Can a Reduced-Dose Prophylaxis Schedule Provide Adequate Coverage Against Respiratory Syncytial Virus Infection?

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(See the Major Article by Weinberger et al on pages 506–14.)

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The current issue of Clinical Infectious Diseases includes an article by Weinberger et al, who have built on previous work documenting the variability of the respiratory syncytial virus (RSV) season in different US localities and correlates of such variability [1]. Using this information, the authors compared various regimens of RSV prophylaxis with palivizumab and found that a regimen of 4 monthly doses tailored to historical local data may provide similar protection to a 5-dose regimen based on either historical local data or the current national recommendations.

Reducing the number of palivizumab doses per eligible infant or child from 5 to 4 in a given RSV season, as proposed by Weinberger et al, appears promising in that it may decrease drug acquisition and administration costs by 20%. However, other alternative regimens or combinations of alternatives deserve consideration. In a recent publication, Gutfraind et al developed a mathematical model that considered the pharmacokinetics, timing of injections, and seasonal patterns of RSV hospitalizations, and proposed a prophylaxis schedule with optimal start dates for 3-, 4-, and 5-dose regimens in combination with a shorter spacing interval between doses 1 and 2 (29 days) and an extended spacing interval between subsequent doses (38 days) [2]. Based on this spacing, a 4-dose regimen would be expected to reduce coverage by only 1 week compared with the standard regimen of 5 monthly doses (143 days vs 150 days). Modified spacing between doses is further supported by epidemiologic studies that showed higher percentages of RSV-related hospitalizations after dose 1 compared with subsequent doses [3], and substantial residual effectiveness beyond 30 days after the last dose [4]. In addition, a pharmacokinetic model suggested modifications in dosing strength in combination with altering the intervals between doses [5]. Focusing particularly on the concern of low serum levels of palivizumab between doses 1 and 2 offered by the current schedule (ie, doses of 15 mg/kg body weight, spaced 30 days apart), Zaaijer et al developed a model to increase serum levels while reducing the cumulative amount of drug needed and providing reasonable serologic protection throughout a season. They accomplished this by making just 2 changes to the current regimen: reducing the time interval between doses 1 and 2 to 23 days, and reducing the strength for doses 2 and beyond to 10 mg/kg body weight.

In contrast to the studies suggesting that a reduced dose schedule may be nearly as effective as the current schedule, a study funded by the manufacturer of palivizumab found that partial prophylaxis during the RSV season led to 21% higher odds for hospitalization compared with full prophylaxis [3], and those authors concluded that reduced and/or delayed dosing is less effective. However, in the Krilov et al study, >30% of children received their first dose after 30 November and the mean gap length was approximately 50 days among doses that were spaced >35 days apart. Thus, the study evaluated the effects of substantial noncompliance with the conventional dosing schedule and not the effects of compliance with an alternative, optimized dosing schedule. However, the Krilov et al study highlights the importance of regular adherence to a dosing schedule, whatever the optimal schedule may be. Arguably, fewer office visits associated with a reduced dose regimen may result in improved adherence.

Any alternative regimen should be designed keeping in mind the importance of...
the start date of prophylaxis, so that children reach immunity during the onset of the season and are well protected during the peak months. In contrast, residual immunity, combined with declining viral activity toward the end of the season, may result in protection well beyond 30 days past the end of the season, may result in poor protection. Randomized clinical trials would provide the most valid evidence to support alternative dosing regimens. However, effect sizes or noninferiority margins in trials that compare different regimens are expected to be small, resulting in the need for very large samples, which makes their conduct unlikely. In the absence of randomized trials, high-quality epidemiologic and modeling studies, such as the ones discussed here, can help support the case for alternative dosing schedules.

Since the American Academy of Pediatrics’ (AAP) palivizumab guidelines were first published in 1998, [6] they have been updated 5 times—most recently in 2014 [7]. Throughout their evolution, the guidelines have gradually moved away from recommending that providers consult local health department, diagnostic virology laboratory, and/or Centers for Disease Control and Prevention data to determine the optimal timing of RSV prophylaxis administration. Current guidelines no longer mention the use of local data (with the exception of Florida) and now recommend that providers consult local geographic areas in the continental United States start prophylaxis in November. This more uniform approach eases the burden on providers to obtain local data; however, it may not be as effective as the former approach that relied partly on real-time or historical local data. The method suggested by Weinberger et al offers a compromise between these 2 approaches by proposing specific, constant RSV prophylaxis start dates that can vary by geographic area. In addition, their results could be readily applied in clinical practice, as optimal start dates for 38 US states and predicted optimum start dates for all US counties are provided in their Table 1 and Supplementary Appendix [1]. Reliance on such fixed, local start dates instead of real-time local surveillance data would allow appointments to be scheduled well in advance and thus provide protection at the start of the RSV season when immunity is likely to be the lowest. Recent publications, including the Weinberger et al study, provide the opportunity for the AAP to determine whether such studies utilize local RSV data in a manner that supports revisions to the palivizumab guidelines, or whether more complex models, observational studies, or clinical trials are needed.

With the proposal of an alternative RSV immunoprophylaxis schedule, the Weinberger et al study has raised an important question for practitioners, public health professionals, policymakers, payers, and manufacturers. Are we as a society willing to increase children’s susceptibility for RSV hospitalization by reducing the palivizumab dosing schedule from 5 to 4 doses when the latter may not be quite as effective as the former? On one hand, although 90%–98% of hospitalizations would have been captured by the reduced-dose schedule suggested by Weinberger et al, due to the high rates of hospitalization among high-risk infants, a sizeable number of children would be at increased risk. On the other hand, given the high drug acquisition cost, a 20% reduction in palivizumab doses per eligible infant or child during each RSV season could make financial resources available to other public health priorities, whose benefits may outweigh the additional number of RSV hospitalizations associated with a reduced-dose regimen. Cost-effectiveness analyses that incorporate RSV seasonality should examine the cost-effectiveness of immunoprophylaxis during the shoulder months of a season to better inform considerations of revised dosage schedules.

Finally, the development and availability of a biosimilar [8] for palivizumab or even an RSV vaccine [9] may reduce costs and mitigate the need for such rigorous evaluation of various drug regimens, some of which may be difficult to implement in practice. In particular, an RSV vaccine would be expected to further reduce both cost of prophylaxis and the burden of RSV disease. In the absence of such interventions, alternative RSV prophylaxis regimens should continue to be explored and considered in future recommendations.

Notes

Disclaimer. C. H. participated in the commentary based on his expertise derived prior to employment with the Food and Drug Administration (FDA). The views expressed are those of the authors and do not necessarily reflect the views of the FDA or the US government.

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