Original Article

The Epidemiology of Admission-Requiring Pediatric Respiratory Infections in a Japanese Community Hospital Using Multiplex PCR

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SUMMARY: Respiratory tract infections (RTIs) are the most common diseases globally among children. This study aimed to assess the epidemiology of admission-requiring pediatric RTI cases and evaluate the effect of the pathogen type on the length of hospital stay (LOS) using the FilmArray® respiratory panel, a multiplex PCR test. The age-specific distribution and seasonality of viruses were investigated between March 26, 2018 and April 12, 2019. Multivariable linear regression analyses were performed to evaluate the effect of pathogen type and coinfection on LOS. Among 153 hospitalized RTI patients, respiratory syncytial virus was the leading cause of hospitalization in infants < 12 months of age (27.7%). Human metapneumovirus and parainfluenza virus were also major causes of hospitalization in patients aged 2–3 years (22.6% and 22.6%, respectively). In the multivariable linear regression model excluding rhinovirus/enterovirus, there was a significant association between viral coinfection and longer LOS (p = 0.012), while single viral infection of any type was not positively correlated with LOS. This study revealed the epidemiology of admission-requiring pediatric RTIs.

INTRODUCTION

Respiratory tract infections (RTIs) are the leading cause of global burden of disease among children (1). The epidemiology of pediatric RTIs reveals a wide variety of causal pathogens and age distributions depending on geographical and seasonal differences (2–5). Therefore, capturing the epidemiological trend of an RTI is important for each country so as to be informed about the appropriate diagnosis, treatment, and infection control measures.

The FilmArray® respiratory panel (FARP; FilmArray®; Biofire), a multiplex PCR (mPCR) test for respiratory infections, detects 17 types of viruses and 3 types of bacteria. It has a 2-min preparation time, 60-min turnaround time, specificity of 89.1–100%, and an overall sensitivity of 84.4–100% (Table 1). The FARP has enabled community hospitals to detect a wide variety of respiratory pathogens quickly. The epidemiology of RTIs using mPCR respiratory panels has been reported in many countries (6–9).

Our previous article assessed the clinical impact of FARP in a pediatric population and showed that it was a potential tool to reduce antimicrobial prescription and improve cost-effectiveness. However, an appropriate stewardship program and avoidance of overuse are very important to achieve positive impacts (10). The Japanese government has approved the clinical use and reimbursement of FARP in Japan for admission-requiring RTIs (11). While results of some previous studies showed no association between the type of respiratory virus and the length of hospital stay (LOS) of the patient, other studies revealed that respiratory syncytial virus (RSV) was related with longer LOS (12,13).

Since an increase in the use of mPCR respiratory panels is expected in Japan, an understanding of the baseline epidemiology of RTIs in the population and the effect of each virus detectable on clinical outcomes is

Table 1. Detectable pathogens in FilmArray® respiratory panel

| Pathogen                          |
|-----------------------------------|
| **Adenovirus**                    |
| **Coronavirus HKU1, NL63, 229E, and OC43** |
| **Human metapneumovirus**        |
| **Rhinovirus/Enterovirus**        |
| **Influenza virus A, A H1, A H3, A H1-2009, and B** |
| **Parainfluenza virus 1, 2, 3, and 4** |
| **Mycoplasma pneumoniae**         |
| **Chlamydia pneumoniae**          |
| **Bordetella pertussis**          |

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also important for the appropriate use of FARP across the nation. The objective of this study was to assess the epidemiology of admission-requiring pediatric RTI cases, including age-specific causal pathogens and seasonality, and evaluate the effect of pathogen type on LOS.

MATERIALS AND METHODS

Design and setting: We conducted a retrospective study of medical records between March 26, 2018 and April 12, 2019 at the Nara Prefecture General Medical Center. During the study period, FARP (FilmArray®, Biofire, Salt Lake city, UT, USA) test was performed on pediatric patients admitted for respiratory infections.

The study participants were patients with RTI who visited the pediatrics department of our hospital during the study period. If a patient with an RTI had clinically severe disease requiring hospitalization after initial assessment by a pediatrician, the FARP test was performed using a nasopharyngeal swab sample. The criteria for admission of patients with RTI were need for oxygen and/or ventilatory support, or requirement of continuous intravenous rehydration. The criteria for discharge were no requirement of oxygen, ventilatory support, or intravenous fluid. Because the FARP test was available only on weekdays from 8:30 to 17:15, patients hospitalized during that time underwent the FARP test and were included in the study. Patients who had immunodeficiency disorders and whose primary clinical diagnoses were not RTIs were excluded from the study.

The age-specific pathological distribution (children aged 0–11 months, 12–23 months, 24–47 months, and 48 months or older) and seasonal distribution of each pathogen among our hospitalized pediatric population were evaluated.

Statistical analysis: Pearson's chi-square and nonparametric tests were performed to evaluate the characteristics of the study population. Then, multivariable linear regression analysis of the 3 models was conducted. The outcome of interest of the models was LOS. In the first model (base-case model), the effect of pathogen type was evaluated using the variables of patient age, sex, and the result of FARP test (all patients). In the second model (viral RTI model), the effect of viral type and viral coinfection were assessed among cases with viral RTIs using variables such as patient age, sex, and number and type of detected viruses. Patients who had all negative FARP results were excluded from the second model because the FARP test could not differentiate coinfection of bacteria and viruses from viral infection. Children with a positive result for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* were also excluded from the second model. In the third model, the effects were investigated after exclusion of rhinovirus/enterovirus-positive cases because a significant proportion of asymptomatic young children may carry rhinoviruses (14–18). In all 3 models, the coefficient (β) with a 95% confidence interval (95% CI) of each variable and the coefficient of determination (R²) were calculated.

All statistical analyses were performed using StataCorp (2015, Stata Statistical Software: Release 14, StataCorp LP, College Station, TX, USA) and Microsoft Excel 2016 (Redmond, WA, USA). A p-value of < 0.05 was considered statistically significant. The study was approved by the Institutional Review Board of the Nara Prefecture General Medical Center, Nara, Japan. Verbal consent was obtained for all cases before performing the FARP test. The reasons for the written consent waiver were the following: the Japanese government approved the clinical use of the FARP test before the start of our study, diagnosis of respiratory pathogens was indispensable to cohort patients in our pediatric ward as our usual practice, and because more than one nasopharyngeal swab had to be obtained for rapid antigen tests in cohort patients before the study; hence, the FARP test was performed instead as it requires only one nasopharyngeal swab and would thereby reduce patient burden.

RESULTS

During the study period, 153 hospitalized patients were analyzed. The patients' backgrounds are shown in Table 2. A total of 132 children (86.3%) had a positive result for at least one pathogen among *B. pertussis*, *C. pneumoniae*, or *M. pneumoniae*, and 21 children (13.7%) had negative results.

Among 129 cases with any type of virus detection, more than 1 pathogen was detected in 27 patients (20.9%). Combinations of coinfection are presented in Table 3. The total and age-specific distributions of each causal pathogen for admission-requiring RTIs are presented in Fig. 1. Among the RTIs, rhinoviruses/enteroviruses were the most frequently isolated pathogens in all age groups, and RSV was the leading cause of hospitalization in infants < 12 months of age (27.7%). hMPV and parainfluenza viruses were also major causes of hospitalization among 24–47-month-old infants (22.6%, respectively). Coronavirus and influenza viruses were uncommon causes of hospitalization (3.3% and 3.9%, respectively) in all age groups. Negative FARP results were seen in 17.0%, 11.5%, 12.9%, and 13.0% for the age groups of 0–11 months, 12–23 months, 24–47 months, and 48 months or older, respectively. The number of pathogens detected by month is presented in Fig. 2. However, it is highly likely that cases were under-reported in the winter season (from November to February) because of a shortage of FARP reagents during this period.

In the multivariable linear regression models, the base-case model showed no significant effect of the type of pathogen on LOS (Table 4, A). The viral RTI model also showed no significant effect of viral coinfection or type of virus among viral RTI cases (Table 4, B). In the rhinovirus/enterovirus-excluded viral RTI model, there was a significant association between viral coinfection and longer LOS (coefficient 4.135 [3.368–7.445]: p = 0.012), while any type of single viral infection was not positively correlated with LOS (Table 4, C).
DISCUSSION

This study revealed the age distribution of common pathogens detected by the FARP test among hospitalized children with RTIs. RSV in infants (< 24 months old) and rhinovirus/enterovirus in all ages were the most commonly detected pathogens; coronavirus and influenza were uncommon causes of admission-requiring RTIs in children. Overall, the type of virus or viral coinfection did not affect the LOS, although viral coinfection was related to prolonged LOS in the rhinovirus/enterovirus-exclusion model.

There was a significant difference in sex distribution between the all-negative FARP and any-positive FARP result groups (33.3% and 63.4%, males respectively; \( p = 0.001 \)). The reason for the sex difference is likely due to the relatively small sample size of the FARP-negative group. There are 2 possible explanations for a negative FARP result among children with RTIs: bacterial infections, such as those caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, and other viral RTIs not captured by the FARP test. The proportion of bacterial infections among pediatric RTIs varies in different populations (19–21). The FARP test used in our study did not test for bacterial infections other than *M. pneumoniae*, *C. pneumoniae*, and *B. pertussis*, and the interpretation of bacterial detection from an upper respiratory sample is controversial (22). Although we could not assess the proportion of bacterial infections, bacterial coinfections, or secondary bacterial infections to viral RTIs, a negative FARP test result in a hospital-requiring RTI case may raise the possibility of a bacterial infection. The detection of a significantly higher procalcitonin level supports

### Table 2. Backgrounds of patients with each pathogen

|                      | Total \((N = 153)\) | All negative FARP \((N = 21)\) | Any positive FARP \((N = 132)\) | \(p\)-value |
|----------------------|---------------------|-------------------------------|-------------------------------|------------|
| Age (year)           | 2.21 ± 2.33         | 2.06 ± 2.43                   | 2.24 ± 2.33                   | 0.430      |
| Sex (male)           | 59.5%               | 33.3%                         | 63.4%                         | 0.001      |
| WBC count \((/μl)\)  | 10,643 ± 50.66      | 9,881 ± 4,047                 | 10,766 ± 5,214                | 0.683      |
| CRP \((mg/dl)\)      | 2.62 ± 3.10         | 3.77 ± 3.40                   | 2.44 ± 3.02                   | 0.115      |
| Procalcitonin \((ng/ml)\) | 0.51 ± 1.08       | 1.23 ± 2.17                   | 0.39 ± 0.73                   | 0.011      |
| Length of stay (days)| 6.85 ± 2.05         | 6.10 ± 1.67                   | 6.93 ± 2.06                   | 0.129      |
| Clinical diagnosis   |                     |                               |                               |            |
| Pneumonia            | 53 (34.6%)          | 6 (28.6%)                     | 47 (35.6%)                    | 0.529      |
| Bronchitis/bronchiolitis | 70 (45.8%)        | 7 (33.3%)                     | 63 (47.7%)                    | 0.219      |
| Upper respiratory tract infection | 22 (14.4%) | 6 (28.6%) | 16 (12.1%) | 0.046 |
| Asthma exacerbation  | 4 (2.6%)            | 0 (0.0%)                      | 4 (3.0%)                      | 0.419      |
| Others               | 4 (2.6%)            | 2 (9.5%)                      | 2 (1.5%)                      | 0.033      |

The values are shown as the average value ± standard deviation. The result for procalcitonin was available in only 63 cases among a total of 153 cases. CRP, c-reactive protein; WBC, white blood cell.

### Table 3. Combination of cases with more than 1 viruses detected

| Combination                     | Number of cases \((N = 27)\) |
|---------------------------------|------------------------------|
| Adeno, Rhi/Ent and RS           | 2                            |
| Rhi/Ent, Paraflu and RS         | 1                            |
| Rhi/Ent and Paraflu             | 7                            |
| Rhi/Ent and RS                  | 6                            |
| Adeno and Rhi/Ent               | 4                            |
| Adeno and Paraflu               | 3                            |
| Corona and RS                   | 2                            |
| Flu and Rhi/Ent                 | 1                            |
| hMPV and Rhi/Ent                | 1                            |

One case was positive for Rhi/Ent and *Chlamydia pneumoniae*.

Adeno, adenovirus; Corona, coronavirus HKU1, NL63, 229E, or OC43; hMPV, human metapneumovirus; Rhi/Ent, rhinovirus or enterovirus; Flu, influenza virus A, A H1, A H3, A H1-2009, or B; RS, respiratory syncytial virus; Paraflu, param influenza virus 1, 2, 3, or 4.
this statement, although this result was not available for all patients (23). One possible explanation for the shorter but insignificant LOS in the negative FARP result group than in the any-positive FARP group may have been that the antimicrobial treatment was effective for the negative FARP result group (for possible bacterial infection) and was not effective for the any-positive FARP group (viral infection). The details of
antimicrobial activity were discussed in our previous paper (10). This suggests that close monitoring and supportive therapy without antimicrobials may be warranted as an initial management for pediatric RTIs with positive virus detection in an mPCR test as long as the patient is clinically stable and presentation does not suggest secondary bacterial infection.

Major viruses that may cause RTIs in children but are not on the FARP test are human bocaviruses (24,25). The causality between human bocaviruses and severe RTI is still controversial, but some studies have shown that the virus is related to symptomatic RTIs in young children (24,25). We excluded rhinovirus/enterovirus detection in the third model of multivariable linear regression analysis because many asymptomatic children may carry a rhinovirus, and majority of the mPCR panels, including the FARP test, cannot differentiate rhinoviruses from enteroviruses (14–18). The possibility that some cases with rhinovirus/enterovirus detection may only carry the virus but have bacterial pneumonia was raised, although there are articles reporting that rhinovirus caused lower respiratory infections (26,27). Therefore, we excluded this in the third model, which revealed that viral coinfection was associated with longer LOS. This result also supports the hypothesis that rhinovirus may not cause severe respiratory infection in a significant proportion of children.

RSV at a young age, such as 6 months or younger, is related to severe RTIs (28). A previous report in Japan showed that 47.4% of children younger than 6 months old with admission-requiring RTIs were confirmed to have an RSV infection (29). Our study also revealed that RSV is the leading cause of hospital-requiring RTIs among children aged 12 months or younger. In our study, RSV was not related to longer LOS after adjusting for age, sex, and other types of positive viruses. However, since we did not have a large sample size, we could not investigate the risk factors for severe RSV infection in specific populations such as neonates and children with underlying respiratory or cardiac conditions. While a previous study showed that hMPV was the most frequently isolated virus in pediatric RTIs in a primary care setting, our study revealed the epidemiology of viral RTIs in a hospital setting (30). The difference between our hospital setting study and the previous outpatient study was due to a different likelihood of contracting severe infection by each virus, although these studies were performed in different geographic locations and at different time periods.

Viral coinfection among RTI cases has been reported in many previous studies (31–33). Although some studies showed that viral coinfection was related to more severe symptoms or longer LOS, a systematic review could not detect any relationship between viral coinfection and clinical outcome (29–31). Our study, with a significant proportion of viral coinfections (20.9% of coinfection among all viral RTI cases), showed a significant effect of coinfection on LOS if rhinovirus/enterovirus was excluded. However, we could not assess what combination of viral coinfection had a greater effect on longer LOS due to the relatively small sample size. Future studies are warranted to investigate the types of coinfection and severity.

Our study had some limitations. First, we could not assess other clinical data, such as duration of symptoms, amount of oxygen required, and radiographic findings. Although these data may have provided some additional information, LOS was selected as the single outcome in our study. Second, there was a shortage of FARP reagents during the winter season, which significantly disturbed the evaluation of the seasonality of viral RTIs throughout the year. Third, the number of detected viruses may not necessarily correlate with the actual coinfection. For example, the FARP test would not be able to detect if a patient had a coinfection with rhinovirus and enterovirus. In the rhinovirus/enterovirus exclusion model, we could not evaluate the impact of coinfection of rhinovirus/enterovirus and another virus. We also had a relatively small sample size after excluding rhinovirus/enterovirus-positive cases. Therefore, further studies with larger sample sizes would strengthen the evidence of the effect of viral coinfection on the severity of illness.

As an increasing number of mPCR tests for RTIs are expected to be performed in Japan, following
government approval of the test, appropriate interpretation of the results and effective use of the mPCR test are crucial. Our study illustrated some important findings, including that viral coinfection may affect patient outcome, except for coinfection with rhinovirus/enterovirus, and a negative FARP result may indicate a possible bacterial infection. Monitoring of antimicrobial use and patient outcomes after mPCR for severe RTI cases is very important.

In conclusion, this study revealed the epidemiology of admission-requiring pediatric RTIs. RSV is the leading cause of hospitalization among infants aged < 24 months, and parainfluenza virus and hMPV are commonly seen among infants aged 24–47 months. This study also showed that viral coinfection, excluding rhinovirus/enterovirus coinfection, was related to prolonged LOS among pediatric viral RTI cases.

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