ABSTRACT

Palivizumab reduces hospitalization for children at risk for respiratory syncytial virus. However, with no significant reduction in the rate of mortality or long-term risk of wheezing or asthma, as well as the high cost of the drug, its use must be carefully controlled. Yet there is evidence that adherence to palivizumab is less than optimal, which could have significant economic implications as well as lead to increased morbidity and mortality. This article discusses the barriers to adherence as well as the implications of the 2009 updated guidelines for the use of palivizumab from the American Academy of Pediatrics. (Adv Stud Pharm. 2010;7(4):105-109)

The primary benefit of respiratory syncytial virus (RSV) prophylaxis with palivizumab is its ability to reduce hospitalization for at-risk children. Unfortunately, there is still no evidence of any significant reduction in the rate of mortality or long-term risk of wheezing. In addition, the high cost of the drug limits its cost effectiveness to children at the highest risk of hospitalization, including those with chronic lung disease, congenital heart disease, and prematurity. A recent study estimated the mean cost of RSV-related pediatric hospitalization in 2007 dollars at $9000 for full-term infants, $13,876 in infants born prior to 33 weeks gestation, and $18,403 for infants born between 33 and 36 weeks gestational age.

Given the cost savings potential of appropriate RSV immunoprophylaxis, most managed care organizations (MCOs) spend considerable effort to ensure that high-risk members receive prophylaxis as directed. What they often cannot control, however, is whether the child receives the injections as authorized once authorization is provided.

A recent literature review of 25 articles and abstracts found that compliance with palivizumab prophylaxis ranged from 25% to 100%, with compliance lower among Medicaid patients (78% Medicaid vs 85% non-Medicaid, P <.001) and African American patients (48% of whom did not receive all dosages), as well as other minorities.

One barrier to successful completion of the prescribed course of prophylaxis is parental perception of its importance. In a survey mailed to the families of 385 high-risk children who were eligible to receive palivizumab, researchers found higher compliance among parents who believed the injections would protect their child against RSV infection “some” or “a lot,” versus those who responded “not at all” or “a little” when asked about their perception of protection (88% compliance in “believers” vs 53% in skeptics [P <.001]). Parents who worried
about their children being infected with RSV were also more likely to be compliant ($P = .03$).

Cost is a factor if parents have co-payments, and negotiating with the insurance company to get the treatment is another concern.\(^{15}\)

Lack of transportation is another significant barrier, with 35% of noncompliant parents versus 15% of compliant parents reporting difficulty with transportation ($P = .004$).\(^{14}\) Studies outside the United States find that compliance tends to improve as the RSV season progresses, perhaps suggesting that parents become more concerned about infection closer to the peak of the outbreak.\(^{16}\) Language difficulties and parental smoking also are associated with non-compliance.\(^{17}\)

We know that parents view the monthly injections as a burden, particularly because their child is not ill. They do not understand that skipping a dose could lead to serious health problems.

For all these reasons, it is important that health plans ensure that once the approval or prior authorization is given for immunoprophylaxis, the patient receives the injections. Although it may reduce cost in the short term, missed opportunities for RSV prophylaxis could increase costs in the long term if that child requires hospitalization.

The physician also has a responsibility in terms of adherence. Some physicians schedule specific days for patients with RSV to receive prophylaxis so all patients receive injections on the same schedule. There is also evidence that providing parental education, including a letter from the primary care physician, can improve compliance.\(^{14}\)

Physicians should also follow up with parents whose child misses a dose. Finally, they should know how to store the medication in the office to ensure an adequate supply.

**Managed Care Implications of 2009 American Academy of Pediatrics Recommendations**

The major implication for MCOs stemming from the 2009 American Academy of Pediatrics (AAP) recommendations for RSV immunoprophylaxis is an expanded population. The new guidelines state that prophylaxis should be given to “infants born at 32 weeks, 0 days through 34 weeks, 6 days . . . born at the start of or during RSV season and who are likely to have an increased risk of exposure to RSV.”\(^{18}\) The risk factors the committee references are present in the majority of children.

It may be difficult to insure discontinuation after 3 doses. Although many providers follow recommendations, some will prefer to give a fourth dose to a child who, under the guidelines, should only receive 3 doses. Thus, it is important that MCOs discuss the AAP guidelines and how they will be implemented within a plan with physicians. In our plan, we told providers that we would consider additional doses if they provided information demonstrating that the child still had a risk of infection. We received a minimum of such requests during the 2009–2010 RSV season.

Another issue that often arises, given the seasonality of RSV, is when to begin prophylaxis. Current literature suggests starting when more than 5% of isolates circulating in the community test positive. Previous recommendations were based on the number of confirmed cases, but the percent of positive isolates appears to trend more closely to the actual amount of virus in the community. The isolate test can be performed with a standard nasal swab and assessed at most reference laboratories.

Another important issue is coordination with the neonatal intensive care unit (NICU). The AAP recommends that hospitalized infants who qualify for prophylaxis during the RSV season receive the first dose 48 to 72 hours before discharge or immediately after discharge. Infants who began the series before hospitalization should continue to receive scheduled dosages while hospitalized.\(^{18}\)

Although a review of 6 studies related to the timing of palivizumab in hospitalized infants found no benefit to providing the first dosage while hospitalized,\(^{19}\) it is common practice that high-risk infants in the NICU receive their first immunoprophylaxis dose just before discharge. The problem occurs if the infant is not discharged due to a relapse or other reason. Should the infant then receive additional prophylaxis while hospitalized? Because if appropriate infection prevention guidelines are followed in the hospital, the risk of RSV infection is very small.

In-hospital administration also results in financial and utilization issues because the drug is often billed under medical expenses as part of the total per-day or diagnosis-related group (DRG) charge unless MCO contracts with the hospital specifically include a carve out. Or, as occurs under some contracts, palivizumab is considered an outpatient drug
so the hospital receives no reimbursement.

In addition, if a child receives the first injection prior to discharge but the information is not communicated to the outpatient physician, the child may receive an additional, unnecessary dose. Ideally, the pediatrician should coordinate prophylaxis after discharge but this is also an area in which the MCO can become involved to ensure appropriate follow-up.11

In conclusion, the revised AAP guidelines will challenge MCOs in several areas, including expanded eligibility for treatment; defined risk factors that are present in a majority of children; difficulty enforcing discontinuation after 3 doses; and tracking utilization and monitoring care and adherence for infants who are eligible for 3 or fewer doses.

DISCUSSION

Dr Buckley: Is there evidence that if patients are not compliant that there is an increase in hospitalization if they only get 3 out of the 5 doses?

Dr Burgoyne: I have not seen any. I doubt if anybody else around the table has seen it. I think it is more our concern, the natural pharmacist response. We expect the patient to be compliant. If he or she is not compliant, it results in poor outcomes.

Mr Calla: That is one of the big debates out there right now. If you do not take the full 5-dose regimen, are you truly increasing hospitalization? It is an unanswered question, at least from what I can see, whether 3 or 5 doses. It is part of why the AAP went down to the 3-dose regimen in that particular set of patients as opposed to 5 doses.

Doug, why do you think the 3-dose regimen will be difficult to enforce? Difficult because somebody may say, “Well, we need a fourth dose,” but not difficult to enforce from a managed care perspective of knowing that that fourth dose may be requested?

Dr Burgoyne: Right. The child is now 3 months old. He has had 3 doses. He was born at 34 weeks and 3 days and the physician says, “We need the fourth dose,” and it is February.

Mr Calla: That you would not give that today in your plan, would you?

Dr Burgoyne: No. But 90 days is not a magical number. It is not as if they turn 90 days and then risk is dissolved. There is still an elevated risk after the 90 days. And I think that is probably more where it is coming from. It also depends on the type of provider because there are providers who follow infectious disease and their recommendations, and then there are those who tend to practice in different ways. So it is having the conversation with the provider that we are going to have to make this decision based on where the infant is at most risk.

And we have told providers we would consider additional doses, but they need to provide us with information that shows that the infant is still at continued risk. That has really been minimal this year.

Dr Rich: So another question I had is you both talked about the start of the season. And we know, obviously, that it varies based on where you are located. How are we determining the start of the season? Are we waiting for a first infection and then we say, “Okay, the season must have started.” Are we doing any type of microbiology?

Dr Buckley: Yes. The most current literature suggests that you start it when more than 5% of isolates tested are positive. Previously, it was number of confirmed cases, but the percent positive seems to trend better depending on the population density of the area.

Dr Rich: So would that be a routine test that would be ordered on a child with any type of respiratory problem too?

Dr Buckley: Exactly. They get a standard nasal swab, particularly this year with concerns about H1N1 influenza.

Dr Lee: We did the same thing. If they came in and thought they had the flu they received complete testing.

Dr Rich: Are there any hospitals that are giving prophylactic doses while the baby is in the NICU rather than just ready to discharge?

Dr Lee: We very much discourage that. It does happen in our hospital, and we end up sending doses before the baby is discharged. Most of the time it is not intentional. But if they think the baby is going home soon and then the baby gets sick again and does not leave, then you have to make the decision because it is hard to stop once you have gotten started in the hospital. So sometimes the baby may be there another 2 months, and then you have to decide, “Well, do they get the next dose or not?” And it is hard to convince the neonatologist not to do that once that baby has started.

Dr Rich: But, would you not be immune from getting RSV just because you are in the hospital?
Dr Lee: Well, you pretty much are if you are adhering to hand washing and there is no RSV outbreak in the hospital. We do not see RSV infection linked to a hospital stay.

Dr Burgoyne: So the trick is how to stop prophylaxis once they start. And from the managed care side, how to find those data, because it could go through under the medical billing. It will end up as a J code somewhere or it is part of a DRG.

Dr Rich: It is completely lost.

Dr Burgoyne: Thus the infant might have had 2 doses accidentally or, in the situation you just described, they thought they were going home and they did not go home.

Mr Calla: So in that situation, the patient could get another 3 doses on top of the 2 doses.

Dr Burgoyne: They could, yes, easily.

Mr Calla: So now you are back to the 5 doses.

Dr Rich: It also would seem there might be a disconnect because when do you transfer care from the neonatologist to the pediatrician?

Dr Lee: That is a good question. And that is something that we have a real hard time with in the hospital. I do not know how you even go about coordinating it when the neonatologist, obviously, wants the dose before they leave the hospital. But it would be beneficial to the hospital because of the cost if the pediatrician took control of the patient before they left so the prophylaxis can be coordinated through their office instead of the hospital providing the dose.

The hospital is not automatically reimbursed for the drug because in Tennessee (under TennCare) it is considered an outpatient drug. So if you give it in the hospital in an inpatient setting, it just falls under the whole patient reimbursement with no additional reimbursement. Thus, it would be nice to be able to coordinate with pediatricians. But we have not figured out how to do that.

REFERENCES

16. Macagno F. Main results of a national multicenter study assessing the compliance of pediatric centers to Italian

