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RSV Immunoprophylaxis: Does the Benefit Justify the Cost?

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KEY WORDS

viral respiratory infection, RSV prophylaxis, palivizumab, asthma

ABBREVIATION

RSV—respiratory syncytial virus

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Respiratory syncytial virus (RSV) is among the last viruses to cause major, predictable worldwide outbreaks of disease and for which no vaccine or broadly effective antiviral drug is available. Annually in the United States, RSV accounts for ~125 000 hospitalizations, 2.1 million outpatient visits to a pediatrician's office or an emergency department, and 250 deaths among children in the first years of life.¹ In addition to the burden of acute disease caused by RSV, severe lower respiratory tract infection early in life is associated with recurrent wheezing during the first decade of life.^{2,3} The unresolved issue of the association between severe viral respiratory illness early in life and subsequent wheezing remains one of the more perplexing issues in pediatrics. Numerous studies have documented that infants hospitalized with viral lower airway disease (especially after rhinovirus or RSV infection) are more likely to experience recurrent wheezing in contrast to infants who do not experience severe bronchiolitis.³⁻⁵ Association of a susceptibility locus on chromosome 17q21, rhinovirus infection in early childhood, and wheezing indicates the existence of a complex interaction between a genetic predisposition and environmental factors.⁴ The unresolved question is whether a severe viral respiratory infection early in life alters normal lung development in a way that predisposes to subsequent wheezing or whether certain infants have a preexisting aberration of the immune response or of airway function that predisposes to both severe bronchiolitis and recurrent wheezing.⁶ If viral lower respiratory tract infections have a causal association with recurrent wheezing, prevention of infection should reduce the incidence of wheezing. If severe bronchiolitis simply identifies an infant who is predisposed to recurrent wheezing from a number of causes, prevention of RSV infection will have little or no impact on subsequent wheezing.

An industry-sponsored report by Yoshihara et al in this issue of *Pediatrics* provides some insight into this issue.⁷ The results of this non-randomized, observational study from Japan compared the incidence of wheezing between 349 preterm infants who received palivizumab prophylaxis in the first 6 months of life with 95 infants who did not receive prophylaxis. The primary end point of the study was physician-diagnosed wheezing during a 3-year follow-up. Twenty-two of 345 infants (6.4%) who received immunoprophylaxis experienced wheezing, whereas 18 of 95 infants (18.9%) who did not receive prophylaxis developed recurrent wheezing ($P < .001$) during the 3-year follow-up period. No difference in hospitalization due to respiratory disease between the 2 groups was found. Concerns with this study design are the lack of randomization and blinding and the absence of standardized enrollment criteria at the 52 participating sites, each of which may have lead to enrollment bias. Nonetheless, the results are consistent with the possibility that avoidance of early RSV infection among

preterm infants decreases the incidence of wheezing in the first few years of life.

A second industry-sponsored trial conducted in the Netherlands addressed the issue of prophylaxis with palivizumab and recurrent wheezing using a different study design. This double-blind, placebo-controlled trial enrolled 429 otherwise healthy late-preterm infants.⁸ Participating infants received monthly prophylaxis with palivizumab or placebo, and the primary end point was parent recorded wheezing during the first year of life. During the first year of life, children in the placebo group experienced 2309 days with wheezing of a total 51 726 patient days (4.5%), whereas those in the palivizumab group had 930 days of wheezing out of 53 075 patient days (1.8%; $P = .01$). This represents an absolute 2.7 fewer days of wheezing per 100 patient days (17.5 wheezing days/1000 days vs 44.6 wheezing days/1000 days = 27.1 fewer wheezing days/1000 days) among infants who received monthly palivizumab in contrast to those who did not receive prophylaxis.

These trials offer preliminary evidence that reduction of RSV lower respiratory tract infection early in life by the use of monthly palivizumab prophylaxis may reduce wheezing episodes in the first, second, or third year of life. It should be noted that in the trial by Yoshihara et al, the reduction in children with recurrent wheezing was modest, from 189 children per 1000 days in the untreated arm to 64 children per 1000 days among recipients of monthly prophylaxis over a 3-year period.⁷ This equates to 125 fewer children with recurrent wheezing per 1000 children receiving prophylaxis, or 12.5 fewer children with an episode of wheezing per 100 children per year over 3 years. The critical question regarding palivizumab prophylaxis has not changed

since this humanized monoclonal antibody was licensed by the Food and Drug Administration in June 1998.⁹ Palivizumab is easily administered, well tolerated, and moderately effective in reducing RSV hospitalization rates, as robustly demonstrated in 2 randomized, blinded, placebo controlled trials conducted from 1996–1997 (Impact-RSV trial) and from 1998–2002 (cardiac trial).^{10,11} The pivotal Impact-RSV trial demonstrated an overall drop in RSV hospitalization rates from 10.6% in the placebo arm to 4.8% among high-risk infants who received palivizumab prophylaxis, a modest absolute reduction of 5.8%, although statistically significant ($P < .001$).¹⁰ The cardiac trial evaluated the safety and efficacy of palivizumab in 1287 children with hemodynamically significant congenital heart disease and demonstrated a reduction in RSV hospitalization from 9.7% in the control arm to 5.3% among palivizumab recipients.¹¹ The absolute reduction in RSV hospitalization in this trial was statistically significant at 4.4% ($P < .003$). The results from the recent studies of wheezing outcomes conducted in Japan and the Netherlands suggest that in addition to this ~5% absolute reduction in RSV hospitalization rates, a small reduction in episodes of recurrent wheezing also may be achieved with palivizumab prophylaxis.^{7,8} The results from both studies regarding a reduction in wheezing reach statistical significance, but are the results of sufficient clinical significance to justify the cost of prophylaxis? The cost-effectiveness of this expensive intervention remains controversial and depends on several base case assumptions including baseline RSV hospitalization rates among different groups of children at high risk, the reduction in RSV hospitalization rates among recipients of prophylaxis in different risk groups in this second decade of the 21st century (which are likely to be

lower than RSV hospitalization rates during the 1990s when the Impact-RSV trial was conducted), the cost of hospitalization (amount saved by avoiding hospitalization), the threshold criteria for hospitalization of a child with bronchiolitis (which differs from country to country and even from pediatrician to pediatrician), the number of monthly doses administered, the weight of an infant who receives prophylaxis, variation in the severity of the RSV season, and the acquisition cost of palivizumab. No difference in mortality rates between control groups and prophylaxis recipients has been found in any clinical trial, so this important driver of cost-saving (life-years gained) cannot be included in a cost-effectiveness analysis. An analysis of the Kids' Inpatient Database regarding bronchiolitis admissions noted that the overall hospitalization rate for all-cause bronchiolitis has declined in the United States by a statistically significant 17% between 2000 and 2009.¹² As the primary end point (RSV hospitalization) becomes less common among infants who do not receive prophylaxis, the cost of prophylaxis to prevent 1 hospitalization increases.

A number of cost-effectiveness analyses have been published regarding palivizumab prophylaxis with dramatically different conclusions.^{13,14} Cost-analyses sponsored by the manufacturer generally show cost neutrality or even cost saving.^{15,16} Among independently conducted cost analyses, the cost of prophylaxis with palivizumab is generally found to far exceed the economic benefit of hospital avoidance, even among infants at highest risk.^{9,17–20} For the highest-risk infants (those born at 23–32 weeks' gestation and who required at least 28 days of supplemental oxygen in the NICU), the number needed to treat to prevent 1 hospitalization in the Impact-RSV trial was 8.5.⁹ For all other infants in the

trial, the number needed to treat to prevent 1 RSV hospitalization ranged from 19 to 170.⁹ The average wholesale cost of 100-mg vial of palivizumab is \$2962 (June 2013). At a monthly dose of 15 mg/kg, assuming no wastage, the per-dose cost of palivizumab is 15 mg/kg $\times$ \$2962/100mg $\times$ 4.8 kg (the mean weight of infants in Impact-RSV trial) = \$2133/dose. If 5 monthly doses are administered, the total direct cost for palivizumab per infant for a single season is \$10 665. Assuming a conservative number of 19 infants need prophylaxis to avoid 1 RSV hospitalization, the acquisition cost at the present time to avoid 1 hospitalization is \$202 635 (19 infants $\times$ \$10 665; Table 1). This figure will be modified by manufacturer's rebates, the number of monthly doses administered, and a number of other factors such as administration fees, reduction in outpatient visits among palivizumab recipients, and perhaps a reduction in episodes of wheezing. The mean charge for 1 RSV hospitalization is \$8530, based on >325 000 patient discharges with bronchiolitis in the United States between 2000 and 2009.¹² Thus, in the United States, the acquisition cost of palivizumab is \$202 635 to save \$8530 in hospitalization cost. Sensitivity analyses show that even with variation in assumptions, the cost of prophylaxis far exceeds a saving from reduced hospitalization rates.^{17,20}

Future studies may confirm or refute a statistically significant reduction in the number of episodes of recurrent wheezing among recipients of prophylaxis. At that time, the cost savings from fewer episodes of recurrent

TABLE 1 Cost and Savings per Patient for Palivizumab Prophylaxis Considering Only the Acquisition Cost of 5 Doses of Palivizumab

	Societal Cost	Societal Saving
Average wholesale cost of 100-mg vial of palivizumab vial	\$2962	—
Palivizumab monthly cost per dose for infant with mean wt of 4.8 kg	\$2133	—
Palivizumab cost for 5 monthly doses (1 RSV season) for 1 infant	\$10 665	—
Palivizumab cost to prevent 1 bronchiolitis hospitalization ^a	$\geq$ \$202 635	—
Mean cost of 1 bronchiolitis hospitalization	—	\$8530

—, not applicable.

^a For all infants except highest-risk infants born after 23 to 32 weeks' gestation who spend $\geq$ 1 month in the NICU.

wheezing among palivizumab recipients may be considered in the complex calculus of a cost analysis of palivizumab prophylaxis. However, even when prevention of asthma is included in a cost-effectiveness model, questions about cost and benefit remain.²⁰ This is because long-term clinical and economic benefits are moderated by the extended time over which the benefit is realized. The critical question will remain: are the statistically significant but modest reductions in hospitalization and wheezing associated with palivizumab prophylaxis of sufficient clinical and societal importance to justify the enormous cost, especially when adverse long-term outcomes such as death are not prevented by passive immunotherapy?²¹

A physician is obliged to act as a patient advocate and to make decisions in a manner that offers maximum benefit to the individual patient being cared for. To act otherwise would be unethical and a violation of the doctor-patient relationship. Another imperative requires a physician to be a responsible custodian of limited health care dollars. It is difficult for a physician to reflect on the needs of other patients who are not under his/her direct care. But it must be

understood that resources spent for one intervention will not be available for other interventions and for other patients who may derive greater benefit for less cost.²²

Cost should not be the sole determinant of any intervention. Assessments of quality of life are difficult to measure but must be considered. A decision to prescribe a specific intervention requires a judgment by the payer or the policy-maker about what is a reasonable expense for an expected benefit. Interventions that provide minimal health benefit are difficult to justify, even if inexpensive and even more difficult to justify if costly. Decision-makers may reach conflicting conclusions because of differences in modeling and in base case assumptions (ie, quality-adjusted life years saved or savings per hospitalization avoided, payer or society perspective, short-term or long-term benefit).²¹ However, as health care costs become increasingly unsustainable, difficult decisions must be made regarding which intervention offers a justifiable return and which does not. Under this scrutiny, palivizumab prophylaxis for most at-risk infants is difficult to justify.

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