Palivizumab Prophylaxis for Healthy Preterm Infants: More Data Supporting American Academy of Pediatrics Guidelines

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As licensed by the US Food and Drug Administration, "palivizumab is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease".[1] The American Academy of Pediatrics (AAP) Committee on Infectious Diseases has endeavored to provide pediatricians and other health care providers with guidance for determining who is at high risk for RSV disease since palivizumab was first licensed in 1998.[2] Over the years, evidence has accumulated regarding the risk of RSV hospitalization and the AAP guidance for palivizumab use has become more restrictive. The most recent recommendations,[3] published in 2014, removed otherwise healthy preterm infants born at or after 29 weeks of gestation from the high-risk groups recommended to receive palivizumab prophylaxis.

In this issue of *Pediatrics*, Farber et al[4] provide data from nine Medicaid managed care health programs in Texas supporting the 2014 recommendation. The investigators evaluated the effect of palivizumab administration on hospitalization for bronchiolitis with or without an RSV diagnosis among healthy preterm infants born at 29 to 36 weeks of gestation during their first RSV season occurring in 2012, 2013, or 2014.[4] These infants did not have conditions known to increase hospitalization rates for RSV, specifically, chronic lung disease of prematurity or congenital heart disease. Although the recommendations to limit use of palivizumab in healthy preterm infants were released in July 2014, the Texas Medicaid program did not fully adopt them until 2015. Interestingly, even though they would have qualified under previous guidelines, the majority of the infants in the Farber study[4] evaluated from 2012 to 2014, did not have paid claims for palivizumab. Overall, only 9.1% of healthy preterm infants born at 29 to 36 weeks of gestation received 1 or more doses of palivizumab; 41.5% of 29–32-week infants and 3.7% of 33- to 36-week-old infants. In addition, ~1 of every 3 infants born at 29 to 32 weeks of gestation received <50% of the recommended doses. These data indicate that in a real-world setting, even before the more restrictive guidelines were published, health care providers were either not prescribing or parents were not obtaining palivizumab for the majority of healthy preterm infants. This finding indicates that the more restrictive guidelines may not substantially change real-world practice.

One important finding of the Farber study is the rate of RSV hospitalization amongst these preterm infants. Of preterm infants evaluated, 4.2% had an RSV hospitalization and the rate of hospitalization was identical for 29-32 week and 33-36 week infants. This result is similar to the rates of hospitalization reported in preterm infants born at

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32–34 weeks in Medicaid populations in Texas (4.5%) and Florida (3.1%) during the years 1999 to 2004, which were modestly higher than for term infants in the same study, who had rates of RSV hospitalization ranging from 1.5% to 2.5%.[5]

In the Farber study,[4] as in other recent studies, the proportion of preterm infants hospitalized for RSV was lower than that observed for the IMPACT-RSV trial (8.1% for preterm infants without bronchopulmonary dysplasia).[6] The IMPACT-RSV trial provided the basis for US Food and Drug Administration licensure of palivizumab and was conducted during the 1996 to 1997 RSV season. In the 2 decades since, criteria for hospitalization have changed, bronchiolitis hospitalizations for all infants have substantially decreased, and mortality associated with RSV has also decreased.[7,8] Specifically for preterm infants, advances in neonatal care have resulted in fewer infants with chronic lung disease. Households are also less likely to expose infants to second hand smoke, breast-feeding rates have increased, and more families are practicing cocooning of infants by immunizing family members against respiratory pathogens, such as influenza and pertussis. All of these interventions may contribute to healthier preterm infants who are less likely to have severe RSV disease and thus less likely to require hospitalization. Because the only known benefit of palivizumab prophylaxis is a reduction in hospitalization, the national trends toward lower hospitalization rates impact the potential utility of palivizumab.

Farber et al[4] did report a small difference in RSV hospitalizations in infants born at 29 to 32 weeks of gestation receiving palivizumab when compared with those who did not receive prophylaxis (3.1% vs 5.0%). A small number of infants who received 80% to 100% total doses of palivizumab accounted for this reduction, indicating that protection is likely related to duration of potential exposure and cumulative effect of repeated dosing. There was no difference in RSV hospitalizations for the 33- to 36-week age group regardless of receipt of palivizumab.

An additional 2.3% of preterm infants had bronchiolitis hospitalizations without a diagnosis of RSV. Although it is possible that these infants had undiagnosed RSV, we believe that this explanation is increasingly unlikely. Rapid and accurate diagnostic testing is available for RSV and is widely used. In addition, new diagnostic testing for a wide variety of respiratory pathogens has demonstrated that multiple viruses, such as coronaviruses, human metapneumovirus, influenza virus, parainfluenza virus, and rhinovirus, circulate at the same time as RSV and cause bronchiolitis syndromes that are indistinguishable clinically from RSV.[9,10]

A unique finding of the Farber study[4] is the identification that palivizumab prophylaxis was associated with hospitalization for bronchiolitis because of viruses other than RSV. This finding is biologically plausible in that multiple respiratory viruses circulate during the winter season and can result in bronchiolitis in susceptible infants. For those infants who have antibody protection against RSV acquired through palivizumab administration and who also have bronchiolitis, the cause may be a virus other than RSV. Bronchiolitis is a common clinical syndrome and the consequences of non-RSV bronchiolitis hospitalizations during infancy are not fully known. For example, a recent publication by Mansbach[11] demonstrated that infants and young children with rhinovirus and bronchiolitis were more likely to develop asthmalike characteristics than those with RSV.

Finally, because the data were obtained from health plans, some financial information was included in the Farber study.[4] As noted by others,[12] the cost of palivizumab administration was high at both the infant and population level ,and the effect of palivizumab was limited. The 29- to 32-week preterm infants had a difference in hospitalization rates of 1.9% between infants who did or did not receive palivizumab. Of the 1186 infants in this age cohort who did not receive palivizumab, this difference translated into ~22 additional hospitalizations over the 3-year study period.

In summary, within the known limitations of a retrospective review of *International Classification of Diseases, Ninth Revision*–coded claims as discussed by the authors, the data presented in this study provide a real life perspective on the use of palivizumab. In this vulnerable Medicaid population of otherwise healthy 29- to 32-week preterm infants, limited utilization and benefits of palivizumab were observed and no benefits were observed for those born between 33 and 36 weeks. Introduction of more restrictive guidelines in 2014 are likely to have had little impact in this population. In an era in which the overall rate of hospitalization for RSV bronchiolitis has decreased, the study by Farber et al[4] lends additional support to the 2014 AAP guidelines for palivizumab prophylaxis.

ABBREVIATIONS

AAP: American Academy of Pediatrics
RSV: respiratory syncytial virus

from BioFire Diagnostics, Inc (Salt Lake City, UT). Dr Munoz is an investigator for clinical trials of an respiratory syncytial virus (RSV) vaccine with Novavax, of an RSV antiviral with Alios, and of an RSV immunoprophylaxis agent with Regeneron. Funds for these efforts are provided directly to Baylor College of Medicine.

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