

Factors associated with recurrent wheezing in the first year of life among premature newborns from Neonatal Intensive Care Units

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Abstract

Objectives: to determine the prevalence and factors associated with recurrent wheezing in the first year of life among premature newborns from Neonatal Intensive Care Units, in the city of Montes Claros, northern Minas Gerais.

Methods: cross-sectional study, with data collection from medical records of a follow-up clinic, interviews with mothers and, eventually, search in hospital records. Bivariate analyzes were carried out between sociodemographic and clinical characteristics and recurrent wheezing. Variables associated up to the level of 20% were analyzed by binary logistic regression, and associations defined by the Odds Ratio and respective 95% confidence intervals. Only variables associated with a 5% significance level were maintained in the final model of logistic regression.

Results: among 277 infants studied, about one fifth (21.3%) were extremely low birth weight preterm and more than half (60.7%) had birth weight below 1500 grams. The prevalence of recurrent wheezing was 14.4% (CI95% = 10.3-18.4). Mechanical ventilation (OR = 2.12; CI95% = 1.09-4.76; p = 0.030) and oxygen therapy time \geq 15 days (OR = 2.49; CI95% = 1.12-5.00; p = 0.010) were the risk factors for the event.

Conclusions: there is a high prevalence of recurrent wheezing in the evaluated group and the associated variables reiterate the risk of prolonged oxygen therapy and mechanical ventilation for premature newborns.

Key words *Infant, Premature, Respiratory sounds, Prevalence, Risk factors*



Introduction

Survival of preterm and low birth weight neonates has been progressively greater with technological advances incorporated into the Neonatal Intensive Care Units (NICU).¹ However, most of these infants suffer many complications after birth, such as respiratory failure with need for mechanical ventilation, infectious and hemorrhagic conditions and need specialized outpatient follow-up after hospital discharge.² The follow-up of infants discharged from the NICU shows many cases of readmissions, growth and development delays, visual and auditory sequelae and respiratory problems in future life.³⁻⁵

The prolonged use of oxygen therapy, with or without mechanical ventilation, the occurrence of neonatal pneumonia and other changes in lung function are examples of factors that make preterm and low birth weight neonates particularly vulnerable to respiratory diseases in the first years of life.^{6,7} The necessary adaptations to the lung development of premature infants (physiological or not) predispose to the emergence of diseases such as asthma and chronic obstructive pulmonary disease in childhood and adulthood.⁷

Bronchopulmonary dysplasia (BPD) represents the main respiratory sequelae for premature infants, presenting with episodes of coughing, wheezing and need for oxygen supplementation, very often evolving with compromised pulmonary function in future life.⁸⁻¹⁰ However, in addition to BPD, the occurrence of wheezing episodes in the first months of life are widely associated with low gestational age and low birth weight and can also significantly compromise the quality of life of these children.^{7,10,11}

In Brazil, there are few studies that investigate the respiratory morbidity of preterm or low birth weight newborns in the first years of life, including, in addition to BPD, pneumonia, hospital admissions for respiratory causes and recurrent wheezing.^{7,12-14} Considering there is an increase in the survival of very premature infant, it is necessary to increase knowledge about the morbidity profile of this group, in order to provide timely guidance to neonatal care services. In addition to lower respiratory tract infections, recurrent wheezing, defined as the occurrence of three or more episodes of wheezing measured by medical diagnosis in the first year of life, represents an important morbidity to be studied, due to its social and economic impact.¹⁵

Some factors have been shown to be associated with greater respiratory morbidity in the first year of life, especially in premature infants, such as changes

or diseases resulting from pulmonary immaturity,¹⁶ use of mechanical ventilation,¹³ respiratory syncytial virus infection, male gender and low birth weight¹⁷ and prolonged use of oxygen therapy.^{9,12} However, there are still few studies that specifically assess the factors associated with recurrent wheezing among preterm infants in the same period.

This study aimed to identify the prevalence and maternal, perinatal, and neonatal factors associated with recurrent wheezing in the first year of life among preterm, high-risk neonates followed up at an outpatient clinic in the north of Minas Gerais State.

Methods

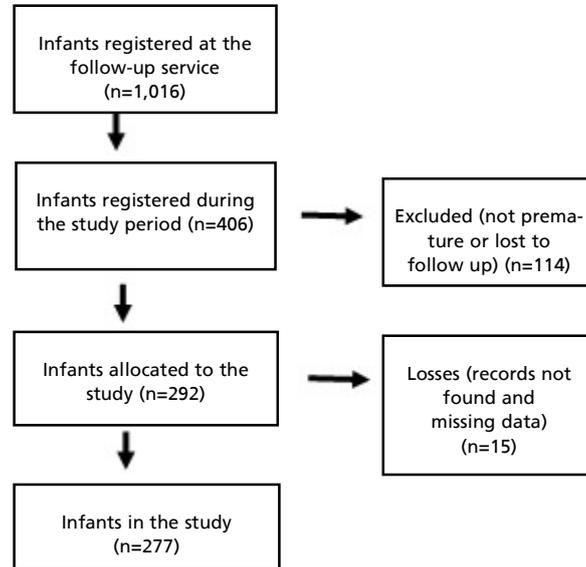
This is a cross-sectional study conducted from the monitoring of newborns assisted at a high-risk infant follow-up clinic bound to the city's health department in Montes Claros, in the north of Minas Gerais. The city has an estimated population of 410 thousand inhabitants and has only one high-risk infant follow-up clinic, where infants from the two public NICUs are monitored with interdisciplinary assistance. The data were obtained by analyzing the medical records of the infants registered after leaving the NICUs, interviews with their mothers and eventual consults in the hospital records (when there weren't medical records available, and the mothers didn't know).

The study included infants registered in the service since 2014, as an attempt to avoid the limitations of older data. For the sample calculation, a prevalence of 17% of recurrent wheezing episodes in the first year of life was considered,¹⁵ with an error margin of 4% and confidence level of 95%, which defined a minimum of 264 infants/records to analyze. The inclusion criteria were infants born prematurely (gestational age < 37 weeks, according to medical record) that had left the NICUs, regularly monitored throughout the first year of life, that is, infants that attended monthly, bimonthly, or quarterly appointments defined by the service. Infants whose mothers did not have precise information about the pregnancy and birth conditions were excluded, as well as those whose most relevant data were not registered in the respective medical records. The flowchart with the process of allocation of the children involved in the study is shown in Figure 1.

Although there is a specific instrument to evaluate recurrent wheezing in infants with family interviews,¹⁸ it wasn't used in the study, since the evaluated group included data that were only researched in previous medical records from infants born

Figure 1

Flowchart of the selection process of the neonates' sample followed up in a high-risk infant follow-up clinic. Montes Claros (MG); Brazil; 2018.



prematurely. The instrument used for collecting data was based on the specific objectives of the study, approaching maternal characteristics, pregnancy and birth conditions and postpartum complications during the NICU stay. Information related to the monitoring of the infants during the first year of life was also collected.

Data collection was performed by two trainee research students, specifically trained to identify data in records and interviews with mothers, and eventually, clarifying information along with the professional team assisting the children. The selection of medical records was performed randomly, by simple random sampling, from the consecutive selection of records, considering for children allocation, the inclusion criterion of complete follow-up in the first year of life. Data collection period was from February to December 2018 and included children assisted between 2014 and 2018.

The dependent variable was the occurrence of at least three wheezing episodes during the first year of life, registered in the child's chart and/or informed by the mother with a report of inhalatory medication. The independent variables were pregnancy and birth conditions and neonatal complications. Descriptive analysis of data was made by frequency distribution. After bivariate analysis, a binary logistic regression analysis (backward method) was made for evalu-

ating all the variables that were associated until the level of 20% ($p < 0.20$) in the initial analysis. The magnitudes of the associations were defined by the odds ratios and their respective 95% confidence intervals. For the final model, the significance level was defined by 5%. The adjusting of the multiple final model was made through the Hosmer-Lemeshow test. All the data collected were codified and analyzed through the software IBM-SPSS for Windows version 22.0.

The research project was appreciated and approved by the Research Ethical Committee of the institution where the study was carried out, with a register of CAAE 58699016.8.0000.5146 and approval protocol nº 1.800.915.

Results

Data from 277 infants were collected, with a slight predominance of male sex (54.2%). Most of mothers had previous deliveries registered (57.8%) and the type of birth was predominantly surgical (68.2%). Gestational records showed that most mothers had complication during pregnancy, and systemic arterial hypertension was the most mentioned (35.7%). The analysis of the gestational age and birth weight revealed that no more than a fifth of the newborns had extreme low weight and over half the newborns

weighed less than 1500 grams (Table 1).

Table 2 shows the frequency distribution of the main complications presented by the evaluated group during the NICU stay. Over two thirds of the infants needed oxygen therapy for more than 15 days (66.5%).

The occurrence of at least three episodes of wheezing (recurrent wheezing) in the first year of life was registered for 40 infants (14.4%). Table 3 shows the result of the bivariate analysis between the studied characteristics of the group and recurrent

wheezing. The variables that were associated up to 20% level ($p < 0,20$) were analyzed by binary logistic regression.

The variables that, after multiple analysis, have shown association with recurrent wheezing were the use of mechanical ventilation ($p=0.030$; OR=2.12; IC95%= 1.09-4.76) and time of oxygen therapy equal or superior to 15 days ($p=0.010$; OR=2.49; IC95%=1.12-5.00) (Table 4).

Table 1

Gestational and delivery characteristics of premature neonates followed up in a high-risk follow-up clinic in the north of Minas Gerais; Montes Claros (MG), Brazil; 2014-2018.

Variables	N	%
Maternal parity		
Primiparous	127	42.2
Multiparous	150	57.8
Pregnancy complications		
Hypertension	99	35.7
Diabetes	13	4.7
Infections	29	10.5
None referred	112	40.4
Others	24	8.7
Prenatal corticosteroid therapy		
Yes	142	51.3
No	135	48.7
Time of rupture of membranes (hours)		
> 18	67	24.2
≤ 18	210	75.8
Childbirth delivery		
Natural	88	31.8
Cesarean surgery	189	68.2
Sex		
Male	150	54.2
Female	127	45.8
Gestational age (weeks)		
< 28	31	11.2
28-32	169	61.0
> 32	77	27.8
Apgar 5 th min		
≥ 7	194	70.0
< 7	83	30.0
Birth weight (g)		
< 1,000	59	21.3
1,000 - 1,499	109	39.4
≥ 1,500	109	39.4
Newborn classification*		
AGA	182	65.7
SGA	85	30.7
LGA	10	3.6

* AGA= Appropriate for gestational age; SGA= Small for gestational age; LGA= Large for gestational age.

Discussion

The results of this study reveal an elevated prevalence of recurrent wheezing among the premature infants that leave NICU throughout their first year of life. However, the prevalence observed was slightly lower than that registered by a large study conducted

by Mallol *et al.*,¹⁵ with over 12 thousand infants in various countries in Latin America. Another follow-up study with moderately premature children (32 to 35 weeks) registered a frequency of 17.8% of recurrent wheezing reported by parents.¹⁹ The results of a Spanish study revealed a prevalence of 18.8%, also within the gestational age of 32 and 35 weeks.²⁰ The

Table 2

Main complications recorded in the NICU for premature neonates followed up in a high-risk follow-up clinic in the north of Minas Gerais; Montes Claros (MG), Brazil; 2014-2018.

Variables	N	%
Oxygen therapy time (days)		
< 7	63	22.7
7 - 14	30	10.8
15-29	124	44.8
> 30	60	21.7
Use of vasoactive amines		
No	190	68.6
Yes	87	31.4
Sepsis		
No	112	40.4
Yes	165	59.6
Blood transfusion		
No	182	65.7
Yes	95	34.3
Neurological complications		
No	226	81.6
Yes	51	18.4

NICU= Neonatal Intensive Care Unit.

Table 3

Association between characteristics of the studied group and recurrent wheezing in the first year of life (bivariate analysis) for premature neonates followed up at a high-risk follow-up clinic in the north of Minas Gerais; Montes Claros (MG), Brazil; 2014-2018.

Variables	Recurrent wheezing				p	OR gross (CI95%)
	Yes		No			
	n	%	n	%		
Sex					0.252	
Female	15	11.8	112	88.2		0.67 (0.34 - 1.33)
Male	25	16.7	125	83.3		1.0
Maternal parity					0.067	
Primiparous	13	10.2	114	89.8		0.52 (0.26-1.06)
Multiparous	27	18.0	123	82.0		1.0
Prenatal corticosteroid therapy					0.607	
No	21	15.6	114	84.8		1.19 (0.61-2.33)
Yes	19	13.4	123	86.6		1.0

continue

OR= odds ratio.

Table 3 **concluded**

Association between characteristics of the studied group and recurrent wheezing in the first year of life (bivariate analysis) for premature neonates followed up at a high-risk follow-up clinic in the north of Minas Gerais; Montes Claros (MG), Brazil; 2014-2018.

Variables	Recurrent wheezing				p	OR gross (CI95%)
	Yes		No			
	n	%	n	%		
Time of rupture of membranes (hours)					0.788	
> 18	9	13.4	58	86.6		0.89 (0.40- 1.99)
≤ 18	31	14.8	179	85.2		1.0
Childbirth delivery					0.227	
Cesarean surgery	24	12.7	165	87.3		1.23 (0.77 – 3.05)
Natural	16	18.2	72	81.8		1.0
Apgar 5 th min					0.137	
< 7	8	9.6	75	90.4		0.54 (0.24- 1.22)
≥ 7	32	16.5	162	93.5		
Resuscitation at birth					0.507	
Yes	21	15.9	111	84.1		1.25 (0.64-2.46)
No	19	13.1	126	86.9		
Oxygen therapy time (days)					0.019	
≥ 15	33	19.9	151	82.1		2.68 (1.14-6.33)
< 15	7	7.5	86	92.5		1.0
Mechanical ventilation support					0.022	
Yes	30	18.5	132	81.5		2.39 (1.12-5.10)
No	10	8.7	105	91.3		1.0
Birth weight (g))					0.259	
< 1,000	12	20.3	47	79.7		1.48 (0.65-3.39)
1,000g - 1,499	12	11.0	97	89.0		0.72 (0.32-1.60)
≥ 1,500	16	14.7	93	85.3		1.0
Gestational age (weeks)					0.048	
< 28	9	29.0	22	71.0		3.09 (1.09-8.76)
28-32	22	13.0	147	87.0		1.13 (0.49-2.59)
> 32	9	11.7	68	88.3		1.0
Use of vasoactive amines					0.102	
Yes	17	19.5	70	80.5		1.76 (0.89-3.50)
No	23	12.1	167	87.9		1.0
Blood transfusion					0.024	
Yes	20	21.1	75	78.9		2.16 (1.10-4.25)
No	20	11.0	162	89.0		1.0
Sepsis					0.449	
Yes	26	15.8	139	84.2		1.31 (0.65-2.64)
No	14	12.5	98	87.5		1.0

OR= *odds ratio*.

variability of the results between the studies can be justified by differences in the evaluated public, considering the inclusion or not of premature infants, the degree of prematurity of the group and the number of episodes that define the recurrent wheezing.

There are few studies in Brazil that approach respiratory morbidity in premature infants, although

several authors highlight the relevance of the subject and approach related subjects in their works.^{10,12-14,16} In a study with premature infants that had been in a NICU during the first year of life, the authors registered a prevalence of 27.8% of airway obstructive syndrome, which was defined by the presence of recurrent wheezing (two or more episodes of wheezes that cause shortness of breath, fatigue or

Table 4

Variables associated with recurrent wheezing in the first year of life (binary logistic regression) for premature neonates followed up at a high-risk follow-up clinic in the north of Minas Gerais; Montes Claros (MG), Brazil; 2014-2018.

Variables	p	OR adjusted (CI95%)
Maternal parity	0.079	
Primiparous		0.47 (0.20-1.09)
Multiparous		1.0
Apgar 5 th min	0.067	
< 7		0.45 (0.19- 1.17)
≥ 7		
Oxygen therapy time (days)	0.010	
≥ 15		2.49 (1.12-5.00)
< 15		1.0
Mechanical ventilation support	0.030	
Sim		2.12 (1.09-4.76)
No		1.0
Gestational age (weeks)	0.138	
< 28		1.96 (0.81-4.75)
28-32		1.02 (0.88-2.20)
> 32		1.0
Use of vasoactive amines	0.463	
Yes		1.32 (0.59-2.97)
No		1.0
Blood transfusion	0.231	
Yes		1.66 (0.72-3.80)
No		1.0

OR= *odds ratio*.

Hosmer e Lemeshow test: $p=0.119$.

respiratory difficulties).¹² In this case, the high prevalence can be attributed to the concept assumed for recurrent wheezing. In a more recent study, the authors registered a prevalence of 27.4% for recurrent wheezing in a year, but though the study included only infants born prematurely, it was not restricted to the first year of life.¹⁴

Another national study made in five Brazilian capitals revealed a much bigger prevalence of recurrent wheezing among low birth weight newborns, which reached 28%.⁶ The circumstances of data collection, however, limit the possibility of comparison with the results of this research, since the referred study was made throughout five years, using only interviews with mothers, without a medical diagnosis confirmation and the analysis restricted to low-birth-weight neonates, which does not define prematurity.

Scientific literature registers an unequivocal association between prematurity and the development of future pulmonary diseases during childhood, regardless of bronchopulmonary dysplasia occur-

rence.^{7,21,22} To Friedrich et al.,¹⁶ both prematurity itself, as well as the interventions and care necessary to maintain the life of preterm infants, apparently alter permanently, to a greater or lesser degree, the development of the respiratory system. Other authors also register the association between prematurity and bronchial hyperresponsivity.²³

The association between prematurity and wheezing is robust, to different studies, even when the concepts of prematurity (different gestational ages) and asthma (medical diagnosis, family, recurrent wheezing) are adjusted.²⁴ The precise mechanisms that would explain the association between prematurity and recurrent wheezing or asthma are still not well understood. In a large study including a systematic revision and meta-analysis that approached the association between prematurity and asthma, the authors concluded that neither a persistent reduced volume in the airways of infants born prematurely, nor the presence of inflammatory cytokines in their airways, nor an eventually faster growth could explain the association consistently.

The authors suggest further studies to improve the knowledge basis of development adaptations in premature lungs.²⁵

In summary, the conclusions of the most robust studies highlight that the association between wheezing in the future life (after the first year of life) and premature birth can be related to the care provided to the newborn.^{24,25} In the analysis of factors associated to recurrent wheezing in this study, which included only infants born prematurely, two variables remained related after multiple analysis and both were associated with the use of resources for respiratory supplementation: the period of oxygen therapy being equal or superior to 15 days and the use of mechanical ventilation.

Regarding the damages associated with the prolonged use of oxygen therapy in the neonatal period, there is already a well-consolidated association with bronchopulmonary dysplasia (BPD). Some studies including animal models have already identified that exposure to high concentrations of oxygen by itself can induce inflammation, fibrosis, and emphysema in immature lungs.^{26,27} For some authors, the abusive use of oxygen tends to cause a larger production of reactive oxygen species, leading to a higher susceptibility to oxidative stress and cellular damage in the alveoli of the immature lung.^{27,28}

The association between respiratory diseases and mechanical ventilation has already been previously registered by researchers who evaluated neonatal risk factors for respiratory morbidity in the first year of life in premature newborns.¹³ However, the study did not evaluate in a distinct way the recurrent wheezing in the first year of life. Some authors point that the use of mechanical ventilation, even for short periods, is sufficient to induce the release of pro-inflammatory cytokines in the newborns' premature lungs, leading to injuries that can be harmful in the future, and recommend alternative means of protection other than conventional mechanical ventilation.²⁹

It is known that the positive pressure and the excessive volume administered through assisted ventilation can cause damage to immature lung from exacerbated inflation of the alveoli, causing cellular damage and inflammation, regardless of the toxicity associated to oxygen therapy.⁹ A recent study done with sheep concluded that there are specific patterns of injuries for a given gestational age, in response to the same mechanical ventilation strategy. The authors conclude that the results found reinforce the need to develop individual respiratory support approaches, specific to the gestational age of the

premature infant.³⁰

Blanken *et al.*¹⁹ carried out a large research on risk factors for wheezing in the first year of life of premature infants, but it was restricted to gestational age from 32 to 35 weeks. In bivariate analysis, the authors reported an association with mothers that smoked and had a history of atopy, male sex infants, ventilatory support in the neonatal period and other variables related to health assistance in the first year of life. Nonetheless, after multivariate analysis, the authors concluded that, for the evaluated group (moderately premature infants), the lack of assistance in childcare was the variable that presented the highest populational risk attributable to recurrent wheezing.

Few national studies evaluate in specific way the respiratory conditions in follow-up of premature infants. In a recent study made with a similar approach, which analyzed infants from three to four years old, the authors concluded that a history of atopy, shorter gestational age and coexistence with two or more children presented a significant association with recurrent wheezing. The authors also reported that infants with a shorter gestational age which received monoclonal antibodies against the respiratory syncytial virus had a higher prevalence of recurrent wheezing than the group of infants with a larger gestational age.¹⁴ In the referred study, the authors did not evaluate the environmental factors during the neonatal period, highlighting mostly post neonatal risk factors associated to recurrent wheezing in infants, which was made in a reduced version in another study.¹⁸

The results of this study should be analyzed considering some limitations: the emphasis of the analysis was for variables related to the conditions of birth and neonatal period, but variables such as the use of surfactants or maximum intensity of mechanical ventilation parameters were not studied. We also did not evaluate socioeconomic factors, use of monoclonal antibodies against the respiratory syncytial virus, family history of asthma, access to health services after discharge from the NICU or clinical conditions associated, such as gastroesophageal reflux, which is relatively common in the population studied. There are other limitations related to the generalization of the data (external validation), considering that the infants evaluated had been to NICU, therefore had a specific profile of prematurity and conditions of survival during the neonatal period. Regardless of the need for other national studies on the subject, the results are relevant and highlight the necessity of a greater vigilance on the use of ventilatory support for premature

newborns.

The results of the present study reinforce the risks of prolonged oxygen therapy and mechanical ventilation in premature neonates, which are related to the development of recurrent wheezing. The authors recommend further studies considering the limitations identified and alert that the success in the care of premature and low weight neonates cannot be based only in their survival, but in their quality of life and future costs for the family and society.

Acknowledgments

The authors are grateful for the financial support of this research by *Fundação de Apoio à Pesquisa do Estado de Minas Gerais* - FAPEMIG (APQ-02030-15) and *Conselho Nacional de Desenvolvimento Científico e Tecnológico* - CNPq (research productivity grant).

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Authors' contribution

Caldeira AP, Pinho L, Carneiro JA: idea conception, data analysis, project management, original manuscript draft, and final writing review. Ramos ACR, Souza RG: data collection, data analysis, and final draft review. All authors approved the final version of the article.

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Received on February 26, 2020

Final version presented on June 21, 2021

Approved on July 19, 2021