Cost-effectiveness Analysis of Palivizumab in Premature Infants Without Chronic Lung Disease

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Objectives: To evaluate the cost-effectiveness of palivizumab as respiratory syncytial virus prophylaxis in premature infants without chronic lung disease and to evaluate the impact on cost-effectiveness of a potential reduction in risk of asthma following respiratory syncytial virus infection among infants receiving palivizumab.

Design: Two decision analytic models were designed, one with and the other without accounting for increased risk of asthma following respiratory syncytial virus infection.

Setting: A hypothetical community or university hospital.

Participants: Hypothetical cohorts of infants without chronic lung disease born at 26 to 32 weeks' gestation.

Interventions: Palivizumab prophylaxis vs no prophylaxis.

Main Outcome Measures: Expected costs and incremental cost-effectiveness ratio expressed as cost per quality-adjusted life-year.

Results: The expected costs were higher for palivizumab prophylaxis as compared with no prophylaxis. The incremental cost-effectiveness ratios were high for all gestations and are not considered cost-effective by today's standards (<$200,000 per quality-adjusted life-year). Both models were sensitive to variation in the cost of palivizumab. The model that included asthma was sensitive to variation in quality of life for children with asthma. In instances where asthma was considered severe with profound worsening in quality of life compared with life without asthma, some infants had an incremental cost per quality-adjusted life-year that was less than $200,000.

Conclusions: Our model supports implementing more restrictive guidelines for palivizumab prophylaxis. Palivizumab was cost-effective for some infants in an analysis that accounted for increased risk of severe asthma following respiratory syncytial virus infection.

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RESPIRATORY SYNCYTIAL VIRUS (RSV) is the most important pathogen in lower respiratory tract infection in infants and young children.1 By age 2 years, approximately 80% to 90% of children experience at least 1 episode of RSV infection. Although the majority of RSV infections resolve uneventfully in otherwise healthy children, high-risk populations such as premature infants may develop severe and sometimes fatal lower respiratory tract infections.1 Long-term complications of RSV infections are unclear. Although there is an established association between RSV infection and recurrent wheezing, a cause-effect relationship has not been demonstrated.2-4 Palivizumab (Synagis; MedImmune, Inc, Gaithersburg, Md), a humanized monoclonal antibody, is effective in reducing the risk of hospitalization secondary to RSV infection.5 The American Academy of Pediatrics (AAP), Elk Grove Village, Ill, developed guidelines6 for the use of palivizumab for RSV prophylaxis in 1998 and revised these guidelines in 2003.7 In part owing to cost concerns, the AAP policy recommended the use of palivizumab only in infants at highest risk for severe RSV infection. A number of economic analyses of RSV intravenous immunoglobulin and palivizumab have been performed in the United States and in other countries.8-20 Multiple economic analyses of palivizumab performed outside of the United States concluded that the use of the prophylaxis is not cost-effective,17-19 but analyses performed in the United States have generated mixed results.8,14,18,20 A systematic review15 of economic analyses of RSV intravenous immunoglobulin and palivizumab found a significant difference in results by funding source (P = .002); all of the 4 studies with pharmaceutical funding reported that...
the prophylaxis was either cost-effective or cost-saving for a high-risk infant population whereas none of the 8 studies without pharmaceutical funding reported similar findings.  

None of these analyses considered potential long-term sequelae, ie, the possible increased risk of asthma following RSV infection in infancy and its impact on quality of life.

The objectives of this study were to evaluate the cost-effectiveness of palivizumab as RSV prophylaxis in premature infants without chronic lung disease and to evaluate the impact on cost-effectiveness of a potential reduction in risk of asthma following RSV infection among infants receiving palivizumab. To our knowledge, our model is the first to study the cost-effectiveness of RSV prophylaxis by specific gestational age, to evaluate the implication of the possible increased risk of asthma with RSV infection, and to integrate measures of morbidity (quality-adjusted life-years).

**METHODS**

**MODEL SETTING AND ASSUMPTIONS**

This study was an economic evaluation using decision analytic modeling. The DATA 3.5 for Healthcare software package (TreeAge Software, Williamstown, Mass) was used to combine data from secondary data sources, including publications and government documents, and to simulate costs and outcomes for the intervention.

A hypothetical cohort of premature infants born at 26 to 32 weeks' gestation was assumed to be discharged from the neonatal intensive care unit at 36 weeks' postconceptional age based on unpublished data from the University of Rochester Medical Center, Rochester, NY (T.P.S., 2003). We assumed that an infant had an equal probability of being discharged from the neonatal intensive care unit at different months of the year. Each infant's weight at the time of discharge was assumed to be 2000 g (10% of the growth curve for an infant at 36 weeks' postconceptional age). The association between RSV infection and asthma remains unclear, we completed 2 sets of analyses, one with and the other without asthma included in the models. The modeling includes asthma used time-dependent Markov processes to allow the risk of asthma to vary with the age of the cohort. Analyses were conducted from the societal perspective and therefore included all of the relevant costs and outcomes regardless of to whom they accrued. A separate decision analytic model was constructed for each gestational age. Sensitivity analyses were performed to test the robustness of the results.

The model combined published data on the risk of RSV hospitalization by gestational age, the seasonal pattern of RSV hospitalization, the efficacy of palivizumab in reducing the risk of RSV hospitalization, national costs of RSV hospitalizations, costs of palivizumab injection visits, costs of emergency department visits, drug costs, and costs of work hours missed by parents for visits and hospitalization. In the base-case analysis with asthma, the model also included the risk of asthma, reduction in quality of life due to asthma, and national estimates of the cost of asthma for a child with the disease. There is no current evidence that palivizumab reduces the probability of death in infants; therefore, we did not include risk of death secondary to RSV hospitalization in the models.

Analyses without asthma had a time horizon of 1 year because palivizumab has not been shown to affect other long-term health outcomes; these were cost-benefit analyses. Cost-effectiveness analyses were performed on the models that included asthma. The model with asthma had a time horizon of 8 years in the base-case analysis and was varied up to 10 years in sensitivity analyses to reflect the length of increased risk of asthma following RSV bronchiolitis. Future benefits and costs were discounted at 3% annually. The use of RSV prophylaxis was evaluated using the incremental cost-effectiveness ratio (ICER), defined as the additional costs associated with the use of palivizumab divided by the additional quality-adjusted life-years associated with its use. Based on recent recommendations, we considered an ICER of less than $200 000 per quality-adjusted life-year to be cost-effective.

**NOCOST PARAMETERS**

The values of noncost parameters included in the model are shown in Table 1. The table shows base-case values and ranges of values used for sensitivity analyses.

### Probability of RSV Hospitalization by Gestational Age

We calculated the probability of RSV hospitalization by specific gestational age and month of neonatal intensive care unit discharge by using gestational age-specific RSV hospitalization rates and the seasonal pattern of respiratory hospitalization. We used gestational age-specific risks (ie, at ≥26, 27-28, 29-30, and 31-32 weeks' gestation) of RSV hospitalization.
as reported by Stevens et al.\textsuperscript{10} in the only study to provide
detailed gestational age-specific risks. We applied a monthly
distribution factor based on the seasonal relationship between hos-
pitalization owing to respiratory illness and month of neonatal
intensive care unit discharge reported by Cunningham et al.\textsuperscript{29}
The probability of RSV hospitalization was varied across the
range of risk reported in the literature\textsuperscript{3,29-33} for premature in-
fants in sensitivity analyses.

We calculated the gestational age-specific estimates of the
efficacy of palivizumab in reducing risk of RSV hospitalization
among infants without chronic lung disease using data from the
IMpact-RSV study,\textsuperscript{7} the only randomized trial of palivi-
zumab. The probability of RSV hospitalization for the no-
 prophylaxis group was calculated as the probability of hospi-
talization without prophylaxis multiplied by (1 - efficacy). In
the sensitivity analysis, we allowed the efficacy of palivizumab
to improve to 95% to determine whether prophylaxis would be
cost-effective with very high efficacy rates.

### Length of RSV Hospitalization

From reported values, an average length of stay of 6.8 days\textsuperscript{30,34,36,37}
for RSV hospitalization was included in our base-case analy-
sis. The entire range of values reported in the literature was
considered in sensitivity analyses.

### Probability of Asthma and Length of Increased Risk of Asthma following RSV Bronchiolitis

We based our estimates of the increased risk of asthma on data
by Sigurs et al.\textsuperscript{26,27} in the only study to prospectively evaluate the
risk of asthma among children who had been hospitalized with
RSV bronchiolitis as infants relative to controls (data shown
in Table 1). A linear extrapolation was performed to calculate the
risk of asthma at ages not included in these articles by
Sigurs and colleagues. In the sensitivity analysis, we consid-
ered the range of values of increased risk of asthma following
RSV bronchiolitis reported in retrospective studies.\textsuperscript{38-46}

### Quality of Life

We assumed 1 parent lost an average of 8 hours of work
per day during RSV hospitalization as well an average of 3
hours of work per day for palivizumab injection visits and
department visits. The national costs of time lost
from work were based on US Bureau of Labor Statistics
data.\textsuperscript{31}
Costs of Asthma

Estimates of per capita costs of asthma for persons younger than 18 years were taken from the study by Weiss et al.\textsuperscript{55} These estimates included the costs of inpatient and outpatient hospital services, emergency department visits, office-based physician services, and pharmaceuticals as well as time lost from work.

TARGETED USE POLICY

In addition to the 2 scenarios and 1-way sensitivity analyses described earlier, we generated estimates for a targeted best-case scenario for the use of palivizumab prophylaxis. The current AAP recommendations for the use of palivizumab prophylaxis result in treating many infants who are at low risk for RSV hospitalization, leading us to conduct additional simulations modifying the current recommendations to seek more cost-effective alternatives using the following parameters: no drug wastage; application of prophylaxis restricted to only the infant's first RSV season; younger chronological age cutoffs, ie, those infants assumed to be discharged from September through March; and infants born at 27 weeks' gestation or earlier if discharged before the RSV season and infants born at 30 weeks' gestation or earlier if discharged during the RSV season.

RESULTS

COST-BENEFIT ANALYSIS ASSUMING NO CAUSAL RELATIONSHIP WITH ASTHMA

The results for the different gestational ages are summarized in Table 3. The results for infants born at 29 and 30 weeks' gestation are reported together since the estimates of the cost and probabilities are identical for infants born at these gestational ages.

Irrespective of the gestational age at birth, we found that the added costs of prophylaxis are greater than the savings from reduced hospitalizations. The expected costs for the prophylaxis group are greatest for infants born at 28 weeks' gestation ($8000 in the model with no increased risk of asthma). Thereafter, the expected costs decrease markedly.

COST-EFFECTIVENESS ANALYSIS ASSUMING A CAUSAL RELATIONSHIP WITH ASTHMA

The ICERs for the different gestational ages are summarized in Table 3. The ICERs are higher than $200 000 per quality-adjusted life-year for all gestations and reach a maximum of $1 855 000 per quality-adjusted life-year for infants born at 32 weeks' gestation when palivizumab is used in accordance with AAP recommendations.

SENSITIVITY ANALYSES

The results of the most significant sensitivity analyses are summarized in Table 4 for the models without increased risk of asthma and in Table 5 for the models with increased risk of asthma. These analyses were shown for 5 different gestational ages to display the trend of varying a specific quantity in the model on ICERs and incremental expected costs. In the model without asthma, the use of RSV prophylaxis did not result in cost savings for any of the sensitivity analyses performed. The model that included asthma was sensitive to varying the quality of life for children with asthma and costs of palivizumab vials. When the quality of life with asthma was reduced to 0.8, the ICER was approximately $200 000 per quality-adjusted life-year for infants born at 26 and 29 to 30 weeks' gestation (Table 5). Reductions in palivizumab costs to 25% of their current values result in an ICER less than $100 000 per quality-adjusted life-year for infants born at 26 and 29 weeks' gestation.

TARGETED USE POLICY

The alterations included in the targeted policy dramatically improved the ICER for the use of palivizumab, with the ICER ranging from $103 053 per quality-adjusted life-year for infants born at 26 weeks' gestation to $280 083 per quality-adjusted life-year for infants born at 29 and 30 weeks' gestation. With the targeted policy, the ICER

<table>
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<th>Variable</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29-30</th>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>1548</td>
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<td>8000</td>
<td>3725</td>
<td>3530</td>
<td>4092</td>
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<tr>
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<td>5589</td>
<td>6452</td>
<td>2527</td>
<td>2852</td>
<td>3414</td>
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<tr>
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<td>0.0042</td>
<td>0.0036</td>
<td>0.0023</td>
<td>0.0018</td>
</tr>
<tr>
<td>ICER†</td>
<td>830 152</td>
<td>1 295 781</td>
<td>1 500 351</td>
<td>675 780</td>
<td>1 212 497</td>
<td>1 855 000</td>
</tr>
</tbody>
</table>

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

*Incremental expected costs = expected costs for prophylaxis group − expected costs for no-prophylaxis group.
†Incremental cost-effectiveness ratio = (cost of palivizumab prophylaxis − cost of no prophylaxis)/(QALY for palivizumab prophylaxis − QALY for no prophylaxis).
This decision analytic model compared the costs and effects of palivizumab prophylaxis for RSV and no prophylaxis for a hypothetical cohort of premature infants without chronic lung disease. Our results show that palivizumab prophylaxis is not cost-effective for these infants. Under the first scenario in which we assumed that RSV had no effect on asthma rates, we found that for all gestational ages, the increased costs associated with the use of prophylaxis were greater than the cost savings from reduced hospitalizations and other costs. The decrease in expected costs for infants born at more than 28 weeks’ gestation reflects the AAP policy for RSV prophylaxis: infants born at 29 to 32 weeks’ gestation receive palivizumab if they are younger than 6 months at the start of the RSV season, and infants born at 26 to 28 weeks’ gestation receive prophylaxis if they are younger than 12 months at the start of the RSV season, ie, infants born at 26 to 28 weeks’ gestation generally received a higher total number of palivizumab injections and, thereafter, a higher cost of RSV prophylaxis than infants born at 29 to 32 weeks’ gestation.27 With the second scenario in which we included the health effects associated with the potential increase in asthma rates among children with RSV infections, we found that the ICERs are greater than $200 000 per quality-adjusted life-year for all gestational ages. Our model was most sensitive to variation in the quality of life with asthma, with ICERs less than $200 000 per quality-adjusted life-year for some gestational ages (infants born at 26 and 29 to 30 weeks’ gestation) when the quality of life with asthma was reduced to 0.80, and to variation in the cost of palivizumab, with ICERs less than $100 000 per quality-adjusted life-year for some gestational ages (infants born at 26 and 29 weeks’ gestation) when palivizumab costs were only 25% of their current values. The cost-effectiveness of the current guideline for RSV prophylaxis does not compare favorably with many accepted interventions,57 numerous vaccinations for children,58,59 or other health care for premature infants.60

Our analyses reveal 2 main explanations for these findings. First, the use of palivizumab results in substantially increased expected costs. Second, the use of palivizumab results in very small increases in expected quality-adjusted life-years for all gestational ages. Our model was most sensitive to variation in the quality of life with asthma, with ICERs less than $200 000 per quality-adjusted life-year for some gestational ages (infants born at 26 and 29 to 30 weeks’ gestation) when the quality of life with asthma was reduced to 0.80, and to variation in the cost of palivizumab, with ICERs less than $100 000 per quality-adjusted life-year for some gestational ages (infants born at 26 and 29 weeks’ gestation) when palivizumab costs were only 25% of their current values. The cost-effectiveness of the current guideline for RSV prophylaxis does not compare favorably with many accepted interventions,57 numerous vaccinations for children,58,59 or other health care for premature infants.60

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Our analyses reveal 2 main explanations for these findings. First, the use of palivizumab results in substantially increased expected costs. Second, the use of palivizumab results in very small increases in expected quality-adjusted life-years for 3 reasons: (1) there is no evidence of, nor did we model, a mortality benefit to the use of the prophylaxis; (2) there is no evidence of long-term improvement in the quality of life associated with its use; and (3) if there is an improvement in quality-adjusted life-years owing to a reduced prevalence of asthma, the
value of the improvement is likely to be small. These explanations for the relatively small potential long-term quality of life effects suggest that the overall welfare effects of the prophylaxis strategy will be driven by the cost consequences. Given the current costs of palivizumab, the reduction in other medical and nonmedical costs is simply not great enough to offset the drug costs. Our formulation of a targeted use policy, however, would be considered cost-effective for more restricted use among infants born at 26 or 27 weeks’ gestation, but it is based on the assumption that drug wastage could be eliminated.

Our study has several limitations. First, the cost and length of hospitalization was assumed to be equal for all gestational ages. This assumption will bias our base-case model findings toward improved cost-effectiveness in the more premature infants and worst cost-effectiveness in the less premature infants. Second, the costs of asthma were based on data collected during 1985 to 1994. Finally, 1 assumption was made in our base-case analysis that deliberately biased our results toward improved cost-effectiveness of RSV prophylaxis. We assumed that the weights of the infant at the time of discharge and the time of injections are at 10% of the growth curve. This assumption will markedly reduce the cost of prophylaxis for different gestational ages.

CONCLUSIONS

In conclusion, our model is the first to our knowledge to study the cost-effectiveness of RSV prophylaxis by specific gestational age, to evaluate the implication of the possible increased risk of asthma on the economic analysis of RSV prophylaxis, and to integrate measures of morbidity (quality of life). We found that the current AAP recommendations for the use of palivizumab as RSV prophylaxis in premature infants without chronic lung disease are not cost-effective by today’s standards. Our analyses support the implementation of more restrictive guidelines for RSV prophylaxis for these infants. Additional studies are needed to identify the best way to target RSV prophylaxis guidelines to enhance the cost-effectiveness of palivizumab. We found evidence that long-term health consequences of RSV are central to the determination of the cost-effectiveness of the intervention. In analyses where asthma following RSV infection was considered severe with profound worsening in quality of life (0.8) compared with quality of life without asthma (0.92), palivizumab was marginally cost-effective only for infants born at 26, 29, or 30 weeks’ gestation.

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Statistical analysis: El-Hassan and Dick. Administrative, technical, and material support: El-Hassan and Sorbero. Study supervision: Hall and Dick.

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“In the midst of your illness, you will promise a goat, but when you have recovered, a chicken will seem sufficient.”
—African proverb