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ORIGINAL ARTICLE

The severity of the first occurrence of bronchiolitis increased the risk of developing asthma symptoms

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Abstract

Aim: The relationship between bronchiolitis and asthma is complex. We assessed whether patients admitted to a paediatric intensive care unit (PICU) with bronchiolitis had a greater risk of developing asthma than patients admitted to a paediatric ward.

Methods: We retrospectively included children under 1 year of age, who were hospitalised for bronchiolitis for the first time at the University Hospital of Caen, France, between 2010 and 2014. The children were divided into two groups: 89 were admitted to the paediatric ward and 89 were admitted to the PICU. We wanted to assess which group developed more asthma before 6 years of age. The Global Initiative for Asthma definition was used.

Results: The median age of the 178 children (55% boys) was 32 (interquartile range 19–56) days. We found that 35% of the PICU group and 19% of the ward group had asthma at 6 years of age. The mean onset of symptoms was 3 years earlier in the PICU group than the ward group ($p < 0.01$). Both these findings were significant.

Conclusion: The severity of the first episode of bronchiolitis increased the risk of developing asthma symptoms. Regular follow-ups are suggested for infants admitted to PICUs for bronchiolitis.

KEYWORDS
asthma, bronchiolitis, intensive care, preschool wheezing, risk factors

1 | INTRODUCTION

The relationship between bronchiolitis and asthma is complex. Bronchiolitis is sometimes considered a potential trigger for asthma but has also been identified as an indicator of an underlying predisposition to asthma development. Both hypotheses appear to be correct.[1] The association between these two diseases can be explained by the interaction between predisposing factors to asthma and a trigger factor. The major predisposing factors are a family history of asthma, bronchopulmonary dysplasia, metabolites and genetic loci.[2,3] A frequently reported trigger factor is early exposure to the respiratory syncytial virus (RSV) or rhinoviruses.[4–6] The functional characteristics of these trigger factors reveal the causative environments in which these predispositions arise.[7] Predispositions to asthma become even more prevalent when subjects are exposed to environments that foster vulnerability, such as passive smoking, a mite-rich environment or obesity.[8]

Abbreviations: PICU, paediatric intensive care unit; RSV, respiratory syncytial virus.

The preliminary results of this study were presented during the French Paediatric Society Congress in May 2021.

Studies have demonstrated that an early episode of bronchiolitis increased the risk of developing asthmatic symptoms before 6 years of age, regardless of the specific virus that caused the infection.[9,10] The risk appeared to be greater in children who had bronchiolitis that required hospitalisation.[11]

The severity of the disease is not the same among these hospitalised children. The less severely affected children go to conventional wards, whereas the most severely affected children go to intensive care units. Limited data exist on how this variation influenced the risk of developing asthmatic symptoms.

Our main aim was to assess whether patients admitted to a PICU faced a greater risk of developing asthma before 6 years old than patients admitted to a paediatric ward. The second aim was to evaluate the impact of the severity of the bronchiolitis on the timing of the onset of asthma. We also assessed whether the possible risk of developing asthma was related to the severity of the bronchiolitis itself or to the care provided in the PICU.

Key Notes

- This study assessed whether the severity of bronchiolitis influenced the development of asthma in 178 patients hospitalised between 2010 and 2014 for their first episode of bronchiolitis.
- We found that 35% of the children admitted to the paediatric intensive care unit (PICU), and 19% admitted to the ward had asthma at 6 years of age.
- The mean onset of symptoms was 3 years earlier in the PICU group than in the ward group.

2 | METHOD

2.1 | Design and settings

This 5-year retrospective study was carried out between 1 January 2010 and 31 December 2014 in the paediatric department of the University Hospital of Caen, a tertiary care teaching hospital in France. It was based on a telephone survey.

We included all infants under 1 year of age who were hospitalised in the paediatric department for their first episode of bronchiolitis during the study period. Bronchiolitis was defined as the presence of shortness of breath with cough, rapid breathing and either auscultatory cracklings or wheezing.[12]

Patients were retrospectively enrolled and their data were obtained from the Department of Medical Information. Individuals who met the inclusion criteria were allocated to the PICU group or the ward group based on their hospitalisation unit.

Our paediatric department followed the guidelines outlined by the French National Health Service.[12] The indications for PICU management were apnoea, a pH of less than 7.34, hypercapnia of more than 45 mmHg, respiratory exhaustion and a rapid increase in oxygen.

We did not include patients with an elevated risk of severe bronchiolitis. This was defined as haemodynamically significant or non-haemodynamically significant congenital heart disease or those with a history of birth before 37 weeks of gestation. Individuals with a history of bronchiolitis were also not included. Children whose parents were unable to participate in our study were subsequently excluded.

2.2 | Ward group

The ward group was established through a 1:1 matching process with patients from the PICU group. The matching criteria included the age at admission, rounded to the two nearest weeks, sex, a family history of atopy and the presence of the virus responsible for bronchiolitis.

Not all viruses were initially tested. Typically, infants who met hospitalisation criteria in the emergency department underwent a rapid diagnostic test for RSV. If the test was negative, the search was expanded to other respiratory viruses using multiplex polymerase chain reaction tests. We used three categories for virus pairing. Patients with a single infection were paired with patients with the same single infection. Those who were coinfected with the RSV/rhinovirus were paired with patients exhibiting the same coinfections and categorised as RSV. Finally, those with a coinfection of RSV/other or rhinovirus/other were paired with patients who also had an RSV or rhinovirus, but the other virus was not considered.

We retrospectively extracted data from medical charts using a predefined standardised form. The collected variables included age and weight at admission, sex, personal history, a family history of atopy and length of hospitalisation. We also recorded the need for respiratory support, such as conventional oxygen therapy, a high-flow nasal cannula, non-invasive ventilation or invasive ventilation. The other variables were the need for enteral nutrition through a nasogastric tube or intravenous hydration and exposure to tobacco during and after pregnancy. Lastly, we recorded the respiratory viruses identified in the initial nasal virology.

We then contacted the parents and carried out a telephone survey, to gather information on their child's respiratory status. The objective was to determine whether an asthma diagnosis had been between their hospital discharge and 6 years of age. The questionnaire (Appendix S1) was devised by two paediatric respirologists (CA and JM) and the design and validity of the content were reviewed by experts in paediatric respiratory issues (BJ) and paediatric intensive care (DB). The survey comprised eight questions. Questions one, two and six were based on the asthma screening questionnaire used by the French agency for the fight against doping (Appendix S2). They are concerned with the search for a diagnosis of asthma. Questions three, four and five came from the questionnaire used by the International Study of Asthma and Allergies in Childhood[13] and related to respiratory symptoms of asthma. We also included two questions about whether the

children had responded to their treatment and exhibited asthma symptoms before 6 years of age.

2.3 | Outcomes

The primary endpoint was parental reports of asthma diagnoses before 6 years of age. Asthma was confirmed if it was diagnosed by a doctor using The Global Initiative for Asthma definition. This was recurrent episodes of wheezing, clinical improvement of shortness of breath or repeated coughing following the use of a short-acting bronchodilator.[14] The secondary endpoints were delays in the onset of asthma symptoms and differences in patients who received PICU care and then were, or were not, diagnosed with asthma.

2.4 | Statistical analysis

Since 2013, the prevalence of asthma in children under 6 years of age in France has been approximately 11%.[15] We needed 170 patients, with 85 in each group, to detect at least a 17% difference between them, with a power of 80% and an alpha risk of 5%. Descriptive data were presented for all patients and compared between the groups. In addition, we compared patients who were or were not diagnosed with asthma to identify differences in care. The quantitative variables are presented as medians and interquartile range and the qualitative variables as numbers and percentages. We compared the PICU and ward groups using the Wilcoxon signed-rank test and the McNemar's test. The Mann–Whitney *U*-test and Fisher's exact test were used to compare those who were and were not diagnosed with asthma.

Multivariable linear regressions were performed to determine risk factors for 6-year-old children with asthma. According to the literature, a family history of atopy, passive smoking and the severity of bronchiolitis are clinically relevant variables in the development of asthma in childhood. In the multivariable model, we followed a backwards procedure with the qualified variables to determine the independent risk factors associated with asthma.

We conducted a survival analysis with the Kaplan–Meier method to assess the time to symptom onset by group. Survival analysis was performed for the entire cohort and for three subgroups, based on the subject's age at the time of their first hospital admission. These comprised children under 1 month, between 1 and 3 months and over 3 months.

A significance level of $p < 0.05$ was used. The statistical analysis was conducted using RStudio software, version 2022.02.2+485 (RStudio Inc., Massachusetts, USA) and SAS software, version 9.4 (SAS Institute Inc., North Carolina, USA).

Ethical approval was granted by the local committee for ethics in health research at the University Hospital of Caen (number 1521). A letter was sent to the parents of the children who were eligible for our study. They were informed of the use of anonymised data and of their right to refuse to take part at any time.

3 | RESULTS

During the study period, 1587 patients were hospitalised for acute bronchiolitis, including 109 patients (7%) in the PICU. We excluded 20 patients from the PICU group, because we could not contact their parents (Figure 1), and matched the remaining 89 patients with the ward group. After matching, the median age of the 178 children (55% boys) was 32 (interquartile range 19–56) days (Table 1). Significant differences were found between the characteristics of the two groups of 89 patients, as expected, such as the amount and duration of care and how long they were hospitalised. Their weight at admission was also significantly different.

Table 2 shows that 35% of the PICU group and 19% of the ward group had asthma at 6 years of age ($p = 0.02$). This difference was significant. In Table 3, the multivariable linear regression analysis revealed two significant risk factors for developing asthma following the first occurrence of bronchiolitis before the age of one. One was a family history of atopy, and the other was severe bronchiolitis requiring admission to the PICU.

The survival analyses are presented in Figure 2. The log-rank test showed that 65% of the PICU group experienced asthma symptoms at 6 years of age, compared with 52% of the ward group ($p < 0.01$). The mean time from the children's first hospitalisation to the onset of symptoms was 2 years in the PICU group and 5 years in the ward group, which was significant ($p < 0.01$).

The subgroup analysis in Figure 3 revealed that the first and third subgroups, under 1 month of age and over 3 months, were significantly more likely to show asthma symptoms at 6 years of age if they were admitted to the PICU rather than the ward. We found that 72% of the PICU admissions under 1 month of age experienced asthma symptoms, compared with 50% admitted to the paediatric ward ($p < 0.01$). The mean time from the children's first hospitalisation to the onset of symptoms was 2 years for the PICU group and 5 years for the ward group ($p < 0.01$). In the third subgroup, 82% of the PICU group over 3 months of age developed asthma symptoms, compared with 40% of the ward group ($p < 0.01$). The mean time from the children's first hospitalisation to the onset of symptoms was 1 year for the PICU group and more than 5 years for the ward group ($p < 0.01$). The second subgroup, covering 1–3 months of age, did not show any differences in the rate of asthma symptoms between each unit or the mean time from the children's first hospitalisation to the onset of symptoms.

Table 4 shows that 65% of patients with asthma have been hospitalised in the PICU, compared with 45% of healthy patients ($p = 0.03$). There was a slightly greater rate of intubation in the asthmatic patients, 15% versus 5% ($p = 0.02$). However, the other types and duration of respiratory support did not appear to impact the development of asthma.

4 | DISCUSSION

This study showed that patients with severe bronchiolitis hospitalised in a PICU had a greater risk of developing preschool asthma

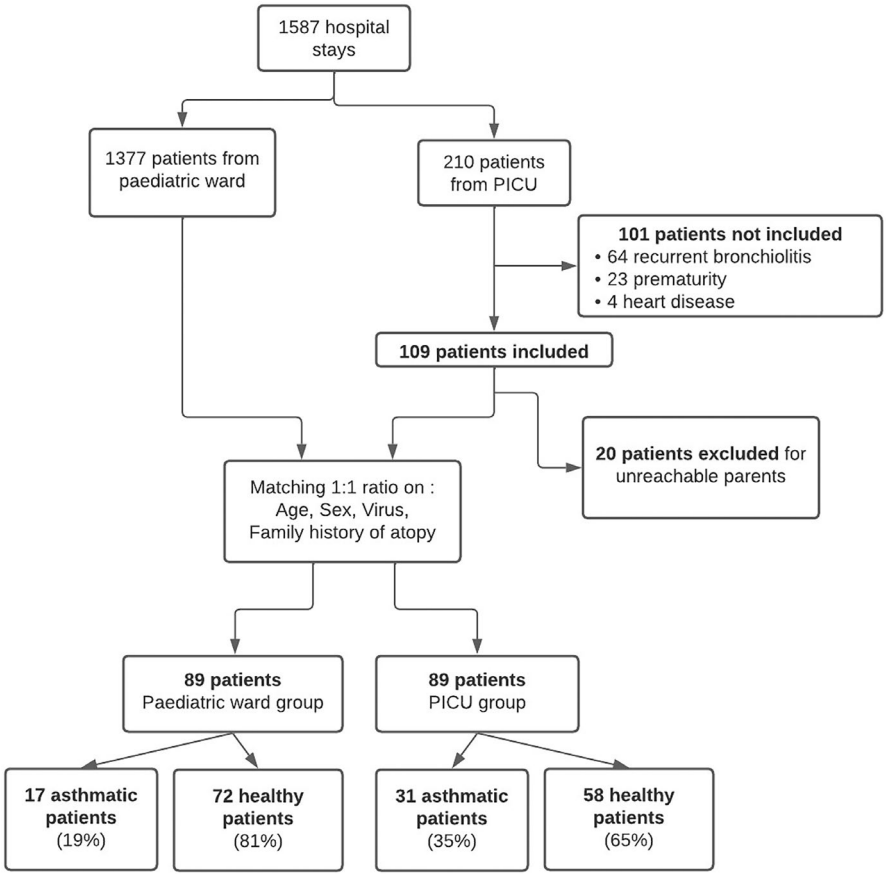

FIGURE 1 Flowchart.

than those with bronchiolitis hospitalised in a paediatric ward. The increased risk of developing asthma before the age of 6 years ranged from 4% to 27% after severe bronchiolitis. Our findings were consistent with the literature despite the fact that most studies did not distinguish between severe and moderate bronchiolitis. They reported that 27–38% of children hospitalised for bronchiolitis before 1 year of age developed asthma.[16–19]

Our multivariable linear regression included adjustments for the three primary asthma risk factors outlined in the literature: family history of atopy, passive smoking and the virus-causing bronchiolitis.[11,18–21] Other variables were excluded from the analysis. Foetal exposure to tobacco is a risk factor for early bronchiolitis but is not commonly associated with an increased risk of developing asthma.[22,23] Age at onset of bronchiolitis was described as a risk factor for asthma, but this was essentially linked to the presence of familial atopy.[24] Additionally, a child's weight and sex are highly variable risk factors over time,[7] and their lack of linear evolution makes them unreliable adjustment variables. Care-related variables, such as the need for and duration of respiratory support, enteral nutrition and intravenous hydration, are direct consequences of the severity of bronchiolitis. Adjusting for these variables could obscure the effect of bronchiolitis severity on the risk of developing asthma.

We examined the potential influence of the care provided on the development of asthma symptoms by comparing asthmatic and healthy patients. While numerous studies have explored the short-[25] and long-term[26] impact of neonatal ventilation on premature infants, there are limited data on the impact of the ventilation of infants for acute respiratory disease. We noticed no significant difference between the rates of children who received supportive care and who did not. Our study suggested that only the severity of bronchiolitis influenced the development of asthmatic symptoms and not the care provided to manage it. However, further studies are needed to verify this conclusion.

The onset of asthmatic symptoms occurred earlier in patients with severe bronchiolitis than in those with moderate bronchiolitis. Our survival analyses revealed minimal variation in this median within subgroups of the PICU group, while it tended to increase within subgroups of the ward group. The association between the severity of bronchiolitis and the risk of asthma aligned with findings from Delacourt's systematic review. Children with severe bronchiolitis who required hospitalisation had a greater risk of developing asthma than did the general population, who were at least 10 years old.[27] Our study contributed to the understanding of this relationship between age groups.

One notable finding was the substantial disparity between patients diagnosed with asthma and those exhibiting symptoms. In the PICU group, 35% of the children were diagnosed with asthma, whereas 64% experienced asthma symptoms. In the ward group, 19% of patients were diagnosed with asthma, whereas 52% had symptoms. These differences may stem from the underdiagnosis of asthma before the age of 6 years. Which is attributed partly to the inherent challenges in establishing the disease caused by the numerous potential differential diagnoses for symptoms such as cough, dyspnoea and wheezing.[28–30]

TABLE 1 Patient characteristics.

	Paediatric ward group, *N* = 89	PICU group, *N* = 89	*p*-value
Age at admission (*d*)	32 (19–57)	32 (19–54)	0.06
Male	49 (55)	49 (55)	1
Weight at admission (*g*)	4240 (3700–5050)	4020 (3470–4710)	0.03
Birth weight (*g*)	3280 (2920–3660)	3190 (2940–3580)	0.24
Prenatal smoking	15 (17)	12 (14)	0.68
Passive smoking	33 (37)	41 (46)	0.33
Family history of atopy	45 (51)	45 (51)	1
Respiratory virus			
RVS	73 (82)	73 (82)	0.58
Rhinovirus	7 (8)	7 (8)	
Other	9 (10)	9 (10)	
Respiratory support	62 (70)	89 (100)	<0.01
Invasive ventilation	-	13 (15)	
NIV	-	49 (55)	
HFNC	-	13 (15)	
Conventional oxygen therapy	62 (70)	14 (16)	<0.01
Respiratory support period (*d*)	4 (2–5)	7 (4–8)	<0.01
Invasive ventilation	-	5 (4–6)	
NIV	-	4 (2–5)	
HFNC	-	3 (1–4)	
Conventional oxygen therapy	4 (2–5)	2 (1–3)	<0.01
Nutrition by NGT	39 (44)	87 (97)	<0.01
NGT period (*d*)	4 (3–6)	5 (4–8)	<0.01
Intravenous hydration	25 (28)	68 (76)	<0.01
Intravenous hydration period (*d*)	3 (2–4)	4 (3–5)	<0.01
Hospitalisation duration (*d*)	5 (4–7)	8 (6–10)	<0.01

Note: Variables are expressed as median (IQR) or as number (percentages).

Abbreviations: HFNC, high flow nasal cannula; NGT, nasogastric tube; NIV, non-invasive ventilation.

TABLE 2 Questionnaire results.

	Paediatric ward group, *N* = 89		PICU group, *N* = 89		
	N	%	*N*	%	*p*-valaues
Asthmatic patients	17	19	31	35	0.02
Patients with at least one symptom of asthma	46	52	57	64	0.13
1 symptom	24	27	24	27	
2 symptoms	18	20	13	15	
3 symptoms	4	5	20	22	
Age at onset of symptomatology					
0 to 1 year	3	3	10	11	<0.01
1 to 2 years	5	6	27	30	
2 to 3 years	5	6	8	9	
3 to 4 years	10	11	6	7	
4 to 5 years	9	10	3	3	
5 to 6 years	14	16	3	3	
Treated patients	28	29	49	55	<0.01
Patients whose treatment has been effective	27	30	49	55	<0.01

TABLE 3 Analysis of asthma risk factors.

	Multivariate analysis	
	Absolute percentage difference [95% CI]	*p*-value
Group		
Paediatric ward	-	-
PICU	+16% [+4% to +27%]	<0.01
Passive smoking	+6% [−9% to +22%]	0.43
Family history of atopy	+24% [+8 to +41%]	<0.01
Virus at the PCR		
RVS	+14% [−3% to +22%]	0.10
Rhinovirus	+6% [−8% to +17%]	0.36
Other	+1% [−18% to +20%]	0.92

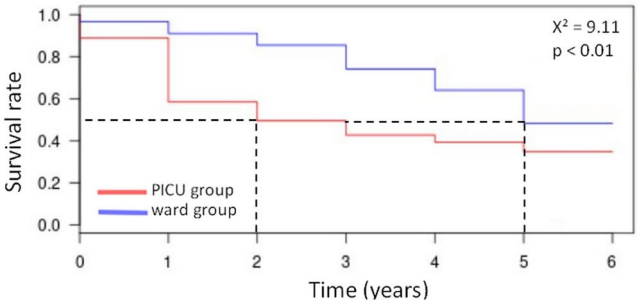

FIGURE 2 Survival analysis of asthma symptoms.

Our results indicated that the severity of bronchiolitis also impacted these respiratory symptoms, whether related to asthma or not.

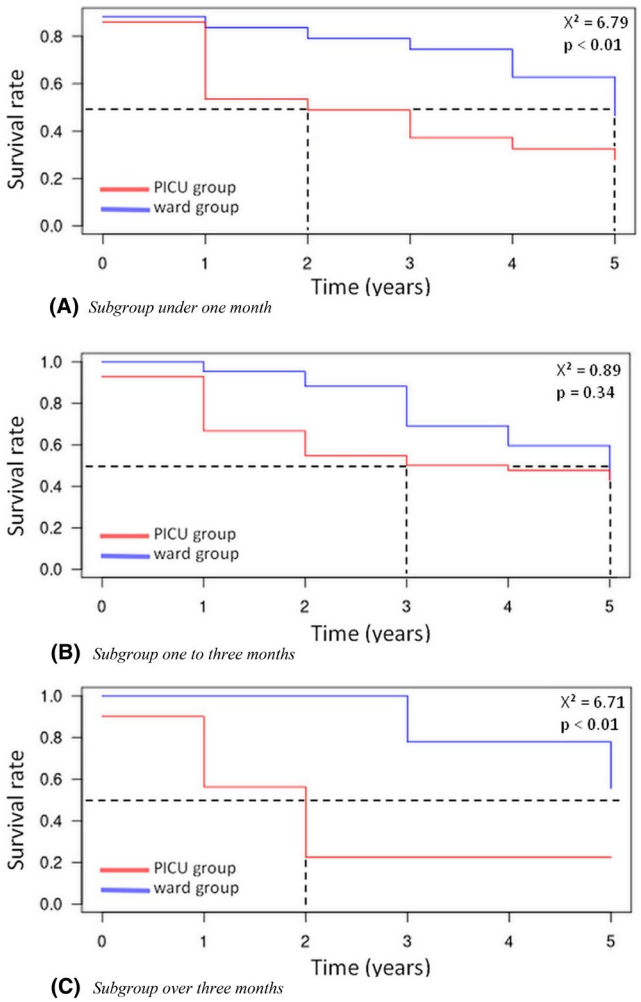

FIGURE 3 Survival analysis of asthma symptoms (subgroups).

4.1 | Strengths and limitations

Our study was original, given the paucity of existing data on the difference between severe and moderate bronchiolitis.

Despite its monocentric design, compliance with French recommendations for the management of bronchiolitis means that our results could be generalised to the whole of France. International application would require evaluation of practices in other countries.

Through rigorous method and a large database on the main risk factors for asthma, our results were strong and consistent with the literature. They need to be confirmed given the lack of data on the asthma phenotype of the children. A complete collection of data from hospital discharge to the age of 6 years would enable us to better characterise the difference between virus-induced asthma and atopic asthma.

In addition to its retrospective design, this study had several limitations. The diagnosis of asthma had been collected 6–10 years after the child's initial diagnosis of bronchiolitis, by a questionnaire. This method introduced the risk of memory bias, and we lacked objective results to validate parental statements.

Lastly, our ward group was not completely representative of the general population. Because we had filled in the necessary number of subjects, only 10% of potentially eligible patients were included. We chose four criteria for matching, the main risk factors for asthma, which greatly reduced the number of possible matches. When a PICU patient-matched several ward patients, the patient whose date of hospitalisation was closest was selected. This was to ensure that the care/environmental conditions were as similar as possible. However, this method included a risk of selection bias. Matching the patients based on the type of virus resulted in a significant imbalance. As a result of this methodology and the diagnostic test used in the emergency department, RSV was possibly overrepresented (Appendix S3). However, it seems that rhinovirus is the main virus responsible for the development of asthma following bronchiolitis.[11]

5 | CONCLUSION

This study assessed the impact of bronchiolitis severity on the development of asthma symptoms before 6 years of age. It showed that

TABLE 4 Asthmatic and non-asthmatic patient characteristics.

	Non-asthmatic patients, *N* = 130	Asthmatic patients, *N* = 48	*p*-value
Age at admission (*d*)	35 (19–54)	28 (19–63)	0.49
Male	67 (52)	31 (65)	<0.01
Weight at admission (*g*)	4105 (3605–4878)	4210 (3565–5000)	0.23
Birth weight (*g*)	3222 (2918–3608)	3245 (2958–3665)	0.88
Prenatal smoking	17 (13)	10 (21)	<0.01
Passive smoking	51 (39)	23 (48)	<0.01
Family history of atopy	57 (56)	33 (69)	<0.01
Respiratory virus			
RSV	103 (79)	43 (90)	0.07
Rhinovirus	11 (9)	3 (6)	<0.01
Other	16 (12)	2 (4)	<0.01
Respiratory support	105 (81)	46 (96)	0.02
Invasive ventilation	6 (5)	7 (15)	<0.01
NIV	34 (26)	15 (31)	<0.01
HFNC	9 (7)	4 (8)	<0.01
Conventional oxygen therapy	56 (43)	20 (42)	<0.01
Respiratory support period (*d*)	4 (2–7)	5 (3–7)	0.27
Invasive ventilation	5 (5–6)	6 (4–8)	0.61
NIV	3 (2–5)	4 (2–4)	0.39
HFNC	3 (2–4)	1 (1–2)	0.12
Conventional oxygen therapy	1 (1–2)	2 (1–4)	0.46
Nutrition by NGT	89 (69)	37 (77)	0.73
NGT period (*d*)	4 (0–6)	4 (2–6)	0.80
Intravenous hydration	66 (51)	27 (56)	<0.01
Intravenous hydration period (*d*)	2 (0–3)	2 (0–3)	0.41
Hospitalisation duration (*d*)	6 (5–9)	7 (5–8)	0.78
Hospitalisation in PICU	58 (45)	31 (65)	<0.01

Note: Variables are expressed as median (IQR) or as number (percentages).

Abbreviations: HFNC, high flow nasal cannula; NGT, nasogastric tube; NIV, non-invasive ventilation.

the more severe the bronchiolitis was, the more likely the child was to develop asthmatic symptoms. In the asthmatic population, the time lag between bronchiolitis and the onset of asthma symptoms seemed to be shorter in those who had severe bronchiolitis.

Given the increased risk of developing asthma after severe bronchiolitis, regular follow-ups are suggested for infants hospitalised in a PICU for bronchiolitis.

AUTHOR CONTRIBUTIONS

Cedric Agossah: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; resources; supervision; data curation; validation; visualization; project administration; formal analysis; software. **Julien Marie:** Conceptualization; writing – original draft; methodology; validation; resources. **Yasmine Bendoukha:** Methodology; validation; software; formal analysis; data curation. **Cecile Vallet:** Validation; writing – review and editing; resources; methodology. **Jacques Brouard:** Conceptualization; methodology; validation; resources; writing – original draft. **David Brossier:** Conceptualization; visualization; methodology; validation; writing – review and editing; resources; supervision; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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