Palivizumab Prophylaxis, Respiratory Syncytial Virus, and Subsequent Recurrent Wheezing

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Objective **Children who experience respiratory syncytial virus (RSV) lower respiratory tract infections (LRTIs) early in life have high rates of subsequent recurrent wheezing. Palivizumab, an anti-RSV monoclonal antibody, has 78% to 80% efficacy in preventing RSV hospitalization in premature infants without chronic lung disease. We hypothesized that palivizumab, by ameliorating or preventing early RSV LRTI in preterm infants, might decrease later recurrent wheezing.**

Study design **A cohort of preterm infants who had received palivizumab and were not hospitalized for RSV (n = 191) or who never received palivizumab (n = 230; 76 who were hospitalized for RSV and 154 who were not), were prospectively followed for 24 months beginning at a mean age of 19 months. The subjects were assessed for recurrent wheezing by caretaker or physician report.**

Results **The incidences of recurrent wheezing and physician-diagnosed recurrent wheezing were significantly lower in the 191 palivizumab-treated subjects (13% and 8%, respectively) compared with all 230 untreated subjects (26%, $P = .001$ and 16%, $P = .011$, respectively) and with the 154 patients in the subgroup not hospitalized for RSV LRTI (23%, $P = .022$ and 16%, $P = .027$, respectively). The effect of palivizumab treatment remained significant after adjustment for potential confounding variables.**

Conclusions **Our study suggests that preventing RSV LRTI with palivizumab may reduce subsequent recurrent wheezing in premature infants.** ***(J Pediatr 2007;151:34-42)***

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Respiratory syncytial virus (RSV) is the most important respiratory viral pathogen in childhood.[1] Although the immediate effects of severe disease are well known, RSV lower respiratory tract infection (LRTI; pneumonia and/or bronchiolitis) in early life has been associated epidemiologically with subsequent recurrent wheezing and asthma later in childhood.[2-6] Prospective studies have demonstrated rates of subsequent airway reactivity 50% to 100% greater in children who developed RSV LRTI in early life than in uninfected controls. Recurrent wheezing has been observed up to 11 years later[4] and may extend into early adulthood.[7]

Preterm infants, even those without chronic lung disease (CLD), develop particularly serious RSV infections in the first year of life,[8] are at higher risk for developing recurrent wheezing or asthma,[9] and have persistent abnormal lung function.[10] It has been demonstrated that the use of a polyclonal immunoglobulin, RSVIG-IV (RespiGam), can prevent serious RSV LRTI in children with CLD.[11,12] In another small study, infants with CLD who had received RSVIG-IV also had less severe chronic asthma, as defined by improved pulmonary function tests, decreased hospital visits, and decreased medication use, compared with control children.[13]

Palivizumab (Synagis), a humanized monoclonal antibody against the RSV fusion protein, has been demonstrated to substantially reduce hospitalization for severe RSV

CI	Confidence interval	LRTI	Lower respiratory tract infection
CLD	Chronic lung disease	RR	Relative risk
HR	Hazard ratio	RSV	Respiratory syncytial virus

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*The members of the Palivizumab Long-Term Respiratory Outcomes Study Group are listed in an appendix, available at www.jpeds.com.

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LRTI in large clinical trials involving preterm infants.[14,15] We hypothesized that the use of palivizumab in preterm infants, by ameliorating or preventing early RSV LRTI, might decrease later recurrent wheezing. We report here on respiratory outcomes in an international cohort of previously preterm infants age 36 months and younger without CLD who received palivizumab in the 1999-2000 respiratory season and were followed up prospectively for 2 years, compared with a matched cohort that had never received palivizumab.

METHODS

Patient Enrollment

Because it is unethical to conduct a randomized placebo-controlled trial in premature infants (in whom palivizumab has been shown to reduce RSV hospitalization), we took advantage of incomplete uptake of palivizumab use and conducted a prospective multicenter, double-cohort, follow-up study in 27 centers in Spain, Germany, The Netherlands, Canada, Poland, and Sweden. The 27 sites were invited to participate in the study based on their use of palivizumab in some premature infants on a compassionate basis in the preceding respiratory season and ability to recruit and retain subjects for the 2-year duration of the study. Investigators reviewed medical records for preterm births and approached all who had received at least 3 doses of palivizumab in the first 12 months of life and had not had an RSV hospitalization (designated the "treated group"). Using chronologic age (±3 months) and gestational age (±4 weeks) for matching, subjects from the large group of premature infants who had not received palivizumab were matched to those in the palivizumab-treated group and were approached for participation in the study (designated the "untreated group"). An attempt was made to recruit equal numbers of RSV hospitalized and nonhospitalized subjects, each matched to 1 subject from the palivuzumab-treated cohort. All study participants were born prematurely (≤35 weeks gestational age) and had no CLD. Other exclusion criteria were mechanical ventilation at enrollment; congenital heart disease; renal, hepatic, or seizure disorder; life expectancy of <6 months; known immunodeficiency; or receipt of other RSV investigative vaccines or therapies. Most of the children (94%) were enrolled between mid-July 2001 and mid-March 2002 and were followed prospectively for 2 years after enrollment. Reasons for use or nonuse of palivizumab were not explored.

Written informed consent was obtained from each subject's parent or legal guardian before the performance of any study-related procedures, after ethical review and approval by the institutional review board at each study site. The study was conducted in accordance with ICH Good Clinical Practice Guidelines and was monitored by Abbott Laboratories, Inc. An independent international steering committee (including the authors) was involved in the study design and data collection, and stipulated and oversaw all analyses reported in this article. At enrollment, a medical and sociodemographic history was obtained, a physical examination was performed, and serum samples were obtained for RSV-neutralizing antibody[16] and IgE levels.[17] The medical history included a validated respiratory questionnaire[2] and a questionnaire on family history, medical history, and underlying diagnosis/disease (RSV) and current medications, demographics (eg, number of people in home, number and ages of siblings, day care, passive smoke), environmental factors (eg, pets, wood-burning stoves), and parental smoking or history of atopy (eg, asthma, allergic dermatitis or allergic rhinitis) in family members.

Patient Follow-Up

Monthly contact with the parents/caregivers was scheduled over the 24 months after enrollment. Visits to the study site were conducted at 6-month intervals; all other monthly contacts were conducted by telephone. Subject illnesses and other medical events occurring during the past month were recorded at each monthly follow-up contact. At 6-month intervals, physician records were reviewed for all intercurrent doctor visits, emergency visits, and hospitalizations for respiratory symptoms.

Respiratory Assessment

Outcomes were assessed clinically using a system adapted from those used in other studies of the long-term respiratory outcome of RSV.[2,3] Wheezing, defined as bronchial obstruction, was assessed at each visit. An episode of wheezing was defined in the protocol as 1 or more consecutive days of wheezing preceded and followed by a nonwheezing, healthy period of at least 1 week. A priori recurrent wheezing was defined as 3 or more episodes of wheezing in the last 12 months but not necessarily verified by a physician. Physician-diagnosed recurrent wheezing was defined as 3 or more episodes of wheezing in the last 12 months verified by a physician at a physician's visit, emergency room visit, or hospitalization. At the study sites, the primary physicians making decisions regarding wheezing were not study physicians. The subjects' parents or guardians were informed at enrollment that they should notify the investigating physician immediately if the child experienced any respiratory symptoms. During unscheduled (sick) visits, an interval medical history was obtained and a physical examination performed.

Statistical Methods

A sample size of 200 patients per group was estimated to provide approximately 80% power for a 2-sided, .05-level test to detect a statistically significant difference in physician-diagnosed recurrent wheezing rates when the true rates are 10% for the untreated cohort and 3% for the palivizumab-treated cohort. Demographics and baseline characteristics were compared using 1-way analysis of variance for quantitative variables and Fisher's exact test for categorical variables. The palivizumab-treated group was compared with both the combined untreated groups and the untreated non-RSV hospitalized group.

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