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RESEARCH ARTICLE

Predictive features of high-flow oxygen supplementation failure in infants with severe acute bronchiolitis

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ABSTRACT

The aim of the study is to describe the clinical course of infants hospitalized with bronchiolitis who underwent high-flow oxygen supplementation via nasal cannula (HFNC) and investigate HFNC failure. We extracted clinical charts of the 130 infants who required oxygen delivered by HFNC and clinical, epidemiological, laboratory, and radiological data were analyzed, out of 824 infants admitted for bronchiolitis over seven epidemic seasons. We ran a multivariate logistic regression analysis (adjusted for age and sex) in order to determine factors associated with HFNC failure. HFNC therapy failed only in 11 (8.5%) out of 130 infants. Infants with HFNC failure were younger with a lower admission weight, and they received more frequently low-flow oxygen before HFNC than patients who underwent HFNC only. Clinical severity score at admission and laboratory findings were similar in the two groups. They showed more frequently complete upper lobe consolidations on chest X-ray (CXR) than infants exclusively supported by HFNC. Moreover, respiratory syncytial virus was more frequently detected in patients with HFNC failure. The presence of complete lobe consolidation was the only significant factor associated with HFNC failure. An early identification of complete lobe consolidation in severe infants with bronchiolitis may guide a personalized management.

HIGHLIGHTS BOX

What is already known about this topic? HFNC is a safe and useful method of non-invasive respiratory support. However, several questions concerning HFNC clinical practice remain unanswered. **What does this article add to our knowledge?** Patients who experienced a failure of HFNC showed more frequently a complete lobe consolidation on CXR than infants in whom HFNC allowed to overcome respiratory distress. **How does this study impact current management guidelines**? An early identification of consolidation with adequate follow-up and proper therapeutic strategies may further reduce the number of children requiring more intensive care. Finally, a CXR could be mandatory on a severe disease respiratory distress.

KEY WORDS

Bronchiolitis; chest X-ray; high-flow nasal cannula; pulmonary consolidation.

INTRODUCTION

Acute bronchiolitis is the most common respiratory illness and the main cause of respiratory failure in infants, often leading to hospitalization with high health-

care costs (1). Bronchiolitis is caused by viruses, particularly by respiratory syncytial virus (RSV), which lead to airway inflammation and obstruction of the lower respiratory tract. Most infants experience mild respiratory symptoms; however, symptoms can get worse and become severe and patients may develop breathlessness, tachypnea, retractions, and hypoxemia with hypercapnia (2). Effective medical treatment is not available; the management is mainly supportive and focuses on respiratory distress, hypoxemia, and dehydration.

A safe and promising method of non-invasive respiratory support is oxygen delivery by high-flow nasal cannula (HFNC). HFNC provides a heated and fully humidified mixture of oxygen and air at a pressure slightly more elevated than the inspiratory peak pressure via a nasal cannula interface. It seems to improve the washout of the nasopharyngeal dead space and mucociliary clearance and decrease metabolic work related to gas conditioning. Moreover, HFNC creates a low level of positive pharyngeal pressure that might help to reduce inspiratory airway resistance (3). Several papers (4-7) demonstrated that infants supported by HFNC have a low rate of pediatric intensive care unit (PICU) admission and a reduced need for escalation of care. Despite these beneficial effects, providing low levels of positive airway pressure, HFNC could not completely overcome airway resistance and atelectasis; moreover, HFNC has not been demonstrated to reduce the length of hospital stay or the duration of oxygen therapy with respect to the oxygen supplementation by nasal prongs. In addition, several questions concerning HFNC clinical practice, such as the optimal timing to initiate HFNC and the features that can predict HFNC failure, which is defined as escalation for more intensive care, remain unanswered. Answering these questions may help in optimize HFNC use.

Over seven epidemic seasons, we retrospectively analyzed the clinical course of infants hospitalized with bronchiolitis who underwent HFNC with the aim of identifying factors associated with HFNC therapy failure.

MATERIALS AND METHODS

Study design and population

Among 824 infants consecutively admitted for bronchiolitis to the Pediatric Emergency Department of Sapienza University of Rome from 2012 to 2019, we have retrospectively reviewed clinical charts of the 130 infants who required oxygen supplementation by HFNC. Bronchiolitis was defined as the first acute lower respiratory tract infection characterized by respiratory distress with tachypnea, cough, retractions, and diffuse crackles on auscultation, in previously health full term babies less than 12 months of age (8). Demographical, clinical and laboratory data such as age, gender, breastfeeding, cigarette smoke exposure, body weight, gestational age, days of illness, length of hospital stay and low-flow oxygen therapy before HFNC, were systematically collected from clinical charts. On hospital admission and just before starting HFNC, we assigned a clinical severity score (from 0 to 8) to each infant according to respiratory rate, oxygen saturation in room air, presence of retractions and ability to feed (9).

HFNC protocol and definition of HFNC failure

According to our internal protocol, patients underwent HFNC for the following clinical indications: presence of severe retractions and/or nasal flaring associated to respiratory rate higher than 70 breaths per minute and heart rate higher than 150 beats per minute and/or oxygen saturation lower than 92%. HFNC was started with a weight-based gas flow rate, starting with 1 L/Kg/min. After 15 minutes, physicians performed a clinical evaluation and, if necessary, gas flow was titrated up to 2 L/Kg and FiO_2 adjusted to target SaO_2 (over 92%). A second clinical evaluation was performed after 60 minutes and then every 3 hours over the next 24 hours. In case of HFNC failure, defined as progressive respiratory distress and inability to keep SaO_2 over 92% with a FiO2 60%, more advanced support was used.

The study protocol was approved by Policlinico Umberto I Ethic Committee (Rif. CE 2377/2012).

Radiological findings

Chest X-ray (CXR) was performed on admission in 105 infants for clinical indications such as severe respiratory distress or when a differential diagnosis was suspected. 31 out of 105 infants (29.5%) performed two CXR at least if a clinical deterioration occurred. An experienced pediatric radiologist (D.P.) evaluated each CXR and described patchy opacities (when multiple ill-defined opacities were present), complete lobar consolidation (areas of increased density which affects a pulmonary lobe) and air trapping (who refers to ex-

cess gas retention in the lungs). Radiologist was blinded to infants' conditions and clinical course, in order to avoid potential bias.

Virus detection

All patients underwent a nasopharyngeal washing (NPW), obtained using 3 ml of sterile saline solution injected into each nostril and collected with a syringe. On NPW, a panel of reverse transcriptase-polymerase chain reaction (RT-PCR) or nested PCR method was used for the detection of 14 respiratory viruses, including RSV, human rhinovirus (hRV), influenza (Flu) A and B, parainfluenza viruses (PIV) 1-3, adenovirus (ADV), human coronaviruses (hCoVs OC43, 229E, NL-63, HUKI), human metapneumovirus (hMPV) and human bocavirus (hBoV), as described (9). All specimens were collected within 24 hours of hospital admission.

Statistical analysis

Statistical analysis was performed using the SPSS Software (version 25.0; SPSS Inc., Chicago, IL). Infants exclusively supported by HFNC and those who required escalation to mechanical ventilation (MV) were divided in two groups and demographic, clinical, laboratory and radiological features were compared. Continuous variables values were expressed as mean ±SD or median and range and compared using T-student or Mann-Whitney tests. Categorical variables were expressed as number and percentages and compared using chi-square test. $P < 0.05$ was considered statistically significant. A multivariate logistic regression analysis (adjusted for age and sex) was performed among features statistically significant in univariate analysis, in order to determine factors associated with HFNC failure.

RESULTS

Among the 824 infants consecutively hospitalized with bronchiolitis in the Pediatric Emergency Department of Sapienza University of Rome, 130 (63.8% males; median age 56.5 days, range 14-319) underwent HFNC and HFNC failure occurred in only 11 infants (8.5%) (**Figure 1**). Concerning demographic and clinical characteristics, infants with HFNC failure were significantly younger and had a lower weight than infants who underwent HFNC only. The percentage of patients who underwent low-flow oxygen therapy before HFNC was significantly higher in infants with HFNC failure compared to infants who were successfully treated only with HFNC. Days of disease and clinical severity score at hospital admission did not show statistically significant differences between the two groups (**Table 1**).

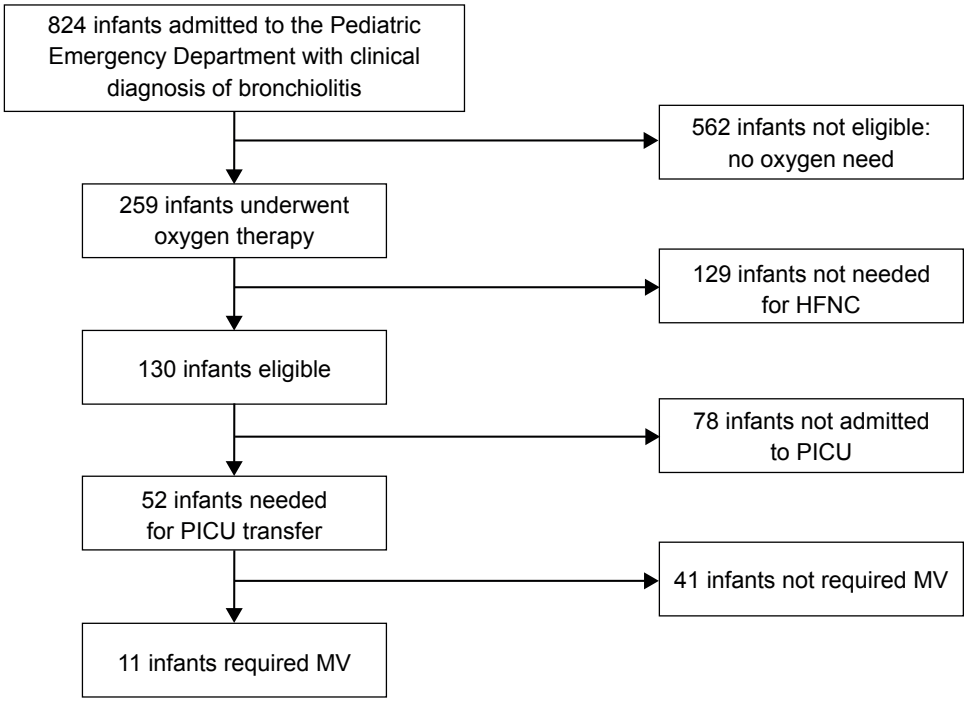

Figure 1. *Study design and study population.*

Comparing laboratory findings, patients with HFNC failure had a slightly lower lymphocyte count than infants who underwent HFNC only (**Table 2**).

Analysing CXR results, complete lobes consolidations were found in 90.9% of infants with HFNC failure compared to 14.9% of patients exclusively supported by HFNC ($p < 0.001$). The upper right lobe consolidation was more frequently detected than the upper left lobe consolidation (**Table 2**).

Analyzing infants with HFNC failure, 9 out of 11 patients underwent at least two CXR before MV. In particular, 8 infants had a gradual development of a complete upper lobe consolidation and in one severe air trapping and diffuse patchy opacities were found.

Analyzing viruses' detections, in all patients with HFNC failure a virus was identified, in particular RSV was detected in 81.8%. In 78.2% infants exclusively supported by HFNC a virus was identified and, among them, RSV was found in 63.4% as a single infection and in 18.3% as RSV-hRV coinfection (**Table 2**).

On multivariate analysis adjusted for age, sex, and RSV detection, the significant independent risk factor for HFNC failure was the presence of a complete upper right lobe consolidation (**Table 3**).

Table 1. *Demographic and clinical features in infants supported by HFNC and in those who required escalation to MV.*

	HFNC (n = 119)	MV (n = 11)	p-value
Age, days (median, range)	60 (14-319)	38 (15-86)	**0.002**
Sex (male)	75 (63%)	8 (73%)	ns
Breastfeeding	90 (75.6%)	9 (81.8%)	ns
Birth weight, g (mean ± DS)	3206 ± 510	3330 ± 351	ns
Weight at hospital admission, g (median, range)	5000 (3000-12000)	4340 (3280-6000)	**0.013**
Gestational age, weeks (mean ± DS)	38.4 ± 1.4	38.1 ± 1.1	ns
Days of disease at hospital admission (median, range)	3 (1-10)	3 (1-7)	ns
Clinical severity score at hospital admission (mean ± DS)	4.2 ± 2	4.1 ± 2.3	ns
Low-flow oxygen therapy before HFNC	62 (53.9 %)	10 (90.9 %)	**0.016**
HFNC hospitalization day (media ± ds)	1.13 ± 1.1	1 ± 1.1	ns

Table 2*. Laboratory and radiological features and virus detected in infants supported by HFNC and in those who required escalation to MV.*

	HFNC (n = 119)	MV (n = 11)	p-value
WBC/mm^3 (median, range)	9590 (3540-28160)	9080 (4860-22520)	ns
Neutrophil count/mm^3 (median, range)	3937 (473-23485)	4153 (2220-14972)	ns
Lymphocyte count/mm^3 (median, range)	4233 (1037-11404)	2742 (1630-10314)	0.063
E # (median, range)	49 (0-1285)	67 (0-247)	ns
PCR (median, range)	0.68 (0.02-9.62)	1.49 (0.29-5.16)	**0.075**
Air trapping	90 (95.7%)	10 (90.9%)	ns
Patchy opacities	55 (58.5%)	1 (9.1%)	**0.002**
Lobes consolidations	14 (14.9%)	10 (90.9%)	**<0.001**
Upper right lobe consolidation	7 (7.4%)	9 (81.8%)	**<0.001**
Upper left lobe consolidation	0 (0%)	3 (27.3%)	**<0.001**
Bilateral upper lobe consolidation	0 (0%)	3 (27.3%)	**<0.001**
Middle lobe consolidation	4 (4.3%)	1 (9.1%)	**ns**
Left lower lobe consolidation	3 (3.2%)	0 (0%)	**ns**
No virus detected	26 (21.8%)	0 (0%)	**0.083**
Virus detected	93 (78.2%)	11 (100%)	**0.036**
- RSV	59 (63.4%)	9 (81.8%)	
- hRV	9 (9.7%)	1 (9.1%)	
- Flu A and B	3 (3.2%)	0 (0%)	
- RSV-hRV coinfections	17 (18.3 %)	0 (0%)	
- hMPV	5 (5.4%)	0 (0%)	
- hBoV	0 (0%)	1 (9.1%)	

***Table 3**. A multivariate logistic regression model of covariates associated with mechanical ventilation.*

Mechanical ventilation	Odds Ratio	Std. Err.	P > z	(95% Conf. Interval)
Upper right lobe consolidation	50.565	51.357	<0.0001	(6.907-370.154)
Age, days	0.193	0.180	0.078	(0.031-1.203)
Sex (male)	2.122	2.367	0.500	(0.238-18.885)
RSV detection	1.022	1.086	0.983	(0.127-8.195)

DISCUSSION

In this large single-centre retrospective study, we sought to identify factors associated with HFNC failure in a homogeneous group of infants hospitalized with severe bronchiolitis. We demonstrated that patients who experienced a failure of HFNC showed more frequently a complete lobe consolidation on CXR than infants in whom HFNC allowed to overcome respiratory distress.

In this study, the main feature associated with HFNC failure was the presence of a complete upper lobe consolidation that affected 90.9% of patients requiring escalation to MV. Perhaps, the underdeveloped collateral ventilation due to the young age, together with a particularly acute angle of the right upper lobe bronchus, may predispose young infants to atelectasis (10). Strong evidence has demonstrated that age less than 3 months and low body weight are significant severe bronchiolitis risk factors (11, 12). In fact, anatomic factors may play a key role: the neonates and young infants' airways are small and more easily may get obstructed, causing respiratory distress and, therefore, the recourse to mechanical ventilation. In case of a complete lobar consolidation with airflow obstruction, airway resistance increases and this aspect, as well as decreased lung compliance, may contribute to respiratory distress (13). Providing low levels of positive airway pressure, HFNC could prevent upper airway collapse and allow alveolar recruitment. Meanwhile, positive end-expiratory pressure generated by invasive mechanical ventilation may also help to overcome airway resistance and atelectasis. Presumably, patients requiring escalation to MV had a severe ventilation/perfusion mismatch of an extent, that HFNC was not able to overcome hypoxemia and respiratory distress. Considering the time necessary to develop, 72.7% of patients who need MV had a gradual development of atelectasis on CXR (**Figure 2**). For this reason, it is essential an early identification of lobar consolidations. A follow-up with a simple, non-invasive, and easy to perform technique, such as for example lung ultrasound could be appropriate (14, 15). The analysis of the clinical severity score showed no differences between the two groups. Moreover, HFNC failure was primarily noticed in infants with low-flow oxygen delivered before starting HFNC. These findings suggest the importance of early use of HFNC in infants with first signs of respiratory distress.

Analyzing possible treatments of this condition, ample evidence reports the efficacy of recombinant human DNase in managing severe RSV bronchiolitis complicated with lung atelectasis (16, 17). Recent reports described that neutrophils, massively recruited in RSV bronchiolitis, release neutrophil extracellular traps (NETs). An excessive NET release has detrimental effects, causing lung injury (18). Nebulised recombinant human DNase (rhDNase) might have a fundamental role in severe bronchiolitis complicated by atelectasis (19): it seems to be able to degrade NET. Supporting these data, one enrolled patient suffering from severe bronchiolitis and supported by HFNC had a segmental upper lobe consolidation on CXR, which clearly improved after nebulised rhDNAse (**Figure 3A, B**).

Another possible therapeutic option could be chest physiotherapy, but in infants with bronchiolitis, the results are conflicting. A recent review shows that chest physiotherapy does not influence clinical course in hospitalized infants with acute bronchiolitis (20). Nevertheless, since airway clearance techniques improve mobilization and transport of secretions reducing airway obstructions by mucus plugs (21), chest physiotherapy could be implemented, particularly in selected infants with bronchiolitis and CXR consolidation.

When we evaluated laboratory data, we demonstrated a slightly decreased number of peripheral blood lymphocytes in infants with higher disease severity and escalation to mechanical ventilation. Several studies show that the immaturity of immune response during

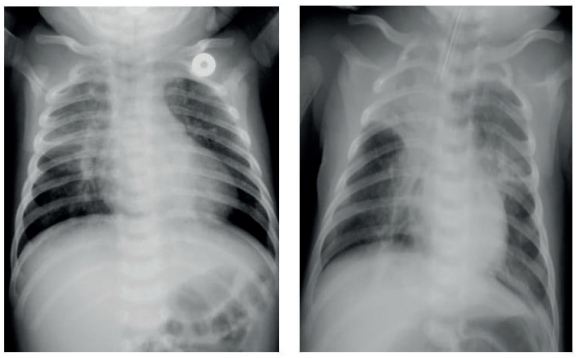

Figure 2. *Gradual development of complete upper right lobe consolidation in infant hospitalized for bronchiolitis.*

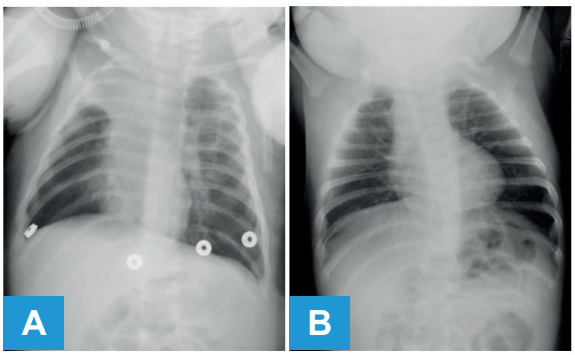

Figure 3. (A) *Segmental consolidation of the upper right lobe in infant with severe bronchiolitis who needed HFNC therapy only;* ***(B)*** *Improved aeration after 3 days of nebulised recombinant human deoxyribonuclease.*

infancy and low level of cellular immunity are important factors in the pathogenesis of severe bronchiolitis (22). Even if in this study has been involved a single institution and has been done a retrospective analysis, more studies are needed to evaluate the association of lobe consolidation with HFNC failure. Moreover, in 14 infants who did not fail on HFNC, no CXR was performed. This could interfere with our findings, but the infants' clinical improvement makes us suppose that complete lobe consolidation was absent.

CONCLUSIONS

In conclusion, our main finding is that complete upper lobe consolidation in young infants is associated with HFNC failure. Further studies are needed to understand if early identification of consolidation with adequate follow-up and proper therapeutic strategies may further reduce the number of children requiring more intensive care.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Authorship

Drs. Enrica Mancino, Raffaella Nenna, Domenico P. La Regina, Luca Cristiani, Greta Di Mattia, Luigi Matera, Daniela Pepino, Antonella Frassanito, Laura Petrarca, Fabio Midulla.

Author contributions

EM had primary responsibility for patient screening, enrolment, outcome assessment, preliminary data analysis and writing the manuscript. DPLR and GDM participated in the development of the protocol and analytical framework for the study and contributed to the writing of the manuscript.

RN and GDM contributed in the same ways as DPLR and LC, who was responsible for patient screening. DP evaluated and described each CXR. FM supervised the design and execution of the study, performed the final data analyses and contributed to the writing of the manuscript.

Ethical approval

Human studies and subjects

The study protocol was approved by Policlinico Umberto I Ethic Committee (Rif. CE 2377/2012).

Animal studies

N/A.

Data sharing and data accessibility

Data available on request from the Authors.

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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