



Respiratory Complications in Children Hospitalized with Respiratory Syncytial Virus Infection

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Abstract

The goal of this study was to define the prevalence of respiratory complications, other than bronchiolitis, such as pneumonia, acute otitis media, and conjunctivitis in children treated in a hospital due to respiratory syncytial virus (RSV) infection, with reference to the plausible risk factors. The study included 111 children, aged up to 22 months (median 3 months). Complications were observed in 68 (61%) children, with 32 (29%) children presenting more than one. The most frequent complication was acute otitis media in 53 (48%), pneumonia in 37 (33%), and conjunctivitis in 12 (11%) out of the 111 children. Children with complications were older than those without complications and had fever that lasted for a significantly longer time, both before and during hospitalization, and the fever was stronger. They also presented a

significantly lower breathing rate at admission. The age over 3 months was a single risk factor associated with the development of otitis media (OR = 9.8, 95%CI: 3.6–26.7) and pneumonia (OR = 2.8, 95%CI: 1.1–7.3). Other factors such as prematurity, birth weight below 2500 g, exposure to tobacco smoke during pregnancy, and the cessation of breastfeeding below age 6 months were statistically irrelevant to this end. We conclude that complications are very frequent in hospitalized children with RSV infection and their risk increases with the infant age.

Keywords

Bronchiolitis · Infection · Otitis media · Pneumonia · Respiratory syncytial virus

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1 Introduction

The respiratory syncytial virus (RSV) is one of the most common infectious agents, responsible for an enormous percentage of acute respiratory tract infections in infants and younger children. The virus causes about 30 m infections each year in low- and middle-income countries and 2.8 m in high-income countries, leading to about 3.2 m hospitalizations. The majority of hospitalizations occur in children below age 5 months, and 45% of

hospitalizations concerns children in the first 6 months of life (European Medicines Agency 2017). There is a high fatality rate of 6.21 deaths *per* 1000 children below age 5 years, yet the deaths occur mainly in lower-income countries (Stein et al. 2017). The lowest fatality rate is observed in high-income countries where it is estimated to be 0.2%, 0.9%, and 0.7% in children aged 0–5 months, 6–11 months, and 12–59 months, respectively (Shi et al. 2017). The RSV causes a major health concern and has a significant impact from the medical care and socioeconomic standpoints. In the outpatient setting, acute otitis media (AOM), which is one of the most frequent complications of respiratory tract infections, turns to be a major cost drawing condition. AOM is variably reported in over 20% (Paramore et al. 2004), 47% (Chonmaitree et al. 2008), 57% (Ruuskanen et al. 1989), and 58% (Heikkinen et al. 2017) of children hospitalized due to RSV-associated bronchiolitis and pneumonia. In general, a leading diagnosis in children hospitalized due to RSV infection is bronchiolitis, which concerns about 70–85% of hospitalized, particularly younger children (Hall et al. 2009). Conversely, RSV is also a major etiological factor of bronchiolitis, responsible for about 60–80% of all bronchiolitis cases (Bamberger et al. 2012; Mansbach et al. 2012; Calvo et al. 2010). RSV also plays a causative role in community-acquired pneumonia (CAP) as about 30% of CAP appears RSV positive (Jain et al. 2015; García-García et al. 2012).

RSV is associated with a risk of developing post-infection wheezing/asthma and as allergic rhinoconjunctivitis. A study by Fujishima (2002) has suggested that the risk of rhinoconjunctivitis increases due to the presence of RSV in conjunctival epithelial cells. A meta-analysis by Shi et al. (2015) has shown that the risk factors of a severe RSV infection course, in the decreasing order of odds ratio, are the following: preterm infants, low birthweight, male gender, having siblings, maternal smoking and history of atopy, and a lack of breastfeeding. Regarding mortality, a higher risk is associated with prematurity; severe comorbidities, including chronic lung disease and congenital heart disease; and nosocomial

acquisition of infection (Welliver et al. 2010). The goal of this study was to define the prevalence of respiratory tract complications, other than nearly universal bronchiolitis, such as pneumonia, acute otitis media, and conjunctivitis in children hospitalized due to RSV-associated respiratory infections, with reference to the plausible risk factors.

2 Methods

The study included 111 children aged up to 22 months (median 3 months, interquartile range (IQR) 1–16 months), who were treated in a tertiary hospital due to RSV infection in the 2017/2018 season. Clinical and laboratory conditions were assessed at admission and then repeatedly in the course of hospitalization. The following variables were recorded: breathing rate, heart rate, serum C-reactive protein (CRP) and procalcitonin, peripheral capillary blood pH, partial carbon dioxide pressure and oxygen saturation, and hematologic profile consisting of white blood cells count (WBC), absolute neutrophil count (ANC), hemoglobin concentration, and platelet count. In addition, we assessed duration of fever prior to hospitalization, the highest level and duration of in-hospital fever, the number of days on oxygen supplementation and antibiotic treatment, and duration of hospitalization.

Acute otitis media (AOM) was defined as the presence of redness, hemorrhagic or cloudy appearance, and bulging of tympanic membrane. In order not to miss an AOM case, since many viral otitis media runs a self-limiting course, patients were prospectively followed up, and otoscopy was performed in each patient at the following time points, admission and then days 3, 5, and 7 post-admission, depending on the patient's length of hospitalization. The other descriptive definitions in the study were as follows: prematurity, gestational age below 37 weeks; low birth weight, below 2500 g; maternal cigarette smoking, any smoking during pregnancy mentioned by parents surveyed at admission; lack of breastfeeding, cessation of breastfeeding below age 6 months; and crowding

condition at home, 1.5 or more persons *per* one room in a household, which was the median value for the whole group of patients. These definitions are generally in line with those used in previous studies (Shi et al. 2015), with some modifications made for a lack of breastfeeding and crowding. The entire lack of breastfeeding is, in our opinion, impossible to ascertain and may be a misnomer, as even mothers who are unwilling to breastfeed make attempts at the very beginning almost in each case. Breastfeeding up to age 6 months is recommended as a desirable goal by the WHO and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (WHO 2019; Agostoni et al. 2009). Thus, we considered the lack of breastfeeding as its cessation below age 6 months. Likewise, overcrowding is difficult to ascertain as it may depend on the number of persons *per* room or household, as well as on other poorly controlled for local circumstances. For instance, crowding has been defined as more than 1.5 persons/room (Bruden et al. 2015), ≥ 2 persons/room plus 4 or more children in the household (Bulkow et al. 2002), and ≥ 10 persons/household or the presence of ≥ 2 siblings aged 3–5 years sleeping in the same room (Weber et al. 1999). Yet others have set the number of siblings sleeping in the same room at ≥ 3 (Okiro et al. 2008). Shi et al. (2015) have used the definition of crowding of ≥ 7 persons/household in their meta-analysis, excluding the studies that failed to meet this criterion. In view of the arbitrariness and lack of fixed rules for what is crowding, we defined it in this study as the number of inhabitants *per* household exceeding the median value.

Data was presented as means \pm SD or medians with lower and upper quartiles. The Shapiro-Wilk test was used to assess normality data distribution. A *t*-test and Mann-Whitney U test were used

to compare the independent variables, as appropriate A *p*-value <0.05 defined statistically significant intergroup differences. Logistic regression analysis was used to calculate the odds ratio (OR) with 95% confidence interval (95% CI). Statistical analysis was performed using a commercial Statistica v13 package (StatSoft; Tulsa, OK).

3 Results

Complications were noticed in 61% of cases (68/111) of RSV-associated respiratory infection, with 29% of children (32/111) presenting more than one complication. There were 30 cases of double complications and 2 cases of the 3 complications above outlined. The most frequent complication was AOM, 48% (53/111), followed by pneumonia, 33% (37/111), and conjunctivitis, 11% (12/111). Referring to the co-occurrence of multiple complications, AOM was accompanied by pneumonia in 25 children and by conjunctivitis in 4 children cases, while in another 3 children, pneumonia and conjunctivitis co-occurred.

At admission, there were 25, 13, and 5 children diagnosed with unilateral, bilateral, and purulent AOM, respectively. On days 3–5, the number increased to 32, 18, and 14 cases, respectively. On day 7, there were 10 unilateral, 7 bilateral, and no purulent AOM case. The peak increases in the number of AOM on days 3–5, when compared to the admission examination, were as follows: unilateral 1.28-fold, bilateral 1.39-fold, and purulent 2.8-fold.

The children with complications, in the main, were older than those without complications (median 6 vs. 2 months, respectively; $p < 0.001$) (Table 1). This age difference between children

Table 1 Baseline characteristics of children with and without complications after respiratory syncytial virus (RSV) infection

Parameter	Complications	No complications	<i>p</i>
Calendar age (months)	6 (2–16)	2 (1–3)	0.001
Gestational age (weeks)	39 (38–40)	39 (39–39)	0.600
Birth weight (g)	3,340 (2,835–3,820)	3,400 (3,030–3,760)	0.100
Crowding (persons <i>per</i> household room)	1 (1–2)	2 (1–2)	0.120

Results are medians (LQ-UQ)

with and without complications concerned both AOM and pneumonia groups (median 7 vs. 2 months, IQR: 3–16 vs. 1–4 months; $p < 0.010$ and 7 vs. 3 months, IQR: 2–16 vs. 1–6 months, respectively; $p = 0.011$). Fever at admission in these children was higher and lasted longer both before and during hospitalization, and they had a lower breathing rate. Children with complications also required longer antibiotic treatment. All these clinical differences between children with and without complications related to RSV infection were significant as presented in detail in Table 2.

The serum CRP level was distinctly higher in children with RSV-associated complications (median 5.45 vs. 1.00 mg/L; $p < 0.001$; with the upper limit of the norm in the hospital laboratory

of 5.00 mg/L). Likewise, neutrophil count was significantly higher in these children (median 4.67 vs. 2.19 k/ μ L; $p = 0.011$). The other blood and biochemical indices investigated did not differ significantly between children with and without complications (Table 3).

Among the risk factors for RSV-associated complications, only the median age over 3 months correlated with the development of complications (OR = 5.2, 95% CI: 2.0–13.5) in the whole group. The correlation was much stronger for AOM (OR = 9.8, 95% CI: 3.6–26.7) than for pneumonia (OR = 2.8, 95% CI: 1.1–7.3). All the other analyzed risk factors, including prematurity, birth weight below 2,500 g, exposure to tobacco smoke during pregnancy, and the cessation of breastfeeding below age 6 months, were

Table 2 Clinical characteristics of children with and without complications after respiratory syncytial virus (RSV) infection

Parameter	With complications	Without complications	<i>p</i>
Fever			
Severity at admission (°C)	37.8 ± 1.0	37.1 ± 0.8	0.001
Total duration (hours)	54.7 ± 55.9	17.8 ± 41.5	0.001
Before hospitalization (hours)	30.0 ± 44.6	11.0 ± 29.5	0.007
During hospitalization (hours)	21.8 ± 27.4	6.2 ± 23.5	0.001
Breathing rate (/min)	50 (40–58)	58 (50–65)	0.031
Heart rate (/min)	138 (130–148)	140 (130–152)	0.064
Oxygen supplementation (hours)	0 (0–36)	0 (0–0)	0.578
Antibiotic therapy (days)	7 (0–10)	0 (0–0)	0.001
Hospitalization (days)	10 (8–13)	8 (7–11)	0.181

Results are means ±SD and medians (LQ-UQ)

Table 3 Laboratory findings in children with and without complications after respiratory syncytial virus (RSV) infection

Parameter	With complications	Without complications	<i>p</i>
Hb (g/dL)	11.8 (10.9–12.3)	11.4 (10.8–12.4)	0.721
WBC (k/ μ L)	11.89 (8.90–13.70)	10.84 (8.49–13.55)	0.317
NEU (k/ μ L)	4.67 (2.22–6.47)	2.19 (1.12–5.08)	0.011
PLT (k/ μ L)	379 (311–472)	439 (344–498)	0.133
CRP (mg/L)	5.45 (1.78–14.58)	1.00 (0.49–4.74)	0.001
PCT (ng/mL)	0.13 (0.09–0.38)	0.12 (0.08–0.15)	0.112
ScO ₂ (%)	92.2 (90.3–94.0)	90.3 (87.2–93.4)	0.077
PcCO ₂ (mmHg)	34.9 (30.9–37.5)	35.5 (32.6–40.9)	0.142
pHc	7.42 (7.40–7.44)	7.41 (7.39–7.43)	0.050

Results are medians (LQ-UQ); *Hb* hemoglobin content, *WBC* white blood cell count, *NEU* absolute neutrophil count, *PLT* platelet count, *CRP* C-reactive protein, *PCT* procalcitonin, *ScO₂* capillary blood oxygen saturation, *PcCO₂* capillary blood partial pressure of carbon dioxide, *pHc* capillary blood pH

statistically irrelevant when analyzed for the whole group of patients with complications, as compared to those without complications, as well as in the subgroups of AOM, pneumonia, and conjunctivitis.

4 Discussion

This study demonstrates a substantial 61% (68/111) rate of complications in children up to 22 months of age, hospitalized due to RSV-associated respiratory infection, with about half of those children presenting more than one complication. Acute otitis media (AOM) clearly prevailed at 48% (53/111), followed by pneumonia, 33% (37/111), and conjunctivitis, 11% (12/111). Otitis media paired with pneumonia also prevailed in case of multiple complication in a child. Despite rather severe and frequent complications, there was no fatality in the investigated group. Our findings are grossly in line with other literature reports. Willson et al. (2003) reported a somehow higher 79% prevalence of complications, but that study focused on infants only, and it investigated a broader array of complications, including cardiovascular and electrolyte disorders which took place in 9% and 19% of infants, respectively. On the other side, Gentile et al. (2019) reported a clearly lower 21% prevalence of complications in non-fatal cases, but about 94% in fatal cases, with many patients having more than one complication. Those authors emphasize that the study was conducted in a hospital, and the complications included respiratory distress, atelectasis, sepsis, and the nosocomial infection; the last one not necessarily being RSV-associated.

The present study focused on respiratory complications that constitute a health hazard in an inpatient setting such as AOM, pneumonia, and conjunctivitis. We purposefully excluded bronchiolitis from the array of RSV-associated complications on the ground that it is the most frequent clinical presentation of RSV infection. Had bronchiolitis been considered a complication, the prevalence of complications would have increased to 98% (109/111). For

comparison, Hall et al. (2009) have found in a prospective, population-based study that 70% of children below age 5 years, hospitalized due to RSV infection, are diagnosed with bronchiolitis. Thus, bronchiolitis should rather be considered a typical clinical presentation of RSV infection in hospitalized children than a complication.

We found that AOM was the predominating complication affecting 48% of children with RSV-associated infection. Previous studies have shown a similar prevalence of AOM: 47.4% in children aged 6 months to 3 years who were prospectively followed up for 1 year (Chonmaitree et al. 2008); 55.6% in children with bronchiolitis, investigated in a study by Gomaa et al. (2012); and 57% in a study by Ruuskanen et al. (1989). Heikkinen et al. (2017) have evaluated the prevalence of AOM by children's age, showing a peak up to age 1 year. Yet it remained at a high level also in children aged 1, 2, and 3–6 years, amounting to 52%, 58%, and 46%, respectively. Likewise, Vesa et al. (2001) have shown the presence of AOM in 57.7% of children hospitalized due to RSV infection. Further, those authors show the predominating occurrence of AOM in the course of any verified viral infection in children aged 6–11 months. A lower prevalence of AOM has been reported in children hospitalized due to RSV bronchiolitis (20.1%) or pneumonia (21.4%) in a review of the American national databases performed by Paramore et al. (2004). However, that study analyzed the final diagnoses unlike the studies outlined above, including the present one, based on a prospective surveillance of RSV-infected children.

In the present study, prevalence of RSV-associated pneumonia was 33%. This figure seems to reflect well the optimum 32% benchmark of clinical care quality concerning the use of chest radiograph in children hospitalized with bronchiolitis, based on the assumption that each X-ray would yield a positive result (Parikh et al. 2014). In a population-based study by Hall et al. (2009), the highest 51% rate of RSV-associated pneumonia has been in children aged 24–59 months. In contrast, in a study conducted in more than 15,000 patients in a tertiary hospital

over an 18-year-long surveillance, Gentile et al. (2019) have reported that atelectasis, which closely reflects pneumonia, is seen only in 3.8% of RSV survivors and in 13.4% of fatal cases. Likewise, Heikkinen et al. (2017) have reported pneumonia in 3% of children with RSV infection aged under 13 years. Therefore, there appears to be an essential age-dependent difference in the prevalence of pneumonia in children with bronchiolitis, with much greater vulnerability in infants and small children.

In a study of Souty et al. (2019) in 6000 patients of all ages, conjunctivitis did not associate with RSV infection in children below age 15 years, although it modestly did with influenza infection, the occurrence of both types of infections being alike – 15% and 17%, respectively. Interestingly, in a study of Sigurs et al. (2005), increased frequency of allergic rhinoconjunctivitis has been reported in children aged about 13 years who had been hospitalized years earlier in infancy due to severe RSV infection when compared to non-hospitalized subjects. The underlying pathomechanism of the effect is unclear, but it might have to do with RSV invading the conjunctival epithelial cells during the infection (Fujishima 2002). If the eye is the primary site for RSV invasion, local inflammation could result in persistent rhinoconjunctivitis. In a murine model, RSV is able to replicate in the eye, with subsequent lower respiratory tract infection that is indistinguishable in terms of the disease course from that acquired through the nose. As a consequence of ocular infection, a mix of chemokines and cytokines are produced. Anti-cytokine treatment reduces local inflammation but does not inhibit RSV replication (Bitko et al. 2007). The presence of RSV-associated conjunctivitis might be a prognostic of future allergic rhinoconjunctivitis, considering the persistent ocular inflammatory response subsequent to viral invasion.

In this study we found that age over 3 months was a single risk factor associated with the development of otitis media and pneumonia. Other commonly considered factors such as prematurity, birth underweight, exposure to cigarette smoke during pregnancy, and the cessation of

breastfeeding below age 6 months did not appear to associate with any of the complications found. For comparison, Hall et al. (2009) have reported that the duration of breastfeeding for less than 1 month of age is a significant risk factor for the development of infectious complications. However, cessation of breastfeeding between 1 and 6 months of age seems irrelevant to this end. Although the risk factors that concern children who are hospitalized each season are well-known, the practical use of this knowledge seems limited. There is a need to increase awareness of the amenable risk factors of RSV infection in the public at large, the factors that basically concern all kinds of respiratory infection. A case in point may be the issue of cigarette smoking during pregnancy. In this study, 20 (18%) out of the 111 children hospitalized with a severe course of RSV infection were exposed to maternal smoking.

Limitations of this study were a relatively small group of child patients and a preselection bias stemming from the fact that all the patients were hospitalized. We also failed to verify the existence of comorbidities, e.g., congenital heart disease, kidney diseases, and others. The presence or lack of a serious comorbidity was established only the basis of anamnesis taken from the child parents/guardians. Despite these limitations we believe we have conclusively shown that RSV infection is related to a high number of complications, which raises a serious health concern and places a substantial burden on healthcare resources. A risk of complications increases with the infant age. Unfortunately, the known risk factors of a severe RSV course do not exactly reflect the development of complications. Therefore, the ill children need to be carefully followed up in order to discern and treat possible complications in a timely manner.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Center of Postgraduate Medical Education in Warsaw, Poland.

Informed Consent Written informed consent was obtained from the parents or legal guardians of all the child patients of the study.

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