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# Respiratory Syncytial Virus Coinfections With Rhinovirus and Human Bocavirus in Hospitalized Children

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**Abstract:** It is not clearly established if coinfections are more severe than single viral respiratory infections.

The aim of the study was to study and to compare simple infections and viral coinfections of respiratory syncytial virus (RSV) in hospitalized children.

From September 2005 to August 2013, a prospective study was conducted on children younger than 14 years of age, admitted with respiratory infection to the Pediatric Department of the Severo Ochoa Hospital, in Spain. Specimens of nasopharyngeal aspirate were taken for virological study by using polymerase chain reaction, and clinical data were recorded. Simple RSV infections were selected and compared with double infections of RSV with rhinovirus (RV) or with human bocavirus (HBoV).

In this study, 2993 episodes corresponding to 2525 children were analyzed. At least 1 virus was detected in 77% (2312) of the episodes. Single infections (599 RSV, 513 RV, and 81 HBoV) were compared with 120 RSV-RV and 60 RSV-HBoV double infections. The RSV-RV coinfections had fever (63% vs 43%;  $P < 0.001$ ) and hypoxia (70% vs 43%;  $P < 0.001$ ) more often than RV infections. Hypoxia was similar between single or dual infections (71%). Bronchiolitis was more frequent in the RSV simple group ( $P < 0.001$ ). Pediatric intensive care unit admission was more common in RSV simple or RSV-RV groups than in the RV monoinfection ( $P = 0.042$ ).

Hospitalization was longer for both RSV simple group and RSV-HBoV coinfection, lasting about 1 day (4.7 vs 3.8 days;  $P < 0.001$ ) longer than in simple HBoV infections. There were no differences in PICU admission. RSV single group was of a younger age than the other groups.

Coinfections between RSV-RV and RSV-HBoV are frequent. Overall viral coinfections do not present greater severity, but have mixed clinical features.

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**Abbreviations:** AdV = adenoviruses, ARI = acute respiratory tract infections, CoV = human coronaviruses, CRPC = reactive protein, EV = enteroviruses, HBoV = human bocavirus, hMPV = human metapneumovirus, NPA = nasopharyngeal aspirates, PCR = polymerase chain reactions, PICU = pediatric intensive care unit, PIV = parainfluenza virus, RSV = respiratory syncytial virus, RT = reverse transcription, RV = rhinovirus, URTI = upper respiratory tract infection, WBC = white blood cell.

## INTRODUCTION

Acute respiratory tract infections (ARIs) are common diseases among children and a major cause of hospitalization, mainly in infants. Viral pathogens play an important role in infants who present ARIs, respiratory syncytial virus (RSV) being the most important virus associated. In addition, children with RSV infections are also exposed to a variety of other respiratory viruses with a similar seasonal pattern, mainly during winter months, such as influenza, rhinovirus (RV), human metapneumovirus (hMPV), and human bocavirus (HBoV).<sup>1</sup> Despite the fact that numerous studies have revealed that an important number of ARI pediatric patients become simultaneously infected with multiple respiratory viruses, there are few studies focused on analyzing viral coinfections. This issue usually becomes a marginal part of the studies.

Over the past few years, several groups, including ours,<sup>2</sup> have described various viral coinfection combinations compared with single ones, with different methodologies, and some of them observed worse prognosis with multiple viral infections,<sup>3-6</sup> whereas others revealed a very similar prognosis for single virus infections.<sup>7,8</sup>

Thus, there is a need of a carefully designed study to shed some light on this issue. We aimed to compare, in a prospective study, clinical characteristics and severity of single versus viral coinfections, defined as simultaneous detection of RSV with RV, hMPV, or HBoV, in a large cohort of hospitalized children.

## PATIENTS AND METHODS

### Clinical Assessment

The study population comprised of all children less than 14 years of age with ARI admitted to the secondary public hospital Severo Ochoa (Leganés, Madrid), between September 2005 and August 2013. The study was approved by The Medical Ethics Committee (Carlos III). Informed consent was obtained from parents or legal guardians. Exclusion criteria were refusal to participate. All patients were evaluated by an attending physician. Clinical characteristics of patients were analyzed. During the hospital stay, and as part of the study, a physician filled out a study

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questionnaire with the following variables: age, sex, month of admission, clinical diagnosis, history of prematurity and underlying chronic diseases, need for oxygen therapy, evaluated via transcutaneous oxygen saturation, axillary temperature ( $\geq 38^{\circ}\text{C}$ ), presence of infiltrates and/or atelectasis in chest radiographs, administration of antibiotic therapy, length of hospital stay, total white blood cell (WBC) count, C-reactive protein (CRP) serum levels, and blood culture results (for those cases in which such tests had been performed). Asthma or recurrent wheezing was not considered an underlying chronic disease.

“Upper respiratory tract infection” (URTI) was diagnosed in patients with rhinorrhea and/or cough and no signs of wheezing, dyspnea, crackles, or bronchodilator use, with or without fever. “Asthma” was diagnosed on the basis of the National Asthma Education and Prevention Program guidelines.<sup>9</sup> All other episodes of acute expiratory wheezing were considered to be “recurrent wheezing.” Acute expiratory wheezing was considered to be “bronchiolitis” when it occurred for the first time in children aged less than 2 years. “Laryngotracheobronchitis” was associated with inspiratory stridor and wheezing. “Laryngitis” was associated with inspiratory stridor without wheezing. Cases with both focal infiltrates and consolidation in chest radiographs were, in the absence of wheezing, classified as “pneumonia.” However, if wheezing were present, even though there was a radiographic infiltrate, the patient was classified as having episodes of wheezing.

### Virus Detection

Specimens consisted of nasopharyngeal aspirates (NPAs) taken from each patient at admission. Each specimen (1 for patient) was sent for virological investigation to the Respiratory Virus and Influenza Unit at the National Microbiology Center (ISCI, Madrid, Spain). NPAs were processed within 24 hours after collection. Upon receipt, 3 aliquots were prepared and stored at  $-70^{\circ}\text{C}$ . Both the reception and the NPA sample processing areas were separate from those defined as working areas.

### Polymerase Chain Reaction Methods for Detection of 16 Respiratory Viruses

Three reverse transcription (RT)-nested polymerase chain reaction (PCR) assays were performed to detect a total of 16 respiratory viruses. In these assays, the RT and first amplification round were carried out in a single tube using the Qiagen OneStep RT-PCR kit (Qiagen, Hilden, Germany). Influenza A, B, and C viruses were detected by using previously described primer sets only to amplify influenza viruses in a multiplex PCR assay.<sup>10</sup> A second multiplex PCR was used to detect parainfluenza viruses 1 to 4 (PIV), human coronaviruses (CoV) 229E and OC43, enteroviruses (EVs) and RVs.<sup>11</sup> Presence of respiratory syncytial virus (RSV) A and B types, hMPV, HBoV, and adenoviruses (AdV) were investigated by a third multiplex RT-nested PCR-BRQ method.<sup>12</sup>

### Statistical Analysis

Continuous variables were described using mean and standard deviation. Categorical variables were described using absolute and relative frequencies. Clinical characteristics of patients with single infections associated with RSV were compared with those associated with coinfections between RSV and hMPV, RSV or RV, and finally with RSV and HBoV.

To compare qualitative variables chi-square test<sup>2</sup> or Fisher exact test was used if there were  $\leq 5$  items of data in a cell. For

quantitative variables, as all of them followed a normal distribution, the means were compared using the Student *t* test to compare the 2 groups. When 2 or more groups were compared, the test of analysis of variance (ANOVA) was used, followed up with post hoc tests to identify which groups differ from the rest. A 2-sided value of  $P < 0.05$  was considered statistically significant. Results were adjusted for age. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 21.0.

## RESULTS

The study population consisted of 2525 children less than 14 years of age who had a total of 2993 episodes of hospitalization for respiratory causes. A total of 2312 episodes (77%) had a positive respiratory viral identification (66.5% were single infections). Among them, 681 episodes were caused by viral coinfection. Out of multiple viral infections, dual infections between RSV and other viruses were analyzed. A comparison between single and dual infections was performed. Viral isolations (single and multiple) are shown in Figure 1.

### Dual RSV Infections

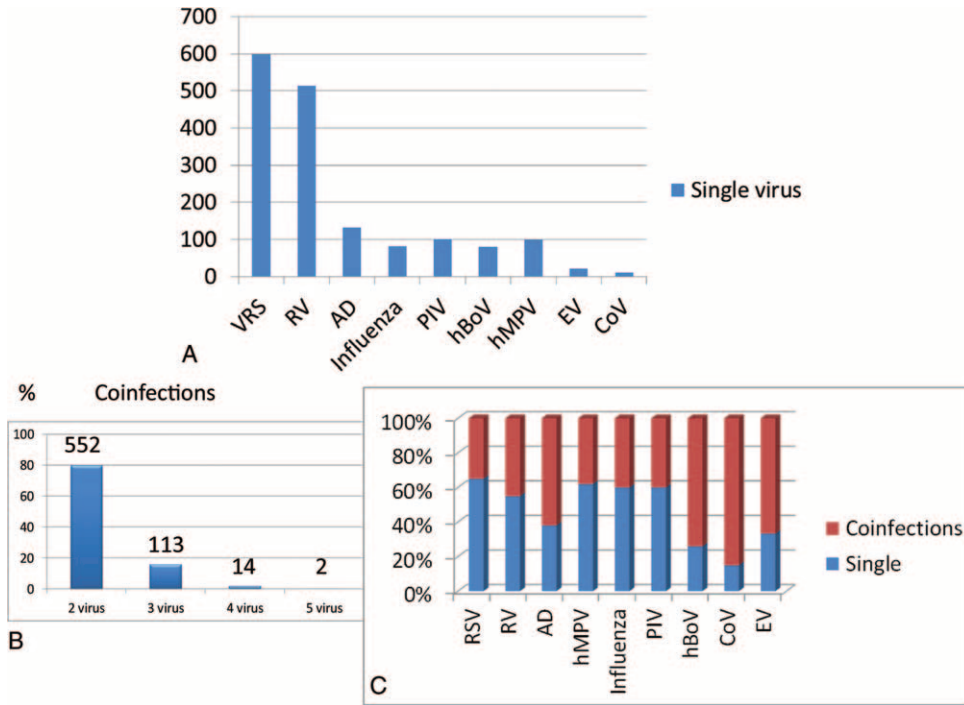
We detected 599 RSV single infections and 326 RSV multiple infections (Fig. 2). We selected dual RSV infections and this group was analyzed and compared with single infections. Out of them, we achieved a significant number of cases for comparing between dual RSV and RV ( $n = 120$  episodes), and between RSV and HBoV ( $n = 60$  episodes). Other dual infections were RSV plus hMPV ( $n = 3$  episodes), RSV plus AdV ( $n = 29$ ), RSV plus influenza ( $n = 11$ ), PIV ( $n = 7$ ), CoV ( $n = 8$ ), and EV ( $n = 13$ ).

### Dual RSV and RV infections

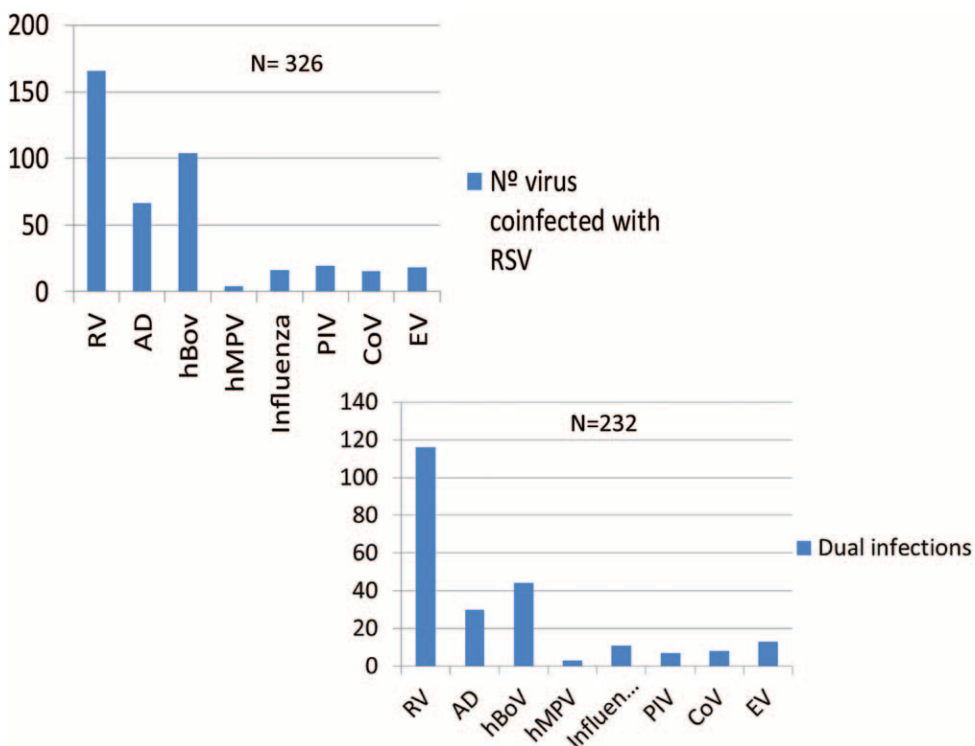
A total of 599 single RSV infections were compared with 120 RSV plus RV infections and with 510 RV single infections (Table 1). The mean age of the children was different between the groups ( $P < 0.001$ ), with 9.5 months on average for RSV, 26 months for RV infections, and an intermediate age of 12.6 months in the coinfection group. The proportion of males (60%) was higher in the RV single group ( $P = 0.045$ ).

Fever was more frequent in children with RSV infection (65%) and coinfections with RV (63%) than in RV ones (42%) ( $P < 0.001$ ). Patients with coinfections had a risk of fever that was 1.9 (confidence interval [CI] 1.4–2.7) times higher than RV infections, and similar to RSV. Also, hypoxia was more prevalent in children with RSV (71%), and RSV plus RV (70%), than in RV single infections (50%) ( $P < 0.001$ ). Risk of hypoxia was twice as high in infants with coinfection, than in RV alone, and similar than in infants with RSV. Duration of hypoxia was 1 day longer in children with RSV alone or in coinfection, than in RV single infections ( $P < 0.001$ ). The clinical picture was also significantly different ( $P < 0.001$ ). RV single infections were mainly associated with recurrent wheezing (62%), whereas RSV single infections were mostly diagnosed with bronchiolitis (65%). Coinfections between them had an intermediate proportion of both clinical diagnoses with 55% of bronchiolitis and 39% of recurrent wheezing or asthma. Pneumonia was more prevalent in children with RV single infections (12%) than in the other groups. Mean CRP ( $P < 0.001$ ) and leukocyte count in blood ( $P = 0.005$ ) were significantly higher in children with RV than in infants with RSV or coinfections (Table 1).

Hospitalization was shorter in RV infection children than in infants with RSV or in coinfection ( $P < 0.001$ ). Admission to



**FIGURE 1.** Viral isolations. A, Single viral infections (absolute numbers); B, coinfections (number of simultaneous isolated viruses); C, percentage of single or multiple infections detected in the different viruses.



**FIGURE 2.** A, Coinfections of RSV with other viruses (n=326); B, dual infections between RSV and other viruses (n=232). RSV = respiratory syncytial virus.

**TABLE 1.** Clinical Characteristics Associated With Infections Caused by Rhinovirus (RV) Single Infections, Respiratory Syncytial Virus (RSV) Single Infections and RV Plus RSV Dual Infections

Clinical Features	RSV (n = 599)	RV (n = 510)	RSV + RV (n = 120)	P
Male	316 (53%)*	307 (60%)*	68(58%)	0.045*
Prematurity	70 (12%)	57 (11%)	11 (7%)	
Temperature >37.9°C	388 (65%)*	216 (42%)*,†	76(63%)*,†	<0.001*,†
		OR = 0.8 (0.78–0.9)	OR = 1.9 (1.4–2.7)	
Hypoxia (SatO <sub>2</sub> <95%)	426 (71%)	255 (50%)*	85 (70%)*	<0.001*
		OR = 0.85 (0.8–0.9)	OR = 2 (1.4–2.8)	
Abnormal X-ray	237 (40%)	144 (28%)*	46 (38%)*	<0.001*
Antibiotic treatment	110 (18%)	106 (21%)	20 (16%)	
Diagnosis:				<0.001
Asthma/recurrent wheezing	181 (31%)	286 (62%)	47 (39%)	
Bronchiolitis	379 (65%)	105 (23%)	66 (55%)	
Pneumonia	19 (3%)	56 (12%)	4 (3.5%)	
Laryngitis	7 (1.2%)	12 (2.6%)	2 (1.7%)	
Highest temperature (SD)	38.7 (0.6)	38.7 (0.6)	38.7 (0.5)	
Leukocytes, cells/mm <sup>3</sup> (SD)	12300 (8000)*	21100 (75780)*	12100 (4460)	<0.05*
C-reactive protein, mg/L (SD)	29 (38)*	58 (91)*,†	35 (47)†	<0.001* 0.036†
Age in months (SD)	9.5 (12.7)*	26 (27)*,†	12.6(18.6)†	<0.001*,†
Days of hospital stay (SD)	4.7 (2.5)	3.4 (1.9)*,†	4.7 (2.8)†	<0.001*,†
Days of fever (SD)	3.1 (2.9)*	2.5 (2)*	2.9 (1.9)	<0–01*
Days of hypoxia (SD)	3.1 (2.2)*	1.9 (1.6)*,†	3.2 (2.6)†	<0.001*,†
Admission to PICU	22 (3.7%)*	7 (1.4%)*,†	5 (4.1%)*	0.042* 0.048†
			OR = 2.2 (1.1–4.4)	

OR = odds ratio (expressed as value and confidence interval), PICU = pediatric intensive care unit, SD = standard deviation. The symbols make reference to the statistic significance of the differences among the groups in each row.

pediatric intensive care unit (PICU) was higher in children with single RSV infection or in coinfection, than in RV single infections ( $P = 0.042$ ). The coinfection RSV plus RV had a risk of admission in PICU 2.2 times higher than the RV single infection (CI 1.1–4.4). Nevertheless, there were no statistical differences between RSV alone or in coinfections to PICU admission.

Monthly distribution of infections was also different among groups ( $P < 0.001$ ), and it is shown in Figure 3. Coinfections between RSV and RV match up with RSV circulation, mainly in January, November, and December, whereas RV single infections occur throughout the whole year, with the highest proportion during September and October.

### Dual RSV and HBoV Infections

A total of 599 single RSV infections were compared with 60 RSV plus HBoV infections and with 81 HBoV single infections (Table 2). Total number of HBoV detections was 310 (13.5% of viral detections), and 230 of them (74%) were coinfections with other different viruses. Mean age of the children was different between the groups ( $P < 0.001$ ), with an average of 9.5 months for RSV, 25 months for HBoV infections, and an intermediate age of 14.5 months in the coinfection group. Proportion of males (65%) was higher in HBoV single group ( $P = 0.045$ ), and coinfections were more frequent in females (53%).

Coinfections of RSV plus HBoV had fever more frequently (80%;  $P = 0.052$ ) than the other groups, and also a higher percentage of hypoxia (75%;  $P < 0.001$ ), whereas the HBoV group had only 52% of the latter and lasting about 1 day less ( $P = 0.03$ ). Clinical diagnosis for the coinfection group was recurrent wheezing and bronchiolitis in approximately equal figures (49% and 44%), and it was different to single infections

( $P < 0.001$ ). Bronchiolitis was the most frequent in RSV infections (65%) and recurrent wheezing was the most common in the HBoV ones (60%). Pneumonia was diagnosed in 22% of the HBoV group. Hospitalization stay was longer and similar in the RSV groups (single infection or coinfection) and nearly 1 day more (4.7 vs 3.8 days;  $P < 0.001$ ) than in HBoV single infections. There were no differences in percentages of PICU admission.

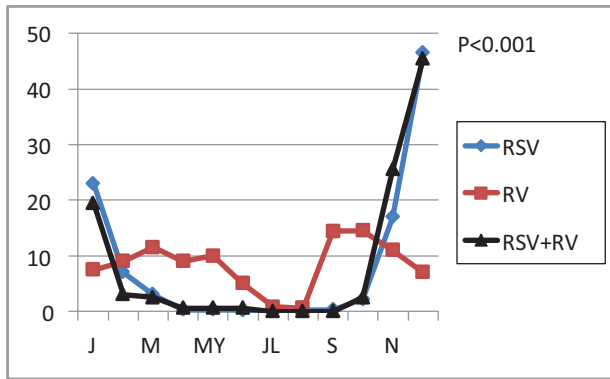
Mean CRP ( $P < 0.001$ ) and leukocyte count in blood ( $P = 0.028$ ) were significantly higher in HBoV infections than in RSV single infections or in coinfections (Table 2). Antibiotic therapy was prescribed more frequently in HBoV infections than in the other 2 groups ( $P < 0.001$ ).

Seasonality of both HBoV infections and HBoV plus RSV coinfections was observed in November and mainly in December (more than half of the coinfections) ( $P < 0.001$ ) (Fig. 3).

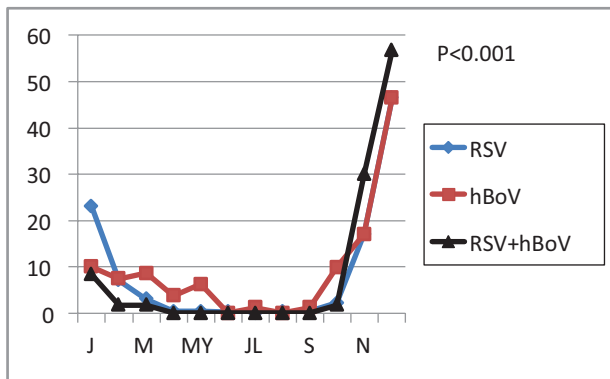
### DISCUSSION

In this study, RSV coinfections were frequent. They were detected in 35% of the analyzed episodes of ARIs caused by this virus. Although they were mainly dual infections, 3 or more viruses were also detected simultaneously. The most frequent dual infection was between RSV and RV, and the second was between RSV and HBoV. Nevertheless, coinfections with all respiratory viruses were detected. Adenovirus coinfections were the third most frequent, but the majority of them were found as multiple viral associations with inadequate dual cases for analysis. There are some systematic reviews about coinfections with different results. We focus our attention towards 1 study conducted in the United States, with data corresponding to a single hospital, and the authors found that dual infections had more ratio of hospitalizations than single infections.<sup>13</sup> However, recently, 2 other reviews have been published and do not find





A



B

**FIGURE 3.** Monthly distribution of viral infections. A, RSV, RV, and RSV plus RV; B, RSV, hBoV, and RSV plus hBoV. hBoV=human bocavirus, RSV=respiratory syncytial virus, RV=rhinovirus.

evidences suggesting that there are any differences in disease severity between coinfections compared to single viral infections.<sup>14,15</sup> Only one of them was performed in children.<sup>14</sup> We agree with the appreciation that coinfections do not increase the severity, and in anyway, we think that studies should focus on dual versus multiple infections, since the different characteristics of the virus can cause a bias when analyzing the results all together. One of the strengths of our study is that we analyzed virus in pairs and only when the number of infected patients to compare was big enough to allow us to draw conclusions. To our knowledge, our study has the highest number of patients in pairs of virus to date.

Dual infections between RSV and RV have different characteristics to single infections of each virus. Children with coinfections were around 1 year old, whereas RSV single infections affected younger infants and RV was found in older children of almost 2 years of age. In our series, coinfections had significantly more proportion of fever, and also more proportion of hypoxia than single infections of RSV or RV. The coinfections had a risk of fever 1.9 times higher than single infections, and the risk of hypoxia was twice as high. The presence of RSV implies a worse prognosis with increased duration of both hypoxia and days of hospitalization, whether in simple infection or in coinfection. The risk of admission in PICU was 2.2 (CI 1.1–4.4) in patients with coinfections versus in those with RV single infections, but there were no differences in patients with RSV single infections. This supports the idea that RSV infection causes the severity. There are few studies focused on coinfections between RSV and RV, and the number of patients analyzed is still small. The most extensive evaluation of the role of RV infections, whether single or multiple in children, is the study by Costa and Queiróz.<sup>16</sup> They analyzed 181 inpatient and outpatient children with RV infections, and 74 of them had coinfections, mainly with RSV. They found that RV single infections were less severe than coinfections RV plus RSV,

**TABLE 2.** Clinical Characteristics Associated With Infections Caused by Human Bocavirus (hBoV) Single Infections, Respiratory Syncytial Virus (RSV) Single Infections and hBoV Plus RSV Dual Infections

Clinical Features	RSV (n = 599)	hBoV (n = 81)	RSV + hBoV (n = 60)	P
Male	316 (53%)	53 (65%)*	28 (47%)*	0.052*
Prematurity	70 (12%)	9 (11%)	9 (15%)	
Temperature >37.9°C	388 (65%)*	56 (69%)*	48 (80%)*	.02*
Hypoxia (SatO <sub>2</sub> <95%)	426 (71%) <sup>†</sup>	42 (52%)*, <sup>†</sup>	45 (75%)*	<0.001* <sup>†</sup>
Abnormal X-ray	237 (40%)	38 (47%)	27 (45%)	
Antibiotic treatment	110 (18%)*, <sup>†</sup>	33 (41%)*	17 (28%) <sup>†</sup>	<0.001*0.058 <sup>†</sup>
Diagnosis				<0.001
Asthma/recurrent wheezing	181 (31%)	48 (60%)	29 (49%)	
Bronchiolitis	379 (65%)	13 (16%)	26 (43%)	
Pneumonia	19 (3%)	18 (22%)	1 (1.7%)	
Highest temperature (SD)	38.7 (0.6)*	38.9 (0.6)	39 (0.6)*	0.005*
Leukocytes, cells/mm <sup>3</sup> (SD)	12300 (8000)*	15500 (7900)*, <sup>†</sup>	12170 (4870) <sup>†</sup>	0.028*0.026 <sup>†</sup>
C-reactive protein, mg/L (SD)	29 (38)*	65 (79) <sup>†</sup>	40 (30)*, <sup>†</sup>	<0.001* 0.04 <sup>†</sup>
Age in months (SD)	9.5 (12.7)*	25 (23) <sup>†</sup>	14.5 (7.8)*, <sup>†</sup>	<0.001* <sup>†</sup>
Days of hospital stay (SD)	4.7 (2.5)*	3.8 (2)*	4.7 (2.8)	<0.001*
Days of fever (SD)	3.1 (2.9)	3 (2.2)	2.9 (1.9)	
Days of hypoxia (SD)	3.1 (2.2)	2.3 (1.5)*	3.2 (2.6)*	0.03*
Admission to PICU	22 (3.7%)	1 (1.2%)	1 (1.7%)	

\*,<sup>†</sup> The symbols make reference to the statistic significance of the differences among the groups in each row.

OR=odds ratio (expressed as value and confidence interval), PICU=pediatric intensive care unit, SD=standard deviation.

requiring less proportion of hospital admission. Patients with single RV were older than single RSV and coinfections, and the most frequent diagnosis was recurrent wheezing. Similar to our series, there were no differences between RSV and coinfections of RV plus RSV with regard to severity.

In our patients, the diagnosis of pneumonia was more common in single RV infection, and these children characteristically had leukocytosis and elevated CRP more frequently than those with simple infections or coinfections of RSV plus RV. Other authors have described the role of viral respiratory infections, and especially RV, as a risk factor to develop invasive pneumococcal pneumonia,<sup>17,18</sup> and we assume that this could explain the high frequency of pneumonia in our series.

Coinfections of RSV and RV in our series had a seasonality that exactly matches up with the RSV circulation during November and December, confirming the importance of RSV in this association.

Dual infections of RSV and HBoV are also frequent and the interpretation of their role is interesting. Up to 75% of the HBoV infections are coinfections with one or more viruses,<sup>19</sup> and have a prolonged viral shedding around 75 days in outpatients,<sup>20</sup> and up to 4.5 months in hospitalized children,<sup>21</sup> which probably explains why HBoV DNA has often been found in asymptomatic cases.<sup>22</sup> This is the reason that explains why some authors consider HBoV as not a pathogenic virus. Nevertheless, the severity of the illness was associated with HBoV infections in children attending daycare,<sup>20</sup> and reinfections contribute to long-term shedding.<sup>23</sup> On the contrary, other studies have suggested that HBoV is the most likely cause of respiratory tract disease if the patient has a single infection, high viral load in NPA, and viremia.<sup>24,25</sup> A severe and life-threatening disease has recently been well documented in an 8-month-old child with acute respiratory distress in Germany.<sup>26</sup> Also, HBoV has been detected as the third agent causing confirmed pneumonia,<sup>27,28</sup> and so, all of them support the pathogenic role of this virus. And finally, serologic diagnosis of HBoV has confirmed that it is a true pathogen in respiratory tract infections in children.<sup>29</sup> Unfortunately, this technique is not yet available in many laboratories including ours.

In our study, clinical features were different in children with HBoV and RSV single infections. The most common clinical diagnosis in children with RSV was bronchiolitis. These children had hypoxia more frequently and a more prolonged stay in hospital than children with HBoV, but there were no differences in terms of PICU admission. In contrast, pneumonia was much more frequent in children with HBoV; this could explain the higher WBC counts and CRP levels in these patients. Dual RSV and HBoV shared clinical characteristics from both viruses, and the most frequent clinical diagnosis in these children was recurrent wheezing. We can show results with our series in which HBoV infections have a pathogenic role. It can also be observed that the coinfections with RSV have different clinical aspects when compared to single RSV infections. A larger number of patients would be needed to conclude if there is any difference in severity between single and multiple infections.

Semple et al<sup>3</sup> and Greensill et al<sup>30</sup> in the United Kingdom found a strong association between coinfections of hMPV and RSV in infants with bronchiolitis and more severity, including admission to the ICU. This series detected that 23 out of 30 ventilated infants had a coinfection in an epidemiologic season. Other prospective studies performed in Europe,<sup>31</sup> and mainly in Holland,<sup>32</sup> did not find this association or any coinfections between RSV and hMPV. In our study, during 8 consecutive

seasons, we only found 3 dual coinfections. The different seasonality pattern of RSV (mainly November and December) and hMPV (mainly in spring) might explain these results. Probably, an atypical circulation of hMPV during the season studied in the United Kingdom allowed the association, but it is not a common condition in respiratory infections in Europe. Therefore, we cannot evaluate if the coinfection RSV–hMPV increases the severity or not.

Other groups of viruses such as influenza, adenovirus, or parainfluenza, not included by us, should be analyzed in future prospective studies. Other limitations of our study are that we have not studied shedding of HBoV or performed serological studies. Despite this, we think that our study provides evidence of the pathogenic role of HBoV, as well as the characteristics of studied coinfections.

Regardless of the viruses studied, it is a common finding in the literature that coinfections present more fever than single infections. This is also the case in our series, both for RSV–RV and RSV–HBoV coinfections. Despite this fact, we cannot conclude that coinfections are more severe than single infections, and the severity in our patients was associated mainly with RSV infection either alone or in combination with other viruses.

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