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Original Article

Respiratory Morbidity in Prematurely Born Children Receiving Palivizumab Prophylaxis of Respiratory Syncytial Virus Disease

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ABSTRACT

Background: Preterm delivery is a risk factor for increased respiratory morbidity in early childhood. This study aimed to quantify respiratory morbidity in preterm survivors, comparing incidence rates among different gestational ages, birth weighst, and current age groups. Additionally, we sought to evaluate variations in respiratory outcomes between groups with and without bronchopulmonary dysplasia (BPD).

Methods: Our study included 89 prematurely born children who were receiving palivizumab prophylaxis for respiratory syncytial virus infection. We categorized the patients based on four criteria: 1) current age of less and more than 1 year, 2) gestational age (GA) of less and more than 30 weeks, 3) birth weight (BW) of less than 1000 g, between 1000 g and 1500 g, and more than 1500 g, 4) with and without BPD. We compared these groups in terms of respiratory morbidity and respiratory therapy.

Results: The average age was 11.9 months, the average GA was 28.9 weeks and the average BW was 1202.4 g. According to the 28-day definition of BPD 75.3% patients had BPD. Around one-third (35.9%) of patients experienced wheezing episodes, 7.8% had pneumonia, 10.1% were hospitalized due to respiratory exacerbation and just 1.1% had RSV infection. There were no statistically significant differences between the different age, GA, BW, or BPD/non-BPD groups in the number of hospitalizations or pneumonia. On the other hand, children older than 12 months and children with BPD had significantly more wheezing episodes. Fifty-nine (66.3%) patients had been receiving inhaled corticosteroids (ICS), all of whom had BPD.

Conclusion: Prematurely-born children receiving palivizumab had significant respiratory morbidity, but majority did not have RSV infection. Further clinical studies are necessary to improve our understanding of the role of ICS in patients with established BPD.

Keywords: Bronchopulmonary dysplasia, Palivizumab, Premature birth, Respiratory infections, Wheezing

Introduction

It is well known that preterm delivery, whether accompanied by bronchopulmonary dysplasia (BPD) or not, is a risk factor for increased respiratory morbidity in early childhood. As the survival of preterm infants has improved in recent years there are now a significant number of children who need long-term respiratory follow-up to reduce the burden of potential complications. Unfortunately, there are scarcely enough studies investigating early childhood respiratory morbidity in prematurely born children post their initial discharge from the hospital. The published studies show a higher incidence of lower respiratory tract infections,

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wheezing, and antibiotic prescriptions in ex-preterm infants, especially those discharged home on oxygen. To address this knowledge gap, further studies are imperative to explore effective strategies for the prevention of respiratory morbidity in this vulnerable population (1).

Prematurely born children, especially those with respiratory morbidities, have increased utilization of healthcare resource over the years with the substantial economic impact (2,3). Furthermore, it has been proven that caregivers of children with BPD had lower caregiver health-related quality of life (4).

Both premature delivery and BPD stand as well-established risk factors for respiratory syncytial virus (RSV) infection, often leading to subsequent complications. Complicated RSV infections in children result in prolonged hospitalization which is then naturally accompanied by a higher percentage of respiratory support, antibiotics, bronchodilators, and steroid usage. Palivizumab is a humanized monoclonal antibody that has been approved for prophylaxis against serious lower respiratory tract infections (LRTIs) caused by RSV infection in high-risk infants (5).

The primary aim of our study was to quantify early childhood respiratory morbidity in preterm survivors, to compare the incidence of respiratory exacerbations in different gestational age, birth weight, and current age groups, and to compare the groups with and without BPD. As our group consisted of infants who were receiving palivizumab the secondary aim was to establish the incidence of RSV infections in these children.

Methods

Our study is a retrospective cohort study. It included 89 children who were born prematurely and who were receiving palivizumab prophylaxis for RSV infection from October 2022 to February 2023. All those children were previously hospitalized in the neonatal intensive care unit and neonatology department of the Institute for Child and Youth Health Care of Vojvodina. After discharge they were regularly controlled and they were receiving palivizumab in the RSV season months. The immunization was done according to the following indications: children born before 29 weeks of gestation aged less than 12 months at the start of the RSV season, children born before 32 weeks of gestation aged less than 6 months at the start of the RSV season, children with BPD aged less than 12 months at the start of the RSV season, children with BPD aged less than 24 months at the start of the RSV season who required therapy 6 months before the start of the RSV season (oxygen therapy, chronic corticosteroid, bronchodilators and/or diuretic usage). Children receiving palivizumab due to other indications were excluded from this study.

Various parameters were analyzed from the patient's medical history, including: gestational age (GA), birth weight (BW), Apgar score (AS), presence or absence of BPD, additional diagnosis during the neonatal period apart from BPD, duration of respiratory support (invasive or non-invasive), duration of supplemental oxygen, surfactant administration, dexamethasone therapy (according to Dexamethasone: A Randomized Trial (DART) study), and prolonged furosemide therapy. To comprehensively asses the respiratory morbidity, and the atopic status of the children at the end of RSV season 2022/2023, we constructed a questionnaire for parents. The questionnaire consisted of the following items: number of wheezing episodes and pneumonia, number of times systemic corticosteroids were used, number of hospitalizations due to respiratory exacerbation, number of RSV infections, presence or absence of chronic cough, chronic nasal secretion, sneezing, itchy nose, eczema, chronic usage of inhaled corticosteroid (ICS) or Montelukast, additional diagnostic to access atopy (IgE, specific IgE, prick test), and exposure to tobacco smoke. The last question was concerning the parents' knowledge about the meaning of bronchopulmonary dysplasia.

We categorized the patients based on four criteria: 1) current age of less and more than 1 year, 2) GA of less and more than 30 weeks, 3) BW of less than 1000 g, between 1000 g and 1500 g, and more than 1500 g, 4) with and without BPD based on the two definitions (need for oxygen therapy at 28 days of age and 36 weeks postmenstrual age (PMA)). These groups were subsequently compared in terms of respiratory morbidity and respiratory therapy.

Statistical Package for Social Sciences - SPSS 21 was used for statistical data processing. Numerical characteristics are presented using mean values (arithmetic mean), and measures of variability (value range, standard deviation). Attributive characteristics were presented using frequencies and percentages. The comparison of numerical values between two groups was performed using the non-parametric Mann-Whitney test, while the

non-parametric Kruskal-Wallis test was used to compare values between three or more groups of data. Testing the difference in frequencies of attributive features was performed using the $\chi 2$ test. Values of significance level $p<0.05$ are considered statistically significant. The effect size is 0.3 (w=0.3).

Ethical approval

The research was reviewed and approved by our institutional ethics committee (Institute for Child and Youth Health Care of Vojvodina Ethics Committee, decision number: 17-11/23), and participation involved informed consent of patient's parents.

Results

Our study included 89 patients who were born prematurely and had been receiving palivizumab due to preterm delivery with or without BPD. There were 49 (55.1%) boys and 40 (44.9%) girls.

The youngest child was 3 months old and the oldest one was 26 months old. The average age was 11.9 months. There were 49 (55.1%) children aged less than 12 months and 40 (44.9%) children aged more than 12 months.

The lowest GA was 24 weeks and the highest was 33 weeks. The average GA was 28.9 weeks. There were 53 children (59.6%) born before 30 weeks of gestation and 36 children (40.4%) born after 30 weeks of gestation. All children born after 33 weeks of gestation had BPD as premature delivery after 32 weeks of gestation without BPD is not a criterion for receiving palivizumab.

The lowest BW was 670 g and the highest was 2100 g. The average BW was 1202.4 g. There were 29 (32.6%) children with BW of less than 1000 g, 42 (47.2%) children with BW of 1000-1500 g, and 18 (20.2%) children with BW of more than 1500 g.

The average AS in the first minute was 5.1, and it increased to 6.6 in the fifth minute. The distribution of AS in the first minute was as follows: 20 patients (23%) had a score of 0-3, 54 patients (62.1%) scored 4-7, and 13 patients (14.9%) scored 8-10. The distribution of AS in the fifth minute was as follows: 5 patients (5.7%) had a score of 0-3, 54 patients (62.1%) scored 4-7, and 28 patients (32.2%) scored 8-10. The AS assessments were not available for two patients as the delivery occurred at home.

According to the most commonly used definition of BPD (need for oxygen therapy at 28 days of age) 67 (75.3%) patients were classified as having BPD. When using the alternative definition (need of oxygen therapy at 36 weeks PMA) the number of children with BPD was 38 (42.7%). No child was on home oxygen therapy. The criteria for receiving palivizumab were made based on the first-mentioned definition of BPD.

Surfactant was administrated in 72 (80.9%) patients, significantly more often in the group of children older than 12 months and those with BPD (based on the 28-day definition). Just one patient with a BW of less than 1000 g didn't receive surfactant, preventing a valid statistical comparison for the BW group. There was no statistically significant difference in surfactant administration between different GA groups.

Systemic corticosteroid therapy (DART) was used in 30 (33.7%) patients. When compared between the groups systemic corticosteroid therapy was used significantly more often in children aged more than 12 months, with GA of less than 30 weeks, with BW of less than 1000 g, and those with BPD (according to both definitions). The long-term furosemide therapy due to BPD was administered to only 1 patient (1.1%).

Respiratory support (both non-invasive and invasive) was conducted in 82 (92.13%) patients. The average duration of respiratory support was 11.71 days, ranging from a minimum of 1 day to a maximum of 43 days. Upon comparison between the groups: children older than 12 months, those with GA of less than 30 weeks, and BW of less than 1000 g, and those with BPD (according to both definitions) experienced a statistically significant longer durations of respiratory support.

The average duration of oxygen therapy was 44.4 days, the minimum duration was 2 days and the maximum time was 115 days. When compared between the groups: children older than 12 months, those with GA of less than 30 weeks, and BW of less than 1000 g, and those with BPD (both definitions) had statistically significant longer durations of oxygen therapy.

The number of children with additional diagnoses apart from BPD is presented in Table 1.

Thirty-two (35.9%) patients had wheezing episodes. The average number of wheezing episodes was 1,1, maximum was 10. Children older than 12 months, and those with BPD (according to both definitions) had significantly more wheezing episodes, while there was no statistically significant difference between the GA and BW groups (Table 2).

Eleven patients (12.3%) received intravenous

Table 1. The diagnoses of preterm children during the neonatal period

Organ system	Disorder	Number of children (percentage)
central nervous system	intracranial haemorrhage	42
	leukomalacia	4
	dystonia	5
	convulsions	3
	meningitis and cerebral ischemia	1
	cerebral cyst	1
		48 (46.1%)
eyes	retinopathy of prematurity	43 (48.3%)
blood	anaemia	72 (80.9%)
cardiovascular system	atrial septal defect	2
	patent ductus arteriosus	13
	congestive cardiomyopathy	1
		21 (23.6%)
respiratory system	pneumothorax	5
	pneumonia	7
		12 (13.5%)
urinary tract	acute kidney injury	2
	hydronephrosis	8
	urinary tract infection	12
		20 (22.5%)
gastrointestinal tract	gastroesophageal reflux	7
	anal atresia	1
	oesophageal perforation	1
	cirrhosis	1
	liver damage	1
	cleft palate	1
		12 (13.5%)
bones	osteopenia	3 (3.4%)
other	sepsis	26 (29.2%)
	jaundice	20 (22.5%)
	combined immunodeficiency	1 (1.1%)
	inguinal hernia	3 (3.4%)

systemic corticosteroids (methylprednisolon) due to wheezing episodes, with a significantly higher incidence in children older than 12 months, and those with BPD (36 weeks PMA definition). No discernible differences were observed between the gestational age (GA) and birth weight (BW) groups.

Seven patients (7.8%) were diagnosed with pneumonia, with no significant difference between the groups.

A single patient (1.1%) contracted an RSV infection in early October, before being started on the prophylactic course of palivizumab.

Table 2. Number of wheezing episodes in different groups of children

		Number of wheezing episodes					Mann-Whitney U / Kruskal-Wallis H*	p
		N	Average	SD	Minimum	Maximum		
Age	<12 months	49	0,53	1,26	0	6		
	>=12 months	40	1,78	2,88	0	10	704,500	0,008
	all	89	1,09	2,22	0	10		
GW	<30	53	0,85	1,90	0	10		
	>=30	36	1,44	2,61	0	10	873,000	0,429
	all	89	1,09	2,22	0	10		
BW	<1000g	29	1,34	2,42	0	10		
	1000-1500g	42	0,83	1,85	0	10	1,381*	0,501
	>1500g	18	1,28	2,70	0	10		
	all	89	1,09	2,22	0	10		
BPD 28 day def.	no	22	0,14	0,35	0	1		
	yes	67	1,40	2,47	0	10	494,500	0,007
	all	89	1,09	2,22	0	10		
BPD 36w PMA def.	no	51	0,43	0,88	0	4		
	yes	38	1,97	3,04	0	10	712,000	0,013
	all	89	1,09	2,22	0	10		

Nine (10.1%) patients were hospitalized due to respiratory exacerbation, all of whom experienced a favorable outcome. There were no statistically significant differences between groups in the number of hospitalizations.

Chronic cough was present in 4 patients (4.5%) and was associated with BPD in all of them.

Symptoms of allergic rhinitis (sneezing, itchy nose) were present in 14 patients (15.7%), without the statistically significant difference between groups.

Eczema was present in 16 (18%) patients, without the statistically significant difference between groups.

A total of 59 patients (66.3%) were under treatment with inhaled corticosteroids (ICS), and all of them were diagnosed with bronchopulmonary dysplasia (BPD). There were no patients using the combination of ICS and long-acting beta-agonist (LABA). ICS were more often used in children older than 12 months, with GA <30 gestational weeks, with BW less than 1000 g, and with BPD (Table 3). A statistically significant longer duration of ICS usage was observed in children older than 12 months and those with BPD based on the 36-week postmenstrual age (PMA) definition. Among the children receiving ICS (59 patients), 24 (40.7%) had a history of wheezing episodes.

Only two (2.2%) patients had been receiving montelukast. Addition atopic analyses turned positive in 3 (3.4%) patients. Seven (7.9%) patients were exposed to tobacco smoke every day while 4 (4.5%) patients were exposed occasionally.

When queried about the meaning of bronchopulmonary dysplasia (BPD), 22 parents (24.7%) confirmed their awareness, 6 parents (6.7%) claimed partial knowledge, and 61 parents (68.5%) admitted having no information about this disease. Importantly, there was no statistically significant difference observed between the group of parents with children having BPD and those without.

Discussion

Respiratory morbidity in preterm children

Prematurely born children, especially those born before 32 weeks of gestation and those with BPD, have a greater risk of respiratory infections, wheezing, and respiratory-related illness hospitalization in the first two years of life compared with children born in term (1,5,6). Respiratory morbidity in these children gradually decreases during the first five years of life but it is still more common than expected (6). The increase in respiratory morbidity is not exclusively limited to the groups of infants with GA of less than 32 weeks; even infants born between 32 to 36 weeks of GA experience considerable respiratory morbidity compared to term infants (7,8). Our study included premature infants who were receiving palivizumab according to the current guidelines which encompass - children born before 32 weeks of GA or those with BPD regardless of GA. The average birth weight (BW) in our study cohort was 1202.4 g, ranging

Table 3. Inhaled corticosteroid usage in different groups of children

		Inahaled corticosteroid therapy						χ^2	p
		no		Yes		All			
		N	%	N	%	N	%		
Age	<12 months	26	86,7%	23	39,0%	49	55,1%	18,275	<0.001
	>=12 months	4	13,3%	36	61,0%	40	44,9%		
	all	30	100,0%	59	100,0%	89	100,0%		
GW	<30	13	43,3%	40	67,8%	53	59,6%	4,941	0,026
	>=30	17	56,7%	19	32,2%	36	40,4%		
	all	30	100,0%	59	100,0%	89	100,0%		
BW	<1000g	5	16,7%	24	40,7%	29	32,6%	7,440	0,024
	1000-1500g	15	50,0%	27	45,8%	42	47,2%		
	>1500g	10	33,3%	8	13,6%	18	20,2%		
	all	30	100,0%	59	100,0%	89	100,0%		
BPD 28 day def.	no	19	63,3%	3	5,1%	22	24,7%	36,261	<0.001
	yes	11	36,7%	56	94,9%	67	75,3%		
	all	30	100,0%	59	100,0%	89	100,0%		
BPD 36 w PMA def.	no	27	90,0%	24	40,7%	51	57,3%	19,774	<0.001
	yes	3	10,0%	35	59,3%	38	42,7%		
	all	30	100,0%	59	100,0%	89	100,0%		

from a minimum of 670 g to a maximum of 2100 g. Similarly, the average gestational age (GA) was 28.9 weeks, with the lowest GA recorded at 24 weeks and the highest at 33 weeks. By receiving palivizumab they were supposed to be protected from RSV infection, so we primarily aimed to investigate the incidence of non-RSV wheezing episodes and pneumonias, treated on an outpatient basis and those requiring hospitalization.

Wheezing episodes occur frequently in prematurely born children, with the highest prevalence occurring in the first 2 years of life, ranging from 46% to 59%. On the other hand, children born in term experience wheezing with the prevalence of about 30% in the first 3 years of life. Wheezing in preterm children can be caused by mechanisms distinct from those causing asthma, such as reduced airway calibre, decreased exhaled nitric oxide, airway malacia, and hyperoxic airway injury (9). The study conducted by Prais et al. reported that extremely premature children receiving palivizumab had reduced wheezing episodes and hospitalizations during the first 2 years of life with only 27% experiencing wheezing compared to 70% in the non-palivizumab group (10). In contrast, the study conducted by Simões et al. reported the higher prevalence of recurrent wheezing in preterm infants who were receiving palivizumab (36.1%), compared to those who did not (27.4%) (11). In our study, which included preterm infants receiving palivizumab, thirty-two (35.9%) patients had wheezing episodes, aligning with the information present in the literature. Eleven patients (12.3%) needed to receive systemic corticosteroids to treat wheezing episodes. Seven patients (7.8%) were diagnosed with pneumonia.

Regarding hospitalizations due to respiratory exacerbation, in our study nine (10.1%) patients were hospitalized, while only 1 patient (1.1%) was diagnosed with an RSV infection. These results are similar to the result from the study conducted by Raguž et al. which reported that 17.1% of 222 infants who were receiving palivizumab were re-admitted to hospital and only one of them had RSV infection (12).

Respiratory morbidity in different groups of preterm children

Given the well-established difference in the risk of respiratory diseases between term, and preterm infants (1, 7, 13), our study focused on comparing various groups of prematurely born children (first versus the second year of life, GA less than 30 weeks versus GA greater than, or equal to 30 weeks of GA, birth weight (BW) less than 1000g versus 1000-1500g versus greater than 1500g, and the presence or absence of bronchopulmonary dysplasia (BPD)).

Hospitalizations, pneumonias, atopic presentation

In our study there were no statistically significant differences between the different age, GA, BW, or BPD/non-BPD groups in the number of hospitalizations or pneumonia, nor in case of atopic presentation (symptoms of allergic rhinitis, eczema). These results are in accordance with the study conducted by Wang et al. and Skromme et al. (5,6). The study conducted by Smith et al. came to different results publishing that BPD infants (according to the 36 weeks PMA definition) had twice the rate of rehospitalization in comparison to the non-BPD population, with 36% of hospitalization attributed to respiratory diagnoses (14). Similarly, the study conducted by Shin et al. found that in the first 2 years of life readmission for LRTIs happened in 53.9% of the BPD and 37.9% of the non-BPD cases. The BPD group also showed significantly higher median rate of hospitalizations and hospital days, oxygen and mechanical ventilation, as well as the asthma prevalence (15).

Wheezing episodes, systemic corticosteroid usage and chronic cough

In our study children older than 12 months and children with BPD (according to both definitions) had significantly higher occurrences of wheezing episodes while there was no statistically significant difference between the GA and BW groups. More patients received systemic corticosteroids in case of wheezing in the group of children older than 12 months, and in the group with BPD (according to 36 weeks' PMA definition) while there was no statistically significant difference between the GA and BW groups. Chronic cough was present in 4.5% of patients, all of whom had BPD.

The higher rate of wheezing episodes observed in children older than 12 months in our study may be explained by the cumulative phenomenon. Children in the second year of life have an additional year to experience respiratory infections, as reflected in our study where we estimated the cumulative number of wheezing episodes experienced by the children so far. The

study conducted by Wang et al. compared respiratory-related illness hospitalization (RIH) and respiratory syncytial virus-positive hospitalization (RSVH) risks in children with chronic lung disease who received palivizumab during the first year (FY, 847 children) versus second year (SY, 450 children). This study showed that FY and SY children had similar risks for RIH and RSVH (5). The study conducted by Tan et al. comparing term and preterm infants concluded that wheezing was more likely to be diagnosed in the first year of life for term infants, but peaked in the second year of life for preterm infants (1).

Concerning wheezing and BPD our data is in accordance with the published studies which show that children with BPD have a higher risk of wheezing episodes (1,6,9,15). The definition of BPD based on the need for oxygen therapy at 36 weeks PMA was found to have the greatest value in predicting serious respiratory morbidity (16). That could explain the higher rate of systemic corticosteroid usage to treat wheezing in this group of children in our study, in contrast to those with BPD defined at 28 days of age.

Regarding the GA and BW groups, our findings differ from those reported by Simões et al. – in this study, one of the risk factors with the greatest chance of recurrent wheezing was birth weight <1000g and gestational age <28 weeks (11).

Use of ICS in BPD

Up to now, the pathophysiology of BPD has been widely discussed and well understood in the scientific literature, but its prevention and management persist to be a huge challenge. So far, there have been a lot of theoretical strategies to prevent or treat BPD, but they have failed to show their potential in clinical work. Many of these strategies lack sufficient evidence and have long-term adverse effects. None of the drugs that are used in current medical practice are labeled by the US Food and Drug Administration for the prevention or treatment of BPD in infants, despite their widespread consistentcy, and usage (17). One of the most frequently used medications in the prevention and treatment of BPD are ICS. Individual studies suggest that prolonged usage of ICS in the first two years of life may reduce respiratory symptoms and bronchodilator usage, increase airway compliance and functional residual capacity, and decrease airway resistance (18). However, ICS usage in BPD is still the object of many clinical trials without any consistent conclusions or clinical guidelines (19). Despite this, multiple observational studies reveal that ICS are frequently prescribed to a large number of preterm infants worldwide for both prevention and treatment, with a substantial variation across different centres (20-23). Clinical trials investigating the usage of ICS to prevent or treat BPD have used a variety of ICS including beclomethasone, budesonide, fluticasone, flunisolide, and dexamethasone, but there have been no clinical trials directly comparing different inhaled ICS in preterm infants (24).

The use of ICS in BPD could be divided into 3 groups, based on indication: to prevent BPD, to treat BPD (e.g., to fasten the weaning off oxygen or to prevent disease progression and frequent respiratory symptoms) and to treat the child with BPD and recurrent wheezing. These indications often overlap leading to confusion amongst healthcare providers about whether they should introduce ICS, as well as when to initiate it, and when to discontinue it. That may explain unnecessary long-term usage of ICS in some patients with BPD (25).

Studies that have been published so far regarding ICS mostly address evolving BPD with the lack of studies that refer to the existing BPD and its long-term therapy (21, 25). The Cochrane Collaboration published systematic reviews in 2012 concluding that ICS have no established role in the prevention or treatment of BPD outside of clinical trials (26, 27). The American Academy of Pediatrics (AAP) in 2022 published official guidelines in 2022 on the use of postnatal corticosteroids (PCSs) to prevent or treat BPD. They came to the conclusion that current research work in not sufficient to support making any recommendations regarding the routine use of PCSs. These drugs may decrease the incidence of severe BPD but they are associated with significant short- and long-term risks of adverse effects. Furthermore, The AAP states that there is no proven advantage of ICS over systemic corticosteroids (24). European Respiratory Society (ERS) published guidelines in 2020 on the long-term management of children with BPD. The ERS does not recommend treatment with inhaled or systemic corticosteroids due to their adverse effects. If the managing pediatrician decide to use PCSs due to a severe clinical picture, the effects of treatment with PCSs should be patiently monitored during a trial period before considering chronic therapy. These recommendations are justified the insufficient data in the existing literature that would prove the effectiveness of ICS and the potential adverse effects of this course of treatment (28).

Apart from the prevention and treatment of BPD ICS can be used to treat recurrent wheezing in preterm infants and children, but their role in preventing wheezing in these patients is not yet clearly established. Most of the randomized clinical trials assessing the usage of ICS in preterm children face significant limitations related to insufficient number of participants, and the absence of standardized, validated clinical symptom scores. These studies have failed to demonstrate the impact of ICS usage on clinically significant outcomes, leading to the recommendation against the use of ICS in preterm children. Nevertheless, the usage of ICS may be warranted in prematurely born children exhibiting symptoms suggestive of asthma (9, 25).

The study conducted by Simões et al. reported that out of 31.2% of premature children who had been using inhaled corticosteroids after the neonatal period, 27.4% exhibited recurrent wheezing, and in the end, 21.3% had been diagnosed with asthma (11). The usage of ICS in our study was significantly higher with 59 patients, or 66.2%, using ICS. Almost all patients with BPD (59 out of 67) were started on ICS during the neonatal period and were continued on ICS after being discharged from the hospital. Among them, 40.7% (24 out of 59) had a history of wheezing episodes. Recent guidelines support a reevaluation of the indications for ICS usage in BPD patients. They emphasize the importance of expediting the discontinuation of ICS, particularly in patients who have never had respiratory exacerbations or a history suggestive of asthma (24, 25, 28).

Exposure to tobacco smoke

Both prenatal and postnatal passive smoking have been shown to have a wide spectrum of effects on mortality and morbidity in children (29, 30). It is well established that postnatal exposure to smoke represents a contributing factor in the onset of asthma, as well as that it leads to more severe lower respiratory illnesses Both prenatal and postnatal passive smoking have been shown to have a wide spectrum of effects on mortality and morbidity in children (29, 30). It is well established that postnatal exposure to smoke represents a contributing factor in the onset of asthma, as well as that it leads to more severe lower respiratory illnesses (29). In the study conducted by Simões et al. 19.6% of preterm children had caregivers who smoked and of those with recurrent wheezing 19.8% were exposed to tobacco smoke (11). In our study 7.9% of patients were exposed every day to tobacco smoke while 4.5% patients were exposed occasionally. We consider this a high percentage, reflecting the necessity for further education of parents on the risks associated with tobacco smoke exposure.

Parental burden and knowledge about BPD

Preterm children with BPD often require continuous home care and re-hospitalization during the first 2 years of life. The burden that comes with taking care of these children may negatively affect caregiver health-related quality of life (4, 31). To our knowledge, there currently no studies that measure parents' knowledge about the diagnosis of their preterm children. In our study, we aimed to asses out parents' understanding of BPD. Of the respondents, parents of 22 patients (24.7%) showed positive awareness when asked about the meaning of BPD, while 6 parents (6.7%) showed partial awareness. There was no statistically significant difference between the group of parents of children with and without BPD. These results imply that the parents may be insufficiently informed about this disease, or it could indirectly imply that they are not burdened with their children's medical condition. Nevertheless, the results highlight the need for additional edification.

Our study faces limitations due to the small number of participants as we included the prematurely born children who were receiving palivizumab, not all prematurely born children. This selection was made because this group of children visited our Institute monthly, to receive palivizumab, allowing a proper follow-up. Simultaneously, this group represents the children at the greatest risk of respiratory status impairment.

Conclusion

Prematurely born children who received Palivizumab exhibited significant respiratory morbidity, with the majority not having respiratory syncytial virus (RSV) infection. Around one-third of them experience wheezing episodes, 7.8% had pneumonia, 10.1% were hospitalized due to respiratory exacerbation and only 1.1% had RSV infection. There were no statistically significant differences between the different age, GA, BW, or BPD/non-BPD groups in the number of hospitalizations or pneumonia. On the other hand, children older than 12 months and those with BPD had significantly more wheezing episodes. The use of ICS in infants with BPD, after being discharged from the hospital, requires careful consideration

as new protocols advise against using ICS as a standard long-term treatment for this disease. If the child does not have any respiratory symptoms, ICS should be discontinued and its reintroduction should be reconsidered only in patients with recurrent wheezing episodes, and a history suggestive of asthma. Our study showed that ICS were used in almost all patients with BPD (59 out of 67), after being discharged from the hospital, while only 40.7% of them (24 out of 59) experienced wheezing episodes despite the usage of ICS. The remaining patients (59.3%) never developed wheezing episodes. Limitations of our study include a small sample size, and the inability to conduct a longer longitudinal follow-up of patients after discontinuing ICS. Further clinical studies are necessary to enhance our understanding of the role of ICS in patients with established BPD.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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