Respiratory syncytial virus infection in children less than five years of age presenting as severe community-acquired pneumonia

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ABSTRACT

Background: Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection in young children in both the community and hospital setting. Ongoing surveillance of the clinical and molecular epidemiology of RSV genotypes is important to characterize prevalent and emerging genotypes that may have impact on vaccine development. **Objective:** To assess the epidemiology of RSV infection in children <5 years of age in a tertiary care hospital. **Materials and Methods:** Children <5 years of age hospitalized with severe community-acquired pneumonia (CAP) were included in the study. Nasopharyngeal aspirate was taken for RSV reverse-transcriptase polymerase chain reaction. **Results:** A total of 100 children were recruited in the study. clinicoepidemiological epidemiological and radiological features were analyzed. The prevalence of RSV infection in children <60 months of age admitted with the features of severe pneumonia in our study was 30% with almost equal proportion of RSV A and B groups. Underlying congenital heart disease and family history of asthma were identified as significant risk factors. There were no significant clinical and radiological features to distinguish RSV from non-RSV disease. **Conclusions:** This study highlights the relevance of RSV infection in hospitalized cases of CAP in our region. Our findings warrant the conduct of further investigations which can help design strategies for controlling the disease. If RT-PCR could be used in children with severe pneumonia who are hospitalized, an accurate diagnosis of RSV bronchiolitis can be made in high percentage of children.

Key words: *Children, Pneumonia, Respiratory syncytial virus, Reverse-transcriptase polymerase chain reaction*

More than 90% of the 150 million new episodes of pneumonia identified per year worldwide occur in the developing countries. Most of these respiratory tract infections in children are due to viruses [1]. According to the World Health Organization (WHO), respiratory syncytial virus (RSV) is the leading etiological agent in 15–40% of children hospitalized with pneumonia or bronchiolitis in the developing world [2]. Globally, RSV accounts for 64 million cases and 160,000 deaths annually [3]. Nearly 60% of all children are infected with RSV within the 1st year of life and almost all by the end of 2nd year. RSV infection is usually limited to the upper respiratory tract and is characterized by profuse rhinorrhea. However, 25–40% of these infants may subsequently develop severe respiratory disease requiring hospitalization [4]. Primary respiratory infection by this virus increases the risk of secondary bacterial pneumonia and viral or bacterial coinfection in approximately 20–30% of episodes [5]. This results in long-term respiratory disorders such as abnormal pulmonary function, asthma, recurrent cough and bronchitis [6,7].

Studies estimating the prevalence of RSV in children hospitalized with severe community-acquired pneumonia (CAP) are limited in the literature [8]. A single study from South India detected viruses in 37% of the children with pneumonia. Children with severe CAP diagnosed as per the WHO guidelines are treated with intravenous antibiotics routinely. Identifying a viral etiological agent in such children can greatly reduce the use of unnecessary antibiotics, at least in hospitalized children. Thus, there is a felt need to study the epidemiology of CAP among hospitalized children in developing countries [9].

RSV is classified into groups A and B based on reactions with monoclonal antibodies against the fusion (F) and attachment glycoproteins (G). Both groups circulate within the community and health-care institutions and predominance of one over the other varies by year and geographic location [10]. Hence, in this study, we aimed to estimate the prevalence of RSV infection in children admitted with severe pneumonia and to correlate the clinical profile with RSV positivity. The currently prevalent RSV group was also analyzed.

MATERIALS AND METHODS

We undertook this analytical cross-sectional study in a tertiary care pediatric hospital in South India from June to December 2016 in children 2–60 months of age hospitalized for severe

pneumonia. Severe CAP was diagnosed according to the WHO 2014 guidelines in children who were symptomatic for <14 days and without prior hospitalization in the past 2 months. Children who had chest in-drawing and fast breathing were classified as "severe pneumonia" and those with any general danger signs were classified as "very severe disease". Children in whom nasopharyngeal aspiration would be a contraindication such as history of recent nasopharyngeal surgery or epistaxis, or refusal of parental consent for participation were excluded.

A convenient sample size of 100 children was chosen. The study protocol was approved by the Institution Ethics Committee. After obtaining informed consent from the parents or the legal guardian, the detailed history, and demographic profile such as age, sex, and nutritional status were recorded. Detailed clinical examination including pulse oximetry was recorded in a structured format on admission. All children had chest X-ray taken on admission as per our hospital protocol. All children diagnosed with severe pneumonia were treated with intravenous antibiotics along with other supportive measures. The children were followed up till discharge/death and the final outcome was also recorded. The RSV-positive and RSV-negative groups were compared for the presence or absence of risk factors such as age, premature birth, low birth weight (LBW), congenital heart disease (CHD), and positive family history of asthma/atopy, clinical, and radiological findings, oxygen requirement, and final outcome. The symptoms such as fever (>100.2 F), coryza, vomiting/refusal of feeds, loose stools,- and hurried breathing were also compared.

Sample collection and RSV detection: A 2" sterile, 8-french nasogastric tube (NGT) was inserted into nasopharynx of the child. A volume of 1–2 ml of normal saline was instilled into the NGT and the same was aspirated through the tube immediately using a sterile syringe. The aspirate was immediately transferred into a sterile transport medium (Himedia, India) provided by the laboratory at Institute of Basic Medical Sciences (IBMS), Chennai. The samples were transported to the laboratory at IBMS for RNA extraction and processing on the same day. Viral RNA in nasal swab was extracted using Macherey-Nagel Viral RNA isolation Kit (MN, Germany). Reverse transcription was done using RevertAid First Strand cDNA Synthesis Kit, (Thermo Fisher Scientific, India), according to manufacturer's instructions. Detection of RSV was done using real-time PCR assay (Qiagen, Germany). Cycle threshold (CT) values <35 were considered positive for RSV. Categorical variables were expressed as proportions and continuous variables were expressed as mean and standard deviations (SD). Statistical significance was considered when the $p<0.05$.

RESULTS

Among the 1100 children hospitalized with the severe CAP during the 6 months period, 843 satisfied the inclusion criteria and were eligible for the study. Among them, 41 were excluded for reasons cited above. Cases were recruited based on availability of the investigator to facilitate the collection and immediate transport of the samples. Thus, 100 children were finally recruited. 59% of them were infants with a male predominance (70%). The prevalence of RSV in the study population was 30 % (95% confidence interval 21–40%) with Group A RSV detected in 16 cases (53%). The rest were RSV B, and there was no coinfection. The mean (SD) age of children with RSV infection (11±7 months) was less than that in the RSV negative group (22.6±23 months). There was a definite male predominance (83.3%) in the RSV positive ($p<0.05$) group.

Age<2 years was a significant risk factor for RSV infection ($p=0.04$). There was no statistical difference in the rates of prematurity ($p=1.000$) or LBW ($p=1.000$) between the groups (Table 1). However, the presence of CHD ($p=0.045$) and a family history of asthma ($p=0.036$) were identified as significant risk factors for RSV infection.

The presence of high fever ($p=0.001$), coryza ($p=0.013$), and vomiting/ feed refusal ($p=0.04$) were significant complaints in children with RSV infection (Table 2). Cough was significantly seen in the non-RSV group ($p=0.039$). Complaints of fast breathing ($p=0.312$) or diarrhea ($p=0.266$) were not statistically significant between the groups. Crackles on auscultation ($p=0.256$) and hypoxia ($p=0.159$) were comparable in both groups, whereas wheeze was predominant in the RSV-negative group ($p=0.032$).

A radiological diagnosis of bronchiolitis ($p=0.0007$) and pneumonia ($p=0.0001$) was significantly common in the RSV negative (Table 3).

Oxygen requirement was more common in the RSV-negative group ($p=0.0252$). The requirement of intravenous fluids between the groups was similar ($p=0.650$). There were no deaths reported in our study. The mean (SD) duration of hospital stay among the RSV-positive children was 5.00±2 days and negative children were 5.07±2.3 days and the difference was statistically insignificant.

DISCUSSION

In our study, 30 among 100 (30%) children hospitalized because of CAP were diagnosed with RSV infection. This is similar to other pneumonia etiology studies that had incorporated detection of viral markers, which show that RSV is the leading viral cause [2]. RT-PCR has shown improved sensitivity in the detection of RSV infection when compared to other methods such as immunofluorescence and should be used as the first choice [11,12]. The RSV groups A and B were almost equally distributed in our study (1.1:1). Although the trends of both groups tend to vary in geographic areas and over the years, Swamy *et al.* in a study determining the RSV subtypes in hospitalized children <5 years from North India had reported a 80% prevalence of RSV B [13]. A study from Chennai done during 2011–2014 which tested samples from patients with influenza-like illness and severe respiratory illness showed RSV A to be the predominant type (68%), although the age groups studied included both children and adults [14].

The mean age in the RSV-positive group was 11 months which was slightly higher than the reported mean age of 2–8 months.

Table 1: Risk factors associated with RSV disease

Variable	RSV status n (%)		p value	Odd's ratio (95% CI)
	Positive	Negative		
Age<2 years	26 (36)	46 (64)	0.0395	3.4 (1.1−10.8)
H/O prematurity	4 (26.6)	11 (73.3)	1.00	0.8 (0.2−2.8)
LBW	10 (31.2)	22 (68.8)	1.000	1.0 (0.4−2.7)
CHD	3 (75)	1 (25)	0.045	7.66 (0.7−76.9)
Family H/o atopy	5 (62.5)	3 (37.5)	0.036	4.5 (0.9−20)

LBW: Low birth weight, CHD: Congenital heart disease, RSV: Respiratory syncytial virus, CI: Confidence interval

Table 2: Clinical symptoms and signs associated with RSV disease

Variable	RSV status n (%)		p value	Odd's ratio (95% CI)
	Positive	Negative		
Fever	26 (87)	37 (53)	0.001	5.8 (1.8–18.4)
Cough	24 (80)	66 (94)	0.039	0.2 (0.06 –0.9)
Running nose	25 (83)	41 (58)	0.013	3.5 (1.2–10.33)
Hurried breathing	24 (80)	51 (73)	0.312	1.5 (0.53–4.2)
Vomiting	9 (30)	9 (13)	0.040	2.9 (1.0–8.3)
Loose stools	5 (17)	7 (10)	0.266	1.8 (0.5–6.2)
Wheeze	26 (36)	46 (64)	0.032	3.4 (1.1–10.8)
Crackles	22 (28)	57 (72)	0.256	0.6 (0.2–1.7)
Hypoxia	2 (67)	1 (33)	0.159	4.9 (0.4–56.5)

RSV: Respiratory syncytial virus, CI: Confidence interval

Table 3: Comparison of radiological features in RSV positive and negative groups

Diagnosis based on chest X-ray	RSV positive n (%)	RSV negative n (%)
Bronchiolitis	22 (38)	36 (62)
Pneumonia	7 (20)	30 (80)
Normal	1 (20)	4 (80)

RSV: Respiratory syncytial virus

However, in a study done in Korea, the mean age of patients was 15 months, with most of the cases being <1 year of age [15]. In our study, 16 (53%) of the RSV cases were infants and almost 87% of the cases were <2 years of age. A similar epidemiology was also reported by Boloursaz *et al*. [16]. Seasonal variation in the incidence of RSV could not be discerned, as the study was done only in the latter half of the year.

Prematurity (GA <37 weeks), LBW <2 500 g, underlying CHD and mother with atopic diseases are considered independent risk factors for RSV infection. In the present study, only underlying CHD and family history of asthma were identified as significant risk factors. This may be due to the fact that children up to 5 years were included rather than only infants, and there are very few studies on risk factors for RSV infection in children beyond infancy [17]. Children with RSV disease were more likely to present with fever, rhinorrhea, and vomiting. A Mexican study which included children up to 18 years of age also had a similar finding [18]. Predominant wheeze was recorded in a third of the cases but was more significantly seen in the RSV negative group. This observation is similar to Oladokun *et al*. who have reported wheeze only in 9% of cases with RSV disease [19]. The non-RSV group also had significant number of children with predominant crackles. Hence, auscultatory findings cannot be taken as a reliable indicator to distinguish RSV disease from other etiological agents.

There was no correlation between hypoxia and RSV disease in our study. Documented hypoxia is an important indication for admitting a child with respiratory distress in most guidelines, and pulse oximetry should be part of the clinical examination of children presenting with pneumonia [20]. X-rays are not routinely recommended in children with bronchiolitis as radiological findings can mimic pneumonia and should not be used to determine the need for antibiotics. Interestingly, a radiological diagnosis of bronchiolitis (generalized prominence of bronchovascular markings in a perihilar distribution, but no confluence consolidation or collapse) was more common in the RSV negative group. This observation may be due to the predominance of non-RSV viral etiological agents in the other group. Interestingly, only 37% of the children admitted as severe pneumonia showed radiological evidence of pneumonia.

The present study shows the limitation of the clinical and radiological findings for the diagnosis of RSV infection in CAP cases. This is similar to the observations made by Almasri *et al*. who studied RSV infection in children with CAP more than 2 years [21]. In a developing country like ours, identifying a definite etiological agent like RSV will avoid considerable economic burden due to prolonged hospital stay and intravenous antibiotics. This will also reduce the emergence of antibiotic resistance due to indiscriminate antibiotic use. Our study has its limitations. The actual prevalence in community may vary because the study was done in a limited number of children attending a tertiary care hospital. Moreover, the seasonal pattern could not be estimated as the study was done in the latter half of the year. The presence of

coexisting bacterial pneumonia was also not evaluated as it requires invasive procedures such as lung aspiration or bronchoalveolar lavage. Moreover, sputum culture in young children may not be representative of the lower respiratory tract. Since the study did not include critically ill children who were admitted directly in the pediatric intensive care unit, the indicators of severity such as ventilator support and mortality could not be studied.

CONCLUSION

The prevalence of RSV infection in children <60 months of age admitted with features of severe pneumonia in our study was nearly 30%. If RT PCR could be used in children with severe pneumonia who are hospitalized, an accurate diagnosis of RSV bronchiolitis can be made in high percentage of children. This would limit the use of antibiotics in a third of children hospitalized with CAP.

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