The Use of Intravenous Palivizumab for Treatment of Persistent RSV Infection in Children With Leukemia

AUTHORS: Roberto P. Santos, MD, Jeffery Chao, MD, Anne G. Nepo, MD, Shafiq Butt, BS, Kathleen A. Stellrecht, PhD, Jennifer M. Pearce, MD, and Martha L. Lepow, MD
Albany Medical Center, Albany, New York

KEY WORDS
children, intravenous palivizumab, leukemia, RSV

ABBREVIATIONS
ALC—absolute lymphocyte count
ALL—acute lymphocytic leukemia
ANC—absolute neutrophil count
hMPV—human metapneumovirus
IV—intravenous
IVIG—intravenous immunoglobulin
LRTI—lower respiratory tract infection
RSV—respiratory syncytial virus

Palivizumab is a humanized monoclonal antibody used to decrease the threat of respiratory syncytial virus (RSV) infection among children at high risk. There are no standard guidelines due to conflicting data on palivizumab’s use in the treatment of RSV lower respiratory tract infections. Intravenous (IV) palivizumab was shown to be well tolerated and associated with decreased mortality in high-risk children who have RSV disease. However, it did not prevent lower respiratory tract infections and did not affect the survival rate of allogeneic stem cell transplant recipients who had RSV infection. We present 2 children with acute lymphocytic leukemia (ALL) and persistent RSV infection while receiving chemotherapy. Patient A is a 4-year-old male with Down syndrome, ALL, and persistent RSV infection for at least 3 months. Patient B is a 3-year-old female with pre-B cell ALL whose chemotherapy intensification phase was delayed due to a month-long RSV infection. RSV infections were determined by using real-time polymerase chain reaction assays from nasopharyngeal swabs before IV palivizumab therapy; patient A was positive for RSV at 36 cycles and patient B was positive for RSV at 29 cycles. RSV infection was cleared in both patients within 72 hours after receiving IV palivizumab (patient A: 16 mg/kg; patient B: 15 mg/kg). IV palivizumab may be a treatment option for persistent RSV infection among immunocompromised patients. Pediatrics 2012;130:e1695–e1699

www.pediatrics.org/cgi/doi/10.1542/peds.2011-1768

doi:10.1542/peds.2011-1768
Accepted for publication Jul 23, 2012

Address correspondence to Roberto Parulan Santos, MD, Department of Pediatrics, Division of Infectious Diseases, Albany Medical Center, 47 New Scotland Ave (MC 88), Albany, NY 12208. E-mail: santosr@mail.amc.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005, Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.
Respiratory syncytial virus (RSV) is responsible for ~120,000 pediatric hospitalizations each year and is the most common cause of lower respiratory tract infection (LRTI) in children aged <1 year in the United States. Palivizumab, a humanized monoclonal antibody directed against the fusion protein of RSV, has been successfully used as prophylaxis in high-risk pediatric populations, such as those with chronic lung disease, preterm birth, congenital heart disease, and immunocompromised states. A study in 2007 found that combining palivizumab with the antiviral nucleoside analogue ribavirin was effective in decreasing the mortality associated with acute RSV infections in certain high-risk children. However, another study in bone marrow transplant patients found that palivizumab alone had no impact on outcome. We report RSV eradication with palivizumab in 2 pediatric patients who were undergoing treatment for acute lymphocytic leukemia (ALL) with persistent RSV infection.

**CASE REPORTS**

Patient A is a 4-year-old male with Down syndrome; he was diagnosed with ALL 14 months previously and was receiving maintenance chemotherapy. He also had a history of reactive airway disease. The patient presented to the hospital with a 1-day history of fever (101.6°F), cough, and congestion. On admission, his absolute neutrophil count (ANC) was 4600 cells/µL and absolute lymphocytic count (ALC) was 580 cells/µL (Fig 1). Chest radiographs were normal, but a nasopharyngeal swab realtime polymerase chain reaction assay tested positive for RSV infection at 23.6 cycles. The number of cycles are inversely related to the amount of RSV RNA detected, with values ≥50 indicating undetectable levels. The results of the blood cultures were negative. The patient was stable and discharged on symptomatic treatment. He was readmitted 1 week later with fever and treated with antibiotics for 48 hours. RSV was still present (27.0 cycles) after antibiotic treatment, but he was subsequently discharged on symptomatic treatment.

The patient returned 2 months later with respiratory distress, fever, tachycardia (153 beats per minute), tachypnea (36 breaths per minute), and pulmonary retractions. His lungs were clear to auscultation bilaterally, and his chest radiograph was normal. White blood cell count was 2300 cells/µL with an ANC of 1470 cells/µL, an ALC of 640 cells/µL, and immunoglobulin G of 400 mg/dL (mean for age: 780 mg/dL). RSV (36.7 cycles) and human metapneumovirus (hMPV) PCR test results were positive. He was started on antibiotic treatment. Forty-eight hours later, after no signs of any clinical improvement and blood culture results were negative, he received a 500-mg dose of intravenous immunoglobulin (IVIG). Approximately 15 hours later, the patient received 16 mg/kg of palivizumab (250 mg). He tolerated treatment well, and rapidly improved clinically and was discharged on the fourth hospital day. Three days after discharge, his PCR assay was negative for RSV (Fig 1). He did not have a recurrence of RSV in that year.

Patient B is a 3-year-old female with a history of pre-B cell ALL diagnosed 7 months earlier, who presented to the hospital for her delayed intensification chemotherapy with fever (101.7°F) of unknown source. She was neutropenic with an ANC of 8 cells/µL and lymphopenic with an ALC of 180 cells/µL. Her chest radiograph showed no evidence of pneumonia. The PCR assay tested positive for RSV infection (27.3 cycles) (Fig 1). Antibiotics were started, and the patient was discharged after the results of initial bacterial cultures were negative.

The patient returned 1 week later; she was febrile (102°F) and tachycardic (121 beats per minute), with nasal congestion and cough. Lungs were clear to auscultation bilaterally. She was anemic, thrombocytopenic, her ANC was 0 cell/µL, and ALC was 500 cells/µL. RSV tested positive (36.7 cycles) and 72-hour antibiotics were empirically started and chemotherapy discontinued. The patient was still febrile after 3 days, with negative results on blood and urine cultures without any major changes in her blood counts. Her PCR assay was still positive for RSV (29.4 cycles). Intravenous (IV) palivizumab at 15 mg/kg (200 mg) was administered. She clinically improved within 24 hours after administration, and her RSV PCR was negative 72 hours after treatment (Fig 1). Her white blood cell count also improved (1900 cells/µL).

**DISCUSSION**

We report the successful use of IV palivizumab for the treatment of persistent RSV infection in children with leukemia who are undergoing chemotherapy. Previous studies have used palivizumab in conjunction with ribavirin and IVIG to treat severe RSV infection. Both patients were severely lymphopenic at the time of palivizumab administration, and both had an undetectable viral RNA using PCR assay within 3 days after therapy.

Previous studies have demonstrated the importance of adequate CD4+ and CD8+ lymphocytes as well as RSV antibodies in terminating RSV replication. Patients who are immunosuppressed, such as those who are premature (<32 weeks' gestation), HIV infected, or undergoing immunosuppressive therapy, are at increased risk for mortality and morbidity from RSV infection due to diminished levels of T lymphocytes. Patients with high titers of maternally derived anti-RSV antibodies or who are
administered palivizumab are better protected against infection.\textsuperscript{9}

The Infectious Diseases Society of America does not routinely recommend treating RSV infections with palivizumab in neutropenic patients who have upper respiratory diseases.\textsuperscript{10} However, this action may be indicated in our patients with recurrent hospitalizations due to persistent RSV infection and severe lymphopenia. It is important to note that after treatment in patient B, there was evidence of bone marrow recovery after administration of palivizumab (Fig 1). This finding supports the use of palivizumab in our patients, as the infection may have contributed to myelosuppression. One study found that up to 80% of upper respiratory infections due to RSV in hematopoietic stem cell transplant recipients and patients with hematologic malignancies can progress to LRTIs.\textsuperscript{11}

Future uses of palivizumab at the time of diagnosis of RSV infection in children with malignancies who are severely lymphopenic should be considered and evaluated for effects on morbidity and prolonged delays in their chemotherapy regimen. Because palivizumab has a long half-life, it could prevent recrudescence as it seemed to do in our patients. Therefore, the use of palivizumab, not only as prophylaxis but in the setting of acute and chronic RSV infection, should be considered. Furthermore, there are cost-effective considerations in decreasing repeat hospitalizations and avoiding delays in chemotherapy with treatment of acute RSV in high-risk populations.\textsuperscript{3}

The main methodologic issue is the relatively small number of patients who can benefit from IV palivizumab for treatment, including patients with leukemia undergoing chemotherapy. Furthermore, patients with Down syndrome have some immunodefiencies, and studies have found that many may have quantitative and qualitative impairments in their lymphocyte levels.\textsuperscript{12} More specifically, it has been found that these patients have decreased absolute numbers of all CD4+ and CD8+ T cells, as well as decreased proliferation and cytotoxicity of T cells in different functional assays.\textsuperscript{13} In addition to prophylaxis, treatment of RSV with palivizumab should be considered in children with Down syndrome, which is an independent risk factor for severe RSV LRTI.\textsuperscript{14} It is important to take this into consideration in future studies, as immunologic issues can influence viral clearance and recovery time.

One issue raised with our patients was the possibility of a concurrent bacterial infection because symptoms seemed to stabilize after antibiotic administration. The likelihood of simultaneous secondary bacterial infection with RSV is low (1%) in the upper respiratory tract of previously healthy children. The most common bacterial coinfection of RSV bronchiolitis is acute otitis media, with an occurrence of 57% to 76% in patients with RSV infection. Neither patient exhibited any signs or symptoms of acute otitis media.\textsuperscript{15} Furthermore, RSV infections in the upper respiratory tract usually last between 7 and 10 days.\textsuperscript{16} With patient A, the time frame between the first and second admission was fairly short (~10 days), which suggests the possibility of persistent infection rather than a new exposure or a secondary bacterial infection. More importantly, the patient’s condition improved after palivizumab therapy.

Another issue is the simultaneous infection with hMPV in patient A. Although we cannot say for certain that the cause of his hospitalization was due to RSV, a few reasons may indicate more strongly that the hospitalization was due to RSV and not to hMPV. First, the patient had a history of hospitalizations due to a persistent RSV
infection. Second, although hMPV and RSV have similar presentations, RSV is more likely than hMPV to cause bronchiolitis. Finally, 1 study reported that RSV and hMPV coinfection leads to an increased severity of disease than when compared with each virus alone. During patient A's third hospital admission, he did not exhibit any significant difference in severity of symptoms compared with previous admissions for RSV alone.\(^1\)

Patient B may also have had a persistent RSV infection at her second admission. The reason the patient was readmitted much earlier may be associated with the fact that she was more lymphopenic than the first patient (Fig 1). However, due to the shortened time intervals between admissions, the infection was most likely a persistent rather than a recurrent infection and may be associated most likely with RSV because palivizumab rapidly improved the patient’s symptoms when broad-spectrum antibiotics did not.

The RSV PCR assay is a qualitative test (Prodesse ProFlu+, Gen-Probe, Inc, San Diego, CA)\(^7\) that can be used semiquantitatively with an inverse relationship between the amount of viral RNA in the respiratory specimens and the cycles reported. It is 1 of the most sensitive (98%) commercial tests for detection of RSV infection and has a specificity >99%.\(^1\) Less than 50 cycles indicates detectable RSV RNA, and this cutoff value is specific to our laboratory. Other cutoff values may vary depending on the assay being used. Compared with other diagnostic methods such as viral culture, enzyme immunoassay, and serology, real-time polymerase chain reaction has allowed for more accurate assessments of RSV infection and correlates well with active or recent infections.\(^7\) In addition, the duration of RSV shedding coincided well with the duration of symptoms among patients with severe immunodeficiency.\(^2\) The issue of PCR detecting dead virus is less of a problem for RNA viruses because RNA is labile, and once a virus is killed, its outer coat will start to break down and expose the RNA to RNases in the human body.

It is important to remember that RSV infection is not limited to the pediatric population. It is also a common cause of adult viral infections in those who have undergone hematopoietic stem cell transplant. The management of RSV in these populations has been limited to ribavirin, IVIG, and palivizumab.\(^2\) IV palivizumab may be an alternative treatment option for other populations with similar vulnerability to RSV infections.

Finally, future studies should determine the usefulness of palivizumab in the prevention or treatment of acute and persistent or recurrent RSV infection in certain high-risk patients. It would be of interest to evaluate other monoclonal antibodies in development such as motavizumab against palivizumab as prevention or treatment.\(^2\)

CONCLUSION

Palivizumab use in 2 children with leukemia demonstrated success in treating persistent RSV infection.

ACKNOWLEDGMENT

This case study was approved under “Expedited Review” by the Committee on Research Involving Human Subjects, Albany Medical Center (November 30, 2010).

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*Pediatrics* 2012;130;e1695; originally published online November 12, 2012; DOI: 10.1542/peds.2011-1768

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