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Nosocomial infection by human bocavirus and human rhinovirus among paediatric patients with respiratory risks

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SUMMARY

Background: Nosocomial infections by respiratory viruses undetected by rapid tests are not often diagnosed. For paediatric patients with background diseases, nosocomial infection could be fatal.

Aim: To determine the relationship between developing symptoms by respiratory viruses undetectable by rapid tests and respiratory risks and to improve the management of infection control.

Methods: Two episodes of nosocomial infection by human bocavirus (HBoV) and human rhinovirus (HRV) were retrospectively investigated in a tertiary hospital paediatric ward in Japan. Viruses were identified by polymerase chain reaction to determine infection control management. When viruses of the same species were detected from different patients, the virus homology was investigated. The relationship between respiratory risks and developing symptoms was statistically investigated.

Findings: Three and four patients with respiratory risks in the HBoV and HRV outbreaks, respectively, developed respiratory symptoms. The nucleotide sequences of two patients in the HBoV outbreak and all four patients in the HRV outbreak were phylogenetically close. In both outbreaks, the patients with respiratory risks developed significantly more symptoms than those without any risk ($P = 0.035$ and 0.018, respectively). After the patients with respiratory infection were separated from those with respiratory risks, no additional nosocomial infection occurred.

Conclusion: Patients with respiratory risks easily develop respiratory symptoms and acquire severe symptoms of nosocomial infection by those viruses. In a paediatric ward, we should adopt not only standard precautions but also isolation management of the patients with respiratory symptoms, even if they have negative results in rapid tests.

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Introduction

In paediatric wards, whereas many patients have multiple comorbidities, including respiratory problems, there are also many patients who have infectious diseases. Because several rapid viral tests, for influenza virus, respiratory syncytial virus, human metapneumovirus, or adenovirus can be performed commercially in Japan, and covered by the Japanese universal insurance system, such tests are often performed on patients with respiratory symptoms [1]. The patients with positive results during rapid viral tests are often assigned to a single room or are cohorted. By contrast, patients with negative results with rapid viral tests are only diagnosed clinically as having common cold and are assigned to general multiple-patient rooms because the hospitals in Japan generally have few single rooms.

The viruses causing common cold symptoms that are not diagnosed by rapid virus tests include human bocavirus (HBoV) and human rhinovirus (HRV). HBoV causes respiratory infection and was first reported in 2005 from Sweden [2]. The epidemiology of HBoV in Japan is not clear. However, in Japan, it was reported that 15.7% of respiratory infections were caused by HBoV [1]. HBoV has the following four different types: HBoV1, HBoV2, HBoV3, and HBoV4. HBoV1 causes respiratory symptoms, whereas the other HBoV types were identified in stool. One report showed that in Japan, HBoV1 causes respiratory symptoms [3]. Some reports showed that HBoV was also detected in asymptomatic patients [4,5]. The incubation period of HBoV is unknown. HRV was found in 1950 and is the most common respiratory virus [6]. HRVs were classified as HRV-A, HRV-B, and HRV-C. A report showed that 47.8% of the patients had HRV-A, 1.4% had HRV-B, and 50.8% had HRV-C among HRV detected with respiratory symptoms in Japan [7]. Some reports showed that HRV was also detected in 12–32% of asymptomatic patients aged <4 years [8–12]. The average incubation period of HRV is two days [6].

Until now, few reports have been available on nosocomial infection by HBoV and HRV because of the difficulty in confirming their diagnoses, although nosocomial viral respiratory infection accounts for 10% of healthcare-related infection [13,14]. Some of the patients without respiratory risks are asymptomatic or manifest only mild respiratory symptoms even if they are infected with HBoV or HRV.

Since polymerase chain reaction (PCR) has become widely used, an increasing number of reports of nosocomial infection by HBoV or HRV have been published [15–20]. It seems that nosocomial infection by these viruses may be widespread.

Pathogenicity of such viruses undetectable by rapid viral tests is not necessarily weak. Whereas otherwise healthy patients are asymptomatic or manifest only mild respiratory symptoms when they are infected with such viruses, patients with underlying respiratory conditions might become symptomatic and easily manifest severe respiratory symptoms.

Here, we report our experience of outbreaks of nosocomial infection by HBoV and HRV causing respiratory symptoms among patients with several respiratory risks. Furthermore, to verify the influence of respiratory risks on infection by such viruses, this study investigated the relationship between respiratory risks and developing symptoms.

Methods

Setting

This study was conducted at multiple-patient rooms in paediatric wards of Keio University Hospital, which is a tertiary hospital in Tokyo, Japan. In this hospital, there were two paediatric wards in different buildings. One paediatric ward had six single rooms and six rooms for four patients, and the other ward had nine single rooms, three rooms for four patients and a paediatric intensive care unit to accommodate seven patients. Each paediatric ward had one large multiple-patient room where children who needed excretion assistance were accommodated. The areas of these multiple-patient rooms were 98.36 and 84.15 m^2, and these rooms accommodated ten and eight patients (infants and young children), respectively. The distance between patients changed according to the occupancy of the room. These rooms were available for a wide variety of patients including those who needed non-invasive respiratory support.

In our institution, when infant patients have a fever or respiratory symptoms at or after admission, we perform rapid viral tests to rule out detectable respiratory viruses, such as respiratory syncytial virus, human metapneumovirus, and influenza virus. After checking that all the rapid test results are negative, we ward such patients into multiple-patient rooms if their family members do not want their children warded into private rooms. In these rooms, medical staff performed the sterile gown technique. Principally, patients in these rooms were managed without parents' supervision. We have previously reported the management for prevention of nosocomial infection by patients who developed influenza virus infection or varicella zoster infection [21,22].

Collecting cases

We reviewed the patients who were diagnosed as having viral respiratory infectious disease by PCR in 2017 and investigated every case and the way in which this infection has been managed retrospectively and non-interventionally. In this hospital, for infection control, the pathogens were identified by performing nasal swab real-time PCR as a standard procedure when nosocomial infection was suspected, and the pathogen was not identified by rapid viral tests. If a nosocomial infection was confirmed by rapid viral test or PCR test, the infection route could be clarified, and the previous infection control protocol could be reviewed and improved.

Identifying the pathogens

Nasal swab real-time PCR was performed to identify the viruses and bacteria. By performing real-time PCR with a Respiratory Tract Infection kit (Code: CY214, CY216, Takara Bio, Shiga, Japan) as described previously, the following 12 pathogens were identified: HBoV; HRV; *Mycoplasma pneumoniae*; *Chlamydophila pneumoniae*; *Legionella pneumophila*; respiratory syncytial virus subtype A (RSV-A) and RSV-B; parainfluenza virus types 1, 2, and 3; Enterovirus (CA9, A16, B5, B6, ECHO-6, ECHO-11, ECHO-30, EV71), human metapneumovirus, influenza virus A and B; adenovirus; and cytomegalovirus [23,24].

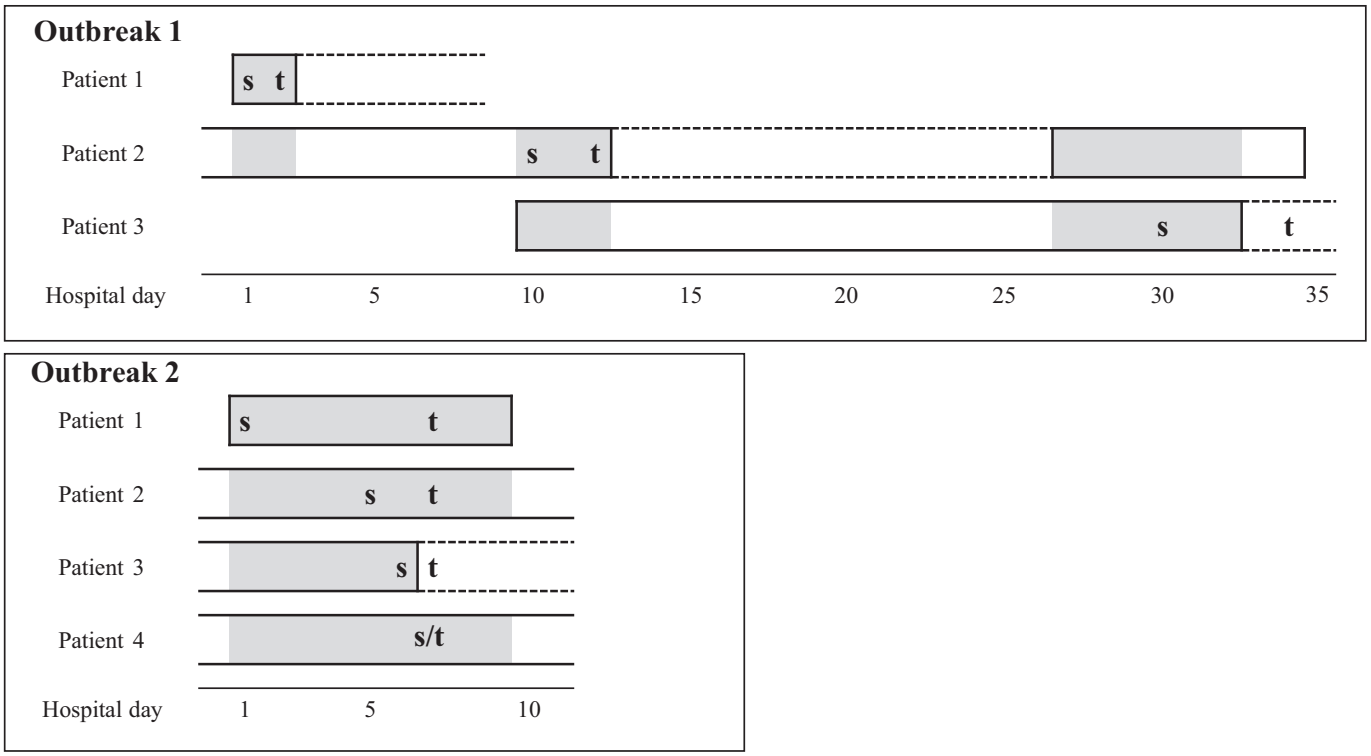

Figure 1. The duration of each patient's stay in the same multiple-patient room. The shaded duration indicates coexistence with other index patients. The duration drawn with dashed line indicates presence in another room. 's', developing symptoms; 't', polymerase test done. All cases with outbreak event 1 (human bocavirus infection) were intubated and were treated in the intensive care unit during intubation.

Investigation of viral homology

When viruses of the same species were detected in different patients, the virus homology was investigated. To construct the phylogenetic trees, we used sequences of all the strains presented in GenBank (https://www.ncbi.nlm.nih.gov/genbank/).

The homology of HBoV was investigated with 5243 base pairs (nucleotides 29–5271) of Primate bocaparvovirus 1 isolate st2, complete genome (accession no. NC_007455.1). The PCR primer pairs and PCR conditions are shown in Supplementary Appendix A. Phylogenetic analysis was performed using Molecular Evolutionary Genetics Analysis Version 7.0 (MEGA7), and a phylogenetic tree was made with the neighbour-joining method by using the 162 samples from our patients and database.

The homology of HRV was investigated using 72 base pairs (nucleotides 469–540) of HRV 1B, complete genome (accession no. D00239.1). The reverse transcription (RT)-PCR primer pairs and RT-PCR conditions are shown in Supplementary Appendix B. Phylogenetic analysis was performed using MEGA7, and phylogenetic tree was made with neighbour-joining method by using 256 samples from our patients and database.

The relationship between respiratory risks and developing symptoms

We defined respiratory risks as having anatomical or functional disorders in the airway, lungs, and/or thorax or having a respiratory disorder caused by other disorders, such as congenital heart disease with high pulmonary blood flow or neuromuscular diseases. We investigated whether respiratory risks were associated with developing symptoms by reviewing the medical records of the asymptomatic patients who were in the same multiple-patient room during the exposure to pathogens.

The observation period for HBoV outbreak was between hospital day (HD) 1 when patient 1 entered the multiple-patient room due to respiratory symptoms and HD 32 when patient 3 was moved from the multiple-patient room. We considered that while all the patients who were in the multiple-patient room between HD 1 and HD 32 were possibly exposed to pathogens because the incubation period and infectious period of HBoV were unknown, the patients who were in the room during the symptomatic period of the cases were more likely to be exposed to pathogens. Therefore, to investigate more thoroughly, we separately focused on the patients who were in the multiple-patient room from the day before the symptomatic patients developed respiratory symptoms to the day when they were intubated and moved to the paediatric intensive care unit for the HBoV outbreak.

In our hospital, the patients who entered the multiple-patient room were checked if they were carrying extended-spectrum β-lactamase (ESBL)-producing bacterium in their stool. The carriers of ESBL-producing bacterium were separated from non-carriers and were nursed by different medical staff. In this way, the distances between the

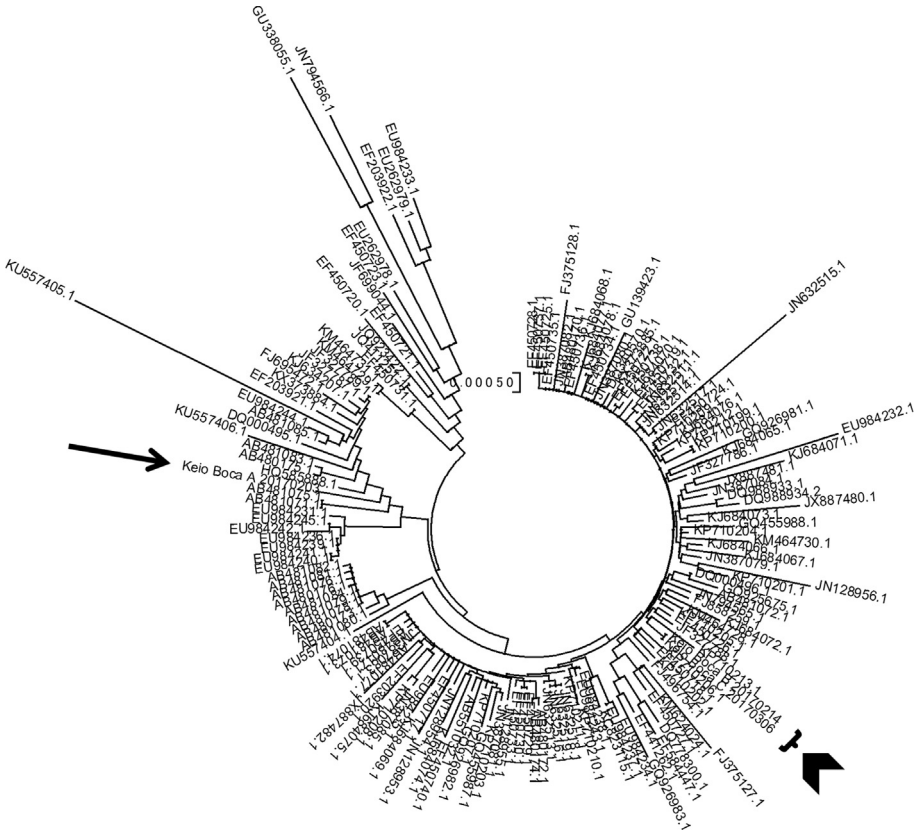

Figure 2. Phylogenetic analysis of human bocavirus isolates with reference sequences. One isolate shown by an arrow was patient 1. Two isolates shown by an arrow head were patients 2 and 3.

ESBL-positive patients and between the ESBL-negative patients were relatively close. Therefore, we also investigated the influence of respiratory risks on developing symptoms among the patients who were carrying ESBL-producing bacterium.

Statistical comparisons were performed using Fisher's exact test and $P < 0.05$ was considered statistically significant.

Ethics

The study conducted was approved by the Ethics Committee of Keio University School of Medicine (approval number: 20160432). Since this was a non-invasive study that used pre-existing clinical laboratory data obtained for management of infection control, informed consent from the patients and their family members was not obtained. To guarantee the patients that they could refuse to participate, the patients were made aware of the contents of this study, and these contents were displayed in our wards.

Results

In 2017, viral examinations were conducted in two outbreak events because of suspected nosocomial infection. One was by HBoV and the other by HRV. The first day of the outbreak of the diseases for each outbreak event (patient 1 of outbreak event 1 and 2, respectively) was defined as hospital day (HD) 1. In 2017, PCR tests for suspected nosocomial infection were performed in these two outbreaks. Figure 1 shows the clinical course of all cases and the duration of each patient's stay in the same multiple-patient room.

Outbreak event 1 (HBoV, in a room with 10 beds)

Patient 1 was a 1-year-old boy with chronic lung disease as a respiratory risk. He was admitted to the hospital following the development of respiratory failure. Wheezing was observed on HD 1. Because several kinds of treatments such as antibiotics (intravenous penicillin) were not effective, he was intubated on HD 2. He needed artificial ventilation by HD 8 and recovered thereafter.

Patient 2 was a 3-month-old girl with hypophosphatasia who had hypoplasia of the thorax as a respiratory risk. She developed fever, tachypnoea, and wheezing and needed much more oxygen than usual on HD 10. Although she received antibiotics (intravenous penicillin), she developed respiratory failure and was intubated on HD 12. She recovered and was consequently extubated on HD 17.

Patient 3 was a 2-year-old girl with double-outlet right ventricle with high pulmonary blood flow as a respiratory risk. She was admitted to the hospital for a cardiac catheter examination on HD 10. She developed wet cough and wheezing on HD 30. Despite antibiotic treatment with intravenous penicillin, her respiratory condition worsened, and she needed intubation on HD 33. She recovered and was extubated on HD 42.

Table I
Outbreak episode 1, nosocomial infection with human bocavirus in the paediatric ward[a]

Respiratory risk	Symptomatic	Asymptomatic
All patients		
High risk	3	4
Low risk	0	19
ESBL-negative patients		
High risk	3	2
Low risk	0	17
ESBL-negative patients who contacted the symptomatic patients		
High risk	3	2
Low risk	0	8

[a] Comparison of the number of symptomatic and asymptomatic patients between respiratory high-risk and low-risk groups among whole patients, non-extended-spectrum β-lactamase (ESBL) patients and non-ESBL patients who closely contacted symptomatic patients (those who stayed in the multiple-patient room from the day before the symptomatic patients developed respiratory symptoms to the day when they were intubated and moved to the paediatric intensive care unit).

These three patients were treated by different medical teams. Some of the doctors were responsible for both patient 1 and patient 2. By contrast, because all three patients were ESBL negative, the same nursing team was responsible for them.

The duration of stay in the multiple-patient room was two days (HD 1–2) for patient 1, 21 days (HD 0–12 and HD 27–34) for patient 2, and 23 days (HD 10–32) for patient 3, respectively. Because initially patients 1 and 2 (two days: HD 1–2), and then patients 2 and 3 (nine days: HD 10–12, HD 27–32) stayed together in the same multiple-patient room due to negativity for ESBL-producing bacterium on admission, nosocomial infection transmission between them was suspected. Viral examination was conducted using PCR on HD 2 in patient 1, on HD 12 in patient 2, and on HD 34 in patient 3. All were positive for HBoV 1 and negative for other pathogens. The base sequences of viruses of patients 2 and 3 were identical, whereas that of patient 1 was different (Figure 2).

The number of patients who were treated in the multiple-patient room during HD 1–42 was 26, including patients 1, 2, and 3 mentioned above. All patients' medical records were reviewed. The number of asymptomatic patients with respiratory risks was four. Median age of those four patients was 80.5 months, and their mean duration of stay with symptomatic patients was 9.3 ± 5.5 days. The number of asymptomatic patients who had no respiratory risks was 19. Median age of those 19 patients was 21 months, and their mean duration of stay with symptomatic patients was 8.1 ± 9.6 days.

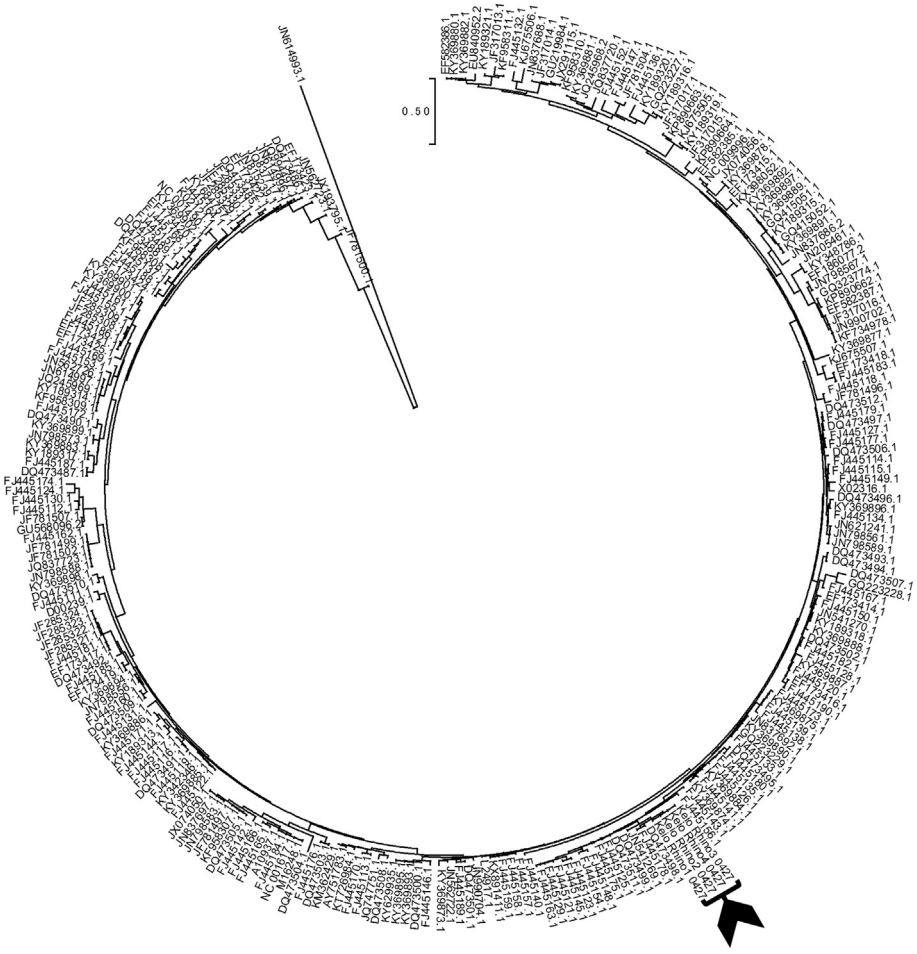

Figure 3. Phylogenetic analysis of rhinovirus isolates with reference sequences. Four isolates shown by an arrowhead were patients 1, 2, 3, and 4.

The relationship between developing symptoms and respiratory risks is shown in Table I. All considerations (among all patients, among ESBL-negative patients, and among ESBL-negative patients who were in close contact with the symptomatic patients) showed that the number of patients with developing symptoms and with respiratory risks was significantly higher than without respiratory risks ($P = 0.013$, 0.006, and 0.035, respectively).

Outbreak event 2 (HRV, in a room with eight beds)

Patient 1 was a 5-year-old girl with *SOX9* mutation, who had upper airway stenosis and bronchial asthma as respiratory risks. She was admitted to the hospital on HD 1 because she developed a fever and wet cough one week before admission. She needed oxygen administration and received antibiotics (oral macrolides). Her fever subsided on HD 6, and she was discharged from the hospital on HD 9.

Patient 2 was a 4-year-old girl with CHARGE syndrome (ocular Coloboma, congenital Heart defects, choanal Atresia, Retardation of growth/development, Genital anomalies, Ear anomalies/deafness). She had hypopharyngeal stenosis as a respiratory risk and she underwent a tracheostomy about one month before. She developed fever, cough, and wheezing on HD 4 and she received antibiotics (intravenous penicillin). Her general condition was good. Her fever subsided on HD 7.

Patient 3 was a 1-year-old boy with a chronic lung disease as a respiratory risk. He needed non-invasive positive pressure ventilator at night only. He developed fever, wet cough, and hypoxia on HD 6; hence he needed a ventilator all day and he received antibiotics (intravenous penicillin). His fever subsided on HD 8; the ventilator was unnecessary during daytime thereafter.

Patient 4 was a 1-year-old boy with VACTERL association (Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, and Limb abnormalities). As a respiratory risk, he underwent Blalock–Taussig shunt operation because of the presence of a tetralogy of Fallot, and he needed nasal airway clearance because of upper airway stenosis. He developed fever and wet cough on HD 7, so he received antibiotics (intravenous penicillin). He had neither dyspnoea nor hypoxia. His fever subsided on HD 9.

Patients 2, 3, and 4 developed fever and respiratory symptoms 3, 5, and 6 days after patient 1 developed respiratory infection respectively; nosocomial infection was then suspected. Viral examinations using PCR were performed on HD 7, and it was revealed that patients 2, 3, and 4 and patient 1 were infected with HRV-A, and only patient 1 was also PCR positive for *Streptococcus pneumoniae*. The base sequences of the viruses of all patients were identical (Figure 3).

The number of patients who were treated in the room during HD 1–9 was nine, including patients 1, 2, 3, and 4 mentioned above. Their medical records were reviewed. Asymptomatic patients had no respiratory risks. The number of asymptomatic patients without respiratory risks was five. The median age of those five patients was 20 months, and the mean duration of these patients staying with symptomatic patients was 4.4 ± 3.5 days. All nine patients were negative for ESBL-producing bacteria.

After these two outbreaks, an effort was made to prevent patients with respiratory symptoms from being admitted into the wards/rooms where patients with respiratory risks were located. Furthermore, the medical staff caring for patients with respiratory symptoms were separated from patients with respiratory risks. These efforts were exerted whenever possible, even when all the rapid viral test results were negative. Consequently, no additional nosocomial infection has occurred for one year after these two outbreaks.

Table II
Outbreak episode 2, nosocomial infection with human rhinovirus in the paediatric ward[a]

Respiratory risk	Symptomatic	Asymptomatic
High	3	0
Low	0	5

[a] Comparison of the number of symptomatic and asymptomatic patients between respiratory high-risk and low-risk groups.

The relationship between developing symptoms after exposure to symptomatic patients and respiratory risks is shown in Table II. The number of patients developing symptoms with respiratory risks was significantly higher than without respiratory risks ($P = 0.018$).

Discussion

We supposed that HBoV was transmitted from patient 2 to patient 3 in the first outbreak and that HRV was transmitted from patient 1 to patients 2, 3, and 4 in the second outbreak. This was confirmed by molecular epidemiologic investigation. From these two outbreaks, it was found that patients who had respiratory risks easily developed respiratory symptoms and consequently respiratory failure by viruses that were known to be the causes of common cold, such as HBoV and HRV infections. Additionally, gene tests were useful to determine whether the patients suffered from nosocomial infection when the same species of virus were detected from different patients. When such patients are in the hospital, special attention to prevent nosocomial infection by respiratory viruses is required. Past report showed that an extremely low birth weight baby with respiratory distress syndrome acquired nosocomial infection by HBoV, and he died eventually [20].

The Centers for Disease Control and Prevention in the USA recommend precautions against droplet infection and contact precautions concerning HRV infection [25]. In the multiple-patient rooms of our hospital, infection control precautions of partitioning and the wearing of gowns and gloves were performed. This protocol, which was stricter than standard precautions, was shown to be effective in decreasing the nosocomial infection rate than when only the standard precaution protocol was performed in a previous report and was thought to be a feasible and reasonable procedure [26]. However, even that protocol did not prevent these outbreaks.

In the paediatric ward with some high-risk patients, partitioning and gown technique in addition to standard precaution seem to be important. Moreover, stricter management should be needed when the patients with respiratory symptoms enter the ward. As the guideline of the Healthcare Infection Control Practices Advisory Committee recommends, isolation from other patients in addition to standard precaution is recommended for patients with respiratory infection if possible [25]. When they cannot be isolated in a single room for some reason, other approaches, for example, protective isolation of high-risk patients or assignment of different medical staff, should be adopted. In our hospital, we decided that patients with

respiratory infection without parents' supervision (meaning that medical staff have more contact with the patients) were not allowed to enter the section containing the patients with respiratory risks without parents' supervision. After adopting this rule, no additional nosocomial infection has occurred. Therefore, this rule might be effective especially in the hospital where patients cannot easily enter into the private rooms and where high-risk patients were accommodated.

We also emphasize the usefulness of molecular tests for epidemiology to determine whether the patients suffer from nosocomial infection when the same species of virus are detected from different patients. This is helpful as part of the explanation to the patients' family members. In our cases, the nucleotide sequences of the isolates from patients 2 and 3 in the HBoV outbreak were phylogenetically very close but that of patient 1 was different. This means that patient 1 had community-acquired HBoV infection and was not the source of infection for patients 2 and 3 in the HBoV outbreak. Viruses that are epidemic in the community (HBoV, end of winter to spring; HRV, throughout the year) may be transmitted in the hospital via asymptomatic patients [27,28]. Patient 2 was suspected to be infected by an unknown asymptomatic patient and transmitted the virus to patient 3.

One of the limitations of this study is that we performed PCR only for seriously unwell patients in the HBoV outbreak and for symptomatic patients in the HRV outbreak. Some patients who were asymptomatic or had only mild symptoms might have had the viruses, but they were not identified in this study. However, the clinical and infection control significance of detecting these viruses from asymptomatic patients or patients manifesting only mild symptoms is unknown. Indeed, there are some reports that the viral load from asymptomatic patients is lower than from symptomatic patients [29,30]. The second limitation is that the detection of HBoV or HRV did not necessarily mean that those were pathogens of the patients. Because both viruses have no specific treatment, we cannot estimate pathogens by the effectiveness of the treatment. Many cases of co-infection of both viruses with other kinds of respiratory viruses have been reported [6,27]. However, in our cases, because we did not find any other viruses and the patients had typical symptoms of those viruses, it is reasonable to regard those viruses as pathogens. The third limitation is that aerosol transmission could not be excluded absolutely because the method of transmission of HBoV has not been known. However, taking into account the presence of HBoV in the nasopharynx with high aerosol concentrations, the reasonable transmission route seems to be droplet transmission like other respiratory viruses [31].

In conclusion, patients with respiratory risks might become symptomatic or acquire severe respiratory distress by respiratory viruses undetectable by rapid virus tests. Because these viruses are easily transmitted to other patients in the hospital, patients with respiratory symptoms should be separated from the high-risk patients as soon as possible. In the paediatric ward, especially in the university hospital or children's hospital having many patients with respiratory risks, this management might be important. Also, nasal swab real-time PCR and investigation of the virus homology are useful ways to detect the pathogens of nosocomial infection.

Conflict of interest statement
None declared.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.05.002.

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