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RSV Prophylaxis: Updates and Recommendations

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The Respiratory Syncytial Virus (RSV) is a prevalent virus within the community, affecting patients of all ages. RSV is common amongst children, causing serious respiratory tract infections in a small percentage of pediatric patients. Although RSV infection usually manifests as upper respiratory tract illness most infected patients are asymptomatic, some conditions may increase the risk and severity of RSV, such as prematurity; cyanotic or complicated congenital heart disease (CHD); and chronic lung disease (CLD, formerly called bronchopulmonary dysplasia).[1]

The Respiratory Syncytial Virus (RSV) season begins nationally between October and December and ends February to mid-April, lasting a median duration of 17 weeks or less.[1] Differences in RSV infections rates are thought to be due to weather conditions affecting the transmissibility and viability of the virus.[2] Population density and other demographic factors may also contribute to the variability seen in RSV seasons throughout the nation. The National Respiratory and Enteric Virus Surveillance System (NREVSS) monitors and reports geographical patterns associated with RSV. In the Northwest Region, consisting of Alaska, Idaho, Oregon and Washington, the RSV season onset is variable, starting anytime between October and December and ending around April.[2]

Within Oregon a variety of population densities and weather variations exist, influencing RSV seasons. This variability has made it difficult to define the most appropriate months to initiate and discontinue immunoprophylaxis vaccinations with palivizumab for high risk pediatric patients. The 2010-2011 RSV season started in the beginning of October.[3] Earliest virus detection, meeting onset criteria, was in the Columbia Gorge/North East Oregon Region, while all other regions had yet to meet onset criteria. All regions experienced RSV onset by late December. Season offset was met initially by the North West Oregon/South West Washington region in the third week of April while other regions still had active RSV rates >10% into May.

Palivizumab

Palivizumab (Synagis®) is a monoclonal antibody currently FDA approved for prevention of serious lower respiratory tract infections caused by RSV in pediatric patients at high risk of RSV disease.[4] Palivizumab is dosed based on body weight, 15mg/kg, and provided in vials of 50mg and 100mg to be injected intramuscularly. Palivizumab is given monthly and concentrations remain high enough to be effective 30 days after the last dose. This translates into 5 doses providing protective concentrations for more than 20 weeks.[1] The safety and efficacy of palivizumab has been demonstrated in infants born at or prior to 35 weeks gestational age, infants with CLD and in children with hemodynamically significant CHD.

Palivizumab effectiveness was evaluated in two randomized, placebo-controlled, double blind trials.[5,6] The IMpact-RSV study was done in 1,502 children who were ≤35 weeks gestation and ≤6 months old at the beginning of RSV season (starting in November) or in children with CLD that were ≤ 24 months at the beginning of RSV season.[5] The primary endpoint was hospitalization with confirmed RSV infection. Palivizumab prophylaxis resulted in an absolute risk reduction (ARR) of 5.8% in RSV-related hospitalizations compared to placebo Patients in the prematurity subgroup benefitted the most from palivizumab prophylaxis with an ARR of 6.3% while children with CLD experienced an ARR of 4.9%, versus placebo.

Feltes, et al, studied palivizumab prophylaxis in children with hemodynamically significant CHD.[6] A total of 1,287 children received 5 weight adjusted doses of palivizumab, starting in November, and followed for 150 days. The primary endpoint was antigen-confirmed RSV hospitalizations. Palivizumab prophylaxis was associated with an ARR of 4.4% (p= 0.003), compared with placebo.

There have been no good quality studies that have shown a decrease in RSV related mortality or recurrent wheezing, after an RSV infection, as a result of palivizumab administration.[1]

2009 Guideline Recommendations

In 2009 the The American Academy of Pediatrics (AAP) updated their guidelines for using palivizumab for RSV prevention, with the goal of targeting those children at highest risk for severe disease. Recommendations changed from previous years by taking into account the seasonality of RSV in different regions and the impact on initiation and termination of prophylaxis; targeting those children with the highest risk of severe disease; reducing the number of risk factors to qualify for prophylaxis and changing the maximum recommended doses for certain populations.

Recommendation for Use of Palivizumab for Prevention of RSV[1]

1. Infants with CHD, CLD of prematurity, or birth before 32 weeks 0 days gestation.
2. Infants with a gestational age of 32 weeks 0 days through 34 weeks 6 days born within 3 months before the start of RSV season or at any time throughout the RSV season with at least one of the following risk factors:
    a. Infant attends child care; OR
    b. 1 or more siblings or other children younger than 5 years live permanently in the child's household.
3. Infants born between 32 weeks 0 days and 34 weeks 6 days gestation without hemodynamically significant CHD or CLD who qualify for prophylaxis should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first). This is a change from previous recommendations of 5 months of prophylaxis.
4. Regardless of the month in which the first dose is administered the maximum number of 5 doses is recommended for all regions.(Table 1)

The AAP has determined a maximum of five monthly palivizumab doses is adequate to provide coverage for most areas of the United States, beginning in November with the last dose in March.(Table 1)

Table 1. Maximum Number of Monthly Doses of Palivizumab for RSV Prophylaxis[1]
Infants Eligible for a Maximum of 5 Doses
Infants with CLD, <24 months of age, and require medical therapy
Infants with CHD, <24 months of age and require medical therapy
Premature infants born at ≤31 weeks 6 days
Certain infants with neuromuscular disease or congenital abnormalities of the airways
Infants Eligible for a Maximum of 3 Doses
Premature infants with a gestational age of 32 weeks 0 days to 34 weeks 6 days with at least 1 risk factor and born 3 months before or during RSV season

Cost

Studies have shown that immunoprophylaxis with palivizumab can reduce hospitalizations, especially during peak viral activity. Due to the cost of palivizumab, which is estimated at $1661-2584 a dose (dependent upon the child's weight), it is important that palivizumab be used judiciously.[7]

Many cost effectiveness analyses on prophylaxis against RSV infection with palivizumab have been preformed.[7,8,9,10,11,12,] Two studies in Medicaid populations have shown reductions in hospitalizations and hospitalization costs, but failed to show cost-effectiveness or decreases in direct costs.[8,9] Systematic reviews have found that cost-effectiveness ratios tend to fall below accepted thresholds, yet, accepted cost-effectiveness has been achieved when high-risk infants with risk factors are targeted.[10,11,12]

Cost-effectiveness analyses are subject to limitations including changing practice recommendations that may influence conclusions. None of the published cost-effectivness studies include the most current AAP recommendations for palivizumab prevention of RSV, which targets children at the highest risk. Additional study limitations are listed below (Table 2).

Table 2. Limitations of Cost-Effective Analyses
1. Cost data sources are variable (acquisition costs and hospitalization costs)
2. Criteria for hospitalization not reported in all analyses.
3. Differences in RSV rates, depending on year and geographic region.
4. Use of sub-group efficacies versus overall efficacies in determining costs.
5. Perspective of analyses varies (society, payer or provider).

A recent example of a study whose conclusions are limited by the above study design issues is a cost-effectiveness analysis by Hampp, et al, which studied palivizumab for RSV prophylaxis for various indications.[7] Data from 159,790 children, ages 0 to 2 years, from the Florida Medicaid system during the 2004-2005 RSV season were analyzed. A decision tree analysis was used to compare children with the following indications: CLD, CHD, or prematurity (≤ 32 weeks gestation) and children with none of these indications. Children were compared using palivizumab prophylaxis versus no prophylaxis with the outcome measure being incremental cost (2010 US dollars) per hospitalization for RSV infection avoided. Medicaid payment amounts, based on National Drug Codes, were used to generate mean palivizumab costs and hospitalization expenses were based on inpatient claims paid by Medicaid.

Almost three thousand children received palivizumab, totaling 9805 doses. Mean palivizumab cost per dose ranged from $1,661 for infants younger than 6 months to $2,584 for children up to 2 years of age. Hospitalizations related to RSV occurred in 1,116 children, with high risk children accounting for 98 visits. Costs associated with RSV ranged from $5,069 in children with no indication to $12,103 in children with CLD. Palivizumab was most cost-effective in children of younger age and with multiple indications. In children 0-2 years old, with an indication for prophylaxis, the incremental cost-effective ratios ranged from $302,103 to over $1.3 million per RSV-related hospitalization avoided. The most cost-effective sub-group was premature infants, 6 months or younger, with no other indications. To prevent one RSV-related hospitalization in this group, palivizumab prophylaxis cost $302,103 (95% Confidence Interval (CI), $141,850-$914,798). Palivizumab immunoprophylaxis would be cost neutral at a per-dose cost of $47, given the mean cost of a RSV related hospitalization in this population being $8,910. This analysis included children identified for prophylaxis according to older guideline recommendations and children that were prescribed palivizumab inappropriately, creating potential bias to favor a less cost-effective scenario. Utilizing Florida demographic data, which is known for a unique onset and offset of the RSV season, may lend the results to being less applicable to other areas of the United States.

The Canadian Agency for Drugs and Technologies in Health (CADTH) examined the data in a 2006 report on palivizumab prophylaxis for RSV. This report included clinical effectiveness data as well as cost and economic evaluations. CADTH concluded that palivizumab should be considered for children at highest risk, such as those with CLD and premature infants, ≤32 weeks gestation.[13]

Summary

Palivizumab is an effective prophylactic measure against RSV in select, high risk patients. AAP guidelines reiterate the importance of utilizing palivizumab in identified high risk infants and children. By identifying infants and children appropriately and limiting the number of palivizumab doses to five a season, palivizumab prophylaxis will be used to its maximum benefit.

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