that, although more expensive, the use of HFNC may have more advantages in reducing the risk of extubation failure in critically ill children, compared to standard oxygen therapy¹⁶.

The positive response to treatment is expressed through a reduction in respiratory rate and respiratory effort, a reduction in heart rate, an improvement in blood oxygenation, an increase in pH and a decrease in pCO₂ in relation to the initial evaluation⁶. Another parameter used to evaluate the therapy response is the PaO₂/FiO₂ ratio, which should increase after the first hour of high flow onset⁴.

It should be noted that regardless of the indication, the assessment of patients after the first hour of therapy is essential for the prognosis and allows distinguishing patients who need more advanced respiratory support methods^{6,11}. Constant monitoring determines the scaling of therapy when necessary, and should be administered every hour in the first six hours of treatment¹¹.

Contraindications and risk groups

Absolute contraindications for HFNC include upper airway abnormalities, life-threatening hypoxia, hemodynamic instability, facial trauma to bones or skull base, and pneumothorax⁷.

Risk groups for therapy failure include children with tachypnea greater than the 90th percentile for age, patients with signs of fatigue, and children with respiratory acidosis (pH <7.3) with pCO₂ buildup above 50 mmHg⁶. A low Initial SpO₂ and PaO₂/FiO₂ ratio lower than 195 in the first hours of treatment are also related to failure to respond to HFNC therapy^{4,6,9}. However, these factors do not contraindicate the use of therapy, but demand constant reassessment.

In addition, HFNC should be applied with care in patients with decreased level of consciousness, congenital heart disease, acute asthma or chronic respiratory failure^{7,9}.

One of the disadvantages of using HFNC is the degree of experience needed to decide which critically ill child would benefit from this form of non-invasive respiratory support over other modes. The decision is important to minimize the delay in using the best tool for the treatment of a child with respiratory distress^{6,11}.

Treatment complications

Most studies did not show significant adverse effects of the use of HFNC^{3,6,7}. A well-known complication of HFNC is barotrauma. However, severe pneumothorax in children has been little reported⁷. In the study by Franklin et al., with 1472 patients, there was only one case of pneumothorax. Despite the low incidence, careful observation is mandatory, as barotrauma has been reported even in low-flow conditions⁷. Mild complications such as epistaxis and mucosal damage have been reported, and abdominal distension can be observed in children^{6,7,9}.

Comparison between HFNC x Non-Invasive Ventilation (NIV)

HFNC, as already mentioned, is an alternative for respiratory support for children with hypoxemic acute respiratory failure, being considered less invasive, better tolerated and allowing the reduction of comorbidities associated with intubation and the use of MV^{17,18}.

Like HFNC, NIV is also used for cases of respiratory failure, both acute and chronic¹⁹. Its benefits are already well described in the literature, such as reduced labored breathing through increased air flow and mass, thus improving alveolar ventilation^{17,19}. However, NIV may not be well tolerated by some patients, mainly due to poor adaptation to the mask¹⁹.

Studies comparing the two modes of respiratory support have been increasingly frequent in the pediatric population. A study by Habra et al.¹⁷ compared HFNC and NIV in the management of children with bronchiolitis and observed that HFNC is associated with a higher failure rate when compared to CPAP/BiPAP. The study by Metge¹⁸ et al. found no difference between HFNC and CPAP in the treatment of severe bronchiolitis.

A study carried out by Santana et al.¹⁹ found that both resources are effective in preventing intubation and preventing hospitalization in a pediatric ICU, with no superiority between them. They also mention that what can interfere in the choice is the acceptance of the patient, and the HFNC can have an advantage due to the lower feeling of claustrophobia (generated by the mask) and the benefit of offering heated air.

PROPOSED FLOW CHART

Patients who arrive at the service with acute respiratory failure must undergo an initial assessment to define those who are indicated to be treated with HFNC.

The age range proposed by the flowchart is from 28 days of life to 14 years of age, which is the age range served by the service. Children who present with at least one of the following criteria should be selected for therapy:

1. Hypoxemia,
2. Hypercapnia,
3. Signs of respiratory distress (use of accessory muscles, subcostal, intercostal, suprasternal retraction, tachypnea, or groaning).

Patients who meet exclusion criteria, such as anatomical abnormalities of the upper airways or facial trauma, or those who present with severe hypoxemia, acidosis, or severe respiratory effort, may require NIV or invasive, and are not eligible for initial treatment with HFNC¹.

The initial flow for use of HFNC in children up to 10 kg should be 2 L/kg/min and for children over 10 kg it should be in accordance with the table shown in the flowchart¹. FiO_2 must be titrated to maintain an O_2 saturation greater than 92%.

Patients should be reassessed hourly for the first six hours. The criteria considered in assessing the response to treatment are: improvement, persistence, respiratory effort, need for $\text{FiO}_2 > 60\%$, $\text{pH} < 7.2$ with $\text{PCO}_2 > 56 \text{ mmHg}$ ¹. Other criteria that should be evaluated are heart rate and respiratory rate. Both must decrease in relation to their initial values, for the treatment to be considered effective. If its values remain or increase, it will be considered a failure in therapy²¹. Er, et al., 2018, also suggests monitoring the $\text{PaO}_2/\text{FiO}_2$ ratio. If the initial value is less than 195, there is a greater chance of therapy failure¹.

Patients who present a reduction in heart and respiratory rate, improvement in respiratory effort and improved blood gas during this observation period can start weaning, gradually reducing FiO_2 and flow, and can be withdrawn from HFNC when FiO_2 is less than 40% and the flow is less than 50% of the initial flow.

Patients who do not achieve a reduction in heart and respiratory rate, have worsening respiratory effort, worsening blood gas analysis, and require FiO_2 greater than 60% to maintain a minimum saturation of 92% should be scheduled for another therapy, which may be another NIV or invasive mode¹.

CONCLUSION

The studies currently available suggest that HFNC is a relatively safe, well-tolerated and easy-to-apply method. Its physiological mechanisms allow a continuous airway distention, which may be the main reason for the improvement of the respiratory effort. The HFNC can also reduce the need for escalation to non-invasive or invasive ventilation therapy, and it is useful for use after extubation. A flowchart to optimize its use in pediatrics can be advantageous for the success of therapy.

FLOWCHART TO USE HFNC IN PEDIATRICS (28 days of life through 14 years)

Patients under acute respiratory failure and without contraindication.

1. HIPOXEMIA

2. HIPERCAPNIA

3. RESPIRATORY EFFORT

Up to 10 kg: Start with 2L/min/kg flow **>10kg:** Follow the flow chart based on the weight
Titrate FiO₂ to maintain saturation higher than 92% (or patient's target saturation)

Monitor the patient's clinical response

Monitor and note: HR, RR, SpO₂ and signs of respiratory distress
Every hour in the first 6 hours of therapy

RESPONDS TO THERAPY

Better respiratory effort
20% reduction in HR and RR

Start HFNC weaning when:

FiO₂ < 40%
Flow < 50% of the initial

Transitioning from CNAF to low flow
O₂ therapy
Titrate FiO₂ to maintain target saturation

DOES NOT RESPOND TO THERAPY

Persistence or worsening of the
respiratory failure, shown by one or
more of the following:
Increase in HR and RR
Worse respiratory distress
FiO₂ > 60%
pH < 7.20 e PCO₂ > 56 mmHg
PaO₂/FiO₂ < 195

Consider indication of:

Non-Invasive ventilation or Invasive
mechanical ventilation

Table with initial flow values¹

Weight (Kg)	Flow (L/min)
< 10	2L/Kg/min
10 – 20	25
20 – 30	30
30 – 40	35

Source: The Authors.

REFERENCES

1. RAMNARAYAN, P. et al. FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): A multicentre pilot randomised controlled trial of high-flow nasal cannula therapy versus continuous positive airway pressure in paediatric critical care. *Critical Care*. 2017;22(1):1–11.
2. LODESERTO, FJ.; LETTICH, TM.; REZAIE, SR. High-flow Nasal Cannula: Mechanisms of Action and Adult and Pediatric Indications. *Cureus*.2018;10(11).
3. FRANKLIN, D. et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *New England Journal of Medicine*. 2018; 378(12):1121-1131.
4. Er A, Çağlar A, Akgül F, Ulusoy E, Çitlenbikh, Yılmaz D, Duman M. Early predictors of unresponsiveness to high-flow nasal cannula therapy in a pediatric emergency department. *Pediatr Pulmonol*. 2018;53(6):809-815.
5. MILÉSI, C et al. A multicenter randomized controlled trial of a 3-L/kg/min versus 2-L/kg/min high-flow nasal cannula flow rate in young infants with severe viral bronchiolitis. *Intensive Care Medicine*. 2018; 44(11):1870–1878.
6. ZIELIŃSKA, A; JASSEM-BOBOWICZ, J; KWIATKOWSKA, Joanna. Oxygen therapy with high-flow nasal cannulas in children with acute bronchiolitis. *Anesthesiology Intensive Therapy*.2019; 51(1):51–55.
7. KWON, JW. High-flow nasal cannula oxygen therapy in children: A clinical review. *Korean Journal of Pediatrics*.2020; 63(1):3–7.
8. MIKALSEN, IB; DAVIS, P; ØYMAR, K. High flow nasal cannula in children: A literature review. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*. 2016; 24(1).
9. YURTSEVEN, A et al. Comparison of heated humidified high-flow nasal cannula flow rates (1-L·kg·min⁻¹ vs 2-L·kg·min⁻¹) in the management of acute bronchiolitis. *Pediatric Pulmonology*. 2019; 54(6):894–900.
10. AL-SUBU, A; HAGEN, S; ELDRIDGE, M; BORIOSI, J. Aerosol therapy through high flow nasal cannula in pediatric patients. *Expert Rev Respir Med*.2017;11(12):945-953.
11. WANG, J et al. Expert Review of Medical Devices High flow nasal cannula in the emergency department: indications, safety and effectiveness. *Expert Review of Medical Devices*. 2018; 00(00):1–7.
12. LYONS, C; CALLAGHAN, M. Uses and mechanisms of apnoeic oxygenation: a narrative review. *Anesthesia*, 2019 (74):497-507.
13. YURTSEVEN, A; SAZ, EU; HENNES, H. Safety and Efficacy of High-flow Nasal Cannula Therapy in the Pediatric Emergency Department. *Turkish Journal of Pediatric Emergency and Intensive Care Medicine*. 2019; 6(3):121–129.
14. MOREEL, L; PROESMANS, M. High flow nasal cannula as respiratory support in treating infant bronchiolitis: a systematic review. *European Journal of Pediatrics*. 2020; 179(5):711–718.
15. BALLESTERO, Y; PEDRO, J; PORTILLO, N; MARTINEZ-MUGICA, O; ARANA-ARRI, E, Benito J. Pilot Clinical Trial of High-Flow Oxygen Therapy in Children with Asthma in the Emergency Service. *J Pediatr*. 2018; 194: 204-210.
16. AKYILDIZ, B; ÖZTÜRK, S; ÜLGİN-TEKEREK, N; DOĞANAY, S; GÖRKEM, SB. Comparison between high-flow nasal oxygen cannula and conventional oxygen therapy after extubation in pediatric intensive care unit. *Turk J Pediatr*. 2018;60(2):126-133.
17. HABRA, BASEL; JANAHI, IA; DAULEH, H. A comparison between high-flow nasal cannula and noninvasive ventilation in the management of infants and young children with acute bronchiolitis in the PICU. *Pediatric Pulmonology*, 2019; 55:455-461.
18. METGE, P et al. Comparison of a high-flow humidified nasal cannula to nasal continuous positive airway pressure in children with acute bronchiolitis: experience in a pediatric intensive care unit. *European Journal of Pediatrics*, 2014; v.173, p. 953-958.
19. SANTANA, SAA et al. Benefícios e comparação na atuação do cateter nasal e da ventilação não invasiva em pediatria: uma revisão sistemática. *Electronic Journal Collection Health*, 2020; (43).
20. VAHLKVIST, Signe et al. High flow nasal cannula and continuous positive airway pressure therapy in treatment of viral bronchiolitis: a randomized clinical trial. *European Journal of Pediatrics*, 2020; 179(3):513–518.
21. LIN, Jilei et al. High-flow nasal cannula therapy for children with bronchiolitis: A systematic review and meta-analysis. *Archives of Disease in Childhood*, 2019:1–13.
22. CHEN DY, ZED; GILDENGORIN, G; FONG, EW. A pilot study of heated and humidified low flow oxygen therapy: An assessment in infants with mild and moderate bronchiolitis. *Pediatr Pulmonol*. 2019;54(5):620-627.
23. KAPUR, Sunil V; OSWAL, Jitendra S.; SARANGI, Bhakti. Efficacy and Safety of High-Flow Nasal Cannula Oxygen Therapy in Moderate and Severe Bronchiolitis. *Journal of Clinical and Diagnostic Research*. 2019;11–14.
24. FRANKLIN, D et. al. Early high flow nasal cannula therapy in bronchiolitis, a prospective randomised control trial (protocol): A Pediatric Acute Respiratory Intervention Study. *BMC Pediatrics*. 2015;15:15-23.