

Failure predictors with oxygen therapy by high-flow nasal catheter in children under 2 years of age with acute lower respiratory infections

Predictores de fracaso de oxigenoterapia por catéter nasal de alto flujo en menores de 2 años con infecciones respiratorias agudas bajas

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What do we know about the subject matter of this study?

The high-flow nasal cannula (HFNC) provides comfort and eventually prevents the use of invasive respiratory support techniques. Some failure factors are elevated pCO₂, prematurity, low birth weight, and low current weight.

What does this study contribute to what is already known?

In this clinical trial, high-flow nasal cannula (HFNC) oxygen therapy in children under 2 years old with acute lower respiratory infection, was not successful in patients with lower gestational age, low birth weight, and higher respiratory rate (RR) before connection. Pre-connection RR to HFNC was the main predictor of technique failure.

Abstract

Acute lower respiratory infections (ALRI) are the main cause of hospitalization during the winter season. High-flow nasal catheter (HFNC) has been established as part of the treatment of these infections. **Objective:** To characterize the population of children with acute hypoxemic respiratory failure treated with HFNC and to determine the predictors of failure of this therapy. **Patients and Method:** Prospective study in children under 2 years of age admitted due to ALRI treated with HFNC at the Pereira Rossell Hospital Center (CHPR), from 20/5 to 20/09 2019. Data were collected from medical records and analyzed with SPSS 21.0 software. The following quantitative variables were analyzed: gestational age, birth weight, current age and weight, respiratory rate, pH, pCO₂, HCO₃⁻, BE, and pre-connection white blood cell count. The qualitative variables evaluated were: sex, comorbidities, radiological alterations, viral antigens, and history of similar episodes. Two groups were defined according to the success or failure of treatment with HFNC, where the following variables were evaluated: sex, weight, age, gasometric alterations, and white blood cell count. **Results:** 449 patients were included,

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of which 274 (61%) were successful with the treatment. Those who failed had lower gestational age ($p = 0.003$), birth weight ($p = 0.046$), and pre-connection higher respiratory frequency (RF) ($p = 0.031$). In the multiple logistic regression model, pre-connection RF predicted failure for HFNC treatment (OR: 1.035 IC 95%: (1.01-1.07)). In the analysis with ROC curves, the area under the curve for RF was 0.558 (CI 0.503-0.613). The RF with the highest sensitivity (53%) and specificity (55%) was 59 breaths per minute. **Conclusion:** Pre-connection RF to HFNC was the main predictor of technique failure. It is necessary to deepen other characteristics to find reliable predictors of failure.

Introduction

The high-flow nasal cannula (HFNC) oxygen therapy provides humidified and heated oxygen at flow rates that exceed the volume per minute requirements. Flow rates of 1 l/kg/min to 2 l/kg/min can provide high oxygen concentrations and some degree of positive intrathoracic airway pressure¹.

Since its introduction to neonatal intensive care units (ICUs) more than 20 years ago, HFNC oxygen therapy has been increasingly used in neonates, infants, and children to treat severe respiratory distress and avoid the need for intubation and mechanical ventilatory support²⁻⁴. Worldwide, this method of respiratory support has been incorporated into the treatment of acute respiratory failure associated with acute lower respiratory infections (ALRI)⁵. In Uruguay, the use of HFNC was extended outside children's ICUs to moderate care wards since 2011, and to emergency services since 2013^{5,6}.

In contrast to low-flow nasal cannula oxygen therapy, HFNC allows 100% oxygen delivery and reduces work of breathing by the clearance of the anatomic dead space in the upper airway and intrathoracic airways. Most of the available scientific evidence regarding the potential benefits of this therapy is derived from infants or young children with bronchiolitis or pneumonia. Studies have suggested a reduced need for intubation but have failed to demonstrate an impact on mortality or ICU admission and/or stay⁷⁻¹². Despite not having demonstrated benefits on variables considered "hard", it has gained wide acceptance due to good tolerance and the possibility of using it outside the ICU.

Unlike other respiratory support techniques, the failure predictors with HFNC in children have not been well established. In retrospective studies, it was observed that elevated pCO₂ and lower levels of oxygen saturation/inspired oxygen fraction (SpO₂/FiO₂) ratio were predictors of failure of this technique^{13,14}. Other factors such as gestational age, birth weight, and current weight may influence the evolution of these patients^{15,16}.

It is important to have tools that allow early detection of the risk of failure of the technique since a delay in intubation could lead to an increase in morbidity

and mortality¹³. The objective of this study was to identify possible predictors of failure of HFNC oxygen therapy in children under 2 years old with acute hypoxemic respiratory failure secondary to ALRI.

Patients and Method

Design

Retrospective observational study in children under 2 years old who received respiratory support with HFNC due to respiratory failure secondary to ALRI between 20 May and 20 September 2019 in the emergency department, intermediate care units, and ICU of the *Centro Hospitalario Pereira Rossell* (CHPR).

The criteria for the use of HFNC were modified TAL score higher than 8 at the time of consultation or higher than or equal to 6 despite treatment, or hemoglobin oxygen saturation less than 90% with conventional oxygen therapy. Impaired consciousness, hemodynamic instability, and pneumothorax were considered contraindications for the use of HFNC⁶.

Patients who received noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV) before the use of HFNC during hospitalization, those with anatomical anomalies of the upper airway (choanal atresia, facial bone or skull base trauma, etc.), neuromuscular disease, and those in whom the indication for HFNC was a cause other than ALRI were excluded from the study.

An air/oxygen blender with a flowmeter coupled to a heated humidifier (Fisher & Paykel®) along with a nasal cannula appropriate to the size of the child was used to provide the support with HFNC. Treatment was started with HFNC at 2 l/kg/min and inspired oxygen fraction (FiO₂) of 60%.

Study variables

The quantitative variables analyzed were gestational age (GA), birth weight (BW), current age and weight, respiratory rate (RR), pH, pCO₂, HCO₃, BE, and pre-connection white blood cell count and the qualitative variables evaluated were sex, presence of comorbidities (broncho-obstructive syndrome, atrial

septal defect, other congenital heart diseases, bronchopulmonary dysplasia, and anemia), radiological alterations (interstitial infiltration, hyperinflation, atelectasis, inhomogeneous opacity, fissure sign), viral antigens detected by immunochromatography (RSV, Influenza A and B, Adenovirus, and Parainfluenza), and history of similar episodes.

Groups conformation

For the analysis, the population was divided into two groups, the group of children who responded to treatment with HFNC (success group) and the group in which the therapy failed (failure group). The first group included those who showed clinical improvement and continued with less complex respiratory support measures. The second group included those who had to escalate respiratory support and required NIV or IMV. The criteria for failure as previously defined in the protocol were: TAL score higher than 8 sustained or increasing, respiratory acidosis with acidemia ($\text{pH} < 7.2$), impaired consciousness, or hemodynamic failure after initiation of HFNC. No time limit was considered in the definition⁶. Children in whom the technique succeeded or failed were compared and, within the latter, those who required NIV were compared with those who required IMV.

The investigators were not involved in therapeutic decisions. The source of data was clinical records.

The protocol was approved by the Ethics Committee of the institution. Informed consent was obtained from the parent or guardian. The information was processed confidentially, and the child's identity was protected.

Statistical analysis

Qualitative variables were described by summary measures (frequencies) and quantitative variables by means and ranges. In the comparison between the success and failure groups, the Chi-square test was used for qualitative variables and the Student t-test for independent samples. In the analysis of the failure predictors, a multiple logistic regression model was applied with the calculation of crude and adjusted Odds Ratio (OR) values. For this model, the sample size was 120 patients estimated by Freeman's formula using 11 as numerical value. The receiver operating characteristic (ROC) curve analysis was applied for the quantitative variables that showed statistical significance in the aforementioned model. p values < 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS 21.0 software for Windows.

Results

449 children under 2 years old with ALRI were

included in the study, 272 (60.6%) corresponded to bronchiolitis and 177 (39.3%) to viral pneumonia. The mean age was 6.3 months (range 0-24 months) and 287 (63.9%) were male.

Respiratory support with HFNC was successful in 274 (61%) and failed in 175 (39%). In the latter group, 110 (62.9%) required NIV, and 65 (37.1%) required IMV (figure 1).

Failure of HFNC therapy was associated with lower GA and BW and higher pre-connection RR. There was a tendency to present more radiological complications in this group and one-third of those who the technique failed were younger than 3 months. Table 1 compares the characteristics of the children from the success group with the failure group.

Table 2 shows the success group and the failure group who required NIV and IMV. Patients in whom the technique failed and required respiratory support with NIV had lower GA, BW, and current weight and those who required IMV presented lower age and current weight and higher pCO_2 . In both groups, RR was higher in the failure group.

In order to determine possible variables that could predict success or failure in treatment with HFNC, a logistic regression model was performed (tables 3 and 4), including the variables that showed an association with failure or success (data from tables 1 and 2).

It was observed that the three variables BW, GA, and pre-connection RR were statistically significant in a simple logistic regression model: RR, GA, and BW but when analyzed in a multiple logistic regression model, it was observed that pre-connection RR and BW were statistically significant as a factor associated with failure. The area under the ROC curve for RR was 0.558 (95%CI 0.503-0.613) and the RR with the best sensitivity (53%) and specificity (55%) was 59 breaths per minute (figure 2).

There were no mechanical complications associated with the use of HFNC in this study. None of the included patients died.

Discussion

This study shows the results of the use of HFNC oxygen therapy in the treatment of hypoxemic respiratory failure in the largest cohort of children under 2 years old reported to date. The size of the sample and the inclusion of children with different types of ALRI are a contribution when interpreting the findings and could be extrapolated to clinical practice.

The findings show that HFNC oxygen therapy represents an effective noninvasive respiratory support modality in these children. Most children under 2 years old with bronchiolitis and viral pneumonia pro-

gressed favorably and had no complications associated with the technique.

It was observed that children with higher GA and BW had a higher success rate of HFNC. In contrast to what has been described in other studies, the absence of comorbidities or underlying diseases was not associated with the success of the technique^{14,17}.

The frequency of failure observed in this study was high (39%), higher than that reported in other series (6 and 19%)^{15,18,19}.

The failure rates reported in other studies are variable. This is probably determined by the definition of failure considered and the characteristics of the population studied¹⁷. Betters et al. and Vareesunthorn et al. reported a failure rate of 6% and 7%, respectively^{20,21}. Also, Kallappa et al. found an intubation rate of 24% in children with ALRI treated with HFNC²².

Several factors may be related to this finding. The criteria used to define failure are not homogeneous. In contrast to this study, in most of the published series, the need for respiratory support with NIV is not considered failure and is limited to IMV. Its inclusion as another criterion increases the failure rate. In addition, there is heterogeneity in the inclusion criteria used, since neonates, patients with chronic pulmonary

diseases, chromosomopathies, and those with a history of orotracheal intubation are frequently excluded. An additional factor that may influence the response to re-

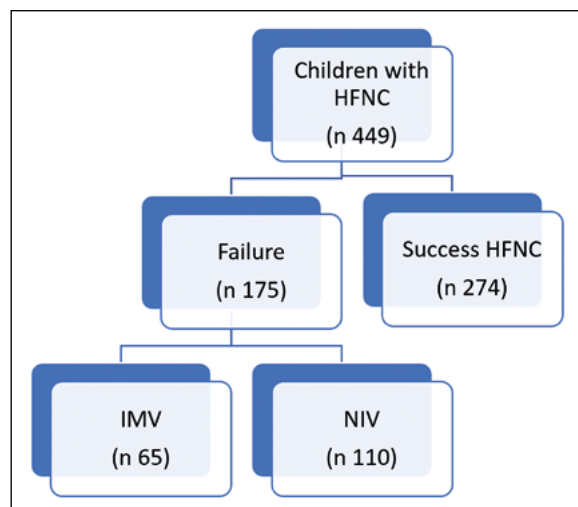


Figure 1. Flowchart for analysis by logistic regression in children under 2 years old admitted due to lower respiratory tract infections treated with high-flow nasal cannula (winter 2019). HFNC: high-flow nasal cannula. IMV: invasive mechanical ventilation. NIV: noninvasive ventilation.

Table 1. Predictors of failure with oxygen therapy by high-flow nasal cannula in children under 2 old with acute respiratory infections. Characteristics of children in whom high-flow nasal cannula was successful and failed (N = 449)

Variable	Success (n = 274)	Failure (n = 175)	p value
Male. n (%)	178 (65)	109 (62.3)	0.564
≤ 3 month. n (%)	74 (27.1)	59 (33.7)	0.129
3-6 months. n (%)	76 (27.8)	39 (22.3)	0.197
6-12 months. n (%)	73 (26.7)	51 (29.1)	0.563
> 12 months. n (%)	49 (18.3)	26 (14.9)	0.392
At least one previous episode. n (%)	107 (40.7)	61 (37.2)	0.473
Previous ICU admission. n (%)	47 (17.2)	33 (18.9)	0.645
Chest radiography complications. n (%) *	45 (18.1)	43 (26.1)	0.052
Gestational age weeks. media ± SD (range)	37.9 ± 2.3 (37.6-38.2)	37.1 ± 3.2 (36.6-37.6)	0.003
Actual age months. media ± SD (range)	6.6 ± 5.5 (5.9-7.2)	5.9 ± 5.0 (5.2-6.7)	0.203
Birth weight grams. media ± SD (range)	3069 ± 643 (2.989-3.151)	2931 ± 738 (2.815-3.047)	0.046
Actual weight grams. media ± SD (range)	7042 ± 2615 (6.715-7.369)	6944 ± 2711 (6.518-7.370)	0.716
pH media ± SD (range)	7.17 ± 1.1 (7.04-7.30)	7.24 ± 0.79 (7.12-7.36)	0.476
pCO ₂ mmHg. media ± SD (range)	42.7 ± 9.35 (41.6-43.9)	43.9 ± 10.7 (42.3-45.5)	0.226
HCO ₃ mmol/L. media ± SD (range)	21.7 ± 3.81 (21.3-22.2)	21.8 ± 3.93 (21.2-2.4)	0.909
BE mmol/L. media ± SD (range)	-3.41 ± 3.51 ((-0.38) - (-3))	-3.32 ± 3.37 ((-3.8) - (-2.8))	0.808
Respiratory rate respirations/minute. media ± SD (range)	56 ± 12 (54.4-57.2)	58 ± 12 (56.5-60.0)	0.031
White blood cells count/mm ³ . media ± SD (range)	12898 ± 5.142 (12.248 -13.547)	13117 ± 6.175 (12.176-14.058)	0.696

ICU: Intensive care unit. *Complications in chest radiography: inhomogeneous opacity, atelectasis, pneumothorax, cisuritis.

Table 2. Predictors of failure with oxygen therapy by high-flow nasal cannula in children under 2 years of age with acute respiratory infections. Características de los pacientes que fracasaron según el soporte respiratorio que recibieron

Variable	Success (n 274)	Failure with non invasive ventilation (n 110)	p value	Failure with invasive mechanical ventilation (n 65)	p value
Male. n (%)	178 (65)	64 (58)	0.213	45 (70)	0.51
At least one previous episode. n (%)	107 (39)	43 (39)	0.743	18 (28)	0.076
Previous ICU admission. n (%)	47 (17)	22 (20)	0.511	11 (17)	0.965
Chest radiography complications. n (%) *	45 (16)	26 (24)	0.127	17 (26)	0.099
Comorbidities. n (%)	73 (27)	36 (33)	0.663	9 (14)	0.046
RSV. n (%)	141 (67.1)	69 (32.9)	0.045	5 (8)	0.000
Adenovirus. n (%)	1 (0.4%)	1 (1%)	0.503	0	0.628
Influenza. n (%)	4 (1.5%)	2 (2%)	0.798	4 (6)	0.327
Gestational age weeks. media \pm SD	37.9 \pm 2.3	36.8 \pm 3.4	0.001	37.5 \pm 2.8	0.239
Actual age months. media \pm SD	6.6 \pm 5.5	7.3 \pm 5.3	0.267	3.7 \pm 3.5	0.000
Birth weight grams. media \pm SD	3070 \pm 642	2901 \pm 752	0.038	2977 \pm 718	0.328
Actual weight grams. media \pm SD	7712 \pm 2.742	7042 \pm 2.615	0.036	5723 \pm 21.2	0.000
pH media \pm SD	7.17 \pm 1.1	7.27 \pm 0.7	0.377	7.19 \pm 0.9	0.921
pCO ₂ mmHg. media \pm SD	42.7 \pm 9.3	42.4 \pm 10.1	0.746	46.5 \pm 11.4	0.006
HCO ₃ mmol/L. media \pm SD	27.8 \pm 3.8	21.7 \pm 4	0.825	22 \pm 3.7	0.595
BE mmol/L. media \pm SD	-3.41 \pm 3.5	-3.3 \pm 3.7	0.804	-3.4 \pm 2.8	0.916
Respiratory rate respirations/minute. media \pm SD	56 \pm 11.6	61 \pm 12.4	0.002	61 \pm 13.3	0.002

ICU: Intensive care unit. RSV: Respiratory syncytial virus. *Complications in chest radiography: inhomogeneous opacity. atelectasis. pneumothorax. cisuritis

Table 3. Simple and multiple logistic regression models for children under 2 years old who required invasive mechanical ventilation. admitted due to lower respiratory infections treated with high-flow nasal cannula

Simple logistic regression for invasive mechanical ventilation					
Variable	B	p value	OR	Confidence interval 95%	
				Upper limit	Lower limit
Age in months	0.115	0.054	1.12	0.998	1.260
Actual weight	0.000	0.811	1	1.000	1.000
pCO ₂	-0.021	0.192	0.979	0.948	1.011
Respiratory rate	-0.028	0.033	0.973	0.948	0.998
Multivariate analysis for invasive mechanical ventilation					
Variable	B	p value	OR	Confidence interval 95%	
				Upper limit	Lower limit
Weight at birth	0.000	0.795	1.00	0.99	1.00
Gestational age	0.098	0.343	1.10	0.90	1.35
Age in months	0.115	0.054	1.12	0.998	1.260
Actual weight	0.000	0.001	1	1.00	1.00
pCO ₂	0.023	0.264	1.024	0.98	1.07
Respiratory rate	0.034	0.037	1.035	1.00	1.07
RSV	1.063	0.14	2.896	1.24	6.78

Cox and Snell coefficient: 0.141. Nagelkerke coefficient: 0.167. RSV: Respiratory syncytial virus. B: Beta coefficient. OR: Odds Ratio

Table 4. Simple and multiple logistic regression models for children under 2 years old who required noninvasive ventilation. admitted for lower respiratory infections treated with high-flow nasal cannula

Simple logistic regression for noninvasive ventilation					
Variable	B	p value	OR	Confidence interval 95%	
				Upper limit	Lower limit
Gestational age	0.104	0.142	1.109	0.966	1.274
Actual weight	0.000	0.012	1	1.000	1.000
Birth weight	0.000	0.724	1.000	1.000	1.001
Respiratory rate	-0.006	0.626	0.994	0.972	1.018
Multivariate analysis for noninvasive ventilation					
Variable	B	p value	OR	Confidence interval 95%	
				Upper limit	Lower limit
Birth weight	0.00	0.795	1.00	0.99	1.00
Gestational age	-0.098	0.343	0.91	0.74	1.1
Age in months	-0.098	0.054	1.12	0.998	1.260
Actual weight	0.000	0.001	1.00	1.00	1.00
pCO ₂	-0.020	0.264	0.98	0.94	1.02
Respiratory rate	-0.034	0.037	0.97	0.94	0.99
RSV	-1.063	0.140	0.345	0.15	0.81

Cox and Snell coefficient: 0.141. Nagelkerke coefficient: 0.167. RSV: Respiratory syncytial virus. B: Beta coefficient. OR: Odds Ratio

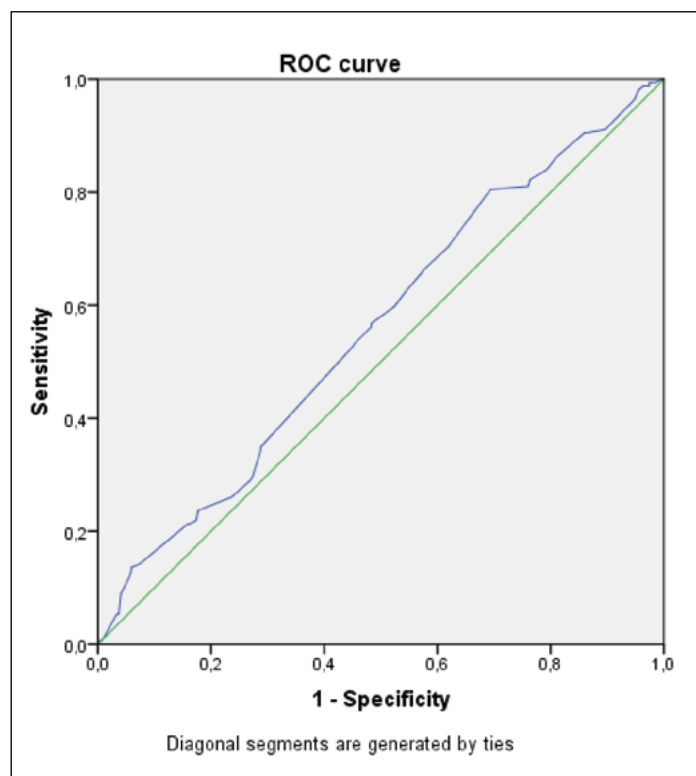


Figure 2. ROC curve for respiratory rate in children under 2 years old admitted due to lower respiratory infections treated with high-flow nasal cannula.

spiratory support technique, is the time from symptom onset, especially from the onset of respiratory distress. This factor was not considered in this analysis, nor was the time factor included in the assessment of the response to the technique. Some studies have found that a decrease of less than 20% in RR after 1 hour of connection to HFNC is an indicator of failure¹⁷.

Finally, it is important to consider that this is a descriptive study, in which the investigators did not participate in clinical decision-making, and without control of other variables that may influence therapeutic response, such as pharmacological treatment, nursing care, physiotherapy, etc. Further analysis of these factors is needed in future studies.

In the univariate analysis, the group of children in whom the technique failed presented lower GA and BW, and higher RR before connection to HFNC. These variables were associated with the need for respiratory support with NIV and IMV. The study by Abboud et al. mentioned that prematurity increases mortality and the risk of respiratory comorbidities, on the contrary, it did not show statistical evidence of increasing the need for escalating therapeutic measures²³. The identification of these characteristics is useful when assessing the response to HFNC and early identification of those patients in whom this modality of respiratory support is most likely to be of little benefit.

In the study by Sunkonkit K et al., the presence of congenital heart comorbidity, lobar infiltration on chest x-ray, the use of HFNC with maximum $\text{FiO}_2 > 0.6$, and a reduction in heart rate and respiratory rate of less than 20% after 1 hour of HFNC use were predictors of failure. However, this study included children from 1 month to 15 years of age, with other pathologies (pneumonia, congestive heart failure, post-extubation stridor)¹⁷. In this series, heart rate before connection was not analyzed, and radiological alterations (inhomogeneous opacity, atelectasis, pneumothorax, fissure sign) were analyzed globally and dichotomously and did not reach statistical significance. It is well known that the presence of pneumonia is a predictor of failure of this therapy, so it would be important to include these aspects in future research²⁴.

It is important to note that, in the overall analysis, no association was observed between the mean values of the parameters in the pre-connection blood gas analysis and the success or failure rate. However, in the analysis according to the type of respiratory support subsequently used, the children who required IMV had higher mean pCO_2 than those in whom HFNC therapy was successful. This is consistent with other publications, which identify pCO_2 as a factor associated with failure¹⁸.

In the simple logistic regression model, GA, BW, and pre-connection RR maintained statistical significance, which increases their association with the risk of HFNC failure. Despite this, the area under the ROC curve for RR showed little discriminatory capacity.

It is necessary to highlight the limitations of the study. One of them is the fact that the decision to connect to HFNC and to escalate respiratory support measures is subjective since it depends on clinical experience. Another consideration is that the statistical significance values in relation to the logistic regression analysis were close to 1 (no difference). Regardless of this, it should be noted that the variables selected are valuable since they are objective and available in routine practice. This study seeks to identify concrete tools to identify which patients have more chances of success or failure with this technique. From these results, it is not possible to make recommendations on the indication for HFNC in case of ALRI.

This study has some limitations when interpreting and extrapolating the results. First, it is a retrospective study, which presents the information and selection biases inherent to this type of design. Secondly, although this study was carried out in a national reference center, with a large sample size and representative of seasonal pathology, it is a single center, where the most vulnerable sector of the population is seen, mainly from the country's capital. Thirdly, in this type of study, the lack of control over key variables such as the indication, initial flow, discontinuation of the HFNC,

and concomitant medical treatment may influence the results. Finally, the lack of analysis of some variables such as duration of respiratory distress pre-connection, heart rate before connection, and response time to HFNC, prevents a better understanding of the factors associated with success or failure.

In conclusion, HFNC represents a useful and safe noninvasive respiratory support measure for the treatment of hypoxemic respiratory failure in children under 2 years old with ALRI. However, children with lower BW and those with higher pre-connection RR should be carefully monitored because of the increased risk of HFNC failure. Special attention should be paid to the pCO_2 level since mean values higher than 45 mmHg are also associated with failure and need for IMV. Future studies, with prospective designs and the inclusion in the analysis of other variables such as heart rate and response time, could be useful to establish scores or predictive models that contribute to optimizing treatment.

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.

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References

- Pinchak María Catalina, Hackembruch Cecilia, Algorta Gabriela, et al. Estrategia de atención hospitalaria de niños con infección respiratoria aguda baja. *Arch Pediatr Urug.* [Internet]. 2007 Mar [citado 2023 Feb 24];78(1):15-22. Disponible en: http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492007000100004&lng=es..
- De Olivera N, Giachetto G, Haller A, et al. Infecciones respiratorias agudas bajas graves en niños menores de 6 meses hospitalizados. Análisis de factores de riesgo de gravedad. *Anales de la Facultad de Medicina*;6(1):109-29. Epub 01 de junio de 2019.<https://doi.org/10.25184/anfamed2019v6n1a4>
- Machado K, Notejane M, Mello M, et al. Infecciones respiratorias agudas bajas en niños menores de 2 años. Hospitalizaciones durante el invierno del año 2014. *An la Fac Med* [Internet]. 2018 Jun 3 [cited 2022 Nov 18];5(1):82-103. Disponible en: http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S2301-12542018000100082&lng=es&nrm=iso&tlng=es
- Noli P, Geymonat M, Muñoz J, et al. Infecciones respiratorias agudas bajas de causa viral en niños hospitalizados en el Centro Hospitalario Pereira Rossell. Características clínicas y terapéuticas. *Arch Pediatr Urug.* [Internet]. 2012 [citado 2023 Feb 24];83(4):250-6. Disponible en: http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492012000400002&lng=es.
- Bae SH, Han M, Kim C, et al. High-flow nasal cannula oxygen therapy can be effective for patients in acute hypoxemic respiratory failure with hypercapnia: A retrospective, propensity score-matched cohort study. *J Korean Med Sci.* 2020;35(10).doi: 10.3346/jkms.2020.35.e67. PMID: 32174065
- Notejane M, Casuriaga A, Vomero A, et al. Aplicación de oxigenoterapia por canula nasal de alto flujo versus oxigenación por bajo flujos. *Arch Pediatr Urug.* [Internet]. 2018;89(4):257-63. Disponible en: <https://doi.org/10.31134/ap.89.4.5>
- Bermúdez Barrezueta L, García Carbonell N, López Montes J, et al. [High flow nasal cannula oxygen therapy in the treatment of acute bronchiolitis in neonates]. *An Pediatr (Barc).* [Internet]. 2017 Jan 1 [cited 2022 Nov 18];86(1):37-44. Disponible en: <https://pubmed.ncbi.nlm.nih.gov/27068070/>
- Franklin D, Babl FE, Schlapbach LJ, et al. A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis. *N Engl J Med.* 2018;378(12):1121-31. doi: 10.1056/NEJMoa1714855.
- Diana-Marcela Barahona Ortega, Lydiana-Ávila De Benedictis AA, Vásquez. Original Uso de cánula de alto flujo en niños menores de 24 meses en salones de pediatría. *Acta méd Costarric.* [Internet]. 2018 Sep [citado 2023 Feb 24];60(3):127-31. Available from: http://www.scielo.sa.cr/scielo.php?script=sci_arttext&pid=S0001-60022018000300127&lng=en.
- Morosini F, Tórtora S, Amarillo P, et al. Cánula nasal de alto flujo en niños con crisis asmática en un servicio de urgencias pediátrico. *Arch. Pediatr. Urug.* [Internet]. 2017 jun [citado 2023 Feb 24];88(3):142-8. Disponible en: http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492017000300142&lng=es.
- Kepreotes E, Whitehead B, Attia J, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *Lancet.* [Internet]. 2017;389(10072):930-9. Disponible en: [http://dx.doi.org/10.1016/S0140-6736\(17\)30061-2](http://dx.doi.org/10.1016/S0140-6736(17)30061-2)
- Wing R, James C, Maranda LS, et al. 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. doi: 10.1097/PEC.0b013e31827122a9.
- Ferlini R, Pinheiro FO, Andreollo C, et al. Characteristics and progression of children with acute viral bronchiolitis subjected to mechanical ventilation. *Rev Bras Ter Intensiva.* 2016;28(1):55-61. doi: 10.5935/0103-507X.20160003.
- Guillot C, Le Reun C, Behal H, et al. First-line treatment using high-flow nasal cannula for children with severe bronchiolitis: Applicability and risk factors for failure. *Arch Pediatr.* [Internet]. 2018;25(3):213-8. Disponible en: <https://doi.org/10.1016/j.arcped.2018.01.003>
- 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). Disponible en: <http://dx.doi.org/10.1186/s13049-016-0278-4>
- Ramos-Fernández JM, Moreno-Pérez D, Gutiérrez-Bedmar M, et al. Predicción de la evolución de la bronquiolitis por virus respiratorio sincitial en lactantes menores de 6 meses. *Rev. Esp. Salud Publica.* [Internet]. 2017 [citado 2023 Feb 24];91:201701006. Disponible en: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1135-57272017000100401&lng=es. Epub 19-Ene-2017.
- Sunkonkit K, Kungsuwan S, Seetaboot S, et al. Factors associated with failure of using high flow nasal cannula in children. *Clin Respir J.* 2022;16(11):732-9. doi: 10.1111/crj.13533. Epub 2022 Aug 29.
- Er A, Çağlar A, Akgül F, et al. Early predictors of unresponsiveness to high-flow nasal cannula therapy in a pediatric emergency department. *Pediatr Pulmonol.* 2018;53(6):809-15. doi: 10.1002/ppul.23981.
- Ruiz VR, Mayer GF, Roux NG, et al. Use of high-flow nasal cannula in the emergency department. *European Respiratory Journal.* 2016 48:PA357; doi: 10.1183/13993003.congress-2016
- Betters KA, Gillespie SE, Miller J, et al. High flow nasal cannula use outside of the ICU; factors associated with failure. *Pediatr Pulmonol.* 2017;52(6):806-12. doi: 10.1002/ppul.23626.
- Vareesunthorn I, Preutthipan A. Modified high-flow nasal cannula in young children with pneumonia: A 3-year retrospective study. *Pediatr Respir Crit Care Med.* 2018;2(3):45. doi: 10.4103/prcm.prcm_2_18
- Kallappa C, Hufton M, Millen G, et al. Use of high flow nasal cannula oxygen (HFNCO) in infants with bronchiolitis on a paediatric ward: A 3-year experience. *Arch Dis Child.* 2014;99(8):790-1. doi: 10.1136/archdischild-2014-306637.
- Abboud PA, Roth PJ, Skiles CL, et al. Predictors of failure in infants with viral bronchiolitis treated with high-flow, high-humidity nasal cannula therapy. *Pediatr Crit Care Med.* 2012;13(6):e343-9. doi: 10.1097/PCC.0b013e31825b546f.
- Celik NB, Tanyildiz M, Yetimakman F, et al. Comparison of high flow oxygen therapy versus noninvasive mechanical ventilation for successful weaning from invasive ventilation in children: An observational study. *Medicine (Baltimore)* [Internet]. 2022 Sep 9 [citado 2022 Nov 18];101(39):e30889. Disponible en: <https://pubmed.ncbi.nlm.nih.gov/3524993/>