Detection and Control of a Nosocomial Respiratory Syncytial Virus Outbreak in a Stem Cell Transplantation Unit: The Role of Palivizumab

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Respiratory syncytial virus (RSV) is a common community-acquired virus that causes upper and lower respiratory tract infections in children, hematologic malignancy patients, and hematopoietic stem cell transplant (HSCT) recipients. Nosocomial transmission of RSV in immunocompromised patients can significantly affect morbidity, mortality, and duration of hospitalization. Stringent infection control measurements are needed to control further hospital transmission. Prophylactic palivizumab was found to result in a significant reduction in hospitalization rates in high-risk children. In this article, we report a nosocomial outbreak of RSV in an adult HSCT unit (4 pods) from January 16 to February 4, 2004, including the infection control interventions used and the prophylactic administration of palivizumab in high-risk patients. Active surveillance identified 5 cases, a substantial increase from previous seasons (2 or 3 cases per season). All infected patients were isolated to 1 nursing pod and placed on contact isolation. All patients on the HSCT unit underwent rapid RSV antigen screening using nasal washes; this was repeated 1 week later, and 1 additional RSV case was identified. Patients identified to be at increased risk for RSV infection received prophylactic palivizumab. Routine screenings of the staff and visitors were undertaken. All patient and visitor areas were thoroughly cleaned with bleach. We educated health care workers about RSV transmission, highlighting proper hand hygiene and contact precautions. Four of 6 patients with RSV infection developed RSV pneumonia, and 2 of these patients died. Staff and visitors with upper respiratory symptoms were screened, and all were negative for RSV. Prophylactic palivizumab was administered in 16 patients who tested negative for RSV, but were considered to be at increased risk for RSV infection. None of these patients developed RSV infections. An RSV outbreak was controlled using prompt preventive measures, including cohorting patients, with a dedicated health care staff; contact isolation of patients; strict adherence to hand hygiene; and screening of visitors, family members, and health care staff for upper respiratory infection symptoms. Immunoprophylaxis with palivizumab, administered to high-risk patients, complemented strict infection control intervention. Thus, the role of palivizumab in the control of RSV hospital outbreaks merits further investigation.

INTRODUCTION

Respiratory syncytial virus (RSV) is a well-known cause of lower respiratory tract infections in young children [1], and is now increasingly recognized as an important cause of respiratory infections in adults, especially in the elderly and immunocompromised patients [2]. By the age of 2 years, almost all children have been infected with RSV [3], but naturally acquired immunity is incomplete, and reinfection is common [4].

The clinical features of reinfections are generally mild in immunocompetent patients, and the duration of viral shedding is relatively short. However, RSV infections have been associated with high morbidity and mortality rates (70%-100%) and prolonged viral shedding in both autologous and allogeneic adult stem cell transplant (HSCT) recipients [5,6]. The
disease incidence varies seasonally, with a peak from November to April in the northern hemisphere. Outbreaks of RSV infections have been reported among nursing home patients and institutionalized young adults [7-9], but few reports have documented nosocomial RSV outbreaks among HSCT patients [10-12].

Active infection control surveillance strategies of RSV and other community-acquired respiratory viruses play crucial roles in identifying nosocomial transmission and controlling outbreaks. Studies have suggested that hand washing after patient contact, the use of gowns and gloves, and cohorting of staff and patients are effective preventive strategies [13,14].

Palivizumab (Synagis. MedImmune, Inc., Gaithersburg, MD, USA) is a humanized monoclonal antibody directed against the F glycoprotein of RSV; it was approved for the prophylaxis of RSV disease in high-risk infants [15-17]. However, its effectiveness in high-risk adults has never been evaluated.

In this article, we describe an outbreak of nosocomial RSV among HSCT unit patients at our institution, which was managed using strict infection control interventions and palivizumab immunoprophylaxis in high-risk adult HSCT patients.

METHODS

Epidemiologic Investigation

The HSCT unit at The University of Texas M.D. Anderson Cancer Center (Houston, Texas) is a 52-bed unit divided into 4 pods (NE, NW, SW, and SE). From October through March each year, we monitor community- or hospital-acquired respiratory viral infections in hematologic malignancy patients. Patients with symptoms of upper respiratory infection undergo RSV and influenza screening, performed using rapid antigen tests and cultures of nasal washes.

At our institution, the incidence of hospital-acquired RSV infection peaks in January and February, with a steady rate of 0.2 and 0.3/1000 patients’ days in 2002 and 2003, respectively (Figure 1). However, in January and February 2004, active surveillance of symptomatic patients identified 5 HSCT patients with nosocomial RSV infections. This number represented a substantial increase in incidence of hospital-acquired RSV (0.74/1000 patients’ days) when compared to that of previous seasons. We initiated strict infection control measures and investigated the outbreak on February 4th.

Identification of Additional Cases

Nasal washes from all HSCT patients on all 4 pods were collected and sent for rapid RSV antigen screening tests on February 4th; the same day strict infection control measures were implemented. All health care workers who reported upper respiratory symptoms were restricted from patient contact and underwent rapid RSV antigen testing. A sign was placed at the entrance of each pod that stated that all visitors and family members were required to check in at the nurses’ station prior to entering patient rooms.

A questionnaire, “Visitor Questionnaire for Upper Respiratory Symptoms,” was distributed to all visitors at the nurses’ station. The questionnaire included 2 questions: “Do you currently have symptoms of a cold, that is, are you sneezing, coughing, have a runny nose, sore throat or fever?” and “Have you had close contact with someone that has a cold within the past 7 days?” All individuals who responded yes to either question were not granted visitation. All visitors who responded no were required to wear a sticker that read, “I have been screened today (date) and I am safe.” The nursing staff kept a record of all visitors who had been screened for upper respiratory signs. This system ensured that everyone entering patient rooms had undergone screening.

One week later after the screening process had been established, all patients underwent follow-up rapid RSV antigen screening of nasal washes.

Definitions

Upper respiratory RSV infection was defined as rhinorrhea, nasal or sinus congestion, otitis media, pharyngitis, or cough with a clear chest radiograph, with or without fever. RSV pneumonia was defined as an acute respiratory illness in association with signs or symptoms of lower respiratory tract disease and new radiographic infiltrates. Infection was considered nosocomial if respiratory symptoms developed >5 days after hospital admission.

Laboratory Methods

Nasal washes were collected for rapid antigen detection using the Light Diagnostics Simufluor RSV/FluA immunofluorescence assay kit (Millipore Corporation, Bedford, MA, USA; catalog no. 3129). All specimens were placed in a viral transport medium on ice or refrigerated immediately and transported to the
laboratory on ice. Specimens were treated and centrifuged into pellets; any specimens that did not contain sufficient respiratory epithelial cells were recollected. Upon treatment with the Simufluor RSV/Flu A reagent, the RSV antigen-antibody complex exhibits an apple-green fluorescence, whereas uninfected cells will stain a dull red [18]. Results were obtained within 2 hours and immediately reported to the clinician. The sensitivity and specificity of this test is between 85% and 100% [18].

RESULTS

Epidemiologic Investigations

On January 16, 22, and 27, 2004, 3 patients admitted to the SW pod were diagnosed with nosocomial RSV infections. Patients 1 and 3 had evidence of pneumonia, whereas patient 2 had an upper respiratory infection with a negative chest X-ray. On January 28, patient 4, admitted to the SE pod, was diagnosed with pneumonia secondary to RSV. Five days later, on February 2nd, patient 5, admitted to the SW pod was diagnosed with RSV pneumonia (Figure 2). This increase in incidence of nosocomial RSV infection was higher than that in previous years, although not statistically significant. We initiated an outbreak investigation as part of our infection control plan when 2 or more nosocomial RSV or other respiratory virus infections are occurring in patients in the same vicinity and around the same period of time (Figure 1). All HSCT patients and health care workers on all 4 pods were screened using a rapid RSV antigen test of nasal washes. Six health care workers were found to have upper respiratory symptoms, but none were positive for RSV antigen. On February 4th, a sixth patient was diagnosed with a RSV upper respiratory tract infection (Figure 2). Table 1 shows the demographic and clinical characteristics of all 6 patients. All patients were treated with aerosolized ribavirin and palivizumab for at least 7 days. Of the 4 patients with RSV pneumonia, 2 died.

Interventions

All RSV-infected patients, along with designated nurses, a respiratory care therapist, and a phlebotomist were moved to the RSV pod (SW). All patients on this pod with or without RSV infection were placed on contact isolation, with masks. No additional patients were admitted to the pod.

All visitors with upper respiratory symptoms or a fever or who had been exposed to individuals with colds within the past 7 days were prohibited from entering patient rooms. The infection control practitioners conducted an intensive educational program for employees on all 4 pods that emphasized proper hand hygiene, and strict adherence to contact isolation with mask. Housekeeping performed environmental decontamination with bleach, and established more frequent, rigorous cleaning schedules for patient rooms, nursing areas, restrooms, break rooms, and waiting areas.

We then identified HSCT patients who may be at high risk for complications if RSV infection is acquired using the following criteria: allogeneic transplantation, preengraftment, graft-versus-host disease (GVHD), high-dose steroids, or neutropenia with absolute neutrophil count <500 cells/mL. Sixteen patients met these criteria. All 16 were negative for RSV antigen and were given a single dose of 15 mg/kg of intravenous palivizumab. One week later, we performed follow-up screening of all HSCT patients; no new cases of RSV infection were identified. None of the 16 high-risk HSCT patients who had received palivizumab developed RSV infections (Tables 2 and 3 summarize all published RSV outbreaks in the pediatric and adult populations).

Twenty days later, control measures were discussed and reviewed. Contact isolation was discontinued for all non-RSV-infected patients. Screening of symptomatic health care staff and visitors was continued. The use of masks and gloves during patient contact was reinforced.

DISCUSSION

RSV is a frequent cause of both acute upper and lower respiratory tract infections, and the severity of clinical manifestation depends on patient age and health status. In immunocompromised patients, such as hematopoietic HSCT recipients, RSV upper respiratory disease may progress to fatal viral pneumonia [19]. In a previous study conducted at our institution,
RSV was isolated in 31% of 343 cases of respiratory illness from July 1, 2000, to July 30, 2002, in leukemia and HSCT patients [20]. Pneumonia developed in 36% (39 of 107) of RSV cases, and 6 of 36 (17%) patients treated for RSV pneumonia died. These high rates of pneumonia and death have been confirmed at other centers [21].

Early treatment (before respiratory failure occurs) with aerosolized ribavirin, alone or in combination with immunotherapy, is key to reducing mortality in patients with established pneumonia [22,23]. Furthermore, the early use of aerosolized ribavirin-based therapy in immunocompromised patients with isolated upper respiratory symptoms can decrease the rate of progression to pneumonia [20]. Thus, routine screening of HSCT patients with upper respiratory symptoms is important, especially during high seasonal peaks.

In this article, we described an outbreak of nosocomial RSV in which 6 HSCT patients developed RSV infections. Two patients had isolated upper respiratory involvement, and 4 developed pneumonia. All 6 patients were promptly started on aerosolized ribavirin treatment, but 2 developed severe respiratory failure and died.

Stringent infection control measures, including cohorting RSV-infected patients and healthy staff members to 1 pod, placing all patients on contact isolation, and screening visitors and staff, were implemented to control the outbreak. RSV is highly contagious, and rapid spread among hospitalized patients has been documented. The virus survives up to 7 hours on countertops, gloves, paper tissues, and clothes and 30 minutes on skin [24]. Transmission occurs primarily through inoculation of nasopharyngeal or ocular mucous membranes after contact with virus containing secretions or fomites [25]. Furthermore, transmission through large aerosol droplets has been implicated [26]. Hence, vigorous handwashing and strict application of contact isolation, including surgical masks and eye protection, may be the most important measures of preventing nosocomial spread [27,28]. Isolating patients and staff, in which patients are placed in private rooms or with other RSV-infected patients and health care workers are restricted from caring for uninfected patients, is extremely effective at controlling further nosocomial transmission [28,29]. Finally, restricting visitors with upper respiratory symptoms from patient contact and continuously educating all personnel and family members should be implemented in every outbreak setting [28].

However, in a recent neonatal intensive care unit RSV outbreak [30], the above infection control measures were not effective at preventing further RSV infections with significant morbidity. Palivizumab therapy was initiated for all infants admitted to the unit, and no further cases were noted. Palivizumab is
a humanized monoclonal antibody that specifically inhibits an epitope at the A antigenic site of the F protein of RSV subtypes A and B. Antibody binding to the F protein has 2 effects. First, it prevents cellular infection by preventing the viral membrane from fusing with the respiratory epithelial cell membrane. Second, it prevents cell-to-cell spread of the virus, which prevents the formation of syncytia and the release of inflammatory mediators in the lungs [31]. These properties provide the rationale for its clinical use. In the Impact-RSV trial [32], a randomized, double-blinded, placebo-controlled multicenter study, prophylactic palivizumab resulted in a significant reduction in hospitalization rates in high-risk children; this finding led to its U.S. Food and Drug Administration approval of palivizumab for RSV prophylaxis in high-risk children in June 1998. Palivizumab was administered intramuscularly each month during the cold season, at 5 doses of 15 mg/kg, in 1502 high-risk children; it resulted in a 55% reduction in the rate of RSV hospitalization (10.6% in the placebo group versus 4.8% in the palivizumab group, \( P < .001 \)). Premature children with no bronchopulmonary dysplasia experienced a 78% reduction in the RSV hospitalization rate (8.1% versus 1.8%, \( P < .001 \)), and children with bronchopulmonary dysplasia experienced a 39% reduction (12.8% versus 7.9%, \( P = .038 \)). Subsequent studies confirmed these results [17,33-39]. The American Academy of Pediatrics acknowledges that palivizumab may be beneficial in children with severe immunodeficiencies [40]. In a decision analysis model designed to determine the effect of prophylactic palivizumab on mortality in pediatric stem cell transplant recipients, the absolute survival rate increased from 83% to 92% with palivizumab [41].

Palivizumab is used, alone or in combination with aerosolized ribavirin, in the treatment of, respectively, upper and lower RSV respiratory tract infections [20,23,42]. However, data on its use in adult HSCT patients remains limited. Palivizumab has an excellent safety profile, and may be beneficial at preventing and treating RSV infections in

### Table 2. Summary of RSV Outbreaks in the Pediatric Population

<table>
<thead>
<tr>
<th>References (No.)</th>
<th>Unit Level of Care (No. of Beds)</th>
<th>Date of the Outbreak</th>
<th>No. of Infants on the Ward at Time of Outbreak</th>
<th>No. of Infants Infected with RSV</th>
<th>No. of Deaths Secondary to RSV Infection</th>
<th>No. of Infants Who Received Prophylactic Palivizumab</th>
<th>No. of RSV Infections after Administration of Palivizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salcedo et al. [45]</td>
<td>NICU (17)/Intermediate care (15)</td>
<td>Jan-00</td>
<td>56</td>
<td>4</td>
<td>0</td>
<td>All infants</td>
<td>0</td>
</tr>
<tr>
<td>Cox et al. [46]</td>
<td>NICU (18)</td>
<td>Nov/Dec 1999</td>
<td>17</td>
<td>7</td>
<td>1</td>
<td>8 (high risk)</td>
<td>0</td>
</tr>
<tr>
<td>Kilani [47]</td>
<td>NICU (20)</td>
<td>2001</td>
<td>20</td>
<td>8</td>
<td>1</td>
<td>All infants</td>
<td>0</td>
</tr>
<tr>
<td>Heerens et al. [48]</td>
<td>Neonatal critical care center (NA)</td>
<td>Feb-98</td>
<td>NA</td>
<td>3</td>
<td>1</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Heerens et al. [48]</td>
<td>Neonatal critical care center (NA)</td>
<td>Apr-98</td>
<td>NA</td>
<td>6</td>
<td>1</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Abadesso et al. [30]</td>
<td>NICU (26)</td>
<td>Nov-98</td>
<td>NA</td>
<td>3</td>
<td>0</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Abadesso et al. [30]</td>
<td>NICU (26)</td>
<td>Apr-98</td>
<td>19</td>
<td>8</td>
<td>1</td>
<td>All infants</td>
<td>0</td>
</tr>
<tr>
<td>Halasa et al. [49]</td>
<td>NICU (37)/Intermediate care (19)</td>
<td>NA</td>
<td>NA</td>
<td>9</td>
<td>0</td>
<td>All not infected</td>
<td>0</td>
</tr>
<tr>
<td>Kurz et al. [50]</td>
<td>NICU (12)</td>
<td>Jan-07</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>All infants</td>
<td>0</td>
</tr>
</tbody>
</table>

NICU indicates neonatal intensive care unit; NA, not available; N/A, not applicable; RSV, respiratory syncytial virus.

### Table 3. Summary of RSV Outbreaks in Adults

#### RSV Outbreaks in Immunocompromised Adults

<table>
<thead>
<tr>
<th>References</th>
<th>Unit Level of Care (No. of Beds)</th>
<th>Date of the Outbreak</th>
<th>No. of Patients on the Ward at Time of Outbreak</th>
<th>No. of Patients Infected with RSV</th>
<th>No. of Deaths Secondary to RSV Infection</th>
<th>No. of Patients Who Received Prophylactic Palivizumab</th>
<th>No. of RSV Infections after Administration of Palivizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrington et al. [11]</td>
<td>BMT unit</td>
<td>Jan/Apr 1990</td>
<td>NA</td>
<td>31</td>
<td>14 (all had pneumonia)</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Jones et al. [51]</td>
<td>Hematology/Oncology ward (14)</td>
<td>Feb/Apr 1997</td>
<td>NA</td>
<td>8 (including 5 posttransplantation)</td>
<td>0</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Abdallah et al. [10]</td>
<td>BMT unit</td>
<td>May/Sep 2001</td>
<td>NA</td>
<td>16</td>
<td>2 (Both had pneumonia)</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Current study</td>
<td>BMT unit</td>
<td>Jan/Feb 2004</td>
<td>52</td>
<td>6</td>
<td>16 (high-risk)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### RSV Outbreaks in Immunocompetent Adults

<table>
<thead>
<tr>
<th>References</th>
<th>Unit Level of Care (No. of Beds)</th>
<th>Date of the Outbreak</th>
<th>No. of Patients on the Ward at Time of Outbreak</th>
<th>No. of Patients Infected with RSV</th>
<th>No. of Deaths Secondary to RSV Infection</th>
<th>No. of Patients Who Received Prophylactic Palivizumab</th>
<th>No. of RSV Infections after Administration of Palivizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorvillo et al. [52]</td>
<td>Nursing home</td>
<td>Mar/May</td>
<td>NA</td>
<td>40</td>
<td>8</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Huang et al. [53]</td>
<td>Psychiatry ward</td>
<td>Aug 2005</td>
<td>25</td>
<td>8 patients and 4 HCW</td>
<td>0</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Caram et al. [54]</td>
<td>Long-term care facility</td>
<td>Jan/Feb 2008</td>
<td>52</td>
<td>22</td>
<td>0</td>
<td>None</td>
<td>N/A</td>
</tr>
</tbody>
</table>

BMT indicates bone marrow transplant; NA, not available; N/A, not applicable; HCW, health care worker; RSV, respiratory syncytial virus.
immunocompromised adults but bearing in mind its prohibitive cost [43]. In the outbreak described in this article, palivizumab was prophylactically administered to all HSCT patients at high risk for RSV infection, including all allogeneic and preengraftment transplant recipients, GVHD patients on high-dose steroids, and severely neutropenic patients (absolute neutrophil count <500). No upper or lower RSV infections occurred in these patients. The use of prophylactic palivizumab may have contributed to preventing the further nosocomial spread of RSV, but the direct benefit from this intervention could not be assessed in our study as other simultaneous infection control measures were implemented as well.

In conclusion, active surveillance of all symptomatic patients and health care workers, especially during RSV season, remains the cornerstone for identifying RSV outbreaks. The prevention strategy should include assiduous handwashing and strict contact isolation and mask use. Patients shed RSV asymptomatically for days before and after resolution of the infection; thus, efforts should be made to isolate these patients and assign designated personnel to care for them. Continuous screening of patients, health care workers, and visitors, especially during outbreaks, is extremely helpful in preventing further nosocomial RSV spread. Furthermore, intensive educational programs help increase awareness of RSV exposure among patients, caregivers, and family members [44]. Our experience suggests that prophylactic palivizumab should be administered to high-risk HSCT patients to contain nosocomial RSV transmission, in conjunction with the simple and inexpensive preventive measure of hand washing. Active surveillance for respiratory viruses should be implemented, as should rapid and strict adherence to all preventative infection control measures. Further studies are needed to assess the role of prophylactic palivizumab in nosocomial RSV and whether this intervention is cost effective.

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REFERENCES


