



## ORIGINAL

## Factors associated to high-flow nasal cannula treatment failure in pediatric patients with respiratory failure in two pediatric intensive care units at high altitude<sup>☆</sup>



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### KEYWORDS

Oxygen inhalation therapy;  
Non invasive ventilation;  
Intensive Care Unit Pediatric;  
Respiratory failure;  
Altitude

### Abstract

**Introduction:** Acute respiratory failure is the leading cause of hospitalization in pediatrics. High-flow nasal cannulas (HFNCs) offer a new alternative, but the evidence and indications are still debated. The performance of HFNCs at high altitude has not been described to date.

**Objective:** To describe the use of HFNCs in pediatric patients admitted with respiratory failure and explore the factors associated with treatment failure.

**Methodology:** A prospective cohort study was carried out in patients between 1 month and 18 years of age managed with HFNCs. The demographic and treatment response data were recorded at baseline and after 1, 6 and 24 h. The number of failures was determined, as well as the length of stay, complications and mortality. Patients with treatment failure were compared with the rest.

**Results:** A total of 539 patients were enrolled. Infants (70.9%) of male sex (58.4%) and airway diseases such as asthma and bronchiolitis (61.2%) were more frequent. There were 53 failures (9.8%), with 21 occurring in the first 24 h. The median length of stay was 4 days (IQR 4); there were 5 deaths (0.9%) and 13 adverse events (epistaxis) (2.2%). Improvement was observed in vital signs and severity over time, with differences in the group that failed, but without interactions. The final logistic model established an independent relationship of failure between the hospital (OR 2.78, 95%CI 1.48–5.21) and the initial respiratory rate (OR 1.56, 95%CI 1.21–2.01).

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*Conclusions:* HFNCs afford good clinical response, with few complications and a low failure rate. The differences found between institutions suggest a subjective relationship in the decision of therapy failure.

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## PALABRAS CLAVE

Terapia por inhalación de oxígeno;  
Ventilación no invasiva;  
Unidades de Cuidados Intensivos  
Pediátricos;  
Insuficiencia respiratoria;  
Altitud

## Factores asociados al fracaso de la terapia con cánulas nasales de alto flujo en pacientes pediátricos con insuficiencia respiratoria en dos unidades de cuidados críticos pediátricos a gran altitud

### Resumen

*Introducción:* El fallo respiratorio agudo es la principal causa de hospitalización en pediatría. Las cánulas nasales de alto flujo (CNAF) ofrecen una nueva alternativa, pero sigue existiendo debate en torno a la evidencia e indicaciones. No se ha descrito su comportamiento en gran altitud.

*Objetivo:* Describir el uso de CNAF en pacientes pediátricos que ingresan con insuficiencia respiratoria y explorar los factores asociados al fracaso de la terapia.

*Metodología:* Estudio de cohortes prospectivo. Pacientes entre un mes y 18 años manejados con CNAF. Se describieron datos demográficos y se evaluó la respuesta al inicio, 1.<sup>a</sup>, 6.<sup>a</sup> y 24.<sup>a</sup> horas. Se determinó el número de fracasos, así como estancia, complicaciones y mortalidad. Se compararon los pacientes con fracaso al tratamiento.

*Resultados:* Ingresaron 539 pacientes. Fueron más frecuentes los lactantes (70,9%) de sexo masculino (58,4%) con afecciones respiratorias como asma y bronquiolitis (61,2%). Se presentaron 53 fracasos (9,8%), 21 en las primeras 24 horas. La mediana de estancia fue de 4 días (RIQ 4), hubo 5 éxitos (0,9%) y 13 eventos adversos –epistaxis– (2,2%). Se observó mejoría de signos vitales y gravedad en el tiempo con diferencias en el grupo que fracasó, pero sin interacciones. El modelo logístico final estimó una relación independiente del fracaso, entre el hospital (OR 2,78; IC95% 1,48-5,21) y la frecuencia respiratoria inicial (OR 1,56; IC95% 1,21-2,01).

*Conclusión:* La CNAF es un sistema con buena respuesta clínica, pocas complicaciones y una baja tasa de fracasos. Las diferencias entre las instituciones sugieren una relación subjetiva de la decisión del fracaso.

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## Introduction

Respiratory conditions are the most common cause for consultation in the routine pediatric practice, and are responsible for the high rates of hospitalization and mortality reported, especially in developing countries.<sup>1</sup> The statistics from the World Health Organization (WHO) show that in 2016 the leading cause of death in children under 5 were respiratory infections.<sup>2</sup> Actually, these are cause for admission in nearly 70% of the causes for admission to the pediatric intensive care unit (PICU).<sup>3</sup> Back in 2027, Colombia reported 11286 PICU admissions due to respiratory infections in children under 5, which amounts to 54.5% of all PICU admissions reported regardless of the age group.<sup>4</sup>

The management of these patients consists of oxygen therapy with or without ventilation assistance (invasive or non invasive).<sup>3</sup> This is achieved using different techniques and interfaces based on their different requirements and risk-benefit ratio.<sup>1,3</sup> Since the beginning of the present century, the use of machines capable of providing condi-

tioning (both heated and fully humidified) gas mixtures at high-flow oxygen through nasal cannulas has become very popular.<sup>5,6</sup> The different hypotheses based on which high-flow nasal cannulas (HFNC) generate ventilation assistance have already been discussed by other authors.<sup>7,8</sup>

Although studies have not come up with a definitive definition yet on the role that this system plays, some pediatric surveys already show the high level of acceptance in the routine clinical practice<sup>9,10</sup> despite the low evidence established regarding its use.<sup>11,12</sup> There seems to be a clinical perception of effectiveness and easiness of use<sup>13</sup>; also, there has been a change of paradigm away from the use of invasive systems to the use of non-invasive ones, thus reducing the impact of conditions like bronchiolitis.<sup>14,15</sup> Some studies back up its effectiveness (clinical response to therapy) among pediatric patients for early ventilation assistance,<sup>16–19</sup> post-extubation,<sup>20</sup> and for the management of different types of conditions that present with ventilatory failure.<sup>18,21,22</sup> However, when compared to other non-invasive ventilatory support devices, its effectiveness is not that high.<sup>11,16,21</sup>

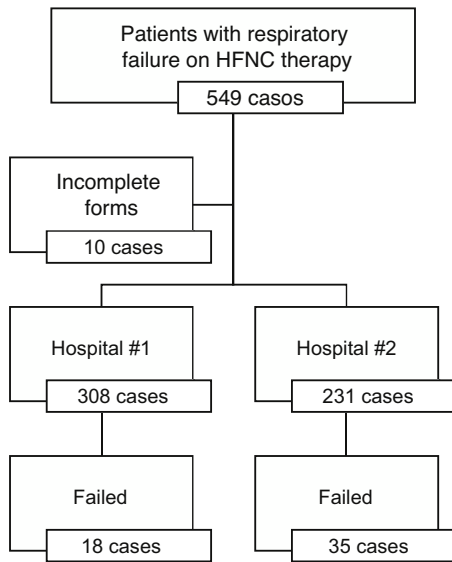


Figure 1 Flowchart of the study cases.

Bogotá, the capital of Colombia, is 2600 m above sea level (ASL), which has important implications to the oxygen pressure available. In altitudes over 1500 m ASL, carotid body stimulation provides higher respiratory rates and tidal volume to compensate for the atmospheric inspired oxygen pressure fall.<sup>23</sup> These changes complicate diagnosis,<sup>24</sup> monitorization thresholds,<sup>25</sup> and the response to the management of patients at high altitudes.<sup>26</sup> Our group has recently published the experience on the use of HFNC in newborn babies and found high fractions of oxygen being used and few signs of severity due to work of breathing.<sup>27</sup> Descriptions of use in middle-income countries with several cities located at moderate and high altitudes have not been reported yet.

Some studies describe factors associated with this therapy failure based on physiological variables upon admission,<sup>28–30</sup> response to these variables,<sup>18,30</sup> severity scales,<sup>28,31</sup> and disease factors.<sup>29</sup> There is even a subjective component in the decisions made based on the type of center.<sup>18</sup> Up to this moment, no study has analyzed these factors in cities at high altitude.

This study will describe the use of HFNC in pediatric patients admitted to pediatric critical care units due to respiratory failure and explore the predictive factors of this therapy failure in 2 units of Bogotá between 2013 and 2016.

## Methodology

Prospective, observational study of patients between 1 month and 18 years of age admitted to the PICUs of the *Sociedad de Cirugía de Bogotá Hospital de San José* and *Clínica Infantil Colsubsidio* Intermediate Care Unit (IMCU), both located in Bogotá, Colombia. These units are exclusively pediatric are located at teaching general hospitals and have 8/13 beds with an average 300/1000 admissions-year. The ratios of health professionals per patient are: 1 nurse for every 6/8 patients, 1 patient care technician for every 3 patients, and 1 respiratory therapist for every unit. Everybody is coordinated by a pediatric intensivist

during daytime and pediatricians on call at night and on national holidays. These units receive medical and surgical populations including cancer patients in one of the units. Also, they assist they population of Bogotá, Colombia. However, these units are not capable of performing cardiovascular surgery, extracorporeal circulation or transplant therapies. Both units use specifically designed high-flow therapy machines bought between 2012 and 2015 with certified and disposable materials. These machines can provide high-flow oxygen rates (Optiflow™; €40 to €70), respiratory circuits (€50 to €150) with integrated heating (50–150 €), and servo-assisted humidifier (F&P 850™ or myAIRVO™ 2; €2500 to €3000). Both units include other non-invasive ventilation systems in conventional machines and interfaces for different ages although with limited variability. From November 2013 through December 2016, all patients with clinical signs of respiratory failure according to the treating physician who prescribed ventilatory support through HFNC were studied. The study only included the first moment of support with the HFNC since some patients required more uses during their hospital stay. Patients referred to a different center 24 h prior to the administration of HFNC or those whose forms had not been properly filled in by their treating physician at the beginning of the follow-up were excluded. Data from each patient was collected at the beginning of therapy and 1, 6, and 24 h into therapy including: demographic parameters like age, weight, and sex, respiratory diagnosis defined by its main pathophysiological mechanism (small airway like bronchiolitis and asthma, occupational lung disease like pneumonia or edema, upper airway like obstructive laryngitis, and neuromuscular conditions like brain related motor failure), and the radiological pattern at admission as described by the treating physician and, when in doubt, by assistant radiologists. Physiological variables like respiratory rate (RR), heart rate (HR), hemoglobin saturation levels measured by pulse-oximetry (SpO<sub>2</sub>), fraction of inspired oxygen (FiO<sub>2</sub>) and its ratio (SpO<sub>2</sub>/FiO<sub>2</sub>), and flow rate administered by kilogram of weight were measured. The degree of severity of the clinical signs was measured using the variables of the Modified Wood's clinical asthma severity scale (M-WCAS) and the correlation between the SpO<sub>2</sub>/FiO<sub>2</sub> ratio, and HR or the Respiratory rate-Oxygenation (ROX) index.<sup>32</sup> Also, the SpO<sub>2</sub>/FiO<sub>2</sub> ratio was grouped in ranges of 100, the M-WCAS scale in categories of severity while both the HR and the RR were categorized as abnormal if outside the 10th and 90th percentiles of age using the data published by Fleming et al.<sup>33</sup> As the well-being measure no scales were used. Instead, the difficulties feeding and the possibility of crying or taking according to age were used as indirect surrogate markers. The continuous variables were expressed as means and standard deviations or means and interquartile ranges (IQR) based on their distribution. The categorical variables were expressed as absolute values and percentages. The changes seen in the variables over time were compared by analyzing repeated measures with the mixed model technique to determine the variance of data. *P* values <.05 were considered statistically significant. Mortality, the PICU stay, and the frequency of occurrence of all adverse events found were measured as well. The «failed case» definition was used to define cases where the HFNC was withdrawn and invasive mechanical ventilation was started; cases were divided into early (first

24h of use) and late cases (>24h of use). A bivariate comparison was made based on the type of failure reported. Then, a multivariate analysis was conducted using a logistics regression model with the relevant or significant variables seen in the bivariate analysis. All data were verified and tabulated in an Excel spreadsheet and processed using the statistical software package Stata 13. Data are presented in tables for better understanding. This study was presented and approved by every center research ethics committees (*Sociedad de Cirugía de Bogotá Hospital de San José* Human Research Ethics Committee [IRB#00011307], September 16, 2013; *Clínica Infantil Colsubsidio* Human Research Ethics Committee, April 4, 2017 [CEI-36-15]). Both authorized an exception to the informed consent since there was no risk involved in the study.

## Results

A total of 549 patients were hospitalized. Ten of these patients were excluded from the study since their data had not been properly collected. A total of 308 patients were hospitalized in hospital #1 (57.1%) and 231 in hospital #2 (42.9%) (Fig. 1).

The overall clinical and demographic characteristics of the admissions are shown in Table 1. Younger newborn babies were more prevalent compared to preschoolers and schoolers. The most prevalent diagnosis was small airway disease followed by occupational lung disease. The radiological pattern seen more often was the presence of opacities followed by signs of lung entrapment. The therapy was more often used for primary support rather than as a post-extubation system. The average flow rate was  $1.3 \pm 0.63$  mL/kg/min with an average FiO<sub>2</sub> ratio of  $0.68 \pm 0.19$ .

## 24-h follow-up

Table 2 and Fig. 2 show the evolution of variables at the follow-up. Within the first hour 2 cases of failed therapy were reported, another 12 cases 6 h later and another 7 within the next 24 h. The cannula was withdrawn due to epistaxis (11 cases) or patient improvement (defined as a positive change in his general state of health) in 16 cases after 6 h and in 48 cases at 24 h. In total, 84.23% of the patients were still using the system at the 24-h follow-up. Both the heart rate and the respiratory rate improved significantly with the passing of the hours and the SpO<sub>2</sub>/FiO<sub>2</sub> ratio was abnormal in most cases with a tendency toward

**Table 1** Demographic and diagnostic description and outcomes of patients on high-flow nasal cannula therapy.

Variable		Overall	
		n	%
Center	Hospital #1	308	57.1
	Hospital #2	231	42.9
Sex	Masculine	315	58.4
	Feminine	224	41.6
Age	Younger newborn baby	300	55.6
	Older newborn baby	82	15.2
	Preschooler	103	19.1
	Schooler	44	8.2
Disease pattern	Teen	10	1.9
	Small airway	330	61.2
	Lung occupation	149	27.6
	Upper airway	30	5.6
Radiological pattern (n = 481)	Neuromuscular	9	1.7
	Non-pulmonary	21	3.9
	Opacity	266	55.3
	Entrapment	114	23.7
Post-extubation cannula	Mixed	68	14.1
	Normal	33	6.9
Failures	Overall	47	8.6
	Early	53	9.8
	Late	21	3.9
Deaths	Late	32	5.9
	Epistaxis	5	0.9
Adverse events	Other	12	2.2
		0	0.0

%; percentage; n: subjects studied; preschooler: 2 to 5 years; older newborn baby: 13 to 24 months; schooler: 6 to 12 years; teen: 13 to 18 years; younger newborn baby: <12 months.

**Table 2** Well-being follow-up within the first 24 h of follow-up in patients on high-flow nasal cannula therapy.

Variable	Beginning			1 h			6 h			24 h			P*
	N	n	%	N	n	%	N	n	%	N	n	%	
<i>Speaks (cries) with the system</i>	538	525	97.6	530	508	95.8	504	486	96.4	443	419	94.6	.014
<i>Mouth feeding (vs. feeding probe)</i>	521	424	81.4	514	388	75.5	498	370	74.3	448	322	71.9	.000
<i>Appearance**</i>													
Good	531	374	70.4	520	374	71.9	484	337	69.6	430	275	64.0	.008
Acceptable		95	17.9		115	22.1		122	25.2		135	31.4	
Poor		62	11.7		31	6.0		25	5.2		20	4.7	

N: subjects studied; n: subjects affected; %: percentage of studied patients.

\* Test statistics comparing the variable to time [continuous] using linear mixed models with random effects (individual). P values < .005 were considered statistically significant.

\*\* Subjective perception of the healthcare personnel.

improvement (Fig. 2). A study was conducted to look for indicators of poor FiO<sub>2</sub> titration. It found that in 33.3% of the data, the SpO<sub>2</sub> was >97%; still, the SpO<sub>2</sub>/FiO<sub>2</sub> ratio analyzed in these groups was low (SpO<sub>2</sub> ≤97%: median 138, IQR 66 vs. SpO<sub>2</sub> >97%: median 152, IQR 64). After studying respiratory severity using the M-WCAS scale some scores, mostly mild and moderate, improved statistically with the passing of the hours, an improvement remained with the use of HFNC. The ROX index started with an average score of 3.5 ± 1.5 and improved up to 4.1 ± 1.9 with a statistically significant difference; however, the cut-off value of 4.8 (reported in the medical literature for adults) was seen in 9.43% of all failed therapies and in 16.2% of the remaining ones. Within the well-being measures, it was found that 95% of the patients can speak or cry with the active system. Significant feeding differences occurred in a variable range (20% to 30%) that were eventually treated with a feeding probe.

### Outcomes

A total of 53 failed cases were presented (9.8%), 21 of which (3.9%) failed before 24 h (early) and the remaining 32 (5.9%) after this timeframe. The average hospital stay was 4 days (IQR 4). A total of 5 deaths were reported, 1 due to early failure, 2 due to late failure, and 2 without failure with limitation of therapeutic effort due to the baseline condition. A total of 12 epistaxes were reported as adverse events that required specific treatment (5 within the first hour, 4 after 6 h, and 3 after 24 h) and the withdrawal of therapy in 11 cases. These events happened in 1 of them (0.33%) in a young newborn baby, 7 (8.54%) in older newborn babies, 3 (2.91%) in preschoolers, and 1 (2.27%) in a schooler.

### Comparison by type of failed therapy reported

When the types of failed therapy and the variables reported were compared, overall differences per hospital, younger age of the patients, higher heart and respiratory rates, and lower ROX index scores were found (Table 3). Regarding these variables, it was studied whether this difference occurred with early or late failures. We saw that, except for the ROX index, the remaining factors were more relevant in late compared to early failed therapies. The multivari-

ate comparison only confirmed the hospital effect and the respiratory rate for overall and late failures (Table 4).

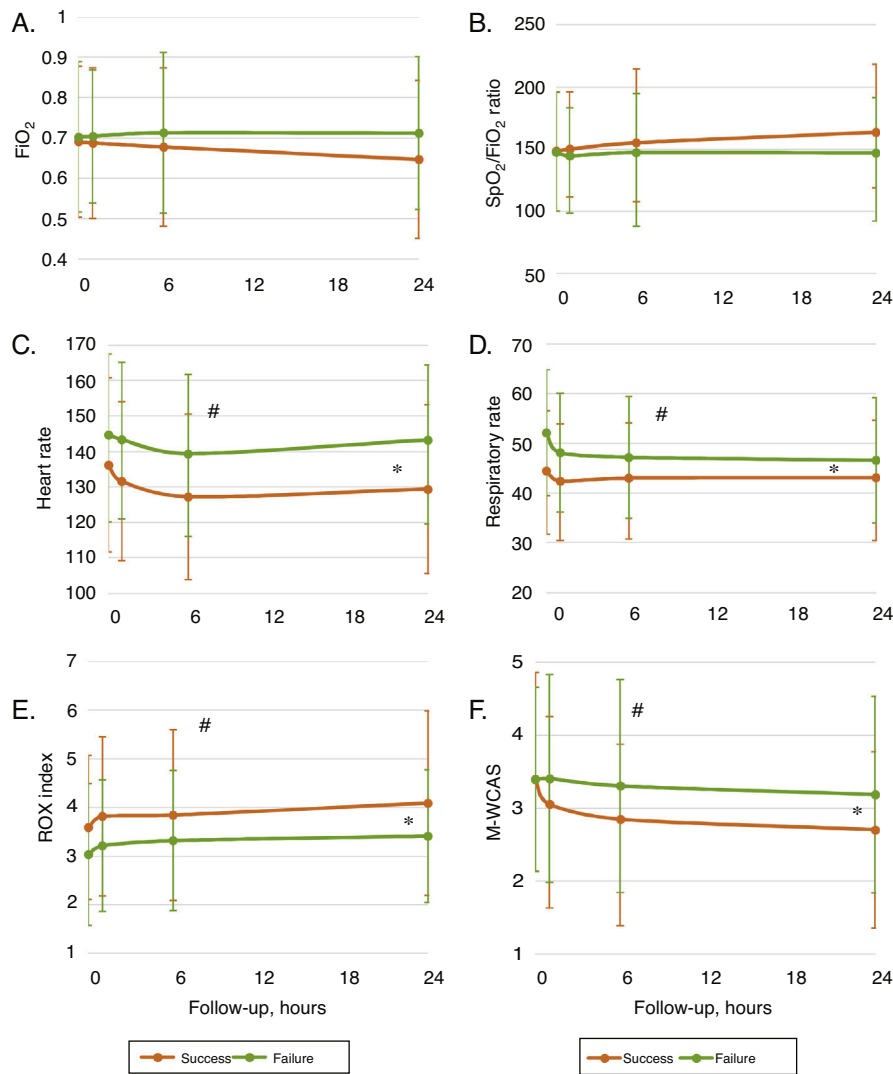
### Discussion

This study shows the management of a cohort of patients from 2 centers located at high altitudes. It found greatly compromised oxygenation and lower ventilation severity according to the M-WCAS scale with clinical variables response and a low percentage of failure within the first 24 h, although with great diversity of patients and outcomes in the study centers.

The demographic make-up by sex, age, and disease pattern is similar to that reported by other cohorts that have been using the HFNC system. For example, back in 2017, Coletti et al. published a cohort of patients monitored in a polyvalent pediatric unit. They confirmed an incidence rate of cases of 44% among females, newborn babies in 49% of the cases, being small airway disease the most prevalent conditions of all (65%).<sup>34</sup> However, there is still great variability of use depending on ages and disease patterns, which is consistent with the differences found between the two centers studied and other cohorts reported in the medical literature that also change over time.<sup>35,36</sup>

The study patients showed much more serious oxygenation disorders compared to the ones reported by other groups: Oto et al. reported a mean FiO<sub>2</sub> of 0.39 ± 0.08,<sup>26</sup> the TRAMONTANE clinical trial on bronchiolitis reported mean values of 0.31 ± 0.1,<sup>37</sup> while Pilar et al. reported mean FiO<sub>2</sub> values of 0.6% and a 0.4% IQR in patients with asthma. Also, Er et al. found early SpO<sub>2</sub>/FiO<sub>2</sub> ratios of 160 ± 57, and failed therapies with SpO<sub>2</sub>/FiO<sub>2</sub> ratios of 195.

These patients' work of breathing was less serious compared to the one reported by Oto et al.<sup>38</sup> based on the M-WCAS scale (8.8 ± 2.5) or by Pilar<sup>21</sup> regarding asthma (median 8; IQR 2), which was consistent with significant respiratory compromise, as reported by Er et al. that described mRAID (modified respiratory distress assessment instrument) severity scores of 9.3 ± 1.4 and also severe respiratory compromise.<sup>22</sup> Other studies like the TRAMONTANE trial<sup>37</sup> on bronchiolitis (M-WCAS score of 4 ± 1) report values that are similar to this study, rather suggesting a different indication (oxygenation due to high altitude) or due to over-use



**Figure 2** Follow-up of patients on high-flow nasal cannula therapy in relation to time. Comparison in relation to failed therapy cases. Chart showing the average behavior and variance of every physiological variable by subgroups of overall success and failure within the first 24h of follow-up. Comparison between variable and time, failure, and time-failure interaction using linear mixed models with random effects (individual). *P* values < .005 were considered statistically significant. Failure differences are shown with an asterisk [\*]; time differences are shown with the pound sign [#]; interacion differences are shown with the dollar sign [\$]. (A) Inspired oxygen fraction ( $FiO_2$ ) ratio. (B) Oxygen saturation through pulse-oxymetry ( $SpO_2$ ) and  $FiO_2$  ratio ( $SpO_2/FiO_2$  ratio). (C) Heart rate (HR) ratio. (D) Respiratory rate (RR) ratio. (E) ROX index ratio (correlation between the  $SpO_2/FiO_2$  ratio and the HR). (F) M-WCAS, Modified Wood’s clinical asthma severity scale.

(therapy was withdrawn in 16% of our patients before the 24h-mark), which may be adding extra-costs for the health-care system (between €100 and €250 in consumables per patient), worries already expressed by other authors.<sup>39–41</sup>

These differences regarding oxygen and ventilation changes can partially explain the low frequency of failed therapies found in this study conducted at high altitudes (2640 m ASL) compared to the variable failed therapy rate reported [40% (21) the highest one and 15% to 20% the lowest one<sup>22,38</sup>] in studies conducted in countries located at low altitudes that used similar or lower  $FiO_2$ , but higher severity scores. We believe that in children who live at sea level hypoxia is indicative of a major respiratory compromise. However, at high altitudes it is rather an indication of a low

inspiratory oxygen content available. This is why they look more hypoxemic, but with lower severity scores in the work of breathing.

The clinical response seen in the vital signs is similar to the one reported by other groups.<sup>22,38</sup> However, the oxygen baseline parameters are much lower compared to other series studied at lower altitudes, suggestive that the cut-off values for abnormality for patients at high altitudes in terms of risk or response to the use of HFNC should be different. This should be studied and confirmed comparatively with centers located at different altitudes.

The ROX index was assessed to test its predictive capabilities regarding clinical response. It showed that the cut-off values of the original study<sup>32</sup> were not good for this cohort

**Table 3** Bivariate analysis comparing the study variables to the different types of therapy failure in patients on high-flow nasal cannula therapy.

Variable		Overall failure			Early failure			Late failure		
		OR	95%CI		OR	95%CI		OR	95%CI	
Center	Hospital #1	Ref								
	Hospital #2	2.88	1.58	5.22	1.22	0.51	2.93	5.22	2.22	12.29
Sex	Feminine	Ref								
	Masculine	1.09	0.61	1.95						
Disease pattern	Small airway	Ref								
	Lung occupation	0.93	0.48	1.80						
Radiological pattern	Normal	Ref								
	Opacity	1.32	0.38	4.58						
	Entrapment	0.75	0.19	3.02						
	Mixed	1.53	0.38	6.05						
Age, years		0.74	0.59	0.92	0.79	0.59	1.07	0.71	0.52	0.96
FiO <sub>2</sub>		1.41	0.30	6.69						
Flow mL/min		1.00	0.93	1.07						
HR/10		1.18	1.04	1.34	1.18	0.97	1.43	1.16	0.99	1.36
RR/10		2.13	1.13	4.02	1.75	0.80	3.82	1.99	1.03	3.87
SpO <sub>2</sub> /FiO <sub>2</sub> ratio		1.00	0.99	1.01						
ROX index		0.72	0.56	0.93	0.63	0.41	0.96	0.80	0.60	1.07
M-WCAS		1.00	0.80	1.24						

Bivariate analysis using the logistics regression model, only by categories if the overall failure rate was statistically significant.

95%CI, 95% confidence interval; FiO<sub>2</sub>, inspired oxygen fraction; HR/10, heart rate grouped by 10 beats; M-WCAS, Modified Wood's clinical asthma severity scale; OR, odds ratio; ref., reference category; ROX index, correlation index between the SpO<sub>2</sub>/FiO<sub>2</sub> ratio and the RR; RR/10, respiratory rate grouped by 10 breathings; SpO<sub>2</sub>/FiO<sub>2</sub> ratio, correlation between pulse-oximetry and FiO<sub>2</sub>.

**Table 4** Multivariate model comparing significant variables based on the different types of therapy failure in patients on high-flow nasal cannula therapy.

Variable	Overall failure			Early failure			Late failure		
	OR	95%CI		OR	95%CI		OR	95%CI	
Hospital #2	2.82	1.50	5.29	1.10	0.45	2.72	5.58	2.25	13.88
Age, years	0.79	0.62	1.00	0.81	0.59	1.10	0.77	0.55	1.09
HR/10	0.99	0.86	1.15	1.08	0.87	1.33	0.94	0.78	1.12
RR/10	1.42	1.03	1.95	0.95	0.59	1.55	1.78	1.20	2.64
ROX index	0.87	0.64	1.17	0.63	0.37	1.09	1.03	0.73	1.45

Multivariate logistics regression analysis with statistically significant variables in the bivariate analysis.

95%CI, 95% confidence interval; HR/10, heart rate grouped by 10 beats; OR, odds ratio; ROX index, correlation index between the SpO<sub>2</sub>/FiO<sub>2</sub> ratio and the RR; RR/10, respiratory rate grouped by 10 breathings; SpO<sub>2</sub>/FiO<sub>2</sub>, correlation between pulse-oximetry and FiO<sub>2</sub>.

because here we are dealing with a pediatric population with higher respiratory rates. Also, because this cohort lives at high altitudes where the critically ill patients' SpO<sub>2</sub>/FiO<sub>2</sub> ratios tend to be much lower. However, values change parallel to the clinical response, which is why additional studies should be conducted to validate these cut-off values in pediatric cohorts living at high altitudes.

Regarding the flow rate used for support purposes, it is consistent with what has been reported by other groups (between 1 mL/kg/min and 2 mL/kg/min). Recently, at least in newborn babies, it is clear what flow rate should be used according to two different studies: one physiological study<sup>42</sup> that has been analyzing responses in the work of breathing of children <3. This study found that flow rates between 1.5 mL/kg/min and 2 mL/kg/min produce the best effect on the work of breathing as determined by the pressure-rate product (PRP). And another randomized clinical trial that showed no differences in the group that used flow rates at 3 mL/kg/min vs. 2 mL/kg/min in patients with bronchiolitis.<sup>17</sup>

The improvement of well-being has not been objectively confirmed or standardized in the pediatric population yet, especially in preverbal patients who are the main users. However, scales like the modified Comfort have confirmed improved scoring.<sup>43</sup> This study found that a great percentage of patients could communicate, speak or cry, which we believe backs up the hypothesis that HFNC systems provide greater comfort to these patients, which is consistent with what has been reported in studies with adults.<sup>44,45</sup> Regarding feeding, many were still being fed through the mouth or probe in case of fatigue, that happened to be a little bit more intense at the end of the follow-up. Still, enteral feeding was secured during the entire therapy without any adverse events being reported. These findings are consistent with those reported by a different study of patients with bronchiolitis that analyzed this aspect of cannulas and found a low rate of adverse events (mostly emesis) unrelated with the intensity of support, but rather with disease onset that is predictive of longer hospital stays.<sup>46</sup>

In the search for failure predictors only the hospital and the early respiratory rate were confirmed as independent predictors. The early respiratory rate is a well-known parameter of risk of respiratory failure among the pediatric population<sup>1</sup>; however, the role that the hospital may be playing suggests that some unmeasured variables, subjective at

times, determined the treating physician's declaration of a case of failed therapy.

The strength of this study is that it was the first large pediatric cohort ever to analyze clinical response in patients treated in cities located at high altitudes. Its multicenter nature and multiple respiratory diagnoses achieved support its findings. Its weakness is that it did not include comparative cohorts at different altitudes for result comparison purposes. Also, the overall great heterogeneity of diseases and ages analyzed.

In conclusion, the use of HFNC in this study at high altitudes behaved clinically different compared to other studies conducted at lower altitudes: we are talking about patients whose FIO<sub>2</sub> requirements are much higher and whose oxygenation improved significantly after the implementation of the HFNC system; ventilation was less compromised than other studies conducted at lower altitudes reported, which should be confirmed in other cohorts studied at different altitudes in order to determine if there is overuse and the associated extra-costs. The factors associated with failure were an initially high respiratory rate and the treating center, suggestive of a not-well defined subjective component in the decision to escalate treatment to invasive ventilation. More comparative studies are needed to define clear criteria of failure. Also, clinical guidelines aimed at pediatric populations living in cities located at high altitudes should be elaborated as well.

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## Authors/collaborators

All authors contributed to the project and deserve to be included as actual authors for their work:

- (1) Designing the study, data mining or analyzing and interpreting the data obtained.
- (2) Writing the draft of the manuscript or doing the critical review of the study intellectual content.



- (3) Approving the final version of the manuscript that was presented here.

## Conflicts of interest

None declared.

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## References

- Hammer J. Acute respiratory failure in children. *Paediatr Respir Rev.* 2013;14:64–9.
- World health statistics 2018: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2018. Available from: [http://www.who.int/gho/publications/world\\_health\\_statistics/2018/en/](http://www.who.int/gho/publications/world_health_statistics/2018/en/) [accessed 20.03.19].
- Schneider J, Sweberg T. Acute respiratory failure. *Crit Care Clin.* 2013;29:167–83.
- Malo DC, Pulido PA. Informe de evento infección respiratoria aguda, Colombia 2017, vol. 31. Bogota, Colombia: Instituto Nacional de Salud; 2018. Available from: <https://www.ins.gov.co/busador-eventos/Informesdeevento/Informe%20IRA%20Final%202017.pdf>
- Sreenan C, Lemke RP, Hudson-Mason A, Osioviich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics.* 2001;107:1081–3.
- Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. *Respir Care.* 2005;50:604–9.
- Ward JJ. High-flow oxygen administration by nasal cannula for adult and perinatal patients. *Respir Care.* 2013;58:98–122.
- Masclans JR, Pérez-Terán P, Roca O. The role of high flow oxygen therapy in acute respiratory failure. *Med Intensiva.* 2015;39:505–15.
- Schmid F, Olbertz DM, Ballmann M. The use of high-flow nasal cannula (HFNC) as respiratory support in neonatal and pediatric intensive care units in Germany – a nationwide survey. *Respir Med.* 2017;131:210–4.
- Miller AG, Gentle MA, Tyler LM, Napolitano N. High-flow nasal cannula in pediatric patients: a survey of clinical practice. *Respir Care.* 2018;63:894–9.
- Lin J, Zhang Y, Xiong L, Liu S, Gong C, Dai J. High-flow nasal cannula therapy for children with bronchiolitis: a systematic review and meta-analysis. *Arch Dis Child.* 2019;104:564–76.
- 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:CD009850.
- Mardegan V, Priante E, Lolli E, Lago P, Baraldi E. Heated humidified high-flow nasal cannulae as a form of noninvasive respiratory support for preterm infants and children with acute respiratory failure. *Am J Perinatol.* 2016;33:1058–61.
- Schlapbach LJ, Straney L, Gelbart B, Alexander J, Franklin D, Beca J, et al. Burden of disease and change in practice in critically ill infants with bronchiolitis. *Eur Respir J.* 2017;49(6).
- Soshnick SH, Carroll CL, Cowl AS. Increased use of noninvasive ventilation associated with decreased use of invasive devices in children with bronchiolitis. *Crit Care Explor.* 2019;1:e0026.
- Vitaliti G, Vitaliti MC, Finocchiaro MC, Di Stefano VA, Pavone P, Matin N, et al. Randomized comparison of helmet CPAP versus high-flow nasal cannula oxygen in pediatric respiratory distress. *Respir Care.* 2017;62:1036–42.
- Milési C, Pierre AF, Deho A, Pouyau R, Liet JM, Guillot 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 (TRAMONTANE 2). *Intensive Care Med.* 2018;44:1870–8.
- Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med.* 2018;378:1121–31.
- Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. *Intensive Care Med.* 2011;37:847–52.
- Testa G, Iodice F, Ricci Z, Vitale V, de Razza F, Haiberger R, et al. Comparative evaluation of high-flow nasal cannula and conventional oxygen therapy in paediatric cardiac surgical patients: a randomized controlled trial. *Interact Cardiovasc Thorac Surg.* 2014;19:456–61.
- Pilar J, Modesto I, Alapont V, Lopez-Fernandez YM, Lopez-Macias O, Garcia-Urabayen Det al. High-flow nasal cannula therapy versus non-invasive ventilation in children with severe acute asthma exacerbation: an observational cohort study. *Med Intensiva.* 2017;41:418–24.
- Er A, Çağlar A, Akgül F, Ulusoy E, Çitlenbik H, Yılmaz D, et al. Early predictors of unresponsiveness to high-flow nasal cannula therapy in a pediatric emergency department. *Pediatr Pulmonol.* 2018;53:809–15.
- Garlick V, O'Connor A, Shubkin CD. High-altitude illness in the pediatric population: a review of the literature on prevention and treatment. *Curr Opin Pediatr.* 2017;29:503–9.
- Lozano JM, Steinhoff M, Ruiz JG, Mesa ML, Martinez N, Dusan B. Clinical predictors of acute radiological pneumonia and hypoxaemia at high altitude. *Arch Dis Child.* 1994;71:323–7.
- Rojas-Camayo J, Mejia CR, Callacondo D, Dawson JA, Posso M, Galvan CA, et al. Reference values for oxygen saturation from sea level to the highest human habitation in the Andes in acclimatised persons. *Thorax.* 2018;73:776–8.
- Niermeyer S, Andrade Mollinedo P, Huicho L. Child health and living at high altitude. *Arch Dis Child.* 2009;94:806–11.
- Vásquez-Hoyos P, Arias-Fernández DA, Barrios-Marengo A, Álvarez-Fonseca YC, Soler-Rincón PJ. Experiencia del uso de la cánula nasal de alto flujo en cuidados intensivos neonatales de un hospital a 2,600 metros sobre el nivel del mar. *Rev Mex Pediatr.* 2018;85:60–5.
- Kamit Can F, Anil AB, Anil M, Zengin N, Durak F, Alparslan C, et al. Predictive factors for the outcome of high flow nasal cannula therapy in a pediatric intensive care unit: is the SpO<sub>2</sub>. *J Crit Care.* 2018;44:436–44.
- Liu J, Li DY, Liu ZQ, Lu GY, Li XQ, Qiao LN. High-risk factors for early failure of high-flow nasal cannula oxygen therapy in children. *Zhongguo Dang Dai Er Ke Za Zhi.* 2019;21:650–5.
- Guillot C, le Reun C, Behal H, Labreuche J, Recher M, Duhamel A, et al. First-line treatment using high-flow nasal cannula for children with severe bronchiolitis: applicability and risk factors for failure. *Arch Pediatr.* 2018;25:213–8.
- Hansen G, Hochman J, Garner M, Dmytrowich J, Holt T. Pediatric early warning score and deteriorating ward patients on high-flow therapy. *Pediatr Int.* 2019;61:278–83.
- Roca O, Messika J, Caralt B, García-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: the utility of the ROX index. *J Crit Care.* 2016;35:200–5.
- Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, et al. Normal ranges of heart rate and respiratory

- rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 2011;377:1011–8.
34. Coletti KD, Bagdure DN, Walker LK, Remy KE, Custer JW. High-flow nasal cannula utilization in pediatric critical care. *Respir Care*. 2017;62:1023–9.
  35. Kawaguchi A, Yasui Y, deCaen A, Garros D. The clinical impact of heated humidified high-flow nasal cannula on pediatric respiratory distress. *Pediatr Crit Care Med*. 2017;18:112–9.
  36. Baudin F, Gagnon S, Crulli B, Proulx F, Jouvét P, Emeriaud G. Modalities and complications associated with the use of high-flow nasal cannula: experience in a pediatric ICU. *Respir Care*. 2016;61:1305–10.
  37. Milési C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Med*. 2017;43:209–16.
  38. Oto A, Erdoğan S, Boşnak M. Oxygen therapy via high flow nasal cannula in pediatric intensive care unit. *Turk J Pediatr*. 2016;58:377–82.
  39. Modesto i Alapont V, Garcia Cuscó M, Medina A. High-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med*. 2018;378:2444.
  40. Riese J, Porter T, Fierce J, Riese A, Richardson T, Alverson BK. Clinical outcomes of bronchiolitis after implementation of a general ward high flow nasal cannula guideline. *Hosp Pediatr*. 2017;7:197–203.
  41. Mayordomo-Colunga J, Medina A. High-flow nasal cannula oxygenation for everyone? Not so fast! *Med Intensiva*. 2017;41:391–3.
  42. Weiler T, Kamerkar A, Hotz J, Ross PA, Newth CJL, Khemani RG. The relationship between high flow nasal cannula flow rate and effort of breathing in children. *J Pediatr*. 2017;189:66–71, e3.
  43. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. *J Intensive Care Med*. 2009;24:323–8.
  44. Mauri T, Galazzi A, Binda F, Masciopinto L, Corcione N, Carlesso E, et al. Impact of flow and temperature on patient comfort during respiratory support by high-flow nasal cannula. *Crit Care*. 2018;22:120.
  45. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. *Respir Care*. 2010;55:408–13.
  46. Slain KN, Martinez-Schlurmann N, Shein SL, Stormorken A. Nutrition and high-flow nasal cannula respiratory support in children with bronchiolitis. *Hosp Pediatr*. 2017;7:256–62.