ORIGINAL ARTICLE

Characteristics of Hospital-Acquired Respiratory Syncytial Virus (RSV) Infection in Young Children Prior to the COVID-19 Outbreak

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Background: Respiratory syncytial virus (RSV) causes healthcare-associated respiratory infections in pediatric patients. Previous studies in developed countries have identified risk factors associated with hospital-acquired RSV (HA-RSV) infection. Those risk factors have a higher mortality rate than the risk factors of community-acquired RSV (CA-RSV) infection.

Objective: To investigate risk factors, clinical characteristics, and outcomes of RSV infection in young children within hospitals.

Materials and Methods: Data from Siriraj Hospital's surveillance system between 2014 and 2018 was used to include children under five with laboratory-confirmed HA-RSV infection. Two control groups were formed, the CA-RSV infection and non-RSV hospital-acquired infections (non-RSV HAI), which were time-matched with the study group as a 1:2 ratio.

Results: Fifty-one HA-RSV cases were identified, with the highest infection rate during the rainy season, which was July to December. HA-RSV patients had higher rates of underlying neuromuscular disease and malignancy. Fever was common in HA-RSV, while upper respiratory and gastrointestinal symptoms were less frequent than CA-RSV. Antibiotic and oseltamivir treatment did not differ significantly. HA-RSV patients had longer stays in the intensive care unit and hospital, but transfer rates and mortality did not differ significantly among the groups.

Conclusion: HA-RSV coincides with community outbreaks, being more severe and affecting vulnerable patients. Targeted surveillance during high RSV seasons is crucial for prevention in hospitals.

Keywords: RSV; Respiratory syncytial virus; Hospital-acquired infection; Healthcare-associated infection

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Healthcare-associated infections (HAIs) have been the most frequent complication during healthcare delivery[1]. HAIs result in a significant impact, including increased morbidity and mortality, prolonged hospital stays, increased rate of antibiotic resistance and overutilization of public health resources[2]. The incidence of HAIs was higher in developing countries, with the estimates of 5.7% to 19.1%[1]. Furthermore, HAI average incidence among the pediatric population is 10.9%[3].

Among HAIs in pediatric patients, compared to those of adult patients, there is a greater risk of nosocomial viral pathogen commonly causing alimentary and respiratory tract infections. As well, pediatric healthcare-associated viral infections lead to increased morbidity and mortality[4-6] compared to those with the infection acquired in the community[7].

Respiratory syncytial virus (RSV) is one of the most common viral etiologic agents of healthcare-associated respiratory tract infections among pediatric patients, particularly in those under five years of age. RSV causes both upper and lower respiratory tract infections with various degrees of severity, from mild symptoms to life-threatening conditions[8,9].

Prior studies conducted in several countries including Thailand revealed that RSV contributed to 50% to 70% of viral respiratory HAIs in pediatric patients, and 30% to 50% of viral lower respiratory

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HAIs[7,10-13]. Other pediatric studies conducted in developed countries demonstrated the risk factors including young age, premature birth, chronic lung diseases, ventilator use, congenital heart diseases, and neuromuscular disorders[14-16]. A study revealed a 15.6-fold increased likelihood of mortality among the patients with hospital-acquired RSV (HA-RSV) infection compared to those with community-acquired RSV (CA-RSV) infection[15].

The authors aimed to investigate the risk factors, clinical characteristics, and patient outcomes associated with HA-RSV infection in the hospitalized pediatric patients aged up to five years at a tertiary care center in Thailand.

Materials and Methods

The authors conducted a retrospective time-matched case control study to investigate risk factors, clinical characteristics, and patient outcomes associated with HA-RSV in the pediatric inpatients aged up to five years, hospitalized between January 2014 and December 2018 at Siriraj Hospital, Bangkok, Thailand. Cases were defined as patients with laboratory-confirmed HA-RSV infection. Two control groups were time-matched with the study cases. Group 1 was those with laboratory-confirmed CA-RSV infection and group 2 was those with non-RSV HAI.

HA-RSV infection was defined as a laboratory-confirmed RSV infection of respiratory tracts that occurred at least six days after hospitalization, which the longest incubation period of RSV[17,18]. However, all RSV infections in neonates hospitalized since birth were defined as HAI.

Data collection

The routine surveillance system of the hospital infection control unit identified and reported all the HAI. Cases of HA-RSV and non-RSV HAI (control group 2) hospitalized during the study period were identified from the surveillance system. The following ICD-10 codes were used to identify the CA-RSV infections hospitalized during the study period (control group 1): B974, J121, J205, and J210. The medical records of the HA-RSV cases and non-RSV HAI and CA-RSV controls were reviewed. The data extracted included demographic and clinical manifestations, length of hospitalization, and treatment outcomes. The RSV laboratory confirmation was by immunofluorescence assay or reverse transcription-polymerase chain reaction. The controls who were hospitalized in the same month as the case were matched to those cases with a proportion of 2 to 1. Therefore, four controls from the two control groups were identified and matched with each case. If numbers of controls exceeded the proportion, they were randomly selected.

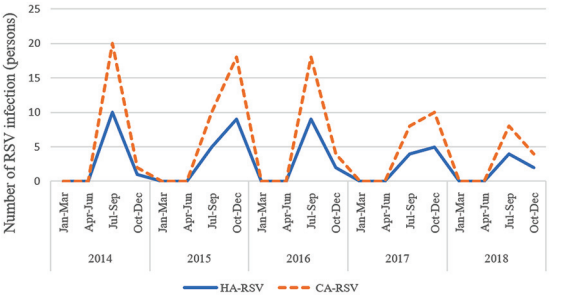

Figure 1. Number of the participants with HA-RSV and CA-RSV by months.

The present study was approved by the Institutional Ethical Committee (Certificate of Approval No. Si 827/2019).

Statistical analyses

As the number of cases was not high, the authors designed a 1 to 2 ratio for cases, with control to provide a robust analysis. Statistical analysis was performed using SPSS version 26. The continuous and categorical variables were reported in medians with interquartile ranges, and absolute numbers with percentages. For the categorical variables, comparisons between the case and control groups were made using chi-square or Fisher's exact test, while comparisons of medians were made by Wilcoxon rank sum test. A p-value of less than 0.05 was considered statistically significant.

Results

Fifty-one pediatric patients with HA-RSV infection were identified during the study period. The cases peaked between July and December each year (Figure 1). Table 1 shows the demographic characteristics of cases and control groups. All cases and controls had a similar age range with predominate in young children less than two years of age. HA-RSV was found to be less frequent in neonates younger than one month compared to non-RSV HAI. Most of both HA-RSV or 86.3% and non-RSV HAI at 80.4% occurred while hospitalized in the general pediatric wards at the median of 17 (IQR of 11 to 51) hospital days and 3 (IQR of 2 to 7) hospital days. The majority of the patients with HA-RSV or 86.3% had underlying diseases, particularly neuromuscular diseases, and

Table 1. Demographics and characteristics of the participants

	(1) HA-RSV (n=51)	(2) Control 1 CA-RSV (n=102)	(3) Control 2 non-RSV HAI (n=102)	p-value (1) vs. (2)	p-value (1) vs. (3)
Age (months); median (IQR)	8.9 (3.9 to 20.9)	8.4 (2.0 to 15.9)	14.0 (2.0 to 31.9)	0.462	0.462
Age group; n (%)					
≤1 month	7 (13.7)	21 (20.6)	25 (24.5)	0.720	0.016
>1 month to 6 months	13 (25.5)	21 (20.6)	13 (12.7)		
>6 months to 1 year	10 (19.6)	25 (24.5)	11 (10.8)		
>1 year to 2 years	12 (23.5)	19 (18.6)	16 (15.7)		
>2 years to 5 years	9 (17.6)	16 (15.7)	37 (36.3)		
Sex; n (%)					
Female	25 (49.0)	46 (45.1)	50 (49.0)	0.647	1.000
Male	26 (51.0)	56 (54.9)	52 (51.0)		
Wards hospitalized; n (%)					
General	44 (86.3)	87 (85.3)	82 (80.4)	0.871	0.368
ICU	7 (13.7)	15 (14.7)	20 (19.6)		
Duration of hospitalization before the HAI (days); median (IQR)	17 (11 to 51)	-	3 (2 to 7)	-	<0.001
Underlying disease; n (%)	44 (86.3)	48 (47.1)	66 (64.7)	<0.001	0.005
Neuromuscular disease	13 (25.5)	11 (10.8)	14 (13.7)	0.018	0.072
Congenital heart disease	8 (15.7)	15 (14.7)	27 (26.5)	0.873	0.134
Chronic lung disease	7 (13.7)	13 (12.7)	5 (4.9)	0.865	0.056
Gastrointestinal	3 (5.9)	3 (2.9)	2 (2.0)	0.377	0.198
Hematologic disease	1 (2.0)	4 (3.9)	4 (3.9)	0.520	0.520
Malignancy	7 (13.7)	-	2 (2.0)	<0.001	0.007
Connective tissue disease	-	1 (1.0)	-	-	-
Primary immune deficiency	2 (3.9)	-	1 (1.0)	0.110	0.258
Chronic kidney disease	2 (3.9)	2 (2.0)	1 (1.0)	0.601	0.258
Metabolic disease	4 (7.8)	5 (4.9)	2 (2.0)	0.482	0.096
Prematurity	10 (19.6)	15 (14.7)	14 (13.7)	0.489	0.355
Growth percentile; median (IQR)					
Weight for age	83.5 (74 to 95)	95.5 (83 to 102)	94.5 (81 to 103)	0.005	0.008
Height for age	96 (91 to 100)	100 (97 to 104)	100 (96 to 104)	<0.001	<0.001
Weight for height	93 (85 to 100)	92 (83 to 100)	90 (83 to 100)	0.532	0.445
Diagnosis at admission; n (%)					
Non-infectious disease	30 (58.8)	0 (0.0)	59 (57.8)	-	0.908
Infectious disease	21 (41.2)	102 (100)	43 (42.2)		
Retain medical devices before HA-RSV infection; n (%)	11 (21.6)	0 (0.0)	10 (9.8)	-	0.046
Endotracheal tube	0 (0.0)	0 (0.0)	4 (3.9)	-	0.302
Central line	11 (21.6)	0 (0.0)	10 (9.8)	-	0.046

RSV=respiratory syncytial virus; HA-RSV=hospital acquired-RSV; HAI=hospital acquired infection; CA-RSV=community acquired-RSV; IQR=interquartile range; ICU=intensive care unit

malignancy, in higher proportion than CA-RSV at 47.1% (p<0.001) or non-RSV HAI at 64.7% (p=0.005) controls. The cases had a significantly lower weight and height percentiles than both control groups and were more likely to retain central line more than controls.

HA-RSV and CA-RSV infection had similar signs and symptoms although HA-RSV cases had more fever at 91.4% versus 77.5% (p=0.011), less upper respiratory such as rhinorrhea at 51.0% versus 81.4% (p<0.001), and nausea/vomiting at 13.7% versus 30.4% (p=0.024). CA-RSV cases had higher frequency of receiving mechanical ventilation at 44.1% versus 15.5% (p=0.001) (Table 2, 3). Antibiotics were dispensed in most patients in both HA-RSV at 86.3% and CA-RSV at 75.5%. Interestingly, oseltamivir was prescribed in a high proportion of patients in both HA-RSV at 60.8%

Table 2. Signs and symptoms of the participants

	(1) HA-RSV (n=51) n (%)	(2) Control 1: CA-RSV (n=102) n (%)	(3) Control 2: non-RSV HAI (n=102) n (%)	p-value (1) vs. (2)	p-value (1) vs. (3)
Symptoms					
Fever	48 (94.1)	79 (77.5)	50 (49.0)	0.011	<0.001
Cough	40 (78.4)	99 (97.1)	29 (28.4)	<0.001	<0.001
Rhinorrhea	26 (51.0)	83 (81.4)	27 (26.5)	<0.001	0.003
Nausea/vomiting	7 (13.7)	31 (30.4)	22 (21.6)	0.024	0.243
Signs					
Tachypnea	29 (56.9)	45 (44.1)	14 (13.7)	0.137	<0.001
Dyspnea	29 (56.9)	75 (73.5)	22 (21.6)	0.037	<0.001
Apnea	-	2 (2.0)	1 (1.0)	0.553	1.000
Respiratory failure	6 (11.8)	6 (5.9)	-	0.202	0.001
Rhonchi	12 (23.5)	31 (30.4)	10 (9.8)	0.373	0.023
Wheezing	9 (17.6)	32 (31.4)	5 (4.9)	0.071	0.016
Crepitation	40 (78.4)	81 (79.4)	13 (12.7)	0.888	<0.001

RSV=respiratory syncytial virus; HA-RSV=hospital acquired-RSV; HAI=hospital acquired infection; CA-RSV=community acquired-RSV

Table 3. Use of respiratory device, antimicrobial agents and outcomes of the participants

	(1) HA-RSV (n=51)	(2) Control 1: CA-RSV (n=102)	(3) Control 2: non-RSV HAI (n=102)	p-value (1) vs. (2)	p-value (1) vs. (3)
Overall respiratory device; n (%)	34 (66.7)	71 (69.6)	36 (35.3)	0.712	<0.001
Low flow nasal cannula	10 (29.4)	46 (64.8)	25 (69.4)	0.001	0.007
High flow nasal cannula	9 (26.5)	14 (19.7)	2 (5.6)		
CPAP	-	-	2 (5.6)		
Conventional ventilator	15 (44.1)	11 (15.5)	5 (13.9)		
High frequency ventilator	-	-	2 (5.6)		
Ventilator duration (days); median (IQR)	13 (7-16)	12 (8-16)	1.5 (1-5)	0.951	0.007
Antimicrobial agents; n (%)	47 (92.2)	85 (83.3)	61 (59.8)	0.212	<0.001
Antibiotics	44 (86.3)	77 (75.5)	58 (56.9)	0.122	<0.001
Oseltamivir	31 (60.8)	56 (54.9)	11 (10.8)	0.489	<0.001
Ribavirin	2 (3.9)	1 (1.0)	-	0.258	0.111
Transfer to ICU after RSV infection; n (%)	10 (19.6)	17 (16.7)	-	0.653	-
ICU duration after RSV infection (days); median (IQR)	19.5 (11-33)	12 (8-16)	-	0.047	-
Length of stay after RSV infection (days); median (IQR)	20 (10 to 47)	6 (4-11)	-	-	-
Outcomes; n (%)					
Improved	50 (98.0)	101 (99.0)	97 (96.0)	1.000	0.664
Dead	1 (2.0)	1 (1.0)	4 (4.0)		

RSV=respiratory syncytial virus; HA-RSV=hospital acquired-RSV; HAI=hospital acquired infection; CA-RSV=community acquired-RSV; IQR=interquartile range; CPAP=continuous positive airway pressure; ICU=intensive care unit

and CA-RSV at 54.9% groups. For those who were transferred to intensive care unit (ICU), which included 19.6% in HA-RSV versus 16.7% in CA-RSV, the HA-RSV patients had a longer ICU stay than CA-RSV with a median of 19.5 days versus 12 days (p=0.047). HA-RSV infection also had a longer hospital stay than CA-RSV infection with a median of 20 (IQR of 10 to 47) days versus 6 (IQR of 4 to 11) days. Despite that, both groups had similar low mortality (Table 2, 3).

Non-RSV HAI primarily refers to non-respiratory infections. The pathogens commonly associated with HAI include coagulase-negative staphylococci, rotavirus, or Acinetobacter baumannii. The patients with non-RSV HAI had less respiratory system involvement, lower proportion received mechanical ventilator at 13.9% versus 44.1% (p=0.007), and none had respiratory failure or transferred to ICU, compared with CA-RSV. They also received less antibiotics at 56.9% versus 86.3% (p<0.001), and

the mortality was similarly low at 4% (Table 2, 3).

Discussion

From the present study, the authors found that the incidence and seasonality of HA-RSV was in parallel with CA-RSV infections, and both occurred mostly in infants. The patients with HA-RSV had more underlying conditions with poorer growth than controls. HA-RSV infection tended to be more severe with higher risk of mechanical ventilation and longer hospital and ICU stay. However, the mortality of HA-RSV patients was similar to the controls.

The authors findings of HA-RSV characteristics were consistent with the previous studies from Thailand[12] and Israel[19]. However, the studies in Germany[15,20] found the median age of HA-RSV to be younger than those with community-acquired infections. This underscores the infection control to prevent HA-RSV in the peak season[21], which is the rainy and cold season[22] in tropical and temperate countries, respectively. RSV is highly contagious and has a long-lasting survival on various surfaces in hospitals. RSV is transmitted via contacts. Therefore, hospitalized patients from the community were the main source of infections that transmitted via healthcare personnel's hands[23].

It was not unexpected that overall co-morbidities particularly neuromuscular diseases and malignancy were found significantly more prevalent in patients with HA-RSV infections. These underlying diseases resulted in long hospital stays and risk of HAI. The other co-morbidities including chronic lung diseases, congenital heart diseases, and prematurity remain inconclusive for risk factors of HA-RSV infection in the present study and those reported from the developed countries[15,19,20]. As the results of more underlying diseases, there were higher proportion of mechanical ventilator use, longer length of stay in both the critical care unit and the hospital among patients with HA-RSV infection than those with CA-RSV infection, consistent with those reported elsewhere[14,15,19,20].

The present study revealed comparable high rates of antimicrobial use in HA-RSV cases and the control groups. Although antibiotics and oseltamivir are not typically rational for CA-RSV, the hospitalized CA-RSV cases in the present study presented with severe symptoms with higher risk of bacterial superinfection warranting empirical treatments. However, RSV-attributed mortality was low and similar between HA-RSV and CA-RSV cases in the previous studies[15,20].

Limitations should be noted. The present study was retrospective and conducted in a single center, potentially introducing bias in case and control patient severity. The findings may not be generalized to other hospital settings due to the study's focus on a tertiary care center. Nonetheless, the present study's strength resulted from using a 6-day incubation period as the cutoff for defining HA-RSV, which differed from other studies that might have over-diagnosed HA-RSV by using the average incubation period of 48 hours as the cutoff[6,10,14,15,19]. Another strength was the inclusion of two control groups, providing a clearer understanding of HA-RSV. It is important to note that the present study was conducted before the COVID-19 outbreak, and the controls were not impacted by COVID-19. Subsequently, the implementation of COVID-19 control measures reduced HA-RSV infections as well as other HAIs. However, following the relaxation of these control measures, CA-RSV infections, as well as HA-RSV infections have resurfaced.

Conclusion

HA-RSV came along with the outbreak in the community. HA-RSV were more severe as it was likely to occur in the most vulnerable subjects as young children with long hospital stay. Targeted surveillance, patient screening particularly during high RSV season[24,25], and contact precautions are crucial for RSV prevention and control in hospital.

What is already known on this topic?

RSV is a frequent viral etiology of healthcare-associated respiratory infections in young pediatric patients. The likelihood of mortality is higher among patients with HA-RSV infection compared to those with CA-RSV infection.

What does this study add?

The young pediatric patients with HA-RSV infections had a higher prevalence of neuromuscular diseases and malignancy. Despite a greater severity of illness indicated by increased risk of mechanical ventilation and prolonged hospital and ICU stays, patients with HA-RSV infection did not have a higher mortality rate than CA-RSV.

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Conflicts of interest

The author declares that no conflict of interest exists.

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