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Nosocomial Transmission of Respiratory Syncytial Virus in an Outpatient Cancer Center

Helen Y. Chu 1,4, Janet A. Englund 2,3, Sara Podczervinski 4, Jane Kuyipers 5, Angela P. Campbell 2,5, Michael Boeckh 1,2,6, Steven A. Pergam 1,2,6, Corey Casper 1,2,6

1 Division of Allergy & Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington
2 Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
3 Department of Pediatrics, Section of Infectious Diseases, Seattle Children’s Hospital, University of Washington, Seattle, Washington
4 Infection Control and Prevention Program, Seattle Cancer Care Alliance, Seattle, Washington
5 Division of Allergy & Infectious Diseases/Department of Medicine, University of Washington, Seattle, Washington
6 Public Health Sciences Divisions, Fred Hutchinson Cancer Research Center, Seattle, Washington

A B S T R A C T

Respiratory syncytial virus (RSV) outbreaks in inpatient settings are associated with poor outcomes in cancer patients. The use of molecular epidemiology to document RSV transmission in the outpatient setting has not been well described. We performed a retrospective cohort study of 2 nosocomial outbreaks of RSV at the Seattle Cancer Care Alliance. Subjects included patients seen at the Seattle Cancer Care Alliance with RSV detected in 2 outbreaks in 2007-2008 and 2012 and all employees with respiratory viruses detected in the 2007-2008 outbreak. A subset of samples was sequenced using semi-nested PCR targeting the RSV attachment glycoprotein coding region. Fifty-one cases of RSV were identified in 2007-2008. Clustering of identical viral strains was detected in 10 of 15 patients (67%) with RSV sequenced from 2007 to 2008. As part of a multimodal infection control strategy implemented as a response to the outbreak, symptomatic employees had nasal washes collected. Of 254 employee samples, 91 (34%) tested positive for a respiratory virus, including 14 with RSV. In another RSV outbreak in 2012, 24 cases of RSV were identified; 9 of 10 patients (90%) had the same viral strain, and 1 (10%) had another viral strain. We document spread of clonal strains within an outpatient cancer care setting. Infection control interventions should be implemented in outpatient, as well as inpatient, settings to reduce person-to-person transmission and limit progression of RSV outbreaks.

INTRODUCTION

Respiratory syncytial virus (RSV) causes substantial morbidity and mortality among hematopoietic stem cell transplantation (HSCT) and oncology patients who are at high risk for progression to lower respiratory tract infection (LRTI)-associated respiratory failure and death [1]. Mortality rates for RSV-associated LRTI range from 15% to 70% [2-3]. Treatment regimens for RSV-associated LRTI include aerosolized ribavirin, often in combination with palivizumab or intravenous immunoglobulin; supplemental oxygen; and respiratory support [4-6]. However, antiviral therapies are expensive, difficult to administer, and have not reliably prevented progression to LRTI [7,8]. With no available vaccine or prophylaxis measures available for adults, infection control practices remain the only effective method to limit RSV outbreaks among adult cancer patients.

RSV may be acquired in a health care setting and has been implicated in outbreaks in inpatient hematology-oncology and transplant wards [9]. Hospital-based outbreaks of RSV infection in HSCT recipients occur through introduction of circulating community strains as well as nosocomial transmission of identical viral strains [10]. The molecular epidemiology of RSV is characterized by sequencing a hypervariable region of the attachment (G) glycoprotein gene [11,12]. Evidence of acquisition of the same viral strain in inpatient cancer care settings has demonstrated the importance of specific infection control policies to prevent nosocomial RSV transmission, although data describing this in the outpatient setting are not available [13]. Studies have shown outpatient transmission of parainfluenza, a respiratory virus also associated with high mortality in immunocompromised cancer patients [14].

Efforts to enhance infection control to prevent RSV spread include strict hand hygiene, use of droplet precautions, cohorting of nursing staff, and symptom screening of employees and visitors [15,16]. Previous studies in inpatient settings have shown that the number of RSV-positive cases decreased after implementation of these infection control interventions [17]. However, most cancer care is now delivered in the outpatient setting. The routine use of antibiotic prophylaxis and hematopoietic growth factors has reduced many risks associated with prolonged neutropenia and prolonged hospital stays [18]. It has been assumed that outpatients generally acquire their respiratory infections in the community through routine daily activities, such as work and exposure to children, and not through contact within the health care setting. Few data are currently available on transmission of RSV infection in outpatient settings.
the outpatient cancer care setting. In this study molecular virologic methods were used to demonstrate nosocomial transmission of RSV during 2 RSV outbreaks at a large outpatient cancer care center.

METHODS

The Seattle Cancer Care Alliance (SCCA) is an inpatient and outpatient cancer care center based in Seattle, Washington. In 2012, 5599 patients were treated for cancer at the SCCA over the course of 72,300 visits. Patients at the SCCA are seen by teams of providers in different physical locations at a single site, divided by type of cancer or therapy, designated as Teams A through F. Allogeneic stem cell transplant recipients were seen by Teams A and B, autologous stem cell transplants were seen by Team C, pediatric patients were seen by Team D, patients in long-term follow-up were seen by Team E, and hematology-oncology patients were seen by Team F providers. The SCCA infection control team tracks incident RSV cases using an electronic system that identifies patients by provider team and location.

Electronic medical records were used to abstract sociodemographic and clinical data for patients with RSV detected during the 2 outbreak periods. Lymphopenia was defined as <500 cells/μL and severe lymphopenia as <300 cells/μL. Respiratory specimens were obtained in patients for testing by nasal washes or from bronchoalveolar lavage fluid when clinically indicated by the primary treatment team [19]. Direct fluorescent antibody detection was performed using RSV-specific mouse monoclonal antibodies (Chemicon, Temecula, CA) on all nasal wash samples before January 21, 2008, and reverse transcriptase PCR was performed afterward at the University of Washington Virology Laboratories using previously published methods [19,20]. All bronchoalveolar lavage samples undergo routine direct testing for RSV using direct fluorescent antibody, shell vial culture, and/or reverse transcriptase PCR testing.

During the 2007-2008 outbreak, all employees at the SCCA were administered a daily 12-symptom respiratory screening paper questionnaire for presence of runny nose, sinus congestion/stuffy nose, postnasal drip, shortness of breath, cough, wheezing or chest tightness, sputum production, sore throat, sneezing, watery eyes, ear pain, or fever (temperature > 100.4°F) and had a nasal wash collected for respiratory viral testing per institutional policy at the time. Testing for RSV and 11 other respiratory viruses, including influenza A and B, human metapneumovirus, parainfluenza 1-4, rhinovirus, human coronavirus groups 1 and 2, and bocavirus were performed on employee samples using previously published methods [19,21]. Employees who had a positive nasal wash for any respiratory virus were not permitted to return to work until complete resolution of all symptoms and clearance by Occupational Health. To compare the outbreak with community data, rates of RSV detected in community samples from the Seattle and Pacific Northwest region were obtained from the University of Washington Diagnostic Virology Laboratory database (http://depts.washington.edu/rspvirus/respiratory.htm).

Sequencing was attempted from residual RSV-positive samples from the 2 respiratory seasons using a semi-nested PCR protocol targeting the second hypervariable region of the attachment glycoprotein coding region [22]. Random residual de-identified RSV-positive community samples collected from subjects seeking medical care during the same respiratory seasons were also sequenced to serve as control subjects. Sequences were submitted to GenBank with accession numbers KC565494 to KC565526. Sociodemographic, clinical, and virologic data were analyzed using Stata 12.0 (STATA Corp, College Station, TX). Nucleotide sequences for 233 and 212 base pair regions of the second hypervariable region of the RSV attachment glycoprotein coding region were aligned using ClustalX2 [23]. Phylogenetic trees were constructed separately for the 2007-2008 and 2012 outbreaks using MEGA5 with evolutionary distances calculated using the maximum likelihood method with 1000 bootstrap replicates [24]. This was performed using the Tamura-Nei model. The tree with the highest log likelihood is shown. When the number of common sites was 100 or less than one-fourth of the total number of sites, the maximum parsimony method was used; otherwise, the BioNJ method with MCL distance matrix was used. The trees were drawn to scale, with branch lengths measured in the number of substitutions per site.

![Figure 1](http://depts.washington.edu/rspvirus/respiratory.htm).

**Figure 1.** Histogram of all RSV cases at the SCCA per day in the 2007-2008 outbreak (A) and only cases where the viral strain was sequenced (B). Histogram of all RSV cases at the SCCA per day in the 2012 outbreak (C) and only cases where the viral strain was sequenced (D). The asterisk represents an identical viral strain for that season. The pattern of the box represents the team of providers seen by the patient.
The analysis involved 32 nucleotide sequences. All positions containing gaps and missing data were eliminated. A total of 233 positions was included in the data set for the 2007 tree and 212 positions in the data set for the 2012 tree. Reference and community sequences were included in the comparison. Community samples included were sequences obtained from community childcare attendees from November 2006 to March 2009 and from random residual de-identified samples collected from adult and pediatric inpatients at the University of Washington and Seattle Children’s Hospital form November to March of each RSV season in the Pacific Northwest from 2006 to 2009 and 2011 to 2012. Ethical approval for the study was obtained from the Fred Hutchinson Cancer Research Center Institutional Review Board.

RESULTS

RSV Outbreak 2007–2008

In November 2007, a cluster of 3 RSV cases at the SCCA prompted the implementation of an active respiratory virus surveillance system (Figure 1A). This plan designated 3 levels of infection control measures (Figure 2), with the immediate enforcement of Level 3 precautions starting January 1, 2008 (Figure 1A). As part of this plan, all patients, staff, and visitors to the clinic were screened for the presence of respiratory symptoms in the prior week using the 12-symptom respiratory screening questionnaire. Symptomatic persons were placed in respiratory isolation and a nasal wash for respiratory virus testing was collected. Of 51 cases of RSV identified in patients, 42 (82%) patients were HSCT recipients and 9 (18%) had hematologic or solid organ malignancies (Table 1). In the week before RSV detection, 33 patients (65%) were seen only in the outpatient clinic, whereas 7 (14%) were hospitalized and 11 (22%) had no associated health care visits. One of 11 subjects with no associated health care visits attended childcare; the others did not indicate recent sick contacts.

Our institutional policy for RSV treatment during this time included the administration of inhaled ribavirin to prevent progression of RSV upper respiratory tract infection to LRTI in patients with severe lymphopenia and the use of palivizumab or intravenous immunoglobulin for documented RSV-associated LRTI. Lymphocyte counts were measured within 1 week of RSV detection in 47 patients; 14 (30%) were lymphopenic and 8 (17%) had severe lymphopenia. Only 4 (8%) were diagnosed with LRTI. Fifteen patients (29%) received ribavirin alone or in combination with intravenous

Figure 2. Our Respiratory Virus Management Plan was implemented January 1, 2008 and included designation of 3 tiers of heightened respiratory viral surveillance and infection control strategies.
Table 1
Sociodemographic and Clinical Characteristics of Patients with RSV Detected in the 2007-2008 and 2012 Outbreaks

| Characteristics                      | 2007-2008 Outbreak [n (%)] | 2012 Outbreak [n (%)] |
|--------------------------------------|----------------------------|-----------------------|
| Patients                             | 51 (68%)                   | 24 (32%)              |
| Median age, yr (range)               | 53 (2-75)                  | 58 (8-69)             |
| Women                                | 25 (49)                    | 14 (28)               |
| Underlying condition                 |                            |                       |
| Malignancy                           | 9 (18)                     | 5 (21)                |
| HSCT recipient                       | 42 (82)                    | 19 (79)               |
| Lymphopenia (≤500 cells/L)*          | 14 (30)                    | 10 (59)               |
| Severe lymphopenia (≤300 cells/L)*   | 8 (17)                     | 6 (35)                |
| Health care location                 |                            |                       |
| Hospital                             | 7 (14)                     | 3 (13)                |
| Clinic                               | 33 (65)                    | 15 (63)               |
| No associated health care visits      | 11 (22)                    | 6 (25)                |
| Specimen type                        |                            |                       |
| Nasal wash                           | 48 (94)                    | 24 (100)              |
| Bronchoalveolar lavage               | 3 (6)                      | 0 (0)                 |
| Ribavirin treatment                  | 15 (29)                    | 3 (13)                |
| LRTI diagnosis                       | 4 (8)                      | 1 (4)                 |
| Follow-up testing performed          | 23 (45)                    | 19 (79)               |
| Repeat testing positive              | 7 (30)                     | 7 (37)                |
| Clinical outcome                     |                            |                       |
| Survival                             | 47 (92)                    | 24 (100)              |
| Death due to other causes            | 3 (6)                      | 0 (0)                 |
| Death attributed to RSV              | 1 (2)                      | 0 (0)                 |

* HSCT indicates hematopoietic stem cell transplant recipient; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.
* Lymphocyte count available within 1 week of RSV detection for 47 patients in the 2007-2008 outbreak and 17 patients in the 2012 outbreak.

immunoglobulin, including 11 with LRTI. Twenty-three patients (45%) had repeat testing performed a median of 13 days later (range, 4 to 32 days) with 7 (30%) having detectable virus. One patient (2%) died due to RSV pneumonia, 3 (6%) died of other causes, and 47 (92%) survived.

Fifty-one cases of RSV were observed over 131 days in the 2007-2008 outbreak (0.39 RSV cases per day; Figure 1A). Residual samples from 19 of 51 patients (37%) in the 2007-2008 outbreak were available for sequencing; 15 outbreak samples (29%) were successfully sequenced, as well as an additional 13 community samples. These included 14 subtype A strains and 1 subtype B strain. During the 2007-2008 outbreak, illness episodes with sequenced samples did not differ by patient age (P = .28) or location of care (P = .43) from those unable to be sequenced, although sequenced samples were collected later in the epidemic (P = .01).

Of the 15 illness episodes sequenced, 10 (67%) were identical, spanning a 43-day period from November 28, 2007 to January 9, 2008 (Figure 1B). Nine of these patients were hospitalized or seen in the clinic in the 7 days before RSV detection, whereas 1 patient had no associated prior health care visits. The first patient with this strain was a pediatric outpatient seen by Team D providers, and the next was seen by Team B providers 5 days later. Of the 10 cases with identical viral strains, only the index case was seen by Team D providers, whereas 2 patients were seen by Team A and 5 by Team B providers. Two of these patients subsequently died with RSV pneumonia as a contributing, although not the primary, cause of their death.

Three other distinct viral strains co-circulated during the outbreak period. One cluster of 2 patients was seen by Team B providers in a 4-day period. In another cluster of 2 patients, 1 was seen in December 2007 by Team B providers and another was seen in February 2008 by Team E providers. No clear epidemiologic link was noted for these 2 patients. One patient seen by Team A providers in December 2007 had a distinct viral strain, similar to circulating community strains from 2009.

Employee Testing Results

Of the daily symptom screenings conducted in 1015 employees who worked during the 2007-2008 outbreak, 254
had respiratory symptoms prompting the collection of a nasal wash. Ninety-one nasal wash samples (34%) had at least 1 respiratory virus detected, including 14 samples (15%) with RSV. Multiple other respiratory viruses detected in employees included human metapneumovirus \((n = 12; 13\%)\), influenza A \((n = 14; 15\%)\), influenza B \((n = 13; 14\%)\), coronavirus \((n = 18; 20\%)\), parainfluenza type 1 \((n = 2; 2\%)\), and parainfluenza type 3 \((n = 2; 2\%)\). Twelve employees had RSV detected from December 20, 2007 to March 13, 2008, with 2 employees positive on repeat testing. Ten (83%) had direct patient contact; 4 of these worked in the transplant or oncology departments. The first employee with RSV detected had no direct contact with patients with documented RSV, although she had been symptomatic since early December with an upper respiratory illness. Of the 12 employees with RSV, only 1 had contact with a patient with documented RSV. However, transmission between the employee and patient seemed unlikely because the timing of symptom onset and diagnosis dates did not indicate an epidemiologic link between the 2 cases.

**DISCUSSION**

Molecular sequencing of RSV strains detected during 2 distinct outbreaks from patients attending a large outpatient cancer care center demonstrated circulation of identical viral strains, suggesting the outpatient clinic can serve as a source of nosocomially acquired respiratory infections. In our center, outpatients are seen by multiple providers in common locations, engage in on-site meetings with other patients, providers, and families, and continue to work and interact with others outside of the medical setting. Traditional infection control interventions shown to be effective in hospital settings, such as the use of strict respiratory isolation and limitation of visitors and staff, may not be as effective as in the inpatient setting due to multiple potential sources to introduce infection [17]. Contact tracing is also more difficult in outpatient environments, making it harder to identify patterns of transmission.

Traditionally, cancer care has been delivered to inpatients until neutrophil recovery and clinical improvement. However, early discharge followed by continued outpatient
Delivering care as an outpatient has multiple advantages, including cost savings, improved quality of life, and potentially reduction of nosocomial infections [25,26]. However, many of these patients are seen routinely in outpatient clinics such as ours, where they continue to interact with health care providers and other patients on a regular basis. Few prior studies have examined nosocomial transmission of respiratory viral infections in the outpatient setting. A study by Nichols et al. [27] conducted at our institution documented outpatient transmission of parainfluenza virus, and a small study by Machado et al. [10] documented clusters of identical RSV strains in an HSCT inpatient and outpatient treatment center in Sao Paolo, Brazil. The Brazilian study used direct fluorescent antibody for RSV diagnosis, a much less sensitive technique that likely limited the sensitivity of detection of RSV among the patients.

In response to the RSV outbreak in 2007-2008, we implemented intervention strategies based on Centers for Disease Control and Prevention guidelines for inpatient infection control settings, with interventions including staff cohorting, employee screening, and hand hygiene [28-30]. In an inpatient study by Lavergne et al. [17], measures that included restriction of visitors with respiratory symptoms, droplet isolation precautions, and use of gowns, gloves, and masks by all patients, staff, and visitors were associated with a 0.9 relative risk of RSV as compared with a more traditional infection control policy. The interventions we implemented in an outpatient setting including heightened symptom surveillance of employees, visitors, and patients at every entry point to the clinic and the strict restriction from access to the clinic based on a positive symptom screen, use of gowns and gloves, and droplet isolation precautions of all clinic patients with respiratory symptoms. We observed that the number of new cases decreased after the intervention in 2008 despite continued high levels of community RSV.
activity as well as steady numbers of patient visits at the SCCA, suggesting that implementation of our strategy was effective in reducing the magnitude of the outbreak. In 2012, the magnitude of the outbreak was limited due to strict reinforcement of Level 2 precautions rather than escalation to Level 3 precautions. It is possible that Level 3 precautions would not have been necessary in 2008 if heightened enforcement of Level 2 precautions had been strictly enforced at that time as well.

In the 2007-2008 outbreak, a respiratory virus was identified in one third of employees with respiratory symptoms, including 12 with RSV. Detection of respiratory viruses would not have been necessary in 2008 if heightened reinforcement of Level 2 precautions rather than escalation of precautions. The magnitude of the outbreak was limited due to strict effective in reducing the magnitude of the outbreak. In 2012, SCCA, suggesting that implementation of our strategy was effective in reducing the magnitude of the outbreak. Further, although we observed decreases in numbers of new cases after implementation of our infection control plan, bias. Further, although we observed decreases in numbers of new cases after implementation of our infection control plan, bias. A study limitation is that we were unable to sequence most samples from the 2 outbreaks. Many samples were inadvertently discarded at the end of the RSV season and were not available for sequencing, including all employee samples. Possibilities for the inability to sequence the remainder of the samples include low viral loads and sample degradation. In the 2007-2008 outbreak in particular, only samples early in the outbreak were sequenced. It is therefore not possible to know whether the cases later in the season were due to continued transmission of the outbreak strain or to sporadic community cases. Additionally, no samples were collected from visitors or family members. These data may have provided additional information regarding the degree of clonal transmission by health care providers and family members in the outbreaks. We also acknowledge no clear epidemiologic data linking outbreak cases. However, in our center, there are multiple sites of potential interaction between patients and care providers, including radiology, phlebotomy, and waiting areas for clinics. Although not documented, we believe these interactions may provide potential exposures of patients to sick employees, and vice versa. It is also possible that the clustering of the RSV strains during the 2 outbreaks was a reflection of the dominant strain circulating during the season in the region. The molecular epidemiology of RSV usually involves 1 dominant strain that circulates over the course of a season [34,35]. However, we found clustering of samples from both outbreaks distinct from co-circulating community strains collected during the same period, making this less likely. Increased sampling and detection during periods of the RSV outbreak may have been partially due to heightened awareness among providers, leading to potential sampling bias. Further, although we observed decreases in numbers of new cases after implementation of our infection control plan, we were unable to document efficacy of the intervention due to the retrospective observational nature of the study.

Molecular sequencing was useful in identifying potential modes of nosocomial spread of RSV in an outpatient cancer care center during 2 separate RSV outbreaks. Infection control interventions used traditionally in inpatient settings should be considered for implementation in outpatient cancer settings to reduce person-to-person transmission and limit progression of RSV outbreaks.

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