Caffeine treatment for bronchiolitis-related apnea in the pediatric intensive care unit

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Short title: Caffeine treatment for bronchiolitis related apnea in the PICU

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What is already known on this topic

- Apnea is one of the main complications of bronchiolitis and one of the primary reasons for the implementation of ventilatory support in bronchiolitis-affected children.
- There is no clinical guideline on the management of bronchiolitis-related apnea.
- Based on neonatal guidelines, some pediatric clinicians consider caffeine to be of great interest in the treatment of bronchiolitis-related apnea.

What this study adds

- This study describes the specific management of bronchiolitis-related apnea and is the largest series of caffeine-treated patients for this indication.
- This study raises the question of the appropriate caffeine dosing regimen for this indication in this postterm population.
- Further studies with prospective randomized controlled designs are warranted.

Abstract:

Introduction: Apnea is commonly encountered in children with bronchiolitis. Despite the lack of recommendations regarding bronchiolitis-related apnea (BRA) management, some pediatric intensive care unit (PICU) practitioners use caffeine treatment based on extrapolation from the recommendations for prematurity-related apnea management. The objectives of this study were to describe the management of BRA in our PICU, evaluate the caffeine prescription rate for this indication, and explore its potential effects on clinical outcomes.

Methods: This was a retrospective study in a university hospital PICU between January 1st, 2009 and December 31st, 2016. All children under 1 year of age admitted to the PICU with a diagnosis of BRA were included. Patients were allocated to a control group or a caffeine group depending on the administration of caffeine.

Results: In total, 54 infants were included and caffeine treatment was administered to 49 (91%) of them. Patient characteristics were similar between the two groups. Ventilatory support was initiated for 50 patients (93%). Supportive care and length of PICU stay were similar between the two groups. Caffeine was not associated with adverse events.

Conclusion: Caffeine treatment in BRA could be considered as a local standard practice. This retrospective study was underpowered to show any benefit of caffeine treatment on clinical outcomes. This treatment was not associated with significant adverse effects. We raised the question of the appropriate caffeine dosing regimen for BRA in this postterm population. Further studies on this topic are warranted.

Keywords: Bronchiolitis; Apnea; Caffeine; Intensive care

1/ Introduction

According to international guidelines, bronchiolitis is defined as a first episode of dyspnea and wheezing before 2 years of age [1–3]. Bronchiolitis is caused by a lower respiratory tract viral infection [1]. Its clinical presentation results from acute airway inflammation and obstruction due to significant mucus production [1]. The symptoms are essentially respiratory (respiratory distress, tachypnea, wheezing, crackling rattles) and of variable intensity depending on the severity of presentation [1]. The recommended management of children with bronchiolitis is essentially supportive and relies on ensuring upper airway patency and providing nutritional support [1–3]. In most severe cases, the affected child needs to be hospitalized and ventilatory support might be necessary [4–6]. Bronchiolitis is a major public health issue throughout the world. In developed countries, bronchiolitis is the main cause of hospitalization before the age of 1 year, and one third of children under the age of 2 are affected [1,2]. The hospitalization rate for bronchiolitis varies between 2 and 17% of diagnosed patients, which represents 20% of global pediatric hospitalizations [7]. It is estimated that 3–11% of hospitalized children with bronchiolitis will need pediatric intensive care unit (PICU) support for severe respiratory distress or apnea [8]. Apnea is one of the main complications of bronchiolitis and is seen in 1.6–5% of cases [2,9–11]. The reported rate of bronchiolitis-related apnea (BRA) is highly variable and reaches 30% in some studies [7,11,12]. The risk factors for presenting with BRA are term infants of less than 1 month of age at diagnosis, less than 48 weeks of postconceptional age for preterm infants, and a history of a previous apnea episode [2,7,11,13]. BRA can occur independently of respiratory distress levels and remains the primary reason for implementation of ventilatory support in bronchiolitis-affected children [14]. BRA can be caused by acute upper airway obstruction, or originate from a central nervous system source, or result from a combination of these two mechanisms. Contrary to apnea of prematurity for which therapeutic management is endorsed by the neonatology medical community and involves a combination

of ventilatory support and caffeine administration [15,16], there is no clinical guideline regarding management of BRA. Based on extrapolation from neonatal practice guidelines, some pediatric clinicians consider caffeine to be of great interest in the treatment of BRA [9,17,18]. To our knowledge, no study has shown a clear benefit of caffeine treatment in BRA [9,18–20]. Published data describing the use of caffeine in the management of BRA are scarce and insufficient to provide a definite answer. Caffeine administration could theoretically reduce the number of episodes and duration of BRA, thus decreasing the need for mechanical ventilation and hospitalization in the PICU. The primary objective of this study was to describe the management of patients under 1 year of age admitted to our PICU for BRA. The secondary objectives were the evaluation of the caffeine prescription rate for this indication and its effect on clinical outcomes.

2/ Methods

2.1/Setting and design

We conducted a single-center retrospective study in the 12-bed medical and surgical PICU of a tertiary care teaching hospital (CHU de Caen, Caen, France). This study was registered at the Commission Nationale Informatique et Libertés (CNIL) on June 6th, 2017 (number 2073447), and was approved by the research ethics committee of the French Society of Pediatrics on September 27th, 2017 (number CERSFP_2017_58).

2.2/Inclusion criteria

Every child under 1 year of age admitted to the PICU and treated for BRA between January 1st, 2009 and December 31st, 2016, was eligible for inclusion in the study. The inclusion criteria were: bronchiolitis defined as a constellation of signs and symptoms related to lower respiratory tract viral infection according to international guidelines [1–3], and apnea observed by medical or paramedical staff or displayed on the patient monitor and documented in the patient medical record, whether the apnea was observed before or after admission to the PICU. In our

institution, apnea is usually defined as a respiratory pause of 20 s or longer, or a shorter pause accompanied with desaturation, cyanosis, bradycardia, or hypotonia, or an apneic episode considered by caregivers as potentially severe [11,14,21,22]. Apnea is, at first, considered as a bronchiolitis complication even when associated with confounding factors.

The exclusion criteria were: apnea reported only by the child's family, pertussis confirmed by polymerase chain reaction analysis, and incomplete or missing medical files.

Patients were selected retrospectively through a request made to the Department of Medical Information (DMI). Patients were included when they met the inclusion criteria and were retrospectively allocated to the caffeine group or the control group, depending on caffeine citrate administration. The decision to start caffeine treatment and the dosing regimen were at the discretion of the attending physician following neonatal standards for caffeine citrate prescription (bolus of 20 $mg.kg^{-1}$ followed by a 5-$mg.kg^{-1}$ daily maintenance dose) [16]. There was no consensus on the duration of treatment. All patients were treated according to the service's standards of practice in terms of monitoring, ventilatory support, nutritional support, antibiotic therapy, analgesia, and sedation. Patient management was left to the discretion of the medical team responsible for the patient. Patients were discharged to other medical wards according to institutional practice in both groups (presence of neurological, respiratory, and hemodynamic stability without need for supportive measures).

2.3/Outcomes

The outcomes were the length of PICU stay, length of hospital stay, noninvasive and invasive ventilation rate, mechanical ventilation duration, and hemodynamic and nutritional supports. Treatment safety was evaluated by documenting the observed adverse effects of caffeine.

2.4/Data sources

Data were extracted from medical charts and collected with a standardized form defined a priori. These data included demographic information (sex, age, weight), patients' past medical

history, predictive score for death (Paediatric Index of Mortality, PIM2) [23], type of medical supportive measures initiated before and during hospitalization in the PICU, patient death, length of PICU and hospital stay, and caffeine-related adverse events (cardiac dysrhythmias, seizure, irritability, feeding intolerance).

2.5/Statistical analysis

Descriptive data were presented for all patients and compared between treatment groups. According to the distribution of the variables (Shapiro–Wilk test), continuous variables are expressed as mean ± standard deviation or median [1st and 3rd quartiles] as appropriate. Categorical variables are expressed as number and proportions. Comparisons between groups were made with the independent samples *t* test or Mann–Whitney test according to the distribution for continuous variables and with Fisher's exact test or chi-squared test for proportions, as appropriate. Intragroup comparisons were performed using Wilcoxon's rank test for continuous variables and McNemar's test for binary discrete variables. Length of stay, total length of apnea-presenting period, and length of respiratory support were represented by Kaplan–Meier curves and compared with a log rank test. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using XLSTAT software (version 19.4).

3/ Results

3.1/ Study participants

During the study period, 371 children under 1 year of age were admitted to the PICU for bronchiolitis. A total of 54 PICU stays were included in the study between January 1st, 2009 and December 31st, 2016 (Figure 1): 35 boys (65%) and 19 girls (35%) (Table 1). The median age was 24 days (18–38) and median weight was 3260 g (2810–3810) (Table 1). The demographic characteristics were similar between the two groups (Table 1).

3.2/ Symptoms and clinical status at admission

The time between the first respiratory symptoms and the first BRA was less than 3 days in 64% of cases. Of the patients, 56%, 44%, and 26% had at least one episode of bradycardia, cyanosis, or hypotonia, respectively, before admission to the PICU. The patients' conditions were similar at admission, as shown in Table 1.

3.3/ Supportive care

In total, 49 patients (91%) received caffeine citrate treatment. A loading dose was administered in 96% of cases (*n*=45). The loading dose was 20 $mg.kg^{-1}$ for all patients except one for whom an additional dose of 10 $mg.kg^{-1}$ was administered (full loading dose of 30 $mg.kg^{-1}$). Maintenance treatment was administered in 81% of cases (*n*=39). The maintenance treatment was a once-daily dosing regimen of 5 $mg.kg^{-1}$, except for two cases: 6.6 $mg.kg^{-1}$and 2 $mg.kg^{-1}$. The median duration of caffeine treatment was 3 days (1–6). Ventilatory support was initiated for 50 patients (93%), with a median duration of 4 days (3–7) (Table 2). Eight patients (15%) required invasive ventilation (median duration: 7.5 days [5–8]). All ventilated patients benefited from noninvasive ventilation at some point (median duration: 3 days [2–5]) and 34 (63%) benefited from high-flow nasal cannula therapy (HFNC). Other supportive measures are summarized in Table 2.

3.4/Patient outcomes

The length of PICU stay was similar between the groups, whereas the length of hospital stay was significantly shorter in the caffeine group (8 vs. 14 days $p < 0.05$) (Table 2). Kaplan–Meier curves are depicted in Figure 2.

3.5/Adverse events

In the caffeine group, the 24-h average heart rate was higher before than after the caffeine citrate loading dose (159 ± 13 bpm vs. 144 ± 13 bpm, $p < 0.01$). Furthermore, 20% of the patients had at least one vomiting episode during their stay. This proportion was not significantly increased

after caffeine treatment initiation (28% vs. 20%, $p = 0.57$). One patient in the caffeine group experienced a convulsive episode without any identified cause.

4/Discussion

Our study shows that 91% of the patients admitted to the PICU of our institution with BRA received caffeine treatment. Respiratory support was given to 93% of patients. Our study also shows that PICU patients with BRA were more often boys (M / F ratio = 1.8), younger than 3 months (median age at admission = 24 days [17.8–38]), and with a gestational age at admission of 41 ± weeks. Caffeine did not have a significant impact on ventilatory support or length of PICU stay.

Flores-Gonzalez et al. published their work in 2017 [24] in which they studied the management of bronchiolitis in PICU patients, without looking at BRA specifically. The patient characteristics in their study were similar to ours with a median age of 1 month, a male predominance (M / F ratio = 1.2), and a family history of atopy in 25% of cases. However, their median weight was higher (4.6 kg vs. 3.3 kg) and the presence of family smoking was less frequent (32% vs. 67%), suggesting a possible influence of these two factors on the risk of BRA.

Our study did not show any impact of caffeine treatment on the use of mechanical ventilation. The majority of our patients (93%) needed invasive or noninvasive ventilatory support, without any difference between the two treatment groups. Our results are consistent with previous publications [9,18]. In 2011, Cesar et al. published a retrospective study (n=25) comparing BRA patients, based on administration of caffeine treatment or not, in a PICU in the United Kingdom. In this study, the authors showed that caffeine tended to protect patients against ventilatory support initiation ($p = 0.0595$) [18]. In 2016, Alansari et al. published a randomized placebo controlled trial (RCT) [9] that focused on children younger than 4 months with BRA. The authors studied the administration of a single loading dose of caffeine citrate (25 $mg.kg^{-1}$) and

concluded that there was no significant reduction in the time needed to obtain a 24-h period without BRA. The frequency of apnea at 24, 48, and 72 h, as well as the need for invasive or noninvasive ventilation, was similar between the two groups. We opted to study different outcomes from the ones chosen by Alansari et al. so as to explore more clinically and economically significant issues such as PICU admission rate, PICU length of stay, and ventilatory support requirement [9]. The study of Alansari et al. did not show significant benefits of caffeine on these aspects of BRA management [9]. Besides, we hypothesize that the previously published studies failed to show the effectiveness of caffeine in BRA because of the potentially inappropriate caffeine dosage considering postnatal maturation of caffeine metabolism in this patient population. In our study, patients received the recommended caffeine citrate dosing regimen for treatment of apnea of prematurity (loading dose of 20 $mg.kg^{-1}$ followed by daily maintenance of 5 $mg.kg^{-1}$) [16]. However, owing to renal and hepatic immaturity, the elimination half-life of caffeine is much longer in premature infants than in term infants. Caffeine clearance is similar in preterm and term neonates, but it accelerates 20-fold by the age of 3 months [14,26]. Studies have shown that using even higher doses of caffeine citrate reduces extubation failures and apnea frequency in premature infants [27]. Satisfactory tolerance has been reported with caffeine plasma levels reaching 70 $mg.L^{-1}$ in premature infants [14]. The lack of documented efficacy of caffeine in BRA as well as its important postnatal pharmacokinetic variations and its large therapeutic index provide arguments for the use of higher dosages for this indication. We hypothesize that administration of the total daily maintenance dose every 12 h instead of every 24 h could provide a better efficacy in this population.

Our work is one of the few studies to describe the specific management of BRA and is the largest series of caffeine-treated patients for this indication [9]. The design used is similar to other studies describing the evolution of children with bronchiolitis [28] especially in cases of

BRA [13,29]. The prolonged and continuous study period prevented any seasonal variations in epidemics and associated bias. Our institution's PICU is representative of general PICUs in France in terms of bed numbers and the patient age group [30].

Our study is limited by the retrospective design and the missing data. In addition, there was no record of continuous cardiac and respiratory monitoring thereby preventing an exhaustive analysis of events (apnea, bradycardia, desaturation). The initial patient selection was made on the basis of ICD-10 diagnosis coding, which is not perfectly exhaustive and could have led to omission of mis-coded patient files. Another limitation of this study is that data from patients with apnea risk factors, such as gastroesophageal reflux or upper airway anomaly, were considered in the analysis. These patients' data were not excluded as we intended to perform a pragmatic evaluation of BRA management. We only considered bronchiolitis episodes treated in the PICU, which led to the selection of the most severe cases. Finally, the small population size and the significant difference in the number of patients in each group (49 patients received caffeine and only five did not) limited the study's statistical power and generalizability as well as its statistical analysis reliability. Thus, the Kaplan–Meier curves and the significant decrease in the rate of fasting lasting more than 24 h as well as the decrease in the length of hospital stay in the caffeine group should be interpreted with caution. This major difference between treatment group sizes was not expected and is impossible to adjust for in the analyses. Statistical analyses were considered a priori when elaborating the protocol before composing the groups. The results of this study should be interpreted as descriptive in their nature and they highlight the fact that despite having no documented clinical benefit in the treatment of BRA, caffeine citrate could be considered a standard of care in some PICUs.

5/Conclusion

Children admitted to the PICU for BRA were mainly boys aged less than 3 months and with a gestational age at admission of 41 weeks. Caffeine citrate is commonly used in our institution

for this population. This retrospective study was underpowered to show any benefit of caffeine treatment on patient outcomes but it is the first to raise the question of the appropriate caffeine dosing regimen for this indication in a postterm population. Further studies with prospective randomized controlled designs are warranted to provide answers regarding the potential benefits of caffeine treatment for BRA.

Conflict of interest: none

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Tables:

Table 1: Demographic and clinical characteristics at admission

Results expressed in numbers (percentages), means ± standard deviation and median [interquartile range]. NS = not significant. NC = not communicated. BP = blood pressure. PIM2 = Pediatric Index of Mortality, revised version.

Parameter	**Total** ***n*** **= 54**	**Caffeine** ***n*** **= 49**	**No caffeine** ***n*** **= 5**	***P***
Male	35 (65%)	32 (65%)	3 (60%)	NS
Age (days)	24 [18-38]	24 [17-36]	28 [18-47]	NS
Gestational age at birth (weeks)	37 [34-38]	37 [33-38]	36 [31-38]	NS
Birth at <37 weeks' gestation	24 (44%)	21 (43%)	3 (60%)	NS
Gestational age at admission (weeks)	41 ± 3	41 ± 3	40 ± 3	NS
Birth weight (grams) [1]	2910 [2215-3403]	2930 [2215-3403]	2590 [1469-3363]	NS
Weight at admission (grams) [1]	3260 [2810-3810]	3350 [2827-3815]	2800 [2560-3650]	NS
Smoking in at least one parent [2]	14 (67%)	14 (67%)	NC	/
Personal medical history				
Congenital heart disease	2 (4%)	1 (2%)	1 (20%)	/
Cardiac dysrhythmia	2 (4%)	2 (4%)	0 (0%)	/
Bronchiolitis	3 (6%)	3 (6%)	0 (0%)	/
Apnea risk factors				
Gastroesophageal reflux	6 (11%)	5 (10%)	1 (20%)	/
Upper airway anomaly	2 (4%)	2 (4%)	0 (0%)	/
Epilepsy	0 (0%)	0 (0%)	0 (0%)	/
Digestive pathology	1 (2%)	1 (2%)	0 (0%)	/
Family history of asthma [3]	9 (21%)	8 (21%)	1 (25%)	/
Parameters at admission				
Respiratory rate (min^{-1})	50 [39-59]	50 [39-59]	42 [35-55]	NS
Heart rate (min^{-1})	151 ± 22	152 ± 22	136 ± 12	NS
Systolic BP (mmHg)[4]	93 ±14	92 ± 14	100 ± 16	NS
Diastolic BP (mmHg)[4]	51 ± 10	51 ± 10	48 ± 12	NS
Temperature (°C)	37 [36.7-37.5]	37.0 [36.8-37.8]	37.0 [36.4-37.6]	NS
Sibilant or crackling [1]	18 (34%)	16 (33%)	2 (40%)	NS
Respiratory distress [1]	32 (60%)	29 (59%)	3 (75%)	NS
Poor general state [5]	15 (33%)	14 (33%)	1 (25%)	NS
Blood gas at admission	35 (65%)	30 (61%)	5 (100%)	NS
pH [1]	7.33 ± 0.07	7.33 ± 0.07	7.32 ± 0.06	NS
pCO_2 (mmHg)	51.7 [49-58.2]	51.2 [48.9-57.3]	53 [50.3-64.9]	NS
HCO_{3-} ($mmol.L^{-1}$) [1]	28.1 ± 3.2	28.0 ± 3.4	28.8 ± 0.9	NS
Lactates ($mmol.L^{-1}$) [6]	2.2 [1.5-3.9]	2.6 [1.7-5.0]	1.6 [1.3-1.6]	NS
PIM2 score at admission (%)	0.9 [0.4-1.2]	0.9 [0.6-1.2]	0.4 [0.3-7.2]	NS

[1] One case of missing data. [2] 31 cases of missing data. [3] 12 cases of missing data. [4] Three cases of missing data. [5] Eight cases of missing data. [6] Performed for 20 patients.

Table 2: Supportive cares and length of stay

Results expressed as numbers (percentages) and median [interquartile range].
NS = not significant. NO = nitric oxide. HFNC = high-flow nasal canula.

Patient care and outcomes	**Total** ***n*** **= 54**	**Caffeine** ***n*** **= 49**	**No caffeine** ***n*** **= 5**	***P***
Ventilation duration (days) [1]	4 [3-7]	4 [2-7]	5.5 [3-11]	NS
Ventilation	50 (93%)	46 (94%)	4 (80%)	NS
Invasive ventilation	8 (15%)	8 (16%)	0 (0%)	NS
Noninvasive ventilation	50 (93%)	46 (94%)	4 (80%)	NS
HFNC	34 (63%)	32 (65%)	2 (40%)	NS
Inhaled NO	1 (2%)	1 (2%)	0 (0%)	NS
Nutritional support	54 (100%)	49 (100%)	5 (100%)	NS
Fasting > 24 h	8 (15%)	5 (10%)	3 (60%)	< **0.05**
Tube feeding duration (days) [2]	4 [3-8]	4 [3-8]	5 [1-8]	NS
Intravenous fluid resuscitation	8 (15%)	8 (16%)	0 (0%)	NS
Inotropic drugs	0 (0%)	0 (0%)	0 (0%)	NS
Vasopressor drugs	1 (2%)	1 (2%)	0 (0%)	NS
Sedative treatment (IV)	9 (17%)	8 (16%)	1 (20%)	NS
Sedative treatment (PO)	22 (41%)	21 (43%)	1 (20%)	NS
Length of stay				
In the PICU (days)	6 [4-8]	5 [3-8]	8 [5-13]	NS
In hospital (days) [3]	9 [6-12]	8 [6-11]	14 [9-27]	< **0.05**
In hospital (days) [4]	9 [6-12]	8 [6-11]	17 [9-37]	< **0.05**

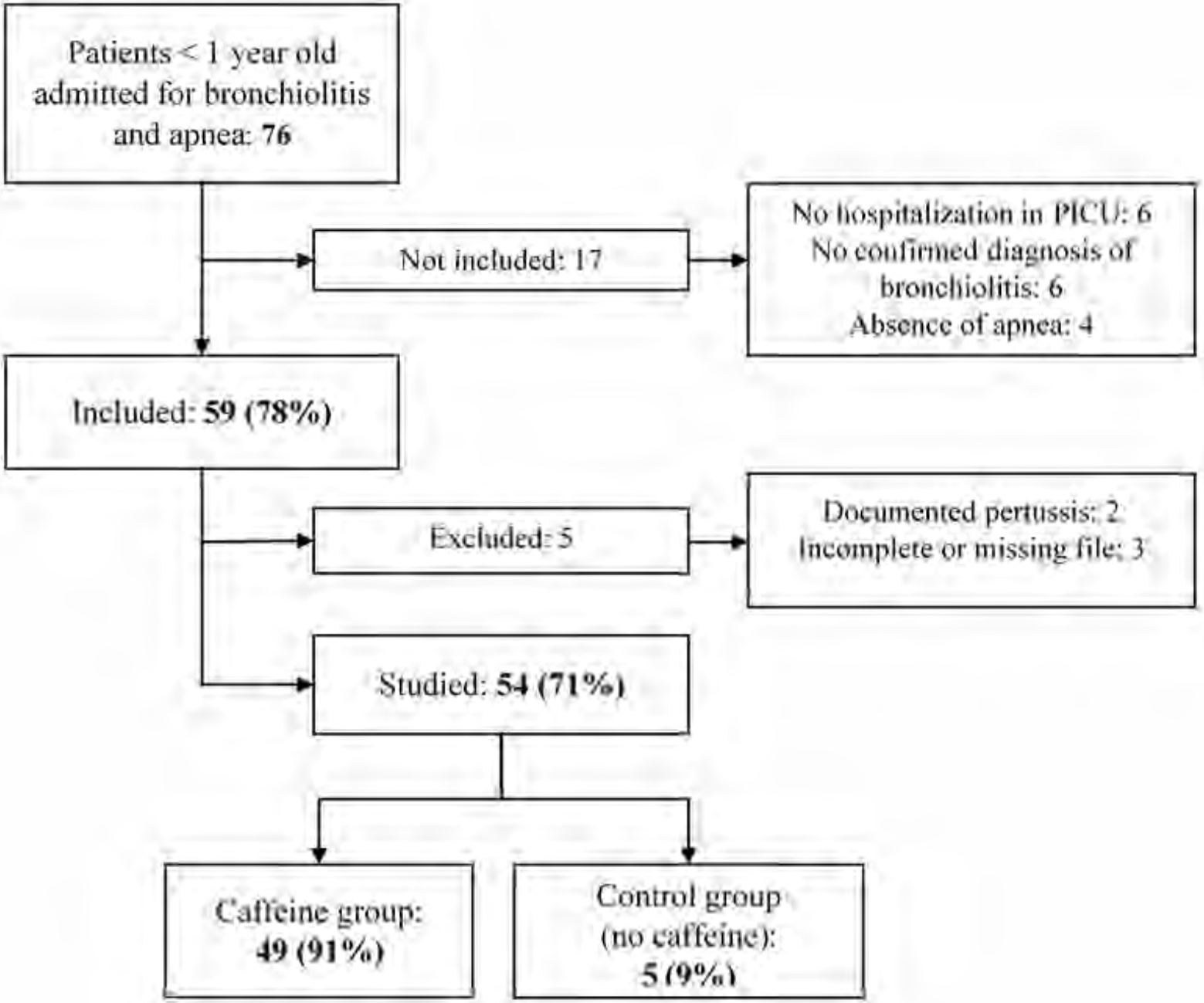
[1] One case of missing data. [2] Seven cases of missing data. [3] Calculated including the five patients of the control group. [4] Calculated excluding a patient in the control group hospitalized on an oncological basis.

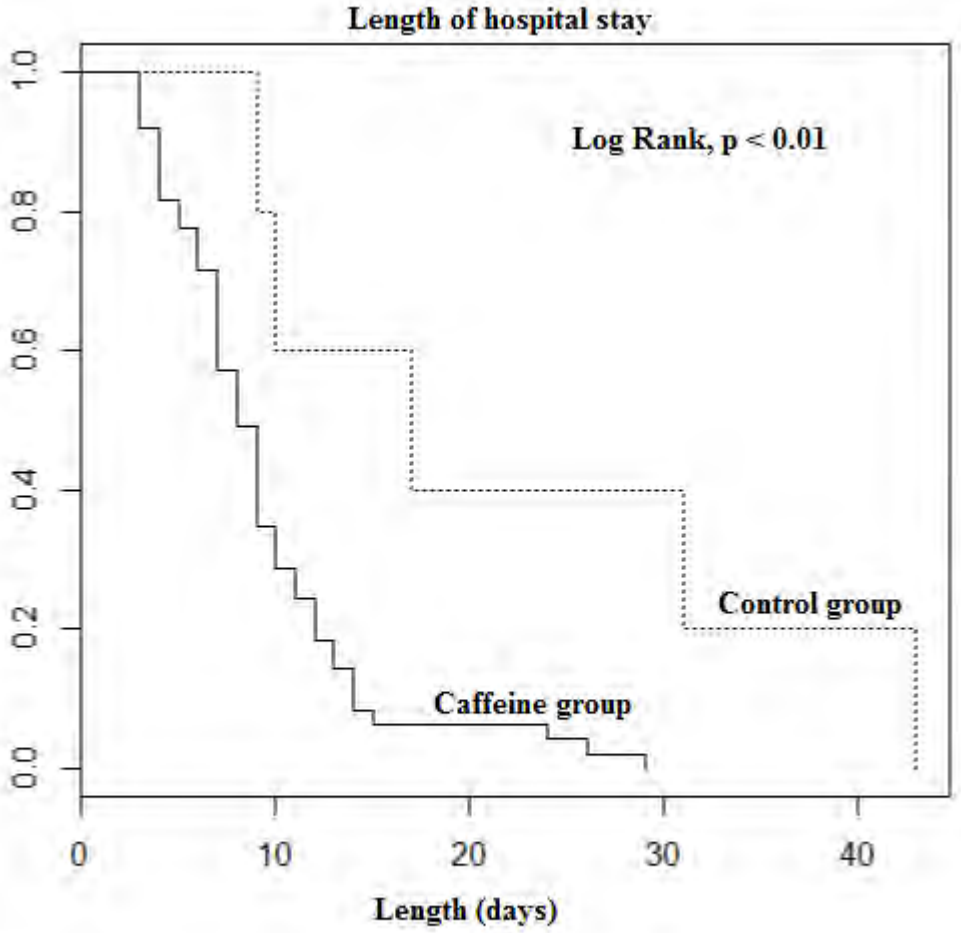
Figures:

1. Flowchart

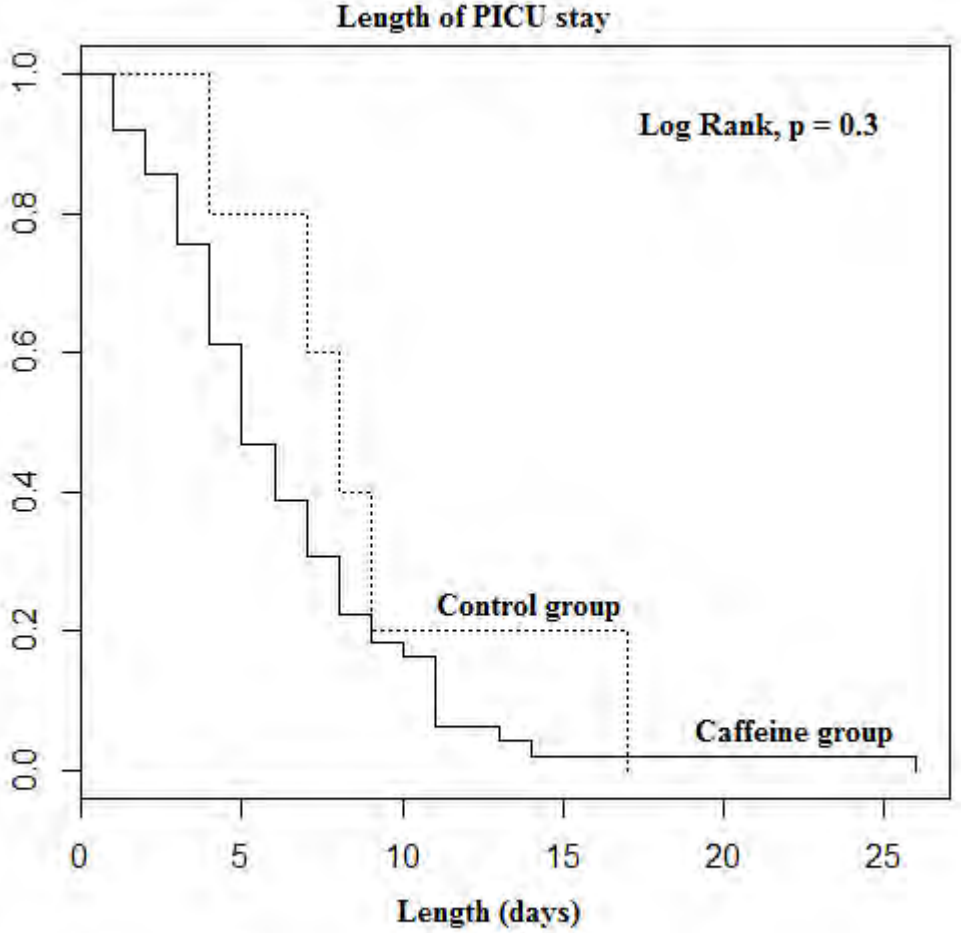
   PICU: Pediatric intensive care unit

2. Lengths. Kaplan–Meier curves

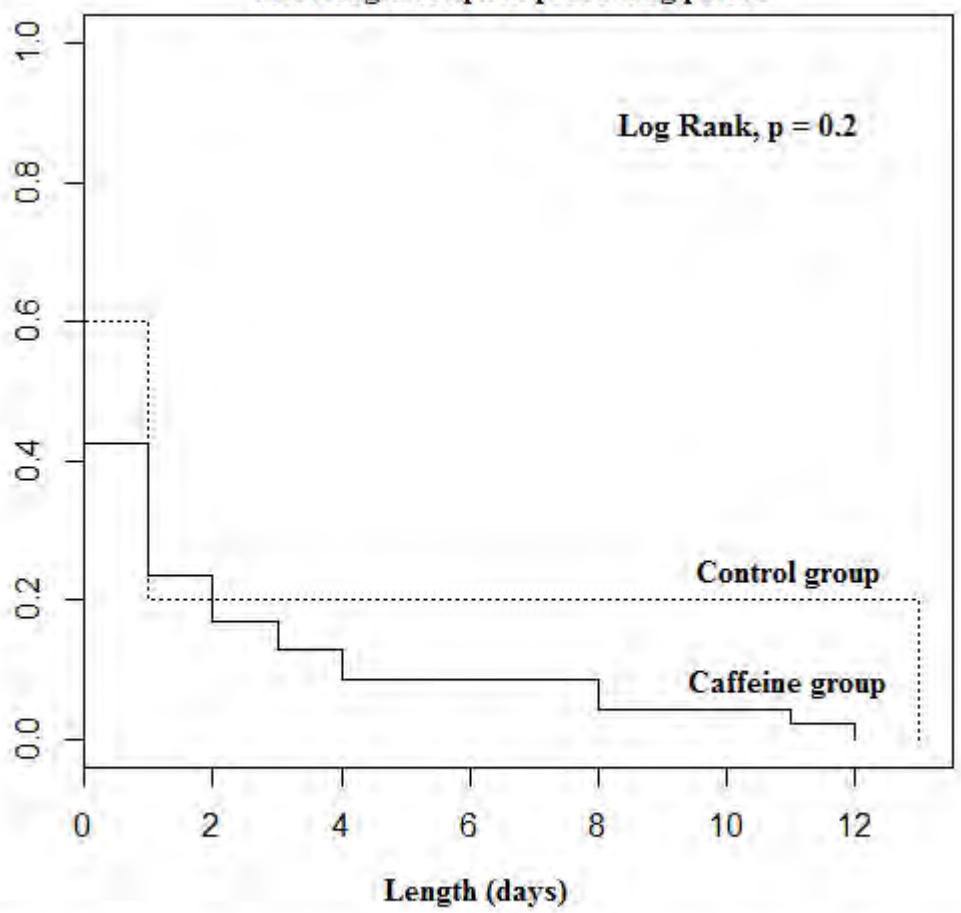

Patients < 1 year old admitted for bronchiolitis and apnea: 76
Not included: 17
No hospitalization in PICU: 6
No confirmed diagnosis of bronchiolitis: 6
Absence of apnea: 4
Included: 59 (78%)
Excluded: 5
Documented pertussis: 2
Incomplete or missing file: 3
Studied: 54 (71%)
Caffeine group: 49 (91%)
Control group (no caffeine): 5 (9%)



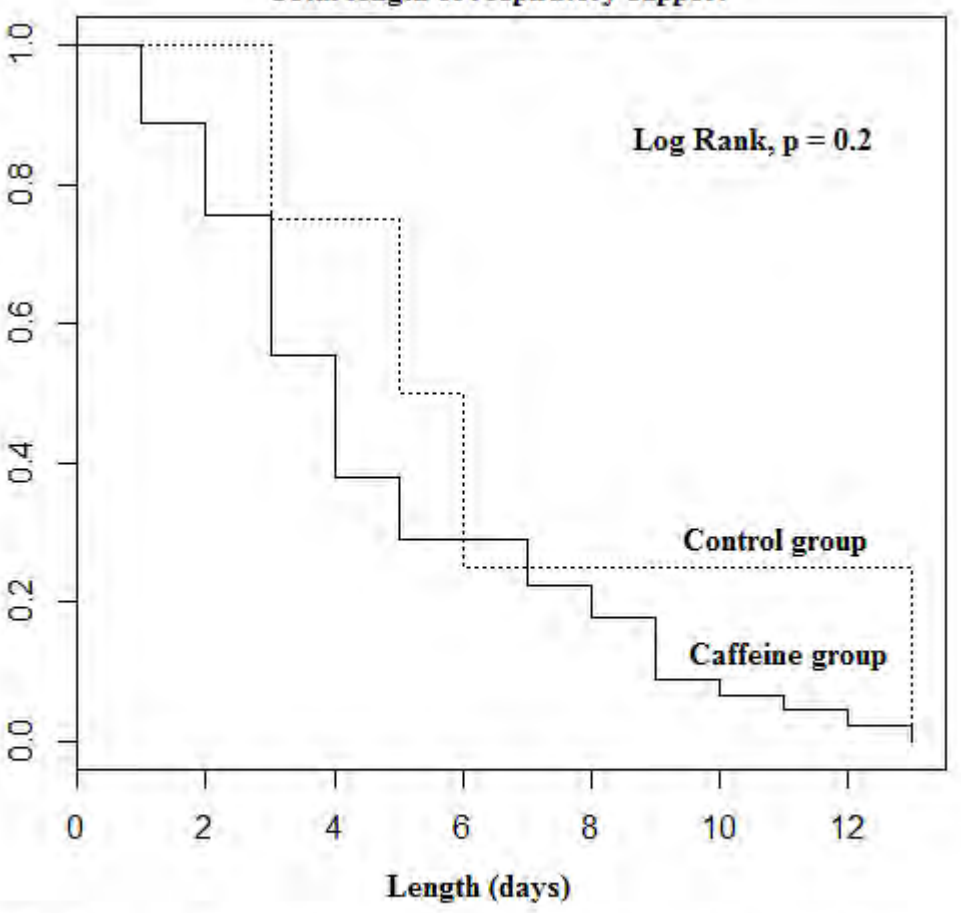
Control	5	4	2	2	1	
Caffeine	49	14	3	0	0	



Control	5	4	1	1	0	0
Caffeine	49	23	8	1	1	1



Control	5	1	1	1	1	1	1
Caffeine	49	8	4	4	2	2	0



Control	4	4	3	1	1	1	1
Caffeine	45	34	17	13	8	3	1