

## High flow nasal cannula oxygen therapy in patients with asthmatic crisis in the pediatric emergency department

### Oxigenoterapia por cánula nasal de alto flujo en pacientes con crisis asmática en un departamento de emergencia pediátrica

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#### Abstract

There are few conclusive studies on the usefulness of High-Flow Nasal Cannula (HFNC) Oxygen Therapy in patients with asthmatic crises. **Objective:** To determine the effectiveness of HFNC in children older than 2 years of age that present severe and moderate asthmatic crises that do not respond to initial treatment. **Patients and Method:** Open controlled randomized clinical trial of patients with asthma exacerbation in the Pediatric Emergency Department. Infection- and comorbidity-mediated crises were excluded. Subjects were randomized as follows: Group 1 HFNC (n:32) and Group 2 Conventional Oxygen Therapy (n:33). Both groups received the usual pharmacological treatment. The first cut-off point was the decrease of more than 2 points of the PIS after 2 hours of treatment; secondary points were PIS decrease at 6 hours, stay time in the Emergency Room, and PICU admission. **Results:** The patient's baseline characteristics were similar in both groups. The proportion of subjects with more than two points decrease in the PIS after two hours of treatment in Group 1 was 43.7% CI 95% (28-60) vs. Group 2 48.4%; CI 95% (32-64) p 0.447. The mean stay time was 24.8 ± 12.3 hours in Group 1 vs. 24 ± 14.8 hours in Group 2; CI 95% (7.56-5.96) p 0.37. We did not find differences in the respiratory effort score measurements every 2 hours. No patients were admitted to intensive care. **Conclusions:** The incorporation of HFNC oxygen therapy in the treatment of patients with asthmatic crises in the Pediatric Emergency Department did not show clinical benefits nor did it diminish the stay time.

#### Keywords:

Acute asthma exacerbations; high-flow nasal cannula; pediatric emergency department; children

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## Introduction

Asthma is a chronic airway disease characterized by coughing, wheezing, and shortness of breath, which is usually reversible, and, in some cases, it appears as a severe clinical picture<sup>1,2</sup>.

Acute asthma exacerbations, which usually occur as a reaction to the exposure to an external agent and/or poor adherence to treatment, are very common reasons for visiting the emergency departments (ED). Also, severe exacerbations may occur in patients with mild or well-controlled asthma<sup>3</sup>.

The main initial treatments include repeated administration of short-acting bronchodilators inhalers, early administration of systemic corticosteroids, and controlled oxygen administration<sup>4,5</sup>.

The standard therapy with  $\beta_2$ -agonists, anticholinergics, oxygen, and systemic corticosteroids may fail to reverse airflow obstruction in children with severe exacerbations, requiring adjuvant therapies<sup>2,6</sup>.

The high flow oxygen system is a form of oxygen support that has been established in recent years as an alternative to non-invasive ventilation (NIV) therapy in patients with moderate and severe respiratory failure<sup>7</sup>.

The high flow nasal cannula (HFNC) therapy was originally described as a type of respiratory support for preterm newborns and it is now increasingly used in the treatment of acute respiratory failure in older infants and children<sup>8,9</sup>. It consists of providing  $O_2$  above the patient's peak inspiratory flow rate through a nasal cannula<sup>10</sup>. The gas is heated and humidified to best match body temperature which clears the nasopharyngeal dead space, generates mucociliary clearance, positive airway pressure and, consequently, a decrease in breathing work<sup>11,12</sup>. It is an effective and safe treatment for acute respiratory events in the pediatric population<sup>13</sup>, however, there are few studies on its application in asthma attacks<sup>14</sup>.

The objective of this study was to determine the effectiveness of the HFNC oxygen therapy in children older than 2 years with moderate asthma attacks that do not respond to initial treatment and in case of severe attacks, determined by the improvement in the clinical respiratory score. Secondary objectives were the decrease in the stay length in the Pediatric Emergency Department (PED) and the need for hospitalization in the Pediatric Intensive Care Unit (PICU).

## Patients and Method

Open-label randomized controlled trial. The study was conducted in the Emergency Department (ED) of a tertiary pediatric hospital from the network of the

Ministry of Public Health and the Ministry of Social Development and Family that takes care of 110,000 children and adolescents per year. Patients older than 2 years with moderate asthma attacks that did not respond to initial treatment and those patients with severe asthma attack at admission were included.

Asthma attacks were defined as patients older than 2 years with history of 2 or more wheezing episodes treated with  $\beta_2$ -agonists who went to the PED presenting an acute exacerbation, defined as a worsening of asthmatic symptoms with an increase in respiratory distress, or a first episode in children with history of atopy<sup>15,16</sup>. The Pulmonary Index Score (PIS) was used to determine the attack severity which assesses five items: respiratory frequency, oxygen saturation, inspiration-expiration ratio, wheezes presence, and use of accessory muscles. Severe asthma attacks were considered as those patients with a PIS score  $> 11$  and moderate asthma attacks those with a PIS score between 7 and 11.

Initial treatment in moderate attack contains inhaled salbutamol and oral prednisone. The salbutamol dose was calculated according to the formula: puff number = patient weight/3, using a maximum dose of 1 mg (1 puff: 100 micrograms) in three cycles every 15 minutes, and oral prednisone 2 mg/kg, with a maximum dose of 60 mg<sup>17</sup>. When there was no decrease or when increasing in PIS score after drug administration, it was considered as non-response to treatment.

Patients with a severe attack were included in the study without receiving prior treatment in the ED. All patients had to have a Glasgow greater than 14.

Patients that present the following criteria were excluded: fever ( $T \geq 38^\circ C$ ) at admission or during treatment, a medical picture compatible with clinically suspected bacterial respiratory infection, those using antibiotics at the time of consultation, and those with comorbidities (cystic fibrosis, congenital heart disease, neuromuscular disorders, and immunodeficiency).

Once parents or guardians signed informed consent, patients who met the inclusion criteria randomly receive one of the two treatments, the HFNC therapy (study group) or conventional oxygen therapy (control group). The envelopes containing the treatment assignment were sequentially-numbered, sealed, and opaque.

All patients included in the study received parenteral hydration and continuous nebulization of salbutamol with nebulizer solution (1 ml/5 mg) diluted in 14 ml of saline solution for one hour. Patients weighing up to 20 kg received 40 drops (10 mg) and those weighing more than 20 kg 80 drops (20 mg). Also, the patients received intravenous dexamethasone at 0.6 mg/kg (12 mg maximum dose) and magnesium sulfate by intra-

venous drip infusion at 200 mg/kg for 4 hours (50mg/kg/hs), (8 gm maximum dose).

According to randomization, the study group received HFNC therapy, using AIRVO™ and AIRVO™ 2 systems (Fisher & Paykel Healthcare), and the Opti-flow™ nasal cannula (Fisher & Paykel Healthcare) suitable for the systems' flow. An initial flow of 1 l/kg was administered with a gradual increase up to 2 l/kg until obtaining a saturation between 93% and 98%. The control group received oxygen therapy through a simple nasal cannula, simple face mask or non-rebreather mask as needed to reach a 93% of saturation.

Demographic variables, nutritional status (Z score according to WHO Anthro), history of previous attacks, and treatment for inter-attacks periods were studied. A time-register form was used for recording PIS score, respiratory rate, oxygen saturation, inspiration-expiration ratio, presence or absence of wheezing, accessory muscles use, and the presence of adverse effects.

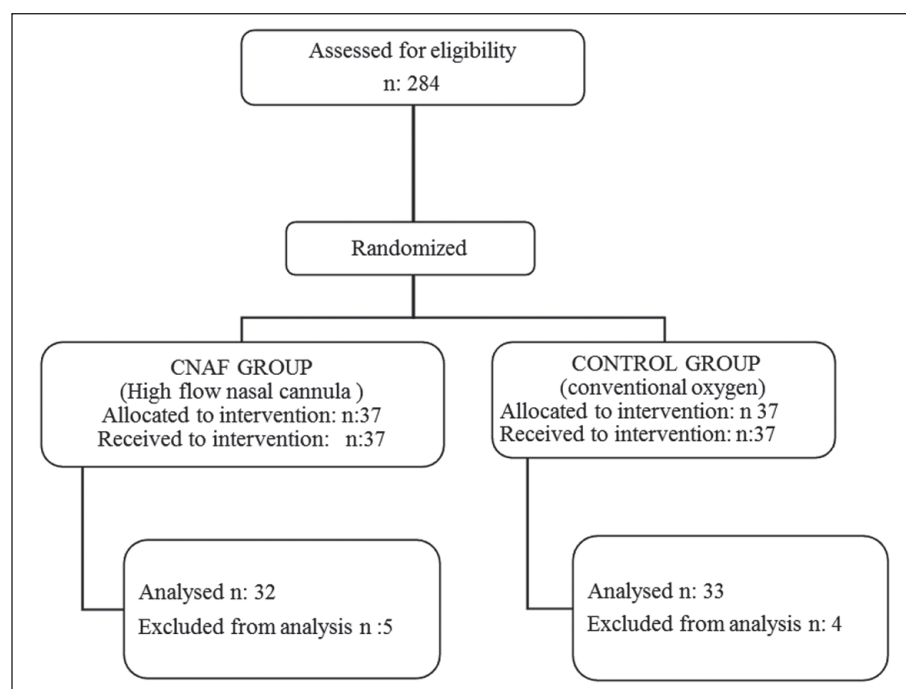
Stopping HFNC therapy was indicated when the patient presents a PIS score  $\leq 6$  and was discharged from the PED with a PIS score  $\leq 5$  without O<sub>2</sub> requirement. The assessment to determine the attack severity and the time improvement in hours was carried out by resident physicians trained for this purpose. The first cut-off point was the PIS score decrease in more than 2 points at 2 hours of treatment initiation and the secondary cut-off points were the PIS score decrease at 6 hours of treatment initiation, the time of stay in the ED, and the admission to the PICU in the study group.

The withdrawal of the HFNC system occurred when the patient presents a score  $\leq 6$  and was discharged from the PED with a PIS score  $\leq 5$ .

For calculating the sample size, the first cut-off point was considered, using the Student's t-test for a magnitude of the analyzed effect of 0.80, with a 0.05 bilateral alpha and a 0.10 beta. 34 patients were needed in each group and 74 patients were recruited considering a 10% loss of patients. The data were analyzed with the SPSS software, and the relationship between the type of oxygen therapy and clinical improvement was obtained using Pearson's chi-square test. Results were expressed in OR with their confidence intervals. The relationship among quantitative variables was determined through the Student's t-test or the Mann-Whitney U test, depending on whether they are or not of normal distribution. The ethics committee of the hospital approved the protocol with informed consent.

## Results

Between April 1 and November 30, 2017, 284 patients with asthma attacks were admitted, of which 74 met the inclusion criteria. 9 patients were excluded, 3 patients due to receive a different treatment than the protocolized one, and 6 ones due to present fever during treatment. 32 patients were included in the HFNC Group and 33 patients in the Control Group (Figure 1).



**Figure 1.** Number of children who were evaluated, assigned to a group and included in the analysis

Demographic characteristics, nutritional status according to z-score, previous attack percentage, and treatment for inter-attack periods were similar in both groups (Table 1). Table 2 shows that the PIS score, respiratory effort score, respiratory rate, and oxygen saturation at admission did not differ either.

There were no significant differences when comparing groups at 2 and 6 hours after treatment started (table 2), nor in the proportion of subjects with a decrease of more than two points in the PIS score at 2 hours of starting the treatment (Table 3).

There were no differences in PIS score, respiratory

**Table 1. Baseline characteristics of the HFNC and Control groups**

Variables		HFNC n (32)	Control n (33)	p
Age	median (range)	5 (2-14)	4 (2-14)	0.537*
Sex	n (%)			
Female		22 (68.8)	17 (51.5)	0.156**
Male		10 (31.3)	16 (48.5)	
Previous crisis	n (%)	30 (93.8)	33 (100)	1****
Maintenance treatment	n (%)	13 (40.6)	15 (45.4)	0.694**
Z Score	mean (SD)	0.45 ± 1.12	0.70 ± 1.53	0.457***
Respiratory rate at admission	mean (SD)	43.8 ± 10.56	46.3 ± 11.62	0.515***
Saturation of O <sub>2</sub> at admission	median (range)	91 (82-99)	92 (80-98)	0.659*

\*Man Whitney; \*\*Chi cuadrado; \*\*\*T student; \*\*\*\*Test exacto Fisher.

**Table 2. Comparison between groups 2 and 6 hours after starting treatment**

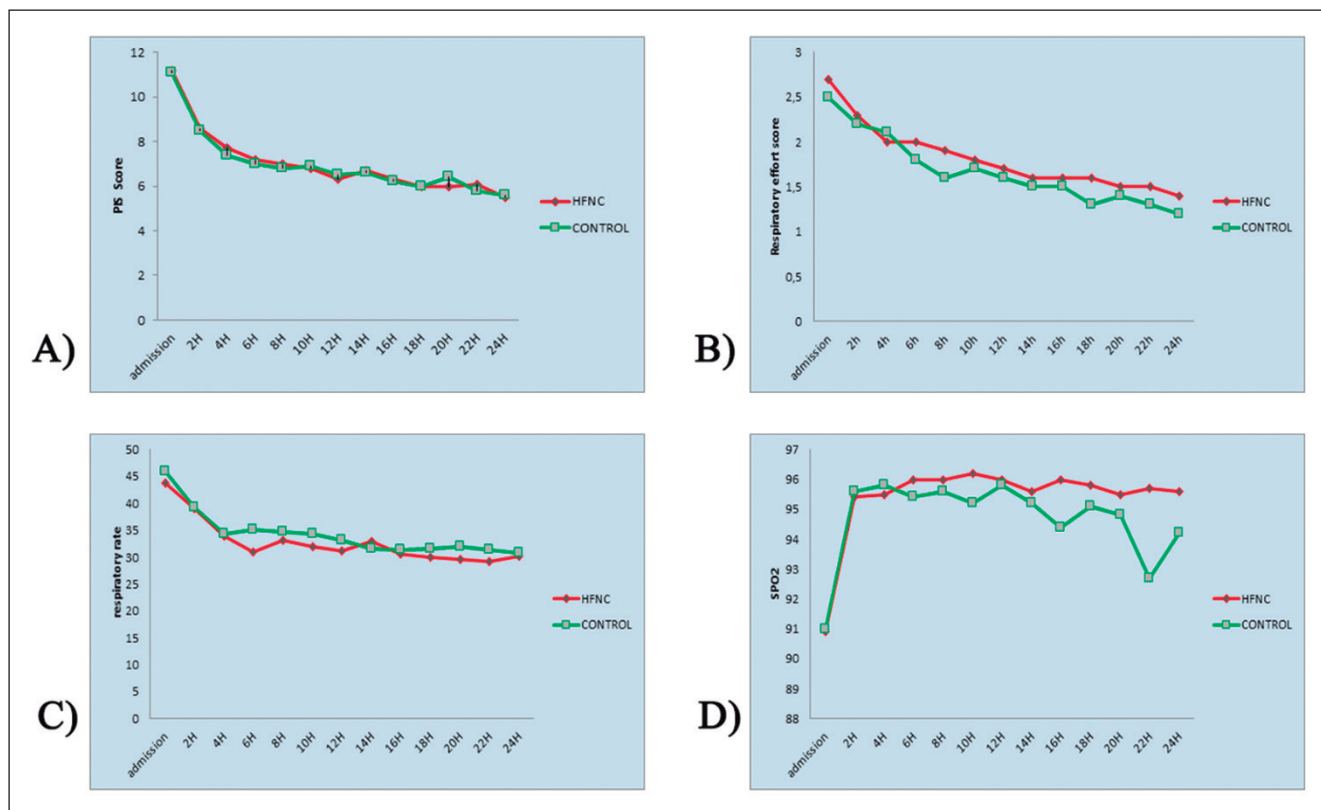
Variables		HFNC n (32)	Control n (33)	p
		mean (SD)	mean (SD)	
Score	2 hs	8.69 ± 1.46	8.55 ± 1.66	0.616*
	6 hs	7.22 ± 1.66	7.06 ± 1.76	0.529*
Respiratory effort score	2 hs	2.34 ± 0.60	2.21 ± 0.59	0.370*
	6 hs	2.00 ± 0.56	1.87 ± 0.73	0.516*
Respiratory rate	2 hs	38.6 ± 10.5	39.0 ± 9.80	0.572*
	6 hs	32.0 ± 7.90	35.1 ± 7.90	0.098*
		median (range)	median (range)	
Oxygen saturation	2 hs	97 (82-99)	96 (89-100)	0.926**
	6 hs	97 (88-99)	96 (85-100)	0.735**

\*T Student. \*\*U Mann Whitney.

**Table 3. Length of stay and proportion of subjects with a decrease of more than two points in the PIS score at 2 hours of starting the treatment**

Variables	HFNC n (32)	Control n (33)	p
	mean (SD)	mean (SD)	
Length of stay (hours)	24.8 ± 12.3	24.09 ± 14.8	0.598*
	n (%)    CI 95%	n (%)    CI 95%	
Decrease > 2 points in the PIS at 2 hours	14 (43.7)    (28-60)	16 (48.4)    (32-64)	0.447
Complications	0	0	ns
Admitted to intensive care	0	0	ns

\*Man Whitney.



**Figure 2. A)** Variation of the Score (PIS), **B)** Comparison of the Respiratory Effort Score, **C)** Variation of the Respiratory rate, **D)** O<sub>2</sub> Saturation Measurements.

effort score, respiratory rate, and oxygen saturation in measurements recorded from admission every 2 hours to discharge or the first 24 hours (Figure 2). The mean length of stay was  $24.8 \pm 12.3$  hours in Group 1 vs  $24 \pm 14.8$  hours in Group 2; 95%CI (7.56-5.96)  $p$  0.598. No patients were admitted to intensive care or presented associated complications.

## Discussion

The HFNC oxygen therapy associated with pharmacological therapy of moderate to severe asthma attacks was not effective in lowering the PIS score at 2 and 6 hours of treatment initiation. Although its use did not add complications or adverse effects, it did not present benefits considering that it is a more expensive therapy than the conventional one.

There is a lack of literature on the use of HFNC in children with asthma. The 2014 Cochrane annual review concluded that there is not enough evidence to recommend the use of HFNC in pediatric respiratory diseases due to the paucity of randomized clinical studies<sup>18</sup>. However, other authors have recently found beneficial effects on asthmatic patients<sup>16,19-21</sup>. This limi-

ted evidences motivated our interest to carry out this study.

In an observational cohort study published in 2017 conducted in the PICU of two Spanish healthcare centers, where they compare the HFNC therapy with the NIV in children with severe acute asthma exacerbation, showed that the HFNC failed more than NIV<sup>20</sup>. We analyzed patients in a very different setting such as the PED.

Most studies did not report adverse effects in children treated with the HFNC oxygen therapy and concluded that its use is safe in a general pediatric ward, in the ED as well as in PICU<sup>9</sup>. Among the possible complications described are atelectasis, nasal septal injury, and pneumothorax. These complications may lead to the need for other forms of respiratory support<sup>22</sup>.

In a pilot study of the high flow oxygen therapy use in the ED in children with asthma published in January 2017, there was a decrease in respiratory effort at 2 hours of high flow oxygen therapy, however, it did not demonstrate that the HFNC is better than conventional oxygen therapy regarding duration of respiratory support, and stay at PICU and in the hospitalization ward. The lower age of the children analyzed in Ballesteros's study could mean a greater possibility of

overlapping pathologies such as bronchiolitis or viral-induced wheeze<sup>16</sup>. Several studies found a decrease in orotracheal intubation and admission to PICU in pediatric patients with respiratory failure, mainly bronchiolitis, after starting the HFNC therapy<sup>23-26</sup>.

Our patients presented a similar clinical improvement in both groups, they did not present complications due to the use of the HFNC and none of the patients of any group required admission to PICU. The stay at the PED was similar, and all were discharged from the PED.

Part of the protocol of our PED is the use of Magnesium Sulfate through intravenous continuous drip infusion for 4 hours in severe and moderate attacks that do not respond to bronchodilator inhalers or the initial corticosteroid therapy. All patients analyzed received high doses of Magnesium Sulfate in continuous drip infusion. The early use of a prolonged infusion of magnesium sulfate in high doses (50 mg/kg/hr/4 hr) for non-infection related asthma attack, accelerates discharges from the ED with a significant reduction in medical care costs<sup>27</sup>. This intravenous bronchodilator therapy could have overlapped some benefit of the HFNC therapy demonstrated in other works such as that of Morosini et al<sup>21</sup>.

This study has several limitations. It was carried out in a single hospital center thus it could not be extrapolated to other populations. Since it is an open-label study, the doctors knew the intervention which could limit its validity, however, the statistical team was blinded. We do not use Ipratropium in moderate attacks that might have added some benefit in the initial treatment, and no hemodynamic variables were compared so we do not know if there would be benefits in these parameters.

## Conclusion

Adding the HFNC oxygen therapy to the treatment of severe and moderate asthmatic patients who did not

respond to the initial therapy did not present clinical benefits or reduce the length of stay.

We think that in respiratory disease outbreaks, it would be reasonable for now to optimize the use of high flow equipment in other causes of respiratory distress, such as severe bronchiolitis, with greater evidence of its benefits, considering costs and equipment availability.

A large randomized controlled multicenter trial is needed to confirm whether or not the HFNC therapy is effective in patients with severe-moderate asthma attacks in PED.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

## References

1. Initiative G, Strategy G, Management A. Global strategy for asthma management and prevention: Prevention. *Rev Fr d'Allergologie d'Immunologie Clin.* 1996;36(6):628-32.
2. Pardue Jones B, Fleming GM, Otilio JK, Asokan I, Arnold DH. Pediatric acute asthma exacerbations: Evaluation and management from emergency department to intensive care unit. *J Asthma.* 2016;53(6):607-17.
3. Powell CV. Acute severe asthma. *ICU Protoc A Stepwise Approach.* 2012;52:691-6.
4. Jones B, Paul A. Management of acute asthma in the pediatric patient: an evidence-based review. *Pediatr Emerg Med Pract* [Internet]. 2013;10(5):1-24. Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=23971269>
5. Babaic N, Valdebenito C, Koppmann A, Prado F. Asma agudo pediátrico. El desafío del manejo escalonado por etapas. *Neumol Pediatr;* 2017 12(3):114-21.
6. Wong JJM, Lee JH, Turner DA, Rehder KJ. A review of the use of adjunctive therapies in severe acute asthma exacerbation in critically ill children. *Expert Rev Respir Med.* 2014;8(4):423-41.
7. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: A critical review of the literature. *Intensive Care Med.* 2013;39(2):247-57.
8. Hutchings FA, Hilliard TN, Davis PJ. Heated humidified high-flow nasal cannula therapy in children. *Arch Dis Child.* 2015;100(6):571-5.

9. Mikalsen IB, Davis P, Øymar K. High flow nasal cannula in children: A literature review. *Scand J Trauma Resusc Emerg Med* [Internet]. 2016;24(1). Available from: <http://dx.doi.org/10.1186/s13049-016-0278-4>.
10. Franklin D, Babl FE, Schlapbach LJ, et al. A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis. *N Engl J Med* [Internet]. 2018;378(12):1121-31. Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1714855>.
11. Milési C, Boubal M, Jacquot A, et al. High-flow nasal cannula: Recommendations for daily practice in pediatrics. *Ann Intensive Care*. 2014;4(1):1-7.
12. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest* 2015; 148:253-61. available from: <http://link.springer.com/10.1007/s00246-002-9361-x>.
13. Ten Brink F, Duke T, Evans J. High-flow nasal prong oxygen therapy or nasopharyngeal continuous positive airway pressure for children with moderate-to-severe respiratory distress? *Pediatr Crit Care Med*. 2013;14(7):e326-31.
14. Baudin F, Buisson A, Vanel B, Massenavette B, Pouyau R, Javouhey E. Nasal high flow in management of children with status asthmaticus: a retrospective observational study. *Ann Intensive Care*. 2017;7(1):1-9.
15. Greenberg RA, Kerby G, Roosevelt GE. A comparison of oral dexamethasone with oral prednisone in pediatric asthma exacerbations treated in the emergency department. *Clin Pediatr (Phila)*. 2008;47(8):817-23.
16. Balletero Y, De Pedro J, Portillo N, Martínez-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* [Internet]. 2018;194:204-210.e3. Available from: <https://doi.org/10.1016/j.jpeds.2017.10.075>.
17. Http: National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma.(NIH publication no. 08-4051). [www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm](http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm) (Accessed on September 01, 2007).
18. Mayfield S, Jauncey-Cooke J, Hough JL, Schibler A, Gibbons K, Bogossian F. High-flow nasal cannula therapy for respiratory support in children. *Cochrane Database Syst Rev*. 2014;2014(3).
19. González Martínez F, González Sánchez MI, Toledo del Castillo B, et al. Treatment with high-flow oxygen therapy in asthma exacerbations in a paediatric hospital ward: Experience from 2012 to 2016. *An Pediatr*. 2019;90(2):72-8.
20. Pilar J, Modesto i Alapont V, López-Fernández YM, Lopez-Macias O, García-Urabayen D, Amores-Hernandez I. High-flow nasal cannula therapy versus non-invasive ventilation in children with severe acute asthma exacerbation: An observational cohort study. *Med Intensiva* [Internet]. 2017;41(7):418-24. Available from: <http://dx.doi.org/10.1016/j.medin.2017.01.001>
21. Morosini F, Amarillo P, Alonso B, Prego J. Cánula nasal de alto flujo en niños con crisis asmática en un servicio de urgencias pediátrico. *Arch Pediatr Urug* [Internet]. 2017;88(3):142-8. Available from: [http://www.scielo.edu.uy/scielo.php?script=sci\\_arttext&pid=S1688-12492017000300142&lng=en&tlng=en#?](http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492017000300142&lng=en&tlng=en#?)
22. Lenglet H, Sztrymf B, Leroy C, Brun P, Dreyfuss D, Ricard J-D. Humidified High Flow Nasal Oxygen During Respiratory Failure in the Emergency Department: Feasibility and Efficacy. *Respir Care*. 2012;57(11):1873-8.
23. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. *Respir Care* 2010; 55:408-13.
24. Kelly GS, Simon HK, Sturm JJ. High-Flow Nasal Cannula Use in Children With Respiratory Distress in the Emergency Department. *Pediatr Emerg Care* [Internet]. 2013;29(8):888-92. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006565-201308000-00003>.
25. Schibler A, Pham TMT, Dunster KR, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. *Intensive Care Med*. 2011;37(5):847-52.
26. Wing R, James C, Maranda LS, Armsby CC. Use of high-flow nasal cannula support in the emergency department reduces the need for intubation in pediatric acute respiratory insufficiency. *Pediatr Emerg Care*. 2012;28(11):1117-23.
27. Irazuzta JE, Paredes F, Pavlichic V, Domínguez SL. High-Dose Magnesium Sulfate Infusion for Severe Asthma in the Emergency Department: Efficacy Study. *Pediatr Crit Care Med*. 2016;17(2):e29-33.