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Clinical course and complications of RSV versus non-RSV bronchiolitis in hospitalised children

Przebieg kliniczny i powikłania zapalenia oskrzelików RSV w porównaniu z nie-RSV u hospitalizowanych dzieci

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Abstract

Introduction and objective: Bronchiolitis in young children often requires hospitalisation. It is mostly caused by respiratory syncytial virus (RSV) and aetiological factors may be associated with clinical presentation and prognosis. We aimed to compare the epidemiology, clinical features, severity and management of RSV and non-RSV bronchiolitis. **Materials and methods:** This cross-sectional retrospective study included hospitalised children under 2 years of age. Children with a positive rapid antigen diagnostic test and/or molecular study were included in the RSV group, while those with a negative result were classified as non-RSV bronchiolitis. We compared patient history, clinical presentation, disease severity including passive oxygen therapy, intensive care unit transfer, death, length of hospital stay, presence of complications, oxygen saturation <92%, acidosis, hypercapnia and treatment used. **Results:** The study included 524 patients (median age 2 months): 462 (88%) RSV and 62 (12%) non-RSV cases. A 7-fold increase in the number of cases was observed between 2010–2011 and 2017–2018. A univariate regression model showed lower odds of family history of atopy (odds ratio, OR = 0.46), higher odds of cough (OR = 4.74), apathy (OR = 2.61), feeding difficulties (OR = 2.03) and vomiting (OR = 3.34) in the RSV group. RSV patients required oxygen therapy (OR = 3.78) and antibiotics (OR = 2.82) more frequently, received inhaled steroid therapy for longer (9 vs. 8 days) and had a higher likelihood of complications (OR = 4.24). A multivariate model showed statistical significance for cough (OR = 6.22), oxygen therapy (OR = 4.43) and complications (OR = 15.95). **Conclusions:** We observed an increasing trend in bronchiolitis hospitalisations, including RSV bronchiolitis, which was associated with a more severe disease course. No significant clinical features were identified to replace laboratory tests.

Keywords: respiratory syncytial virus, bronchiolitis, children, complications

Streszczenie

Wprowadzenie i cel: Zapalenie oskrzelików u małych dzieci często wymaga hospitalizacji. W większości przypadków jest wywoływane przez syncytialny wirus oddechowy (*respiratory syncytial virus*, RSV), a czynniki etiologiczne mogą być związane z obrazem klinicznym i rokowaniem. Celem pracy było porównanie epidemiologii, cech klinicznych, ciężkości i leczenia zapalenia oskrzelików wywołanego przez RSV i nie-RSV. **Materiał i metody:** To przekrojowe badanie retrospektywne obejmowało hospitalizowane dzieci w wieku poniżej 2 lat. Dzieci z dodatnim wynikiem szybkiego testu diagnostycznego antygenu i/lub badania molekularnego zostały włączone do grupy RSV, podczas gdy te z ujemnym wynikiem zostały sklasyfikowane jako zapalenie oskrzelików nie-RSV. Porównano wywiad u pacjenta, obraz kliniczny, nasilenie choroby, w tym tlenoterapię bierną, przeniesienie na oddział intensywnej opieki medycznej, zgon, długość pobytu w szpitalu, obecność powikłań, wysycenie tlenem <92%, kwasicę, hiperkapnię i zastosowane leczenie. **Wyniki:** Do badania włączono 524 pacjentów (mediana wieku 2 miesiące): 462 (88%) z RSV i 62 (12%) nie-RSV. W latach 2010–2011 i 2017–2018 zaobserwowano 7-krotny wzrost liczby przypadków. Model regresji jednoczynnikowej wykazał niższe prawdopodobieństwo atopii w wywiadzie rodzinnym (iloraz szans, *odds ratio*, OR = 0,46), wyższe prawdopodobieństwo kaszlu (OR = 4,74), apatii (OR = 2,61), trudności z karmieniem (OR = 2,03) i wymiotów

(OR = 3,34) w grupie RSV. Pacjenci z RSV częściej wymagali tlenoterapii (OR = 3,78) i antybiotyków (OR = 2,82), dłużej otrzymywali wziewną terapię sterydową (9 *vs* 8 dni) i mieli większe prawdopodobieństwo powikłań (OR = 4,24). Model wieloczynnikowy wykazał istotność statystyczną dla kaszlu (OR = 6,22), tlenoterapii (OR = 4,43) i powikłań (OR = 15,95). **Wnioski:** W badaniu zaobserwowano rosnący trend hospitalizacji z powodu zapalenia oskrzelików, w tym RSV, co wiązało się z cięższym przebiegiem choroby. Nie zidentyfikowano istotnych cech klinicznych, które mogłyby zastąpić testy laboratoryjne.

Słowa kluczowe: syncytialny wirus oddechowy, zapalenie oskrzelików, dzieci, powikłania

BACKGROUND

Acute bronchiolitis (AB) is one of the most common causes of hospitalisation in paediatric wards, and the major aetiological factor for AB is human respiratory syncytial virus (RSV)[1]. Worldwide, RSV is responsible for approximately 101,000 deaths in children under 5 years of age each year; the majority of deaths occur in low- and middle-income countries, but RSV is also a significant socioeconomic problem in high-income countries[2,3]. Overall, approximately 33 million cases of RSV are reported each year in children under 5 years of age, of which 3.6 million require hospitalisation; a large proportion of infections and a higher proportion of hospitalisations are seen in children aged 0–6 months (6.6 million and 1.4 million cases, respectively)[2]. Similarly, in Poland, the highest hospitalisation rates are observed in the youngest group of patients (reaching 11.32/1,000 in children under 1 year of age), and a sharp increase in the number of hospitalised RSV cases has been observed over the last decade[4].

To date, guidelines for the management of AB do not recommend routine RSV testing, as it does not lead to a change in management – there is currently no causative treatment, but the use of microbiological testing may be justified on epidemiological grounds, for example to implement patient isolation or cohorting[5–7].

In addition to the epidemiological significance, there are some practical implications of establishing the aetiology. The literature on this topic is rather scarce, but studies comparing RSV and non-RSV bronchiolitis associated RSV with a more severe course of disease, more frequent need for oxygen therapy or respiratory support, transfer to the intensive care unit (ICU) or longer hospital stay[8–11]. Furthermore, some authors have suggested a higher use of medications, both inhaled therapeutics and antibiotics, in children with RSV AB[11]. The question of treatment response has also been raised, as a systematic review showed a positive trend towards shorter hospital stays in children with non-RSV AB treated with systematic corticosteroids, although no conclusions can be drawn due to lack of statistical significance[12]. Nevertheless, only supportive therapy is currently recommended, including nasal aspiration, oxygen treatment (either low-flow oxygen therapy – LFOT, or high-flow nasal cannula – HFNC) or, in the most severe cases, non-invasive ventilation (NIV) or mechanical ventilation (MV)[13]. The prospects for causal treatment and prophylactic measures are promising, with a number of vaccines (and other vaccine candidates), monoclonal antibodies and potential drugs being intensively studied in preclinical and clinical trials, although it must be emphasised that from a global perspective, vaccines appear to be the most effective methods[14,15].

Accurate knowledge of the actual epidemiological situation and RSV circulation is needed to guide the use of prophylactic monoclonal antibodies in at-risk groups as precisely as possible; the importance of changing epidemiology was highlighted by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic[16]. To date, a relatively stable and repeatable seasonality has been observed in Europe, with increased RSV activity mainly in winter, with the RSV season starting later and lasting longer with increasing northern latitude, peaking between January and March[11,17,18]. The non-pharmacological interventions against the SARS-CoV-2 pandemic rapidly reduced the spread of RSV infection, but as restrictions were relaxed, significant changes in RSV epidemiology were observed, including the presence of RSV outside the previously typical RSV season[16,19]. As changes in seasonality may require rapid changes in prophylactic strategies, such as shifting the start date of monoclonal antibody administration, the need for enhanced epidemiological surveillance correlated with clinical data and real-time information sharing between relevant institutions becomes apparent[20].

Due to expected differences in clinical features and disease course, the main rationale of this analysis was to provide a comprehensive assessment of RSV versus non-RSV bronchiolitis. We aimed to compare the epidemiology, clinical presentation, course and treatment of acute bronchiolitis.

MATERIALS AND METHODS

This retrospective cross-sectional study included patients admitted to hospital with a diagnosis of acute bronchiolitis between January 2010 and January 2019. Patients with ICD-10 (International Classification of Diseases, 10th Revision) final diagnosis codes: J21.0 (AB due to RSV), J21.8 (AB due to other specified organisms) and J21.9 (AB, unspecified) were eligible for the study. The medical records of patients admitted to the paediatric ward of the Bielanski Hospital, Warsaw, Poland, were searched and the extracted records were reviewed for final diagnosis. Inclusion criteria also included age (under 24 months) and a relevant clinical diagnosis of AB according to the official Polish guidelines for the treatment of lower respiratory tract infections (LRTI): acute

inflammatory process of the bronchioles preceded by an episode of upper respiratory tract infection with a first episode (in life) of expiratory dyspnoea with rales and/or wheezing; the Polish guidelines recognise AB in children under 2 years of age[7]. The RSV AB group included only patients with laboratory-confirmed RSV infection; the aetiological factor was confirmed in a nasopharyngeal swab specimen using the Alere BinaxNOW RSV Card rapid antigen test (Alere Scarborough, Inc., Scarborough, Maine, USA) or NADAL RSV Test (nal von minden GmbH, Moers, Germany, in the period September–November 2017) and/or cartridge-based nucleic acid amplification test (CBNAAT) – Cepheid GeneXpert (Sunnyvale, California, USA). Diagnostic testing was performed according to the manufacturer's instructions. Patients in the non-RSV group had at least one negative (and no positive) rapid antigen test and/or molecular study result. Exclusion criteria were age 2 years and older and lack of complete clinical follow-up data, including discharge at the request of parents/legal guardians.

Laboratory procedures

Blood was taken from the patients on admission and the following tests were performed:

- capillary blood gas (CBG) – an incision site was disinfected and without prior warming, an initial puncture was made with a needle to obtain a capillary blood sample, then the samples were checked for the presence of air bubbles and analysed using the Roche Cobas b 121 and b 221 analyser (Roche Diagnostics Ltd., Rotkreuz, Switzerland) until 26 January 2016 and using the Siemens RAPIDLab 348EX blood gas system (Siemens Healthcare Diagnostics, Marburg, Germany) from 27 January 2016;
- procalcitonin (PCT) measurement using the Cobas e 411 (Roche Diagnostics Ltd., Rotkreuz, Switzerland) until 4 August 2016 and the Cobas 6000 (Roche Diagnostics Ltd., Rotkreuz, Switzerland) since 5 August 2016 with a detection limit of 0.02 ng/mL;
- C-reactive protein (CRP) measurement using Cobas 6000 (Roche Diagnostics Ltd., Rotkreuz, Switzerland) with a detection limit of 0.1 mg/L;
- white blood cell (WBC) count with absolute neutrophil count (ANC) using Sysmex XT2000i and Sysmex XN1000/Sysmex XN550 (Sysmex Corporation, Kobe, Japan) since 10 April 2014.

Interview-based baseline characteristics included sociodemographic data (sex, age, gestational age, birth weight, lowest Apgar score during the first 10 minutes, maternal age, feeding method, living conditions estimated by density – the number of persons per room) and history of atopy (patient history, family history – first-degree relatives, or any history, i.e. patient or family). In line with the risk groups age subgroups contained patients aged 0–<3 months, 3–<6 months, 6–<12 months and 12–23 months[5–7].

The comparative analysis considered 3 groups of endpoints: 1) a clinical picture, 2) a disease severity, 3) a treatment.

1. The clinical picture included the following primary endpoints: presence of fever, fever level, duration before/during hospitalisation and total duration, coryza, cough, dyspnoea, apnoea, apathy, feeding difficulties (fatigue/exhaustion), presence of foamy mucous in the mouth, history of aspiration, vomiting, diarrhoea.
2. Disease severity was assessed by primary endpoints – need for oxygen therapy, ICU transfer, fatal outcome, prolonged (above median) length of stay (LOS), presence of sequelae: pneumonia or purulent otitis media, oxygen blood saturation below 92% on pulse oximetry, acidosis (i.e. pH <7.35) on CBG or hypercapnia (i.e. pCO_2 >45 mm Hg). Secondary endpoints – duration of oxygen therapy, length of stay, and clinical parameters (respiratory rate, heart rate, oxygen pulse oximetry on admission) and laboratory parameters (CBG parameters – pH, pCO_2, and inflammatory markers – PCT, CRP, WBC, ANC).
3. The treatment comparison included the use of corticosteroids (inhaled and systemic), inhaled bronchodilators and (separately) inhaled alpha-mimetics (epinephrine/adrenaline), hypertonic saline and antibiotic treatment.

Statistical analysis

Nominal variables are presented as numbers (*n*) and percentages, while continuous variables are presented as mean with standard deviation (*SD*) in the case of normal distribution or median with interquartile range (IQR) in the case of skewed data distribution. Distribution was tested using the Shapiro–Wilk test, and appropriate parametric (Student *t*-test) or non-parametric (Mann–Whitney *U* test) tests were used for direct comparisons, while the nominal data were compared using Fisher's exact test or chi-squared test. Univariate and multivariate logistic regression models were fitted to calculate the odds ratio (OR) with 95% confidence interval (95% CI); the numerical data were categorised according to the median. Variables that were statistically significant in both uni- and multivariate analyses were furtherly analysed in age subgroups. A significance level of alpha = 0.05 was used. Statistical analysis was performed using Statistica 13.1 software (Statsoft, Tulsa, OK, USA).

The study received a positive opinion from the Bioethics Committee and was granted approval number 32/PB/2019 (issued on 13 March 2019). The study was conducted in accordance with the tenets of the Declaration of Helsinki and its amendments. Informed consent was waived as patients underwent only standard procedures and were not exposed to any additional procedures, the study did not influence disease management and was retrospective in nature.

RESULTS

During the study period (January 2010 – January 2019), there were 16,195 hospitalisations in the paediatric ward of the Bielanski Hospital, Warsaw, Poland; among vthese

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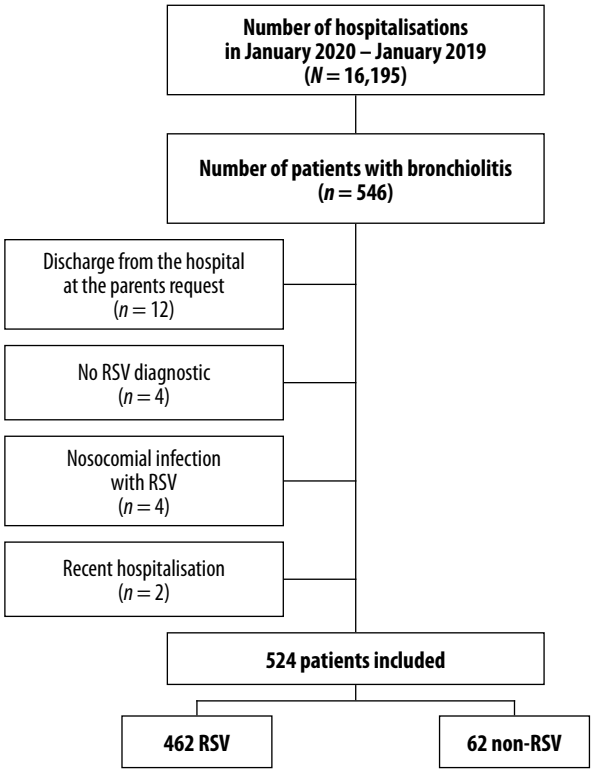

Fig. 1. A flowchart of the patients in the study

patients, 546 children were diagnosed with acute bronchiolitis, 12 were discharged at the request of legal tutors, 4 were not tested for RSV, 4 patients were excluded because of a nosocomial infection and 2 because of a possible nosocomial infection due to a hospitalisation within a short period before the bronchiolitis hospitalisation (Fig. 1).

Demographic characteristics of the study group

Finally, 524 patients were included, including 298 boys (56.9%) and 226 girls (43.1%) aged 7 days to 23 months (Tab. 1 A). No fatal cases took place, whereas 3.2% of the patients required ICU transfer (Tab. 1 B). Antibiotic therapy was implemented in 18.7% of the patients, mostly due to pneumonia (9.4%) and acute otitis media (4.2%) (Tab. 1 C). RSV infection was laboratory confirmed in 462 (88.2%) children, while 62 (11.8%) patients with a negative RSV test were included in the non-RSV group. The median age was 2 months (IQR: 1–4); the median age of patients in the RSV and non-RSV groups was also 2 months, and the differences were not statistically significant; no statistically significant differences were observed with regard to gestational age, birth weight, Apgar score, or maternal age, but a small difference was observed with regard to mixed breastfeeding

Variable		*n* (% of group)	Median	IQR (Q1;Q3)
Patients, *n* (%)		524 (100)		
Sex, *n* (%)	Female	226 (43.1)		
	Male	298 (56.9)		
Age, months, median (Q1;Q3)			2.0	1.0;4.0
Hbd, weeks, median (Q1;Q3)			39.0	38.0;40.0
Preterm, *n* (%)		75 (14.3)		
Birth weight, g, median (Q1;Q3)			3,400.0	3,035.0;3,730.0
Apgar score, point, median (Q1; Q3)			10.0	10.0;10.0
Complicated course of pregnancy, *n* (%)*		231 (44.1%)		
Mother's age, years, median (Q1;Q3)			31.0	28.0;34.0
Feeding method, *n* (%)	Breastfeeding only	309 (58.9)		
	Breastfeeding + modified milk	78 (14.9)		
	Modified milk only	124 (23.7)		
	No data	13 (2.5)		
Number of persons in household/number of rooms, median (Q1;Q3)			1.5	1.3;2.0
Patient atopy, *n* (%)		11 (2.1)		
Family atopy, *n* (%)		53 (10.1)		
Any atopy, *n* (%)		61 (11.6)		
Chronic diseases, *n* (%):				
Respiratory system diseases		12 (2.3)		
Cardiological diseases		21 (4.0)		
Neurological diseases		5 (1.0)		
Down syndrome		1 (0.2)		
Immune disorders		4 (0.8)		
Genetic diseases		2 (0.4)		

Hbd – weeks of pregnancy; **IQR** – interquartile range.
* Cervical insufficiency, premature rupture of membranes (PROM), vaginal haemorrhage, placental pathology, hypertension, cholestasis, thyroid diseases, diabetes, anaemia, thrombocytopenia, serological conflict, viral/parasitic infections in pregnancy (HBV, HCV, HIV, VZV, *Toxoplasma gondii*), maternal arrhythmia, foetal supraventricular tachycardia, foetal hypotrophy/macrosomia, oligo-/polyhydramnios, foetus hydrothorax, maternal nicotinism, chemotherapy, antiphospholipid syndrome/thrombosis in pregnancy, pre-eclampsia/eclampsia.

Tab. 1 A. Baseline characteristics of patients: sociodemographic data and a history of atopy

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Variable		*n* (% of group)	Median	IQR (Q1;Q3)
Patients, *n* (%)		524 (100)		
Fever (°C), *n* (%)	<37.7 37.7–<38 38–<39 39–<40 ≥40	352 (67.2) 75 (14.3) 77 (14.7) 19 (3.6) 1 (0.2)		
Fever duration before hospitalisation, days, median (Q1;Q3)			0.0	0.0;0.0
Fever duration during hospitalisation, days, median (Q1;Q3)			0.0	0.0;0.0
Total fever duration, days, median (Q1;Q3)			0.0	0.0;1.0
Passive oxygen therapy, *n* (%)		157 (30.0)		
Passive oxygen therapy, days, median (Q1;Q3)			3.0	2.0;5.0
ICU transfer, *n* (%)		17 (3.2)		
Deaths, *n* (%)		0		
Length of hospitalisation, days, median (Q1;Q3)			9.0	8.0;11.0
Respiratory rate on admission to the hospital, /min, median (Q1;Q3)			60.0	50.0;64.0
Heart rate on admission to the hospital, /min, median (Q1;Q3)			140.0	130.0;152.0
Saturation on admission to the hospital, %, median (Q1;Q3)			96.0	94.0;97.0
Rhinitis, *n* (%)		424 (80.9)		
Cough, *n* (%)		496 (94.7)		
Dyspnoea, *n* (%)		374 (71.4)		
Apnoea, *n* (%)		15 (2.9)		
Apathy, *n* (%)		91 (17.4)		
Feeding difficulties, *n* (%)		247 (47.1)		
Foamy mucus in the mouth, *n* (%)		218 (41.6)		
Aspiration, *n* (%)		10 (1.9)		
Vomiting, *n* (%)		70 (13.4)		
Diarrhoea, *n* (%)		36 (6.9)		
ICU – intensive care unit; **IQR** – interquartile range.				

Tab. 1 B. Baseline characteristics of patients: clinical course and severity of the disease

Variable	*n* (% of group)	Median	IQR (Q1;Q3)
Patients, *n* (%)	**524 (100)**		
pH in capillary blood, median (Q1;Q3)		7.41	7.39;7.43
pCO_2 in capillary blood, mm Hg, median (Q1;Q3)		36.0	33.0;40.4
PCT, ng/mL, median (Q1;Q3)		0.10	0.07;0.13
CRP, mg/L, median (Q1;Q3)		1.10	0.23;4.26
WBC, 1×10^3/μL, median (Q1;Q3)		10.40	8.40;13.10
ANC, 1×10^3/μL, median (Q1;Q3)		2.10	1.19;3.64
PLT, 1×10^3/μL, median (Q1;Q3)		419.0	341.0;499.0
Inhaled steroids, *n* (%)	379 (72.3)		
Inhaled steroids, days, median (Q1;Q3)		9.0	7.0;11.0
Systematic steroids, *n* (%)	32 (6.1)		
Bronchodilators, *n* (%)	335 (63.9)		
Bronchodilators, days, median (Q1;Q3)		9.0	6.0;12.0
Adrenaline, *n* (%)	363 (69.3)		
Adrenaline, days, median (Q1;Q3)		9.0	8.0;12.0
Hypertonic salt, *n* (%)	340 (64.9)		
Antibiotic therapy, *n* (%)	98 (18.7)		
Indications for antibiotic treatment*:			
• Pneumonia	49 (9.4)		
• Acute otitis media (AOM)	22 (4.2)		
• Severe clinical condition	9 (1.7)		
• Lack of clinical improvement	4 (0.8)		
• Urinary tract infection	9 (1.7)		
• Other	8 (1.5)		
Antibiotic therapy, days, median (Q1;Q3)		10.0	7.0;10.0
ANC – absolute neutrophil count; **CRP** – C-reactive protein; **IQR** – interquartile range; **pCO_2** – partial pressure of carbon dioxide; **PCT** – procalcitonin; **PLT** – platelets; **WBC** – white blood cells. * In some cases more than one indication for antibiotic therapy was present.			

Tab. 1 C. Baseline characteristics of patients: test results and treatment

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Variable		RSV patients	Non-RSV patients	*p*-value
Patients, *n* (%)		462 (88.2)	62 (11.8)	
Sex, *n* (%)	Female	193 (41.8)	33 (53.2)	0.09
	Male	269 (58.2)	29 (46.8)	
Age, months, median (Q1;Q3)		2.0 (1.0;4.0)	2.0 (1.0;2.0)	0.12
Hbd, weeks, median (Q1;Q3)		39.0 (38.0;40.0)	39.0 (38.0;40.0)	0.27
Preterm, *n* (%)		66 (14.3)	9 (14.5)	0.83
Birth weight, g, median (Q1;Q3)		3,410 (3,050.0;3,730.0)	3,345 (2,920.0;3,700.0)	0.48
Apgar score, point, median (Q1; Q3)		10.0 (10.0;10.0)	10.0 (10.0;10.0)	0.65
Complicated course of pregnancy, *n* (%)*		200 (43.3)	31 (50.0)	0.32
Mother's age, years, median (Q1;Q3)		31.0 (28.0;34.0)	31.0 (29.0;34.0)	0.84
Feeding method, n (%)	Breastfeeding only	274 (61.0)	35 (56.5)	0.49
	Breastfeeding + modified milk	62 (13.8)	16 (25.8)	**0.01**
	Modified milk only	113 (25.2)	11 (17.7)	0.24
	No data	13 (2.8)	0	–
Number of persons in household/number of rooms, median (Q1;Q3)		1.5 (1.3;2.0)	1.3 (1.0;2.0)	0.23
Patient atopy, *n* (%)		10 (2.2)	1 (1.6)	0.78
Family atopy, *n* (%)		42 (9.1)	11 (17.7)	**0.03**
Any atopy, *n* (%)		49 (10.6)	12 (19.4)	**0.04**
Chronic diseases, *n* (%):				
Respiratory system diseases		8 (1.7)	4 (6.5)	**0.02**
Cardiological diseases		20 (4.3)	1 (1.6)	0.31
Neurological diseases		4 (0.9)	1 (1.6)	0.57
Down syndrome		1 (0.2)	0 (0.0)	0.71
Immune disorders		2 (0.4)	2 (3.2)	0.71
Genetic diseases		1 (0.2)	1 (1.6)	0.09

Hbd – weeks of pregnancy.
* Cervical insufficiency, premature rupture of membranes (PROM), vaginal haemorrhage, placental pathology, hypertension, cholestasis, thyroid diseases, diabetes, anaemia, thrombocytopenia, serological conflict, viral/parasitic infections in pregnancy (HBV, HCV, HIV, VZV, *Toxoplasma gondii*), maternal arrhythmia, foetal supraventricular tachycardia, foetal hypotrophy/macrosomia, oligo-/polyhydramnios, foetus hydrothorax, maternal nicotinism, chemotherapy, antiphospholipid syndrome/thrombosis in pregnancy, pre-eclampsia/eclampsia.

Tab. 2 A. Group comparison between RSV bronchiolitis versus non-RSV bronchiolitis: sociodemographic data and a history of atopy

Variable		RSV patients	Non-RSV patients	*p*-value
Patients, *n* (%)		462 (88.2)	62 (11.8)	
Fever (°C), *n* (%)	<37.7	310 (67.1)	42 (67.7)	0.99
	37.7–<38	67 (14.5)	8 (12.9)	
	38–<39	67 (14.5)	10 (16.1)	
	39–<40	17 (3.7)	2 (3.2)	
	≥40	1 (0.2)	0	
Fever duration before hospitalisation, days, median (Q1;Q3)		0.0 (0.0;0.0)	0.0 (0.0;1.0)	0.24
Fever duration during hospitalisation, days, median (Q1;Q3)		0.0 (0.0;0.0)	0.0 (0.0;0.0)	0.08
Total fever duration, days, median (Q1;Q3)		0.0 (0.0;1.0)	0.0 (0.0;1.0)	0.70
Passive oxygen therapy, *n* (%)		150 (32.5)	7 (11.3)	**<0.01**
Passive oxygen therapy, days, median (Q1;Q3)		3.0 (2.0;5.0)	2.0 (1.0;7.0)	0.80
ICU transfer, *n* (%)		15 (3.2)	2 (3.2)	0.99
Deaths, *n* (%)		0	0	N/A
Length of hospitalisation, days, median (Q1;Q3)		9.0 (8.0;12.0)	9.0 (7.0;10.0)	0.12
Respiratory rate on admission to the hospital, /min, median (Q1;Q3)		60.0 (50.0;64.0)	54.0 (46.0;64.0)	0.58
Heart rate on admission to the hospital, /min, median (Q1;Q3)		140.0 (130.0;152.0)	140.0 (131.0;150.0)	0.91
Saturation on admission to the hospital, %, median (Q1;Q3)		96.0 (94.0;97.0)	96.0 (95.0;97.0)	0.33
Rhinitis, *n* (%)		374 (81.0)	50 (80.6)	0.95
Cough, *n* (%)		444 (96.1)	52 (83.9)	**<0.01**
Dyspnoea, *n* (%)		328 (71.0)	46 (74.2)	0.60
Apnoea, *n* (%)		15 (3.2)	0	0.24
Apathy, *n* (%)		86 (18.6)	5 (8.1)	**0.04**
Feeding difficulties, *n* (%)		227 (49.1)	20 (32.3)	**0.01**
Foamy mucus in the mouth, *n* (%)		198 (42.9)	20 (32.3)	0.11
Aspiration, *n* (%)		10 (2.2)	0	0.62
Vomiting, *n* (%)		67 (14.5)	3 (4.8)	**0.04**
Diarrhoea, *n* (%)		32 (6.9)	4 (6.5)	0.89

ICU – intensive care unit.

Tab. 2 B. Group comparison between RSV bronchiolitis versus non-RSV bronchiolitis: clinical course and severity of the disease

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Variable	RSV patients	Non-RSV patients	*p*-value
Patients, *n* (%)	462 (88.2)	62 (11.8)	
pH in capillary blood, median (Q1;Q3)	7.41 (7.39;7.43)	7.42 (7.39;7.44)	0.20
pCO_2 in capillary blood, mm Hg, median (Q1;Q3)	36.1 (33.1;40.5)	34.4 (31.7;38.2)	0.08
PCT, ng/mL, median (Q1;Q3)	0.10 (0.07;0.13)	0.08 (0.06;0.12)	0.05
CRP, mg/L, median (Q1;Q3)	0.95 (0.23;3.49)	1.47 (0.41;6.63)	0.07
WBC, 1×10^3/μL, median (Q1;Q3)	10.15 (8.20;12.80)	12.30 (10.00;14.75)	**<0.01**
ANC, 1×10^3/μL, median (Q1;Q3)	1.99 (1.15;3.64)	2.64 (1.79;3.82)	**0.03**
PLT, 1×10^3/μL, median (Q1;Q3)	415.0 (339.0;494.5)	451.0 (366.0;514.0)	0.09
Inhaled steroids, *n* (%)	333 (72.1)	46 (74.2)	0.73
Inhaled steroids, days, median (Q1;Q3)	9.0 (7.0;12.0)	8.0 (5.0;9.0)	**0.04**
Systematic steroids, *n* (%)	31 (6.7)	1 (1.6)	0.12
Bronchodilators, *n* (%)	301 (65.2)	34 (54.8)	0.11
Bronchodilators, days, median (Q1;Q3)	9.0 (6.0;12.0)	7.5 (1.0;9.0)	0.08
Adrenaline, *n* (%)	322 (69.7)	41 (66.1)	0.57
Adrenaline, days, median (Q1;Q3)	9.0 (8.0;12.0)	9.0 (7.0;10.0)	0.13
Hypertonic salt, *n* (%)	297 (64.3)	43 (69.4)	0.43
Antibiotic therapy, *n* (%):	93 (20.1)	5 (8.1)	**0.03**
Indications for antibiotic treatment*:			
• Pneumonia	48 (10.4)	1 (1.6)	0.09
• Acute otitis media (AOM)	22 (4.8)	0	**0.03**
• Severe clinical condition	9 (1.9)	0	0.27
• Lack of clinical improvement	2 (0.4)	2 (3.2)	0.27
• Urinary tract infection	7 (1.5)	2 (3.2)	0.27
• Other	8 (1.7)	0	0.30
Antibiotic therapy, days, median (Q1;Q3)	10.0 (7.0;10.0)	7.0 (7.0;10.0)	0.54

ANC – absolute neutrophil count; **CRP** – C-reactive protein; **IQR** – interquartile range; **pCO_2** – partial pressure of carbon dioxide; **PCT** – procalcitonin; **PLT** – platelets; **WBC** – white blood cells.
* In some cases more than one indication for antibiotic therapy was present.

Tab. 2 C. Group comparison between RSV bronchiolitis versus non-RSV bronchiolitis: test results and treatment

and formula feeding (more frequent in the non-RSV group, 25.8% vs. 13.8%, $p = 0.01$). The RSV group was less likely to have a positive family history of atopy (9.1% vs. 17.7%, $p = 0.03$) or any history of atopy (10.6% vs. 19.4%, $p = 0.04$), while no significant differences were found regarding individual history of atopy; detailed comparison between RSV and non-RSV group with regards to sociodemographic data, history of atopy, clinical course, test results and treatment is presented in Tabs. 2 A–C.

The majority of patients were younger than 6 months, including 310 patients (59.2%) aged 0–<3 months, 155 (29.6%) aged 3–<6 months, 50 (9.5%) aged 6–<12 months and 9 (1.7%) aged 12–23 months. RSV was predominant in each group: 262/310 cases (84.5%) in patients aged 0–<3 months, 145/155 (93.5%) in 3–<6 months, 46/50 (92%) in 6–<12 months and 9/9 (100%) in 12–23 months (Fig. 2).

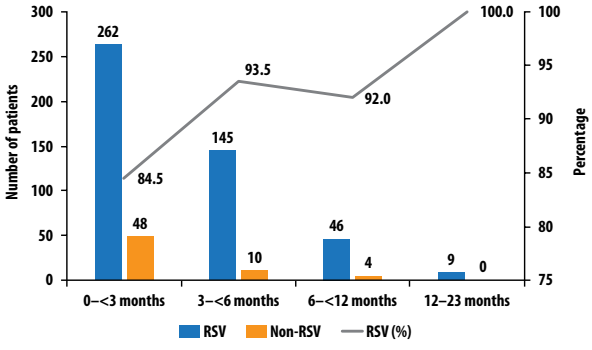

Fig. 2. The number and the percentage of RSV and non-RSV bronchiolitis cases by the age groups

Seasonality

We observed a significant increase in the number of hospitalised cases of bronchiolitis; a comparison of the first 2 years of the analysed period (2010–2011, $n = 23$) and the last 2 years (2017–2018, $n = 161$) showed a 7-fold increase in the number of AB hospitalisations, with a relatively stable percentage of RSV cases, but an increasing absolute number of hospitalised RSV cases (Fig. 3). A clear seasonality

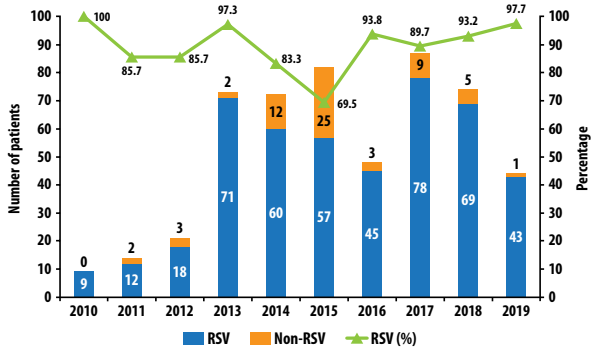

Fig. 3. The total number of bronchiolitis hospitalisations and the percentage of RSV bronchiolitis cases during the study period

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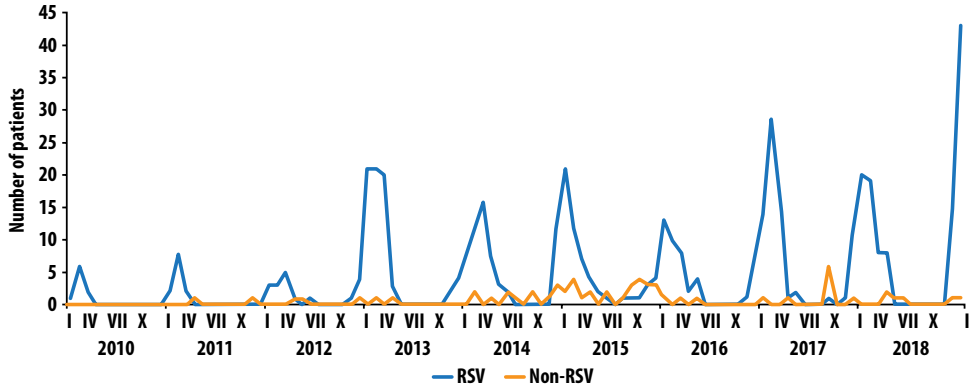

Fig. 4. A month-by-month number of RSV and non-RSV bronchiolitis hospitalisations in the consecutive study years

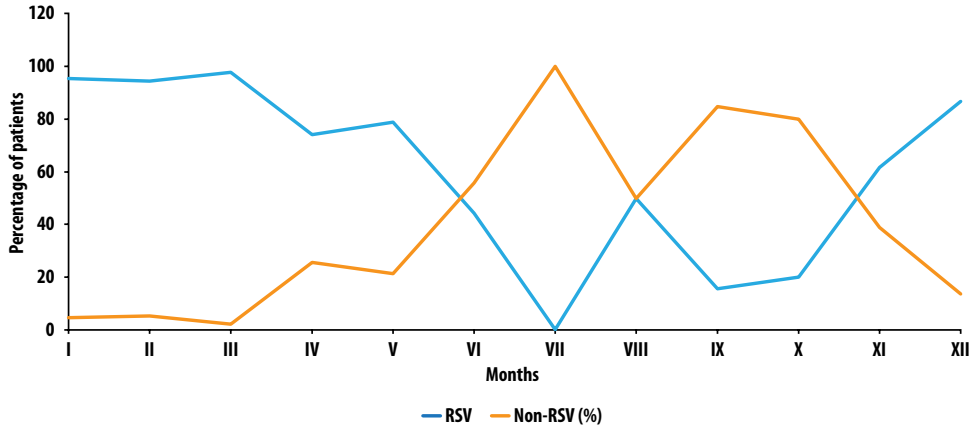

Fig. 5. An accumulated month-by-month graph of RSV and non-RSV bronchiolitis hospitalisation percentages based upon the 2010–2018 period (data from January 2019 were not included due to lack of a whole year 2019 analysis)

was observed, with 86.4 to 97.7% of the total annual number of hospitalisations (94.1% on average) occurring during the peak RSV season, i.e. December, January, February and March. The number of non-RSV AB cases was low and varied only slightly; outside the RSV season, the non-RSV proportion of bronchiolitis cases increased to 21–85%, reaching 100% in the summer months, although only single hospitalisations occurred then (Figs. 4 and 5).

Clinical course

Regarding the clinical course, univariate analysis showed higher odds for cough and vomiting (OR = 4.7 and OR = 3.3, respectively), apathy (OR = 2.6) and feeding fatigue (OR = 2), whereas multivariate analysis showed only higher odds only for cough in the RSV group (OR = 6.2), with no statistically significant differences between the other characteristics (Tabs. 3 and 4). The groups did not differ with regard to the other parameters analysed, including fever or apnoea, although all 15 cases of apnoea were seen in the RSV group. The subgroup analysed presence of cough (statistically significant in both uni- and multivariate regression model): the odds of cough in patients with RSV under 3 months of age was statistically significantly higher ($p = 0.0003$) (Tab. 5).

Patients with severe clinical course

Patients in the RSV group had more severe disease, as assessed by: higher odds of oxygen therapy (OR = 3.8 in univariate and OR = 4.4 in multivariate analysis) and higher odds of sequelae (OR = 4.2 and OR = 16, respectively) (Tabs. 3 and 4). There were no statistically significant differences in terms of ICU transfer, with 15 patients in the RSV group and 2 patients in the non-RSV group being transferred to the ICU; however, those in the non-RSV group who were transferred to the ICU had only a rapid antigen test performed without molecular testing. There were no deaths in the study arm. The odds of passive oxygen therapy were significantly higher in children with RSV infection aged 0–<3 months (OR = 4.73, $p = 0.0015$) and the odds of complications were higher in children aged 3–<6 months (OR = 18.9, $p = 0.0056$) (Tab. 5).
Among the secondary endpoints assessing disease severity, children with RSV infection had lower WBC (10.15 vs. 12.3, $p < 0.01$) and ANC (1.99 vs. 2.64, $p = 0.03$) with no differences in CBG parameters (Tab. 2 C).

Treatment

The groups differed in terms of treatment: RSV infection was associated with higher odds of antibiotic treatment (OR = 2.8

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	Univariate regression model		
Characteristic	**OR**	**95% CI**	***p*-value**
Atopy history			
Patient atopy	1.35	0.17–10.73	0.7768
Family atopy	0.46	0.22–0.96	**0.0376**
Any atopy	0.49	0.25–0.99	**0.0473**
Clinical course			
Fever	1.06	0.60–1.87	0.8307
Rhinitis	1.02	0.52–2.00	0.9539
Cough	4.74	2.08–10.82	**0.0002**
Dyspnoea	0.85	0.47–1.56	0.6012
Apnoea	4.35	0.26–73.60	0.3084
Apathy	2.61	1.01–6.70	**0.0465**
Feeding difficulties	2.03	1.16–3.56	**0.0138**
Foamy mucus in the mouth	1.58	0.90–2.77	0.1141
Aspiration	2.90	0.17–50.11	0.4639
Vomiting	3.34	1.02–10.95	**0.0470**
Diarrhoea	1.08	0.37–3.16	0.8896
Disease severity			
Passive oxygen therapy	3.78	1.68–8.49	**0.0013**
Length of passive oxygen therapy >median	0.99	0.21–4.59	0.9921
ICU transfer	1.01	0.22–4.51	0.9930
Length of hospitalisation >median	1.55	0.90–2.69	0.1135
Complications (Pneumonia/AOM)	4.24	1.30–13.87	**0.0167**
Saturation <92%	1.05	0.43–2.57	0.9136
pH <7.35 (capillary blood)	1.49	0.34–6.48	0.5987
pCO_2 >45 mm Hg (capillary blood)	1.63	0.56–4.68	0.3679
Treatment			
Inhaled steroids	0.90	0.49–1.64	0.7267
Systemic steroids	4.39	0.59–32.72	0.1492
Bronchodilators	1.54	0.90–2.63	0.1142
Adrenaline	1.18	0.67–2.07	0.5678
Hypertonic salt	0.80	0.45–1.41	0.4331
Antibiotics	2.82	1.10–7.25	**0.0310**

95% CI – confidence interval; **AOM** – acute otitis media; **ICU** – intensive care unit; **OR** – odds ratio; **pCO_2** – partial pressure of carbon dioxide.

Tab. 3. Disease course and treatment in RSV vs. non-RSV bronchiolitis: the results from the univariate regression model

in univariate model, not significant in multivariate model) (Tabs. 3 and 4), patients with RSV received inhaled steroids for a longer period (9 vs. 8 days, $p = 0.04$) (Tab. 2 C).

DISCUSSION

Acute bronchiolitis is one of the most common causes of paediatric hospitalisation, and aetiological factors may lead to differences in clinical presentation, disease course or prognosis. Our study shows several important differences related to RSV as a specific aetiological factor.

RSV was the predominant aetiological factor in acute bronchiolitis (88% of all AB hospitalisations in our series of patients), as might have been expected from published studies, although the percentage of RSV-caused AB is even higher than in previous reports, which found RSV in 60%[11] – 62.7%[9] – 66%[8] of AB hospitalisations. Furthermore, due to the observed seasonality, RSV was responsible for 86.4% (December) to 94.5–97.7% (January–March) of the hospitalised cases during the peak season of RSV incidence. Studies conducted in Europe have shown that the vast majority (up to 97%) of RSV hospitalisations occur during the season of increased RSV activity; the seasonality in the modern climate of the northern hemisphere used to be typical and repeatable with only minor variations, and the peak incidence was observed between December and March, although a significant change with high RSV morbidity outside the typical season was observed after the SARS-CoV-2 pandemics[9,16,18].

The number of non-RSV bronchiolitis cases was low and relatively balanced throughout the year, with a clear decrease during the summer months, probably due to a generally lower incidence of infectious diseases in Poland during this season.

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	Multivariate regression model		
Characteristic	**OR**	**95% CI**	***p*-value**
Atopy history			
Patient atopy	2.83	0.17–46.0	0.4636
Family atopy	0.85	0.29–2.53	0.7765
Any atopy	0.49	0.23–1.06	0.0709
Clinical course			
Fever	0.61	0.26–1.43	0.2551
Rhinitis	0.71	0.31–1.61	0.4072
Cough	6.22	2.24–17.30	**0.0005**
Dyspnoea	0.55	0.27–1.12	0.1019
Apnoea	N/A*		
Apathy	2.89	0.96–8.69	0.0586
Feeding difficulties	1.63	0.83–3.20	0.1530
Foamy mucus in the mouth	1.45	0.73–2.91	0.2921
Aspiration	N/A*		
Vomiting	4.52	0.98–20.87	0.0529
Diarrhoea	0.79	0.23–2.72	0.7100
Disease severity			
Passive oxygen therapy	4.43	1.53–12.82	**0.0061**
ICU transfer	N/A*		
Length of hospitalization >median	0.81	0.41–1.61	0.5483
Complications (Pneumonia/AOM)	15.95	1.58–160.89	**0.0188**
Saturation <92%	0.89	0.29–2.74	0.8421
pH <7.35 (capillary blood)	1.25	0.14–11.05	0.8401
pCO_2 >45 mm Hg (capillary blood)	0.75	0.19–3.00	0.6884
pCO_2 >45 mm Hg (capillary blood)	1.63	0.56–4.68	0.3679
Treatment			
Inhaled steroids	0.49	0.22–1.10	0.0834
Systemic steroids	N/A*		
Bronchodilators	1.91	0.94–3.87	0.0727
Adrenaline	1.44	0.69–3.00	0.3315
Hypertonic salt	0.80	0.40–1.61	0.5325
Antibiotics	1.54	0.45–5.26	0.4895

95% CI – confidence interval; **AOM** – acute otitis media; **ICU** – intensive care unit; **OR** – odds ratio; **pCO_2** – partial pressure of carbon dioxide.
* Not run due to insufficient number of events.

Tab. 4. The results of the multivariate regression model regarding atopy history, clinical course, disease severity and treatment in RSV versus non-RSV bronchiolitis

Aetiological differences may influence the diagnosis and definition of the disease. Differences in the definition of bronchiolitis include the age of the patient; whereas the American approach defines AB as a disease in those under 2 years of age[5], some European definitions are limited to patients under 12 or even 6 months of age[14,21,22]. This is at least partly due to age-related differences in aetiology – whereas RSV predominates in infants, rhinovirus bronchiolitis is particularly prevalent in those over 1 year of age[23]. In our series of patients, the vast majority of AB cases occurred in the first year of life, and in this age group RSV infections were highly predominant (Fig. 2). However, it must be emphasised that we did not observe any cases of non-RSV bronchiolitis in children aged 12–23 months.

There is a paucity of published work directly comparing RSV and non-RSV.

The clinical course of bronchiolitis may differ depending on the aetiological factor. Ramagopal et al. included 80 infants aged <1 year and showed that patients with RSV presented more often with wheezing (89.7% vs. 41.5%), but there were no differences in fever, coryza, cough, dyspnoea, cyanosis, chest indrawing, tachypnoea, tachycardia or decreased oxygen blood saturation[10]. On the contrary, we found (in both univariate and multivariate models) higher odds of cough and (in the univariate model only) vomiting; the latter may play a role (unlike cough, which does not seem to be a significant discriminator in the case of LRTI). Previous work has described more frequent vomiting in children with RSV disease[24], a probable association

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Age groups	OR	95% CI	*p*-value
Cough			
0–<3 months	5.82	2.22–15.21	**0.0003**
3–<6 months	3.11	0.33–29.53	0.3229
6–<12 months	1.38	0.06–31.22	0.8392
Passive oxygen therapy			
0–<3 months	4.73	1.81–12.36	**0.0015**
3–<6 months	1.58	0.32–7.74	0.5747
6–<12 months	3.26	0.16–65.01	0.4380
Complications (Pneumonia/AOM)			
0–<3 months	12.26	0.74–204.02	0.0807
3–<6 months	18.90	2.37–150.90	**0.0056**
6–<12 months	3.26	0.16–65.01	0.4388

95% CI – confidence interval; **AOM** – acute otitis media; **OR** – odds ratio.
* OR for the age group 12–24 months was not included due to the lack of non-RSV cases in this group.

Tab. 5. Age subgroups comparison between the RSV and non-RSV groups regarding variables statistically significant in uni- and multivariate analysis of the whole study group

with RSV A infection has been raised (our study did not distinguish between RSV A and RSV B infection)[25], and a suggestion has been made to include vomiting in the disease severity scoring system, especially vomiting unrelated to cough episodes[26]. Contrary to Ramagopal et al.[10], we did not assess the frequency of wheezing because the Polish definition of bronchiolitis already includes wheezing as one of the main features of AB[7].

Another significant feature of the clinical course of RSV bronchiolitis reported in the univariate models was apathy (OR = 2.6) and feeding fatigue (OR = 2). Although these features were classified in the clinical course, it must be emphasised that the presence of any of these features could be an important signal of a more severe course of the disease, and feeding difficulties or inadequate (decreased) oral fluid intake should prompt consideration of hospital referral[7,27]. Particular attention should be paid to apnoea, which is also often cited as one of the signals that a patient should be referred to hospital[7,27]. Although we found no statistical significance in our material, all patients with apnoea episodes (n = 15) had RSV infection, and the lack of statistical significance may be due to the large imbalance in the number of patients per group.

Analysis of disease severity showed that aetiology may also be associated with prognosis and is therefore of significant value. We observed a more severe of disease course in children with RSV bronchiolitis, which is in line with previously published data[8,9,11]. Apart from the aforementioned apathy and fatigue during feeding, we observed a higher likelihood of oxygen therapy in RSV-positive children (OR = 3.8 in univariate analysis and OR = 4.4 in multivariate analysis); similarly, a higher need for oxygen supplementation in RSV bronchiolitis was reported by García et al. in his study of 4.800 children under 2 years of age[8]. Hervás et al. included 2,384 patients under 24 months of age and showed a higher oxygen requirement in RSV disease[9]. In addition, Christou et al. included 491 children under 1 year of age and showed prolonged oxygen use in RSV-infected infants[11], although our analysis found no statistically significant association between aetiological factor and prolonged oxygen treatment. In contrast to our study, some authors also suggested a longer hospital stay in RSV bronchiolitis, which may also indicate a more severe course of the disease[8,9,11]. We also did not confirm a higher risk of ICU transfer, which has been suggested in RSV infections[8,9,11], but we have to note that both patients in the non-RSV group had only negative RSV results in rapid antigen diagnostic tests, but no molecular study was performed in any of them. Some authors have also suggested that a higher risk of mechanical ventilation was also increased[8], although we did not assess the type of respiratory support used in the ICU.

Of note, a higher likelihood of sequelae due to RSV-associated bronchiolitis was observed in our group of patients, which may be due to the characteristics of the virus; previous studies have shown that RSV is associated with a high risk of both pneumonia and acute otitis media, estimated to affect up to 33% of patients (in the case of pneumonia as a complication) and up to 50–77% of RSV-infected patients (in the case of otitis media)[28–30].

Analysis of laboratory parameters revealed lower WBC and ANC values in RSV bronchiolitis, which does not seem to be crucial from a practical point of view, but it must be emphasised that we did not observe worse capillary blood gas parameters, although some of the previous studies found an association between higher pCO_2[31,32] and/or lower pH with increased risk of respiratory failure or ICU transfer[32].

Regarding treatment, RSV patients were more likely to receive antibiotics (OR = 2.8 in the univariate model and not significant in the multivariate model), which may also be indirectly related to disease severity. One of the main reasons for the use of antibiotics in patients with bronchiolitis has been shown to be concern about the severity of the patient's condition and further treatment without

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antibacterials in circumstances that may lead to bacterial co-infection[33]; accordingly, a study in the ICU showed that patients with more severe conditions (e.g. requiring mechanical ventilation) were more likely to receive antibiotic therapy, although these groups cannot be directly compared[34]. However, the issue of antibiotic therapy is more complex and the influence of several factors should be considered; it is not only the lack of sufficient experience with severe patients or the lack of knowledge of current bronchiolitis management guidelines that contribute to antibiotic use, although they need to be recognised, but also parental expectations and a general belief that "something has to be done", together with the hope of potential benefits with a low risk of adverse effects, lead to antibiotic overuse[35]. The observed higher odds of antibiotic therapy in the RSV versus non-RSV comparison may be related to the more severe condition of patients with RSV bronchiolitis, but may also be driven by the higher risk of otitis media, which can reach 50–77% during the course of RSV disease and is the main reason for antibiotic use in many cases[29,30,36]. Similarly, Christou et al. found more frequent use of antibiotics and inhaled epinephrine in children with RSV bronchiolitis[11], whereas Ramagopal et al. found more frequent use of antibiotics, bronchodilators or corticosteroids in non-RSV patients[10]. We found no differences in the use of bronchodilators, but a longer duration of inhaled steroid therapy in the RSV group; however, it should be remembered that this approach is not a recommended treatment[5,7,27]. The reasons for prolonged inhaled steroid therapy remain controversial and may be due to lack of clinical improvement, but also to local therapeutic practices; however, overuse of steroid therapy is a commonly reported problem and implementation of guidelines, supported by educational programmes, improves bronchiolitis management and reduces unnecessary use of therapeutics[37–39].

It is noteworthy that in García's et al. study[8], the number of diagnosed cases of bronchiolitis increased (the period analysed was 2002 to 2007) and an increase in RSV infections was also observed; similarly, in Poland there has been a sharp increase in the number of hospitalised RSV patients in recent years[4]. Our study found a similar trend, with a 7-fold increase when comparing the last 2 years of the study with the first 2 years analysed, and although the percentage of RSV cases remained stable, a significant increase in the number of RSV cases was noted. Certainly, increased viral activity, virulence and/or spread could be a possible explanation, but there are several possible explanations for this trend, including increased awareness of RSV, wider availability of diagnostic methods, improved performance of rapid antigen tests and the practical benefits of establishing aetiology[8]. Further increases in diagnosed RSV cases could be predicted, as diagnostic testing is still relatively infrequent and the true burden of RSV disease is greater than thought, with modelling studies suggesting that the incidence is underestimated by 30–57%[40].

The study is limited by the lack of multicentre analysis, which makes these findings less generalisable, despite the relatively large number of patients included. Secondly, we did not perform molecular studies in each patient, and a classification into RSV versus non-RSV group based only on a negative rapid antigen test result is questionable; antigen tests are characterised by high specificity (above 90%) but lower sensitivity, reaching about 70%, although there are studies showing both much higher and much lower sensitivities[41–44]. The lack of identification of other aetiological factors is, in our opinion, the most important shortcoming of the study, as it would not only reduce the risk of false negative RSV test results, but also the differentiation between certain agents (generally classified as non-RSV) may play a crucial role in the future. Diagnostic possibilities were limited in our study, but the improved availability and development of diagnostic methods, especially molecular tests, guarantee further investigations on this topic.

CONCLUSIONS

RSV is the predominant aetiological factor in hospitalised cases of bronchiolitis and is associated with a more severe course of disease, including a higher likelihood of oxygen therapy. Clinical features do not differ sufficiently to identify the aetiological factor of bronchiolitis, and targeted diagnosis is the only method of verification. A much debated issue is whether to continue with the guideline recommendations to avoid RSV testing as the test result does not change management – in our opinion, although the search for the aetiological factor does not currently influence the treatment itself, it facilitates the prevention of nosocomial RSV spread, helps to better assess disease-related risks and improves our understanding of the RSV burden; in-depth knowledge of RSV epidemiology is urgently needed for the purposes of implementing prophylaxis or pharmacoeconomic evaluation of potential interventions.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

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Data availability

The datasets generated during and/or analysed during the current study are not publicly available due to legal reason, but are available from the corresponding author on reasonable request.

Ethics approval

The study was conducted in accordance with the Helsinki Declaration with later amendments, and granted permission by the local Ethics Committee at the Centre of Postgraduate Medical Education in Warsaw (permission number 91/PB/2020 issued on 15 June 2020). Patient's and parent's/tutor's consent were waived due to the retrospective character.

Informed consent statement

Patient's and parent's/tutor's consent were waived due to the retrospective character.

Consent to participate

Informed consent was obtained from legal guardians of all individual participants included in the study.

Author contributions

Original concept of study: MK, TJ, AW. Collection, recording and/or compilation of data: MK. Analysis and interpretation of data: MK, AW. Writing of manuscript: MK, AW. Critical review of manuscript: TJ, AW. Final approval of manuscript: TJ.

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