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Original article

Clinical course of children with postinfectious bronchiolitis obliterans with versus without comorbid bronchopulmonary dysplasia

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Background: Postinfectious bronchiolitis obliterans (PIBO) is a rare chronic obstructive pulmonary disease that occurs after a respiratory infection. Its diagnosis is generally based on clinical history, respiratory symptoms, and computed tomography (CT) findings.

Purpose: Here we evaluated the frequency of exacerbations, clinical progress, and inhaled corticosteroid (ICS) usage in children diagnosed with PIBO with or without comorbid bronchopulmonary dysplasia (BPD).

Methods: This retrospective observational study was conducted in Rouen, France. The inclusion criteria were as follows: child diagnosed with PIBO (history of respiratory infection, airway obstruction with no or poor response to bronchodilation treatment, and/or mosaic pattern or trapping on chest high-resolution CT) in 2009–2024 treated with intravenous corticosteroid pulses.

Results: Fifty-seven patients were included: 13 (23%) with BPD and 44 (77%) without BPD. The mean age at diagnosis was 7.0±3.6 months, with no significant intergroup difference. We observed a significant reduction in exacerbations following corticosteroid pulse treatment as soon as 6 months (P<0.001), with persistent effects observed up to 24 months (P=0.02). We also noted a reduced daily ICS dose starting at 12 months (P=0.03). Respiratory syncytial virus is the most commonly identified causative virus, followed by rhinoviruses and adenoviruses. The viral codetection rates were 18% and 61% in the BPD and non-BPD groups, respectively.

Conclusion: In our cohort, intravenous corticosteroid pulse treatment effectively treated PIBO, with a rapid and long-lasting reduction in exacerbations and ICS requirements. BPD was a significant comorbidity of PIBO.

Key words: Postinfectious bronchiolitis obliterans, Respiratory viruses, Child, Respiratory outcome, Bronchopulmonary dysplasia

Key message

Question: Postinfectious bronchiolitis obliterans (PIBO) is a chronic respiratory disease that typically develops in children after a severe respiratory infection. Bronchopulmonary dysplasia (BPD) is often comorbid in patients with PIBO.

Finding: Corticosteroid pulse therapy effectively manages PIBO with or without comorbid BPD, significantly reducing exacerbations and decreasing the daily requirement for inhaled corticosteroids.

Meaning: Therapeutic effects of corticosteroid pulses are rapid and sustained over time, in both groups.

Introduction

Postinfectious bronchiolitis obliterans (PIBO) is a rare, chronic obstructive lung disease in infants and in children, usually following a severe respiratory infection. Characterized by inflammation and fibrosis in the terminal bronchioles, it leads to airway blockage. The condition typically affects infants under 12 months, and while the exact prevalence is unknown, PIBO is underreported among pediatric respiratory diseases.[1)] Frequence of PIBO is probably underestimated, but the disease belongs to the group of rare diseases.[2)] Viruses, particularly adenovirus, are the primary triggers for PIBO, although bacteria like Mycoplasma pneumoniae have also been implicated.[3-6)] Diagnosis is generally based on typical clinical history, respiratory symptoms (tachypnea, cough, wheeze) and computed tomography (CT) imaging (mosaic perfusion), as lung biopsy is often too invasive for routine pediatric practice.[4,7)] Treatment lacks standardized guidelines, but intravenous corticosteroid pulses are commonly used,

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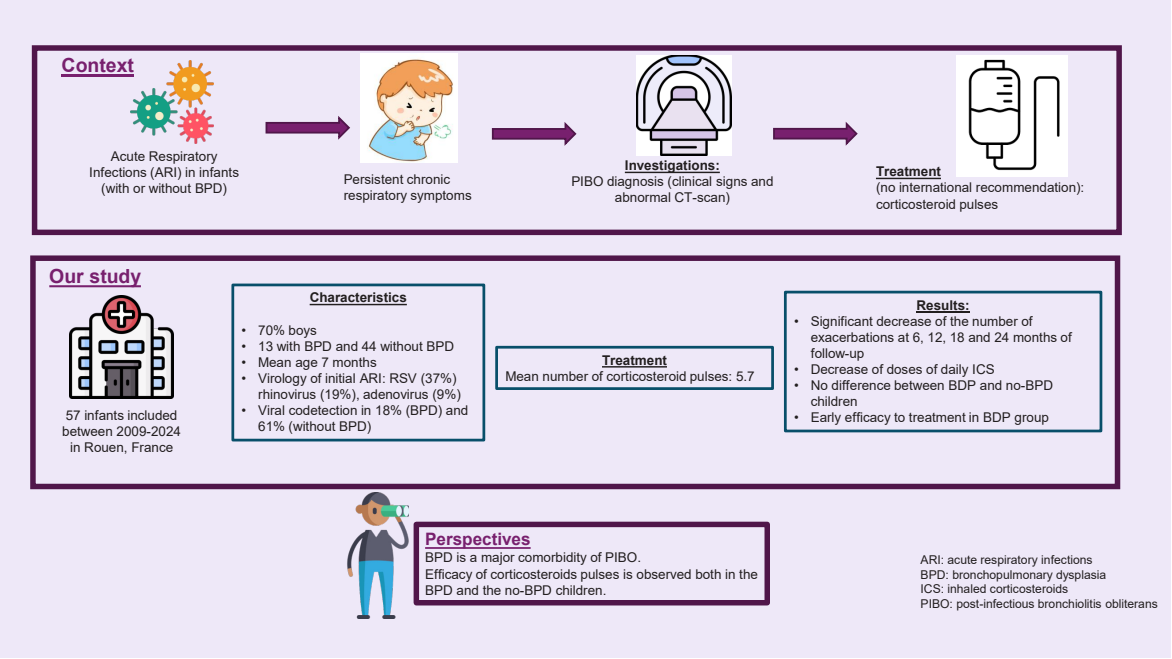

Graphical abstract

with some studies showing the effectiveness of combined treatments with inhaled corticosteroids (ICS), montelukast, and low-dose azithromycin.[8,9] PIBO's prognosis remains unclear, as existing studies are limited and sample sizes are small.[10] Bronchopulmonary dysplasia (BPD) is a frequent complication of prematurity, increasing in frequency and severity with the degree of prematurity. Immature lungs are highly susceptible to be attacked, particularly by respiratory viruses, and few articles in the literature study the link between BPD and the development of PIBO. The pathophysiology remains unexplained.

This study examines a larger cohort of infants with PIBO, primarily evaluating the effectiveness of intravenous corticosteroids, and secondarily exploring the impact of BPD as a comorbidity.

Methods

1. Study design

This observational, retrospective, single-center study was conducted at the Rouen University Hospital's Department of Pediatrics. We included children diagnosed with PIBO from January 2009 to January 2024 who received corticosteroid pulses. The study's inclusion criteria were: children with a history of respiratory infection, an obstruction of the airway with no or poor response to the treatment with bronchodilatation, and/or mosaic pattern or trapping on chest high-resolution CT. Exclusion criteria included asthma, cystic fibrosis, primary ciliary dyskinesia, severe pulmonary BPD requiring corticosteroids for oxygen cessation, and immune deficiencies. Data were collected at 6-month intervals, tracking exacerbations (defined as an acute episode requiring the use of bronchodilators, or short courses of oral corticosteroids, or hospitalization, or onset or worsening of respiratory symptoms) and daily ICS dosage.

PIBO was defined as persistent respiratory symptoms lasting 4–6 weeks after acute bronchiolitis, confirmed by characteristic CT results and excluding other diagnoses.

The corticosteroid pulse regimen involved monthly injections of prednisone equivalent (300 mg/m²/day) over 3 days. The first reassessment took place at 3 months, and the pulses were discontinued when the child no longer presented respiratory symptoms at rest or during exercise. Children with mild PBD (defined as oxygen therapy for the first 28 days of life and weaning at less than 36 weeks corrected age) were also included in this study. The primary objective was to evaluate the efficacy of intravenous corticosteroids. The secondary objective was to study the impact of BPD as a comorbidity.

2. Statistics

The quantitative variables were compared with a Student t test or with Mann-Whitney test between the "PIBO with BPD" group and the "PIBO without BPD" group. For qualitative variables, the 2 groups were compared with a chi square test or exact Fisher test depending on the theoretical workforces. For continuous measurements, data are presented as mean±standard deviation or median with interquartile ranges (25th and 75th percentiles). For qualitative parameters, data are presented as the number

of case n (percentage (%) of patients). All tests were 2-sided and a *P* value of <0.05 was considered to be statistically significant. Statistical analyses were performed using DATAtab® et EasyMedStat®.

3. Ethics

The study was reviewed by Rouen University Hospital's research committee and does not fall within the scope of Jardé's law. All patient data were anonymized.

Results

1. Baseline characteristics

Among the 57 children who met the inclusion criteria, we identified a group of 13 patients (22.8%) with BPD. The average age at diagnosis was 7.0±3.6 months, with no significant age difference between the 2 groups (BPD and no-BPD). Initial clinical data are reported in the Table 1. Respiratory symptoms began earlier in the no-BPD group (*P*=0.041), with high rates of hospitalization and an average ICS dose of 1,810±552 µg at diagnosis. The clinical sign most often found at diagnosis was polypnea (93%), with signs of respiratory distress (93%). Permanent wheezing and cough were frequent too (respectively 60 and 53%). CT scans were abnormal in 84% of cases, commonly showing air trapping (56%) and mosaic perfusion (16%).

2. Virology

Respiratory syncytial virus (RSV) was the most frequently detected virus, followed by rhinovirus and adenovirus (Table 2). Multiplex polymerase chain reaction (PCR) was negative in about 30% of cases in both groups. Viral codetection was higher in the non-BPD group, present in 61% of cases. RSV, metapneumovirus and influenza viruses were mostly mono-detected. Results of explorations at the inclusion are summarized in the Table 2.

Table 1. Clinical characteristics at diagnosis of the total cohort, PIBO with BPD, and PIBO without BPD groups

Characteristic	Total cohort (n=57)	With BPD (n=13)	Without BPD (n=44)	*P* value
Male sex	40 (70)	9 (69)	31 (70)	>0.999
Age of PIBO diagnosis (yr)	7.0±3.6	8.88±4.05	9.61±9.51	0.219
Age of first symptoms (yr)	4.44±4.36	5.31±3.52	4.19±4.63	**0.041**
Age of first bronchiolitis (yr)	4.11±4.02	4±4.46	4.5±2.29	0.119
No. of bronchiolitis	2.4±1.6	2.6±1.5	2.3±1.68	0.378
No. of hospitalizations				
Standard unit	1.1±0.92	1.3±0.855	1.1±0.95	0.203
Intensive care	0.4±0.59	0.5±0.519	0.4±0.625	0.689
Daily dose of ICS (µg)	1810±552	2000±0	1755±625	0.168
Corticosteroids pulses		n=13	n=40	
Age at the first pulse	7.9±3.92	9.5±4.56	7.3±3.64	0.071
No. of pulses	5.7±3.86	6.9±4.6	5.2±3.61	0.158
Term of birth	34.2±4.97	33.9±5.10	34.1±6.71	**<0.001**
Full-term newborns (≥37 WG)	29 (51)	0 (0)	28 (64)	
Premature	28 (49)	13 (100)	16 (36)	
Birth weight (g)	2,340±1,056 (n=47)	1,259±834 (n=12)	2,710±874 (n=35)	**<0.001**
Neonatal respiratory distress	21 (37)	12 (92)	9 (20)	**<0.001**
Neonatal disease				
BPD	13 (23)	13 (100)	0 (0)	
Esophageal atresia	4 (7)	1 (8)	3 (7)	0.999
Cardiac malformation	9 (16)	3 (23)	6 (14)	0.412
Diaphragmatic hernia	1 (2)	1 (8)	0 (0)	0.228
Respiratory symptoms				
Wheezing	34 (60)	8 (62)	26 (59)	>0.999
Crackles	6 (11)	2 (15)	4 (9)	0.611
Cough	30 (53)	9 (69)	21 (48)	0.216
Signs of respiratory distress	52 (93)	12 (92)	40 (91)	>0.999
Polypnea	53 (93)	12 (92)	41 (93)	>0.999
Oxygen therapy	7 (12)	2 (15)	5 (11)	0.653
Initial growth delay	26 (46)	8 (62)	18 (41)	0.220

Values are presented as number (%) or mean±standard deviation.
PIBO, postinfectious bronchiolitis obliterans; BPD, bronchopulmonary dysplasia; ICS, inhaled corticosteroids; WG, week gestation.
Boldface indicates a statistically significant difference with *P*<0.05.

Table 2. Results of exams in the total cohort at diagnosis, and comparison between the "PIBO with BPD" and "PIBO without BPD" groups

Characteristic	Total cohort (n=57)	With BPD (n=13)	Without BPD (n=44)	*P* value
Virological results				
Positive PCR	39 (68)	9 (69)	30 (68)	>0.999
Codetection	16 (28)	8 (61)	8 (18)	0.12
Negative result	18 (32)	4 (31)	14 (32)	>0.999
RSV positive	21 (37)	4 (31)	17 (39)	0.748
RSV alone	15 (72)	1 (25)	14 (82)	0.15
Codetection RSV/HRV	3 (14)	1 (25)	2 (12)	0.547
Codetection RSV/other	3 (14)	2 (50)	1 (6)	0.547
HRV positive	11 (19)	4 (31)	7 (16)	0.251
HRV alone	3 (27)	0 (0)	3 (43)	>0.999
Codetection HRV/other	8 (73)	4 (100)	4 (57)	0.547
ADV positive	5 (9)	2 (15)	3 (7)	0.319
ADV alone	2 (40)	0 (0)	2 (67)	>0.999
Codetection ADV/HRV	1 (20)	1 (50)	0 (0)	0.228
Codetection ADV/other	2 (40)	1 (50)	1 (33)	0.407
BLA	(n=51)	(n=12)	(n=38)	
Total cellularity (10^5 cells/mL)	1.43±1.35	1.06±1.24	1.54±1.4	0.302
Lymphocytes (%)	4.38±3.45	4.46±4.07	4.36±3.35	0.885
Macrophages (%)	58.85±24.71	67.08±17.19	56.32±26.57	0.244
Neutrophils (%)	26.27±30.93	18.67±29.47	28.55±31.74	**0.044**
Eosinophils (%)	0.27±1.21	0.167±0.444	0.308±1.37	0.766
Positive bacterial culture	31 (57)	5 (38)	18 (41)	0.191
Immunoglobulins (g/L)	(n=47)	(n=10)	(n =37)	
IgG	5.31±2.32	5.72±3.18	5.18±2.09	0.517
IgA	0.44±0.31	0.315±0.29	0.475±0.32	**0.047**
IgM	0.86±0.42	0.932±0.60	0.835±0.37	0.856
Blood neutrophils (G/L)	0.27±0.27	0.265±0.29	0.297±0.21	0.318
Anomaly at bronchoscopy	33 (58)	7 (54)	26 (59)	0.47
Inflammation	30 (53)	6 (46)	24 (55)	0.521
Anatomic malformation	4 (7)	2 (15)	2 (5)	0.144
Malacy	18 (32)	4 (31)	14 (32)	0.593
Secretions	8 (14)	2 (15)	6 (14)	0.63
Abnormal CT scan	48 (84)	11 (85)	37 (84)	>0.999
Atelectasis	24 (42)	7 (54)	17 (39)	0.357
Mosaic perfusion	9 (16)	1 (8)	8 (18)	0.668
Air trapping	32 (56)	9 (69)	23 (52)	0.35
Bronchiectasis	10 (18)	2 (15)	8 (18)	>0.999
Other	10 (18)	4 (31)	6 (14)	0.213
Echocardiography: PHT	2 (4) (n=36)	0 (0) (n=12)	2 (5) (n=24)	NA

Values are presented as number (%) or mean±standard deviation.
PIBO, postinfectious bronchiolitis obliterans; BPD, bronchopulmonary dysplasia; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; HRV, heart rate variability; ADV, adenovirus; BLA, broncho-alveolar lavage; CT, computed tomography; PHT, pulmonary hyper tension.
Boldface indicates a statistically significant difference with *P*<0.05.

3. Follow-up

Of the 57 patients, 41 (72%) were followed for 24 months, including 11 patients with BPD. At inclusion, infants had had a mean of 2.34 exacerbations before the treatment with high-dose intravenous corticosteroid pulses. There was a significant decrease in the number of exacerbations over time in the total cohort (*P*<0.001) (Table 3). Exacerbations decreased significantly after corticosteroid pulse treatment, with no significant difference between BPD and non-BPD groups (*P*=0.772). ICS dosages were also significantly reduced during follow-up, indicating sustained therapeutic effects from corticosteroid pulses (*P*<0.001). No significant difference was found between the "PIBO with BPD" and "PIBO without BPD" groups over time (*P*= 0.092). However, we note a more rapid decrease of the treatments in the "PIBO with BPD" group (Fig. 1).

Table 3. Evolution of the number of exacerbations in the total cohort over time

Study period	Mean difference (95% IC)	*P* value
M0–M6	1.34 (0.81–1.87)	**<0.001**
M0–M12	1.56 (0.99–2.13)	**<0.001**
M0–M18	1.27 (0.59–1.95)	**0.005**
M0–M24	1.12 (0.44–1.81)	**0.020**
M6–M12	0.22 (-0.39 to 0.82)	1.000

M0: onset of the treatment by steroids pulses, M6, M12, M18 and M24: respectively 6, 12, 18 and 24 months after the onset of the treatment by steroids pulses.
Boldface indicates a statistically significant difference with *P*<0.05.

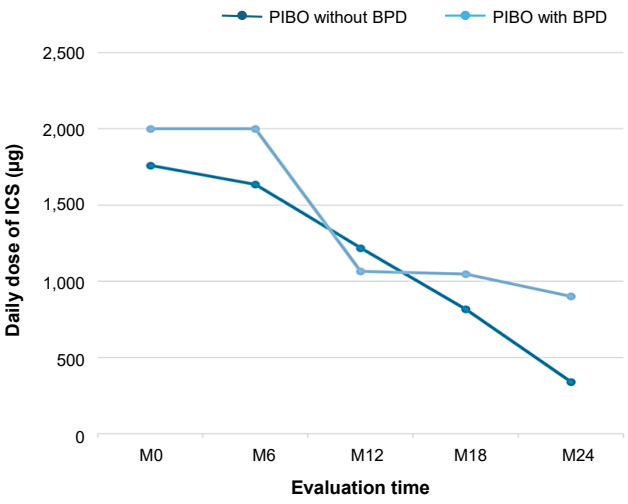

Fig. 1. Evolution of daily ICS dose in the PIBO with BPD versus PIBO without BPD groups over time. ICS, inhaled corticosteroids; PIBO, postinfectious bronchiolitis obliterans; BPD, bronchopulmonary dysplasia; M, month.

Discussion

Our study described the clinical and functional characteristics of a cohort of 57 children with PIBO treated with methylprednisolone pulses. Our main objective was to determine the evolution in the first 2 years of life. We compared the clinical course of these children in the 24 months following diagnosis of PIBO, and highlighted a subgroup of patients with a history of BPD. To our

knowledge, we report here one of the few European cohorts, most articles being of South American and Asian origin.[11,12] The diagnosis of PIBO was made according to currently accepted criteria, and 85% of our patients had a CT scan with the presence of abnormalities indicative of bronchiolar involvement.[1] The demographic characteristics of our patients were comparable to those described in the literature. Indeed, the mean age at diagnosis of PIBO was less than 12 months.[3] Although male gender has not been identified as a risk factor for the development of PIBO, more than two-thirds of the cohort were boys, as observed in other series.[3,5] This rate is much higher than that observed in other infant respiratory diseases.[13,14] We have shown that the presence of pulmonary comorbidities is not negligible in this cohort, particularly the presence of BPD. Indeed, half of our cohort was premature, and 20% of them had presented with BPD. Tomikawa et al.[15] reported 12.5% prematurity in their cohort of 40 children. Moreover, in the BPD subgroup, the onset of chronic respiratory symptoms was later. This is explained by the fact that these premature infants were discharged from hospital later, and had a delayed exposure to respiratory viruses.

We found about 30% of malacia in our cohort. Malacie is common in the first years of life, and almost always has a favorable outcome. It may be responsible for an increased cough, with a characteristic noise, but it is not responsible for bronchial obstruction and mosaic scan abnormalities. It was not therefore possible to be responsible for the clinical presentation of our patients.

We report that the first viral etiology identified is RSV, followed by rhino-enteroviruses, with adenovirus only in third place. This frequency is in line with the epidemiological descriptions we reported in a large study of acute bronchiolitis.[16] All viruses are known to be associated with bronchiolitis obliterans, but the predominance of RSV has not been reported.[12] In the German study by Jerkic et al.,[11] RSV accounted for only 2 of 21 cases. Also, the frequency of coinfections, found in more than one in 4 cases, is less frequent in the BPD group. The rate of viral codetection in our study is high, particularly for rhinoviruses and bocavirus, and especially in the "PIBO with BPD" group. Several studies show that the presence of viral codetection does not increase the severity of infection.[17] Indeed, studies using the PCR technique have shown that viruses can be excreted for prolonged periods without associated clinical symptoms.[18,19] Consequently, codetection is not systematically synonymous with coinfection. Other studies showed that the prognosis of respiratory infections can be altered, positively or negatively, by specific viral interactions.[20,21] In a third of cases, no virus was detected, as described in other cohorts.[11]

We report on a cohort treated with methylprednisolone pulses, with an early start to treatment, lasting an average of 6 months. We observed a 58% reduction in the number of exacerbations from the first 6 months, which was maintained during the 2-year follow-up. Concomitantly, we also showed that at 6 and 12 months of evaluation, the number of children presenting no exacerbation during the follow-up period increases from 39% to 61%, and stabilizes for 50% of the population at 18 and 24 months. Very few studies have reported the efficacy of methylprednisolone pulses. Only Tomikawa et al.[15] describes the number of exacerbations: they showed a reduction during the first 6 months, which is maintained up to 18 months. In this series, only 33% of patients were exacerbation-free at 24 months. This may be explained by different populations: in Tomikawa's study, patients were more heterogeneous in age, and the diagnostic delay was much longer (up to 32 months). In our study, this rapid reduction in exacerbations is important, as exacerbations have been shown to be a major factor in lasting impairment of respiratory function. At the same time, we observed a reduction in the dose of ICS administered to children over the follow-up period. This decrease became significant from 12 months onwards, reflecting a consolidation of the therapeutic effect of pulses at 6 months.

In conclusion, this study demonstrates the effectiveness of intravenous corticosteroid pulses in treating PIBO, with sustained improvements in respiratory health over 24 months. Our findings support the role of BPD as a comorbidity in PIBO, with corticosteroid therapy beneficial for children with and without BPD.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Author contribution: Conceptualization: CM, HP; Data curation: LM, JG; Formal analysis: LM; Methodology: LM, JG, CM, HP; Writing - original draft: LM; Writing - review & editing: JG, CM, HP

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