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ORIGINAL ARTICLE

Factors associated with pediatric intensive care transfer after ion-invasive respiratory support in general wards

Factores asociados a derivación a cuidados intensivos pediátricos luego de aplicación de soporte respiratorio no invasivo en salas generales

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

The use of noninvasive respiratory support (NIRS) systems in general pediatric wards is a growing practice, but the risk factors related to their failure are poorly described.

What does this study contribute to what is already known?

Children with acute respiratory failure supported with NIRS outside the PICU had an ICU referral rate of 14.2%, with younger age, prematurity, congenital heart disease, and higher initial heart rate as risk factors for failure.

Abstract

The application of Non-Invasive Respiratory Support (NIRS) has been increasingly used outside the pediatric intensive care units (PICUs). Early identification of disease progression or poor response to therapy is crucial for timely referral. **Objective:** To describe the use of NIRS in general pediatric wards and to evaluate the risk factors associated with therapy failure and PICU referral. **Patients and Method:** Retrospective, observational, single-center study in children under 24 months with acute lower respiratory tract infection (LRTI) who received NIRS in general wards during the winter seasons of 2021-2022. NIRS included high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP). Each event was individually charac-

Keywords:
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terized, documenting the type of support and its clinical response (success or failure). Failure was defined as the need for PICU admission. Demographic factors, clinical characteristics, and types of support used were compared between these groups using bivariate analysis and multivariate logistic regression. **Results:** Out of a total of 415 patients, 14.2% experienced therapy failure. The main predictors of failure were age (adjusted OR = 0.87; 95% CI: 0.81-0.94), prematurity (adjusted OR = 2.52; 95% CI: 1.07-5.96), the presence of congenital heart disease (adjusted OR = 5.92; 95% CI: 2.13-16.42), and a higher heart rate (adjusted OR = 1.25; 95% CI: 1.06-1.48). Clinical outcomes did not vary according to the type of NIRS used. Regarding the type of NIRS received, HFNC was used in 68.6% of the events, followed by CPAP (25.3%) and BiPAP (6.1%). **Conclusions:** The use of NIRS in general pediatric wards prevented PICU referral in 85.8% of cases. The identified risk factors for referral included younger age, prematurity, the presence of congenital heart disease, and a higher initial heart rate. HFNC emerged as the most commonly used respiratory support technique, followed by CPAP and BiPAP, which were primarily used as rescue strategies.

Introduction

Worldwide, lower respiratory tract infections (LRTIs) are a major cause of morbidity and mortality, especially in developing countries[1]. In Latin America, respiratory diseases cause seasonal care overload at all levels of the healthcare system[2-4]. The incorporation of different noninvasive respiratory support (NIRS) systems in general pediatric wards, including high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP), has proven to be a safe health strategy associated with a decrease in the number of admissions to pediatric intensive care units (PICU)[5-10].

In Uruguay, some public referral hospitals, such as the *Centro Hospitalario Pereira Rossell*, have been using NIRS since 2009 in general wards prepared for this purpose[6]. One of the most important points for the success of NIRS applied to acute respiratory failure (ARF) is the adequate patient selection and early detection of those children with a greater probability of clinical deterioration who will require timely referral for invasive support in the PICU[2]. Pediatric evidence regarding its use in general wards is still scarce and needs to be better characterized.

The main objective of this study was to describe the use of NIRS in general pediatric wards during the winter campaigns of 2021-2022 and to evaluate the risk factors related to therapy failure and subsequent PICU referral. Secondarily, we aimed to characterize the NIRS events and describe the cohort of patients treated with this modality outside the PICU during the periods studied.

Patients and Method

Observational, retrospective cohort study in general pediatric wards prepared during the winter to provide NIRS ("NIRS wards") at the *Hospital Pediátrico Centro Hospitalario Pereira Rossell* (HP-CHPR). HP-CHPR is a public pediatric hospital with 152 general pediatric inpatient beds and a PICU with 20 intensive and intermediate care beds. The NIRS units have a total of 21 beds prepared during the winter to provide different NIRS modalities. The medical staff responsible for patient care in these wards includes four on-duty physicians (licensed general pediatricians or pediatric fellows). The nursing staff consisted of one professional nurse and one nurse assistant for every 3 patients. All patients under 24 months of age admitted to NIRS wards with a diagnosis of LRTI and ARF, who received during their hospitalization some method of NIRS, were included. Those patients who were referred from PICU to these wards, children < 1 month old or < 3.5 kg, tracheostomized children or with previous chronic ventilatory support, and cases with an order not to resuscitate or not to refer to PICU due to limitation of therapeutic effort were excluded. The study period corresponded to the opening and closing of NIRS units in the hospital, from May 20 to September 20, between 2021 and 2022.

Variables and primary outcomes

We obtained basic demographic data, clinical information, and main healthcare outcomes. Regarding the definitions of the comorbidities of our patients, prematurity was considered as those children with a perinatal history with birth before 34 weeks of gestational age; hemodynamically significant heart diseases that required pharmacological treatment before the current disease were considered congenital heart disease; clinically significant airway pathologies such as anatomical and functional airway malformations before the current disease were considered airway disease; bronchopulmonary dysplasia was considered if there was a history of previous diagnosis of chronic bronchopulmonary disease with onset in the perinatal stage before the current disease; malnutrition (acute or chronic) was considered as any variation from the growth percentiles curves based on the World Health Organization percentiles for age, weight, and height before the current admission; and the diagnosis of encephalopathy was considered in those children with severe alterations in cognitive development before the current admission.

We used two different units of analysis: 'admissions', which represent the set of NIRS interventions performed on a patient during their hospital stay until it was determined whether PICU transfer was necessary or whether they could be discharged, and 'events', which refer to each individual application of NIRS following an episode of clinical deterioration. Each event was assessed to identify whether it resulted in clinical improvement, thus allowing discontinuation of NIRS, or if, on the contrary, it was associated with further deterioration needing transition to a more advanced respiratory support modality. Failure was defined as the need for transfer to the PICU. Only NIRS events following a previously identified deterioration were included in the analysis.

We identified the clinical diagnoses of disease that determined ARF, isolated germs, and indicated medications. We documented the hospital sector where NIRS was initiated and duration of use, and mapped the support pathways using a Sankey diagram, showing the trajectories to referral to the PICU or discharge.

Regarding NIRS data, for HFNC, we report the maximum flow (L/kg/min) and the maximum fraction of inspired oxygen (FiO2) (%); for CPAP, we report the peak pressure used and the peak FiO2; and for BiPAP, we document the maximum low and high pressure used and the maximum FiO2. The operational definitions used to define each NIRS modality are those agreed upon for pediatric mechanical ventilation[12].

The criteria used to define LRTI, type of LRTI, and ARF were those described in the clinical history and used operationally by the on-duty physicians during the care process. The NIRS wards admit children with exclusively acute respiratory pathology. In our hospital, the decision to refer to the NIRS ward is determined by the clinical judgment of the on-duty general pediatrician in the ward and the on-duty pediatrician in the NIRS sector. The criteria for initiating and selecting the NIRS method, as well as the failure variables of the different techniques, were those determined by the on-duty NIRS ward physicians. Similarly, referral to the PICU was based on the judgment of the on-duty medical team. The usual general criteria for PICU referral recommended in NIRS wards are respiratory distress, hypercapnia, hypoxemia, shock, and altered state of consciousness. The judgment of the on-duty clinical physician is prioritized during decision-making.

Data were extracted from the admission records of patients referred to the PICU, including the reason for referral, length of stay in the PICU, and the need for invasive mechanical ventilation (IMV) or inotropes. This includes both hospital admissions and those for which information was obtained from PICUs outside the center where the study was conducted.

Data source and management

Data was extracted from hospital electronic clinical records, managed using Research Electronic Data Capture (REDCap) software[13], and analyzed using the STATA 17 statistical package. To visualize the progression and outcomes of NIRS events, SankeyMATIC was used to create a Sankey diagram. This diagram represents patient flows from the initiation of NIRS to its outcome, whether improvement, deterioration, hospital discharge, or transfer to the PICU.

Statistical Method

The units of analysis included hospital admissions, considering that a patient could have multiple admissions, as well as individual NIRS events within each admission for those patients who received more than one NIRS support, regardless of whether they presented improvement or deterioration.

For numerical variables, the appropriate measure of central tendency was selected according to the nature of the variable, and the normality of the distributions was assessed using the Shapiro-Wilk test. Contingency tables were constructed to explore the frequencies of the categorical variables.

For the analysis of risk factors for PICU referral, appropriate statistical significance tests were used according to the type of variable; for continuous variables with normal distribution, the Kolmogorov-Smirnov test was applied, and they were processed with Student's t-test, expressing the results as mean ± standard deviation (SD). For variables without normal distribution, the Mann-Whitney U test was used, and the results were presented as median differences with interquartile ranges (IQR) of 25% and 75%. Categorical variables were analyzed with the chi-square test and expressed as absolute frequencies and percentages.

In addition, simple logistic regression was used to calculate associations, followed by the development of a multivariable model which was constructed by including only those variables that collectively maintained their statistical independence, to simplify the model through a step-up approach. In this context, both crude and adjusted Odds Ratios (OR) were determined for the significant variables.

To describe the flow of NIRS use at each admission, a Sankey diagram was used. A sample size of 400 events was estimated for a 95% confidence interval, 5%

precision, and an expected frequency of referral to the PICU due to NIRS failure of 15%, according to previous analysis of the literature and experience of the investigators.

Ethical considerations

The study was registered with the Ministry of Public Health of Uruguay and approved by the Institutional Management and the Ethics Committee of the HP-CHPR (number 1362023).

Results

Out of the 571 children admitted to NIRS wards during the study periods, 390 met the inclusion criteria, resulting in 415 hospital admissions. Among these, 24 patients had two admissions, and one patient had three. A total of 609 events of NIRS use were registered, with a median number of events per admission of 1 (IQR 1-2). The maximum number of NIRS events recorded for a single admission was seven. The attached Sankey diagram (Figure 1) describes these data.

Table 1 shows the clinical and demographic characterization of hospital admissions to NIRS wards. Bronchiolitis (276 cases, 66.5%) and viral pneumonia (121 cases, 29.2%) were the most common conditions. Respiratory syncytial virus (RSV) was identified in 233 cases (56.1%), being the most frequent germ. A higher detection of adenovirus was observed in patients referred to the PICU (3 cases, 5.1%) compared to those not admitted to the PICU (1 case, 0.3%). Detection of rhino/enterovirus, bocavirus, and metapneumovirus was less frequent, and SARS-CoV-2 or RSV infection was not identified as a risk factor for failure. In addition, most patients had no pre-existing comorbidities (357 cases, 86.0%), and the median age was 6 months (IQR 3-10).

Table 1 also details baseline and post-treatment vital signs, including changes (delta), and treatments administered. The mean baseline heart rate, recorded at 140 bpm (IQR 130-155), was turned into frequency per 10 beats to facilitate the interpretation of ORs. The mean respiratory rate was 55 breaths per minute (IQR 46-62), and the mean peripheral oxygen saturation was 97% (IQR 95-98). Regarding treatment, bronchodilators were the most commonly used, being present in 95.4% of admissions.

Referral to the PICU was necessary in 14.2% of the 415 admissions, of which 30.5% were referred to an external PICU. Of the 59 cases, IMV was used in 47.5%, although in 8 cases the ventilatory support received in the PICU could not be registered. The main reason for referral of these 59 cases was increased work of breathing, present in 91.5%, followed by hypoxemia and hypercapnia, each in 8.5%. It is important to note that some cases presented simultaneously with more than one condition. In addition, of the 59 children referred, 2 required inotropes due to shock, and one had seizures. In one admission, the reason for referral was not registered. The mean length of stay in the PICU was 5.5 days (IQR 4-8), in the NIRS wards was 3 days (IQR 2-4), and the mean length of hospitalization was 6 days (IQR 4-8).

Table 2 shows how the different NIRS systems were used in the 609 individual events, highlighting their independence from hospital admissions. HFNC was established as the predominant initial method, applied in 68.6%, with a median use of 48 hours (IQR 21-68). A mean flow rate of 2 ml/kg/min and a maximum mean FiO_2 of 60% were used. Of the 140 HFNC events that presented deterioration and required increasing the level of respiratory support, CPAP was used in 110 (78.6%), and, of these, in 29 cases, it was escalated to BiPAP with adequate response in 12 (41.4%). This transition of support was frequently performed in the same ward, avoiding transferring the patient to the PICU. In the events that used CPAP (25.3%, 154/609), the median pressure support was 7 cmH_2O (IQR 6-7) and for the events with BiPAP (6.1%, 37/609), IPAP was 9 cmH_2O (IQR 9-10) and EPAP was 7 cmH_2O (IQR 6-7).

Only 5 cases with adverse effects were reported, with discomfort being the most frequent (4/5 cases). No deaths were recorded during the study period. Regarding sedation, it was necessary in 23 events (3.6%), mostly used in positive pressure systems. Benzodiazepines were administered in most cases (22 events), dexmedetomidine was used in one event, and antipsychotics in two.

Bivariate analysis showed that age and weight at admission had an inverse and significant association with failure (Table 1). The presence of adenovirus [OR 19.02 (1.94-186.05)] and metapneumovirus [OR 19.02 (1.94-186.05)] was also related to a higher probability of failure. In contrast, the lack of identified pathogens was associated with a lower tendency to failure. The absence of comorbidities was associated with a lower probability of failure, whereas prematurity and congenital heart disease increased this risk. Vital signs such as higher heart rate and respiratory rate at admission were associated with failure, although other factors showed no significant differences.

After analyzing all the factors that initially showed a significant association, the best multivariate model was established, including only those that retained their independent statistical significance. In this refined model, age at admission emerged as a key predictor since each additional month of life decreases the risk of failure by 13% (adjusted OR = 0.87; 95% CI: 0.81-0.94).

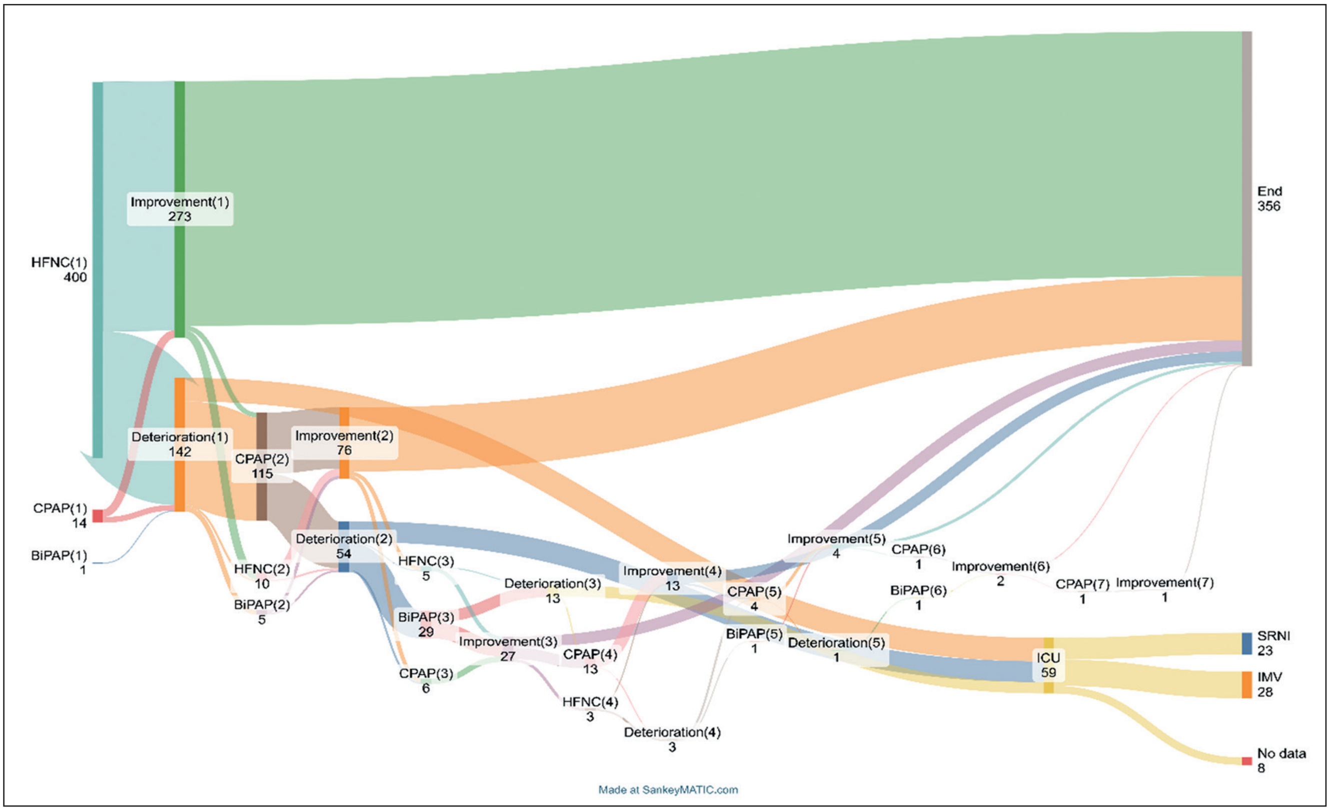

Figure 1. Sankey diagram of non-invasive respiratory support (NIRS) progression in pediatric patients with lower respiratory tract infections (LRTIs)–This diagram represents the 609 events of NIRS distributed in 415 admissions during 2021/2022. Trayectories represent the evolution towards clinical improvement or deterioration until PICU referral (where some children required invasive mechanical ventilation (IMV) or hospital discharge Numbers attached to each connection show the number of patients who followed each specific route. NIRS: Non Invasive Respiratory Support, HFNC: high flow nasal cannula, CPAP_ Continuous Positive Airway Pressure, BiPAP: Bilevel Airway Possitive Pressure, rescue: second NIRS technique, ICU: Intensive Care Unit, IMV: Invasive Mechanical Ventilation.

Table 1. Global description of demographic and clinical characteristics of hospital admissions to Non Invasive Respiratory Support (NIRS)and its association with the need of pediatric Intensive Care Unit (PICU) transfer

Admissions	Admissions N = 415	Success N = 356	Failure N = 59	p-value	OR (IC95%)	ORa (IC95%)
				0,796		
One admission per patientUn ingreso por paciente	390 (94.0)	335 (94.1)	55 (93.2)		Ref.	
Two admissions per patient	24 (5.8)	20 (5.6)	4 (6.8)		1.22 (0.40-3.70)	
Three admissions per patient	1 (0.2)	1 (0.3)	0		NA	
Age (m)	6 [3-10]	6 [3-11]	3 [1-7]	< 0.001	0.88 (0.82-0.94)	0.87 (0.81- 0.94)
Weight (kg)	7 [5-9]	7 [6-9]	5.1 [4.5-8]	< 0.001	0.77 (0.68-0.88)	
Sex	H 271 (65%)	H 229 (64.3%)	H 42 (71.2%)	0.376	Ref.	
	M 144 (35%)	M 127 (35.7%)	M 17 (28.8%)		0.73 (0.40-1.33)	
Respiratory Diagnosis						
Bronchiolitis	276 (66.5)	232 (65.2)	44 (74.6)	0.701	Ref.	
Viral Pneumonia	121 (29.2)	107 (30.1)	14 (23.7)		0.69 (0.36-1.31)	
Laringeotracheobronchiolitis	11 (2.7)	10 (2.8)	1 (1.7)		0.53 (0.07-4.22)	
Bacterial Pneumonia	6 (1.5)	6 (1.7)	0		NA	
Cold	1 (0,2)	1 (0,3)	0		NA	

Germ						
None	153 (36.9)	140 (39.3)	13 (22.0)	0.011	0.44 (0.23-0.84)	
RSV	233 (56.1)	200 (56.2)	33 (55.9)	0.972	0.99 (0.57-1.72)	
SARS CoV2	17 (4.1)	13 (3.7)	4 (6.8)	0.281	1.92 (0.60-6.10)	
Rinho/Enterovirus	9 (2.2)	3 (0.8)	6 (10.2)	< 0.001		
Influenza	6 (1.4)	4 (1.6)	2 (3.4)	0.204	3.08 (0.27-22.03)	
Adenovirus	4 (1.0)	1 (0.3)	3 (5.1)	0.01	19.02 (1.94-186.05)	
Metapneumovirus	4 (1.0)	1 (0.3)	3 (5.1)	0.01	19.02 (1.94-186.05)	
H. Influenzae	3 (0.7)	1 (0.3)	2 (3.4)	0.054	13.32 (3.23-54.87)	
Pneumococcus	2 (0.5)	1 (0.3)	1 (1.7)	0.264	6.12 (0.38-99.22)	
Bocavirus	2 (0.5)	0	2 (3.39)	0.02	NA	
Parainfluenza	1 (0.2)	1 (0.3)	0	1	NA	
Comorbidities						
None	357 (86.0)	316 (88.8)	41 (69.5)	< 0.001	0.06 (0.28-0.11)	
Bronchopulmonar Dysplasia	8 (1.9)	6 (1.7)	2 (3.4)	0.318	2.05 (0.40-10.39)	
Preterm (<34w)	35 (8.4)	25 (7.0)	10 (17.0)	0.02	2.70 (1.22-5.97)	2.52 (1.07-5.96)
Congenital Heart Disease	19 (4.6)	10 (2.8)	9 (15.3)	< 0.001	6.23 (2.41-16.07)	5.92 (2.13-16.42)
Airway Disease	6 (1.5)	4 (1.1)	2 (3.4)	0.204	3.09 (0.55-17.25)	
Encephalopathy	4 (1.0)	3 (0.8)	1 (1.7)	0.46	2.03 (0.21-19.84)	
Malnutrition	11 (2.7)	9 (2.5)	2 (3.4)	0.66	1.35 (0.28-6.42)	
Baseline vital signs						
HR / 10	14 [13-15.5]	14 [13-15.5]	15 [13-16]	0.004	1.28 (1.10-1.49)	1.25 (1.06-1.48)
RR	55 [46-62]	54 [46-60]	60 [52-64]	0.004	1.03 (1.01-1.06)	
SpO_2	97 [96-98]	97 [95-98]	97 [96-98]	0.098	1.08 (0.95-1.24)	
Fever	211 (50.8)	183 (51.4)	28 (47.5)	0.502	0.90 (0.76-1.07)	
Response signs						
HR/10	13 [12.2-14.5]	13 [12-14]	14 [13-15.4]	0.003	1.31 (1.11-1.54)	
RR	44 [38-50]	42 [36-50]	50 [43-60]	< 0.001	1.06 (1.03-1.09)	
SpO_2	98 [98-99]	99 [98-99]	98 [98-99]	0.129	0.88 (0.78-1.00)	
FiO_2	60 [60-60]	60 [60-60]	60 [60-60]	0.833	0.99 (0.96-1.02)	
Delta						
HR	10 [-5. 20]	10 [-5. 20]	10 [-5. 20]	0.855	1.00 (0.99-1.02)	
RR	10 [2-18]	10 [2-18]	9 [0-15]	0.169	1.00 (0.99-1.00)	
Theprapies						
None	13 (3.1)	13 (3.7)	0	0.23	NA	
Antibiotics	117 (28.2)	96 (27.0)	21 (35.6)	0.173	1.50 (0.84-2.68)	
Steroids (respiratory)	145 (34.9)	127 (35.7)	18 (30.5)	0.441	0.79 (0.44-1.44)	
Salbutamol/Aminophilline	396 (95.4)	338 (94.9)	58 (98.3)	0.253	3.09 (0.40-23.58)	
Anticholinergics	10 (2.4)	8 (2.3)	2 (3.4)	0.64	1.53 (0.32-7.37)	
Epinephrine (inhaled)	27 (6.5)	25 (7.0)	2 (3.4)	0.4	0.46 (0.11-2.02)	
First NIRS type				0.173		
HFNC	400 (96.4)	344 (96.6)	56 (94.9)		Ref.	
CPAP	14 (3.4)	12 (3.4)	2 (3.4)		1.02 (0.22-4.70)	
BiPAP	1 (0.2%)	0	1 (1.7)		NA	
Where NIRS starts				0.0169		
Emergency Room	198 (47.7)	172 (48.3)	26 (44.1)		Ref.	
General Ward	10 (2.4)	9 (2.5)	1 (1.7)		0.74 (0.09-6.04)	
NVI Unit	105 (25.3)	85 (23.9)	20 (33.9)		1.56 (0.82-2.95)	
HFNC Unit	93 (22.4)	82 (23.0)	11 (18.6)		0.89 (0.42-1.88)	
Prehospital (from ambulance)	1 (0.2)	0	1 (1.7)		NA	
Another hospital	8 (1.9)	8 (2.3)			NA	

m (months), kg (kilograms), M (Male), F(Female), RSV (Respiratory Syncytial Virus, and PICU (Pediatric Intensive Care Unit) , SARS CoV2 (Severe acute respiratory syndrome coronavirus 2), HFNC: high flow nasal cannula, CPAP_ Continuous Positive Airway Pressure, BiPAP: Bilevel Airway Possitive Pressure , HR(Heart Rate) , HR/10 (Heart Rate divided by 10) , RR (Respiratory Rate) , SpO2 (Pulse Oxymetry Saturation, FiO_2 (Inspired Oxygen Fraction), NA (Does Not Apply). **Note:** The data are presented as numbers (%) for categorical variables and as medians [interquartile range] for continuous variables. OR corresponds to the Odds Ratio, and ORa to the adjusted Odds Ratio, adjusted for identified confounding variables, with Ref. indicating the reference category used for the calculation of ORs. p-values less than 0.05 were considered statistically significant. The 95% confidence intervals are presented in parentheses.

Regarding comorbidities, children with congenital heart disease are at nearly six times the risk of failure (adjusted OR = 5.92; 95% CI: 2.13-16.42), and preterm infants (≤ 34 weeks of gestation) are at more than double the risk compared to non-preterm infants (adjusted OR = 2.52; 95% CI: 1.07-5.96). With respect to basal vital signs, a 10 bpm increase in basal heart rate indicates a 25% increased risk of failure (adjusted OR = 1.25; 95% CI: 1.06-1.48).

Discussion

Our results showed that the application of NIRS in general wards (outside the PICU) of our center in children under two years of age with LRTI had a failure rate of less than one-sixth. Failure was found to be associated with easily identifiable risk factors such as younger age, lower weight, history of prematurity ≤ 34 weeks, and the presence of congenital heart disease. On the other hand, the absence of previous diseases in admitted children acted as a protective factor.

Our results need to be compared with the available literature. First, it confirms the high degree of healthcare impact of RSV infection as the main agent of severe LRTI, mainly bronchiolitis in children under 2 years of age requiring NIRS[7,14]. We also found that the most commonly used NIRS is HFNC, which is in line with different reports both inside and outside of national and international PICUs[15,16]. The finding that physicians select HFNC as the initial respiratory support over other methods of NIRS is interesting, as it points to a clear contemporary preference of physicians for HFNC in the PICU setting and may be the

Table 2. Summary of Individual Events of Non-Invasive Respiratory Support (NIRS) by Location, Type of Support, and Clinical Outcomes

	Total	HFNC	CPAP	BiPAP
NIRS Events	609	418 (68.6)	154 (25.3)	37 (6.1)
Location				
Emergency Room	201 (33)	200 (47.9)	1 (0.7)	0
General Ward	10 (1.6)	10 (2.4)	0	0
NIV Unit	289 (47.5)	100 (23.9)	152 (98.7)	37 (100)
HFNC Unit	99 (16.3)	98 (23.4)	1 (0.7)	0
Prehospital (from Ambulance)	1 (0.2)	1 (0.2)	0	0
Another hospital	9 (1.5)	9 (2.2)	0	0
Suspension				
Due to improvement	396 (65)	278 (66.5)	96 (62.3)	22 (59.5)
Due to deterioration	213 (35)	140 (33.5)	58 (37.7)	15 (40.5)
Adverse Events	5 (0.8)	3 (0.7)	2 (1.3)	0
Air leak	1	0	1	0
Discomfort	4	3	1	0
Sedation				
Some	23 (3.6)	1 (0.2)	16 (10.4)	6 (16.2)
Benzodiacepine	22	0	16	6
Dexmedetomidine	1	1	0	0
Antipsychotics	2	0	1	1
Total Hours de uso	43 [16-65]	48 [21-68]	36 [9-58]	15 [5-28]
Hours until improvement			52 [35-75]	26 [15-31]
Hours until deterioration	11 [6-21]	14 [8-24]	6 [3-13]	5 [3-10]
Maximum parameters				
Flow (ml/kg/min)	2 [2-2]	2 [2-2]		
PEEP (ePAP), cm H2O	7 [6-7]		7 [6-7]	7 [6-7]
PIP (iPAP), cm H2O	9 [9-10]			9 [9-10]
FiO2	60 [60-60]	60 [60-60]	NA	NA

NIRS (Non-Invasive Respiratory Support), HFNC (High-Flow Nasal Cannula), CPAP (Continuous Positive Airway Pressure), BiPAP (Bilevel Positive Airway Pressure), PEEP (Positive End-Expiratory Pressure), PIP (Peak Inspiratory Pressure), FiO2 (Fraction of Inspired Oxygen), N/A (Not Applicable). Note: The data are presented as numbers (%) for categorical variables and as medians [interquartile range] for continuous variables. In this table, each NIRS event is counted individually and not as a hospital admission.

subject of future research and/or interventions to improve quality of care. We found a high prescription of pharmacological therapies that current international guidelines do not recommend[17]. This phenomenon of pharmacological over-prescription may be due to the variability of care practices recognized in this type of cohort of children with more severe disease and that merits future study[18].

The failure rate in NIRS found in our cohort was consistent with that reported in the previous decade by investigators from our own hospital[5,6]. However, the subsequent IMV rate reported by Alonso et al in 2012 was lower than ours (19.4%) and that of Morosini et al in 2015 was similar (55%)[5,6]. Internationally, a Spanish report showed that the failure rate of NIRS and PICU referrals was 20% of which 20% required IMV[9]. Likewise, Suessman et al in the United States found that in children under 24 months of age with bronchiolitis after the use of HFNC in emergency rooms, 10.2% of patients required IMV within 48 hours of hospital admission[19]. In other reports in which NIRS were provided directly in intensive care, the percentage of patients requiring IMV is not so different. In a multicenter study conducted in the United States, Canada, and Saudi Arabia, it was found that 28% of children with bronchiolitis admitted with HFNC or NIV required IMV; and that initial treatment with NIV (vs. initial treatment with HFNC) was associated with a greater need for IMV[20]. In another retrospective study, conducted in Australia, it was found that 32% of patients under 2 years of age hospitalized with RSV infection required IMV and that this percentage increased to 39% if patients with comorbidities were considered[21]. This last finding of the impact of the presence of comorbidities on failure is in line with our results, which showed that the absence of comorbidities is a factor that can be considered protective.

The risk factors for failure closely associated with deterioration in the use of NIRS that we observed in our cohort also align with findings from other studies. Pinchack et al showed that in patients exposed to HFNC outside the PICU, age younger than three months is a predictor of the need for a PICU referral[7]. Prematurity is also a major risk factor previously reported[22,23]. Betters et al. described as risk factors for failure of HFNC outside the PICU having required high FiO2, a history of heart disease, and/or having required previous IMV[8]. However, the failure criteria defined (need for intubation or cardiorespiratory arrest) by the investigators were different from ours (referral to PICU) making comparisons difficult.

Abboud et al. did not find that prematurity or age were risk factors for failure of HFNC and concluded that patients with higher pCO2 as well as lack of respiratory rate decrease after initiation of HFNC were at higher risk of failure[11]. However, the study was in the PICU setting so extrapolations to other care settings such as ours are complex. As we found in our cohort, other investigators also found that the presence of heart disease is a good predictor of NIRS failure[24]. Other variables identified in the literature as risk factors for NIRS failure in patients with HFNC or NIV were pCO2[13,25,26,27] and PaCO2/PaO2[26], lower SatO2/FiO2, respiratory acidosis[28], and pH < 7.30[27].

The protocol used in the NIRS wards of our hospital (HFNC default start with flow of 2 L/k/min and FiO2 of 60%), could explain why no significant difference was found in these parameters between patients who experienced success or failure[29]. Our investigation did not obtain sufficient quality granular data on the characteristics of most of the physiological variables mentioned and, as was previously discussed, physiological changes after initiation of NIRS are difficult to interpret given the characteristics of our cohort and research design to include in detail for this analysis. Among the variables well captured in our cohort (such as heart rate variability after initiation of NIRS), we were able to find similar findings to the study by Pons-Odena M et al, in which an increase in this variable two hours after initiation of NIRS was a clear risk factor for failure[30]. However, that work was conducted in the PICU setting, and failure was defined as the need for IMV, a clinical scenario and definition of failure different from our work, so future studies should confirm our data. An interesting finding in our cohort and poorly reported previously is that failure of the first selected NIRS behaved as a risk factor for PICU referral.

It is worth noting that our data show that the application of NIRS is a safe health strategy, with very few adverse effects reported, as shown in previous reports from our hospital[5,7]. This may be due to the adequate learning curve in these NIRS wards for more than a decade in our center, which also reflects a paradigm shift towards different NIRS systems in pediatrics[9,31]. However, better patient selection needs to be adjusted, since a failure of these techniques may be associated with worse care outcomes and the need for timely invasive therapies[24,31].

Our study has important limitations. First, the weaknesses inherent to the retrospective design prevented us from having physiological data of sufficient quality to include them all in our analysis and to accurately detect risk factors associated with known failure as we previously analyzed. We were also unable to access an adequate registry of other minor adverse events of NIRS such as nasal and skin lesions. It was not possible to access specific data on children who were treated in out-of-hospital PICUs, which may affect the course of the disease and the outcomes. In addition, we were also unable to describe in detail the reasons for referral to the PICU, and, actually, many overlap. We note that, like many of the decisions we physicians make during care (e.g., referring a child to PICU due to respiratory distress), they are part of the subjectivity inherent to contemporary clinical practice. In any case, these points should be further explored in future studies. However, the data source was unique, electronic, and known to the researchers, which allowed us to have little data leakage of the selected variables and to have greater consistency at the time of the final analysis. We were also able to analyze 100% of the NIRS events of use outside the PICU during the study period.

Second, our study excluded infants under one month old and under 3,500 grams, which are populations at particular risk of poor outcomes in LRTI[32]. Third, it is known that there may be differences in the effectiveness of HFNC, CPAP, and BiPAP in the respiratory support of this type of patient[33]. Although in our cohort the use of different modalities was a frequent occurrence, the bias of the high use of HFNC cannot be ignored. Also, when thinking about the external validity of the study, it should be considered that the setting of the study is in a center with a lot of experience in the use of NIRS outside the PICU, so extrapolation of our results should be made cautiously in other hospital contexts. Despite these limitations, our study has strengths such as the large sample size and, to our knowledge, is one of the largest reported cohorts on the use of NIRS outside the PICU. It also represents a sample of actual clinical care contemporary practices.

Conclusion

The use of NIRS outside the PICU in units prepared for this purpose in our hospital had a low failure rate and was comparable with the available literature. This strategy was again shown to be a safe strategy to prevent PICU admission in many children during two respiratory epidemics. Multiple risk factors were identified, such as younger age, weight, and comorbidities, especially prematurity and heart disease. Our findings should help to better optimize the selection of patients in NIRS wards outside the PICU, as well as to timely detect those patients who will require PICU admission. In the future, it would be important to carry out new studies that include the analysis of other variables associated with the risk of failure during NIRS.

Note: Preliminary data of this work have been presented at the XXXIV Uruguayan Congress of Pediatrics under the title: ¨Hospitalizations due to Acute Respiratory Infection in a Pediatric Reference Hospital. Non-Invasive Respiratory Support outside the Intensive Care Unit: risk factors for failure and clinical evolution. Years 2021-2022¨. Date 14-09-2023

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: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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