Reassessing the Cutoff Level for Poliovirus Antibody in Patients after Successful Chemotherapy for Leukemia or Hematopoietic Stem Cell Transplantation

To the Editor—The serologic profile of poliovirus neutralizing antibody in patients with acute leukemia prior to vaccination against poliovirus and after treatment for leukemia revealed that almost 11% of patients had protective antibody to all 3 poliovirus serotypes. After 12 months of vaccination, only 47% of patients had protective antibody to all 3 poliovirus serotypes. The antibody titer cutoff used to label disease protection was \( \geq 1:8 \) [1]. Identical susceptibility in children after hematopoietic stem cell transplantation before and after vaccination was 29% and 92%, respectively [2]. With the imminent global control of polio, the antibody titer cutoff level in patients after completion of successful chemotherapy for leukemia or after hematopoietic stem cell transplantation would be worth scrutiny. The prevailing \( \geq 1:8 \) titer might be responsible for false confidence.

The existing cutoff level of \( \geq 1:8 \) has been known to be protective against wild or Sabin attenuated poliovirus strains. This titer might not be adequate against any budding vaccine-derived poliovirus isolates. Recently, type 2 and type 3 evolving or highly divergent vaccine-derived poliovirus isolates were isolated from sewage in Israel. Neutralization data on these isolates demonstrated viral genetic diversity and antigenic divergence. During their neutralization, there was an average 3.3-fold decrease in geometric mean titer, even though the protective antibody titers for Sabin and wild strains exceeded \( \geq 1:8 \). Moreover, 10 (7%) of 150 individuals aged 20–50 years had titers below the minimum protective level of \( \geq 1:8 \) against \( \geq 1 \) vaccine-derived poliovirus strain [3].

Prospective studies to work out the use of simpler vaccination schedules for any earlier vaccinations after successful chemotherapy or transplantations [1, 2] should aim to express polio antibody quantum in international units, rather than use an arbitrary dilution figure. Prospective comparison of inter- and intralaboratory serologic data would be better illustrated with the use of international units. The antibody content would be more explicit if expressed in international units, rather than using an arbitrary dilution figure. Serologic data on representative post-OPV serum samples from Germany were expressed in such units [4].

Acknowledgments

Potential conflicts of interest. S.C.A and N.A.: no conflicts.

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References

Pneumococcal Vaccination of Children after Hematopoietic Stem Cell Transplantation: Timing Is Crucial

To the Editor—We read with great interest the report by Patel et al. [1] regarding serologic responses to the current British reimmunization schedule among children who have undergone autologous (8 children) or allogeneic (30 children) hematopoietic stem cell transplantation (HSCT). The article elegantly demonstrates that vaccination with tetanus, Haemophilus influenzae type B, meningococcus C, measles, poliovirus serotypes 1, 2, and 3, and heptavalent pneumococcal conjugate vaccines provides a high level of protection against these vaccine-preventable diseases. In the study by Patel and colleagues, vaccination was initiated at \( \geq 12 \) months after autologous and HLA-identical sibling HSCT and at \( \geq 18 \) months after unrelated donor HSCT. On the basis of the significant morbidity and mortality associated with invasive pneumococcal disease within the first year after allogeneic HSCT, we are, however, greatly concerned about the timing of pneumococcal vaccination in the British schedule, in which vaccination was started not earlier than 15 and 21 months after HLA-identical sibling and unrelated donor HSCT, respectively. In this regard, we agree with Chisholm [2], who concludes that the study by Patel and colleagues provides a platform on which further studies should evaluate the earlier start of reimmunization after allogeneic HSCT.

We have recently completed the prospective IKAST vaccination trial (NCT00169728) among pediatric recipients of allogeneic HSCT, in which we aimed to start vaccination as early as 6 months after transplantation. In the
IKAST trial, children and adolescents aged \( \leq 18 \) years were vaccinated with 3 doses of heptavalent pneumococcal conjugate vaccine (Prevenar, Wyeth Pharma), along with a hexavalent tetanus, diphtheria, pertussis, poliovirus, *Haemophilus influenzae* type B, and hepatitis B combination vaccine. In contrast to the study by Patel et al. [1], vaccination was supplied irrespective of donor type (i.e., HLA-identical sibling donor or unrelated donor) and the presence of immunosuppressive medication and/or graft-versus-host disease. In our study [3], we provide the first evidence that early vaccination with heptavalent pneumococcal conjugate vaccine, along with a hexavalent combination vaccine, is safe and elicits protective antipneumococcal antibody responses against all vaccine serotypes within the first year after transplantation in the majority of pediatric recipients of related or unrelated donor HSCT. Thus, our data strongly suggest that all children undergoing allogeneic HSCT should receive heptavalent pneumococcal conjugate vaccination starting as early as 6 months after transplantation.

**Acknowledgments**

Potential conflicts of interest. R.M. and D.D. have received research grant support from Wyeth Pharma (Munster, Germany) and GlaxoSmithKline Pharma (Munich, Germany).

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Clinical Infectious Diseases 2007;45:297–8

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**Reply to Arya and Agarwal and Meisel and Dilloo**

To the Editor—We thank Drs. Arya and Agarwal for their letter [1] and agree that, in principle, the development of the World Health Organization international antibody standards, such as that available for polio neutralizing antibody assays, is valuable for standardizing results between laboratories.

In our studies [2, 3], we measured polio neutralizing antibodies according to the World Health Organization microneutralization procedure [4]; this procedure reports neutralizing antibody titers. The presence of serotype-specific neutralizing antibody detected in this assay at a serum dilution of 1:8 is interpreted as indicating immunity. We have acknowledged in our articles that, although this antibody titer is used as the protective threshold, it may not necessarily apply to immunocompromised hosts. A subsequent World Health Organization document recommended the use of the international standard for polio antibody to allow results to be reported in terms of international units [5]. This recommendation has not been widely adhered to, however, because a protective threshold in terms of international units has not been clearly established [6]. Expressing polio neutralizing antibodies in terms of international units would, therefore, have not made a contribution to our study, because we were aiming to describe the proportions of children achieving protective antibodies and/or titers against a range of vaccine antigens.

We also thank Drs. Meisel and Dilloo for their letter [7]. We agree that, in view of the increased susceptibility of hematopoietic stem cell transplant (HSCT) recipients (particularly allogeneic HSCT recipients) to pneumococcal disease within the first year after HSCT, it would be preferable to be able to administer the pneumococcal conjugate vaccine earlier than is currently recommended in the British schedule [8]. The British schedule has been based primarily on expert opinion and on the limited published studies available. Our study [3] evaluated the immunogenicity of the British schedule, and our intention has been to use these data as a platform for further studies. We welcome the publication from this group and their very promising data regarding earlier revaccination with pneumococcal conjugate vaccine [9].

Our study [3] demonstrated that the conjugate vaccines, *Haemophilus influenzae* type b and *Neisseria meningitidis C* vaccines, when administered earlier (at 12 months after HSCT for autologous and HLA-matched allogeneic graft recipients and at 18 months after HSCT for other allogeneic graft recipients) than pneumococcal conjugate vaccine in the schedule evoked protective antibody responses. We would, therefore, expect similarly good responses to pneumococcal conjugate vaccine when administered earlier. In the study by Meisel et al. [9], 55% of patients achieved protective antibody responses against all 7 serotypes when 2 doses were administered as early as 6–9 months after HSCT. The response rate increased to 74% when 3 doses were administered at monthly intervals. Our study [3] demonstrated that 2 doses of pneumococcal conjugate vaccine administered at a median time of 23 months after HSCT resulted in 92% of patients achieving protective antibody responses against all 7 serotypes (albeit, using a lower “protective” threshold of 0.35 μg/mL). Additional studies are warranted to support these data, and consideration might be given to the implementation of early 2-dose schedules (with doses given 2 months apart),