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Vaccination of Children following Allogeneic Stem Cell Transplantation

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INTRODUCTION

Despite guidelines from the Centers for Disease Control (CDC) [1] and European Blood and Marrow Transplant (EBMT) center [2], most centers do not consistently revaccinate patients following hematopoietic stem cell transplantation (HCT) nor know the efficacy of these guidelines in their patient population [3]. The current guidelines advocate initiation of posttransplant vaccination at 6-12 months post-HCT, irrespective of an individual's level of immune competence (Figure 1). Nevertheless, the kinetics of T and B cell reconstitution following a related or unrelated transplant (Figures 2 and 3), affected by age and the presence or absence of graft versus host disease is variable. Although vaccination of all transplant patients using a standard time table may be a simple and less costly intervention, proof that it is efficacious for all vaccine types is lacking. Over the last decade improved disease-free survival (DFS) following HCT [4-8] has resulted in increasing numbers of HCT survivors returning to school and the workplace. Whereas immunization of healthy children and young adults is considered protective because of the >90% seroconversion rates observed (reviewed in [9]), the ability of HCT patients to respond to childhood vaccines is less well known (reviewed in [3]). A number of studies have demonstrated that in the absence of revaccination, levels of preexisting antibody titers wane with time post-HCT (reviewed in [3]). By 2 years post-HCT, most patients will have lost protection against tetanus [10], although approximately 50% will have persistent titers against measles, mumps, and/or rubella [11]. This unfortunately lulls physicians into omitting measles, mumps, and rubella (MMR) revaccination in patients capable of response [12], most of whom will have lost seroprotection within 3 to 5 years post-HCT [11]. During the last decade, outbreaks of measles [13,14], mumps [15], pertussis [16], and varicella [17] have occurred in the United States. The index cases were either unimmunized individuals [13-15] or previously immunized individuals [17] who lost protective antibody. Breakthrough outbreaks of varicella have occurred. These outbreaks stress the continued vulnerability of inadequately vaccinated HCT patients and the need for proven vaccine trategies.

Vaccine preventable infections, including, but not limited to pneumococcus [18-20], influenza [21], and varicella [22-24] remain a significant cause of morbidity, rehospitalization, and mortality late after successful HCT. A European survey [18] reported invasive pneumococcal infections in 12.2/1000 alloHCT recipients, 10 times the reported incidence in healthy individuals, excluding infants and the elderly. Eighteen percent of pneumococcal infections were fatal. Chen et al [20] evaluated the incidence of pneumonia in 1375 patients following HCT. With a median follow-up of 2 years, 25% of patients developed at least 1 episode of pneumonia after discharge home. Bacterial pneumonia, of which pneumococcus was the most frequent isolate, accounted for 22% of cases in which a specific etiology could be identified [20]. In a study by Machado et al [21], influenza occurred in 30 of 118 consecutive alloHCT patients. Although yearly influenza vaccination is recommended for all patients >6 months post-HCT, only 44% of vaccine eligible patients were immunized. Influenza A developed in 2 of 19 vaccinated patients compared to 12 of 24 unimmunized patients ($P < .05$). Varicella represents a significant cause of morbidity post-alloHCT [22-24]. The estimated cumulative incidence of varicella zoster virus (VZV) in 151 patients was 13% at 12 months, 32% at 24 months, and 38% at 28 months [22]. In another study of 100 consecutive adults undergoing allogeneic BMT, 41 patients (41%) developed VZ reactivation [23]. Among the 47 patients in this study who survived more than 2 years post-HCT, 59% developed Zoster. Forty percent of patients with VZV reactivation required admission with a mean hospital stay of 7.2 days. Two patients developed encephalitis, and 1 died despite antiviral therapy. Postherpetic neuralgia and peripheral neuropathy developed in 68% of patients. A retrospective analysis of VZV infection in children demonstrated that 33 of

CDC

- **Td, IPV, Hib** x 2 doses
  - 12,14 mos
  - boosters at 24 m
- – **PPV23** x 2 doses 12, 24m
- – **Hepatitis B** is optional
- – **MMR** at 24 months

EBMT

- **Td, IPV, Hib** x 3 doses
  - 6-12 months
  - boosters at 24m
- – **PPV23** x 2 doses, 6-12m
- – **HepB** is recommended
- – **MMR** at 24 months

Figure 1. Summary of re-vaccination schedules recommended by the CDC versus European Blood and Marrow Transplantation Association following HCT.

109 consecutive patients developed VZV post-HCT (24). The 2000 CDC [1] guidelines do not recommend the live attenuated varicella vaccine, Varivax, in any patient, including those who have never been vaccinated or infected with varicella. Studies have shown that Varivax is safe and effective in children with ALL in remission [25] and in pediatric solid organ transplant recipients, despite their need for life-long immunosuppression [26]. Vaccination in these populations was not associated with an increase in the incidence of herpes zoster [24-26]. Administration of the live attenuated varicella, Varilrix, was safe and effective in 15 children vaccinated 12-23 months following HCT [27].

IMMUNOGENICITY OF VACCINES POST-HCT

Current literature on vaccine efficacy following alloHCT has often been limited by a small number of heterogeneous patients, use of inconsistent vaccination schedules, and lack of long-term follow-up. These studies have shown conflicting results even between adult and pediatric recipients of an unmodified HLA-matched sibling BMT (reviewed in [3]). Ljungman et al [28] demonstrated that only 42%, 36%, and 21% of patients immunized with 1 IPV developed a 4-fold rise in titer against serotypes 1, 2, and 3, respectively. Following 3 IPV doses, 50% of patients responded to all 3 serotypes [28]. This contrasts with a study by Parkkali et al [29] in adult HLA-matched sibling BMT recipients, in which all patients responded

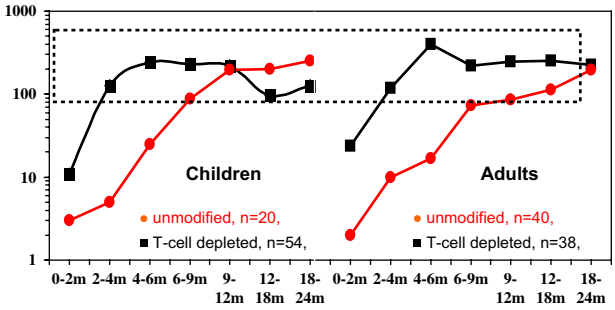

Figure 2. Median B Cell Recovery following T cell depleted or T-replete Unrelated HCT.

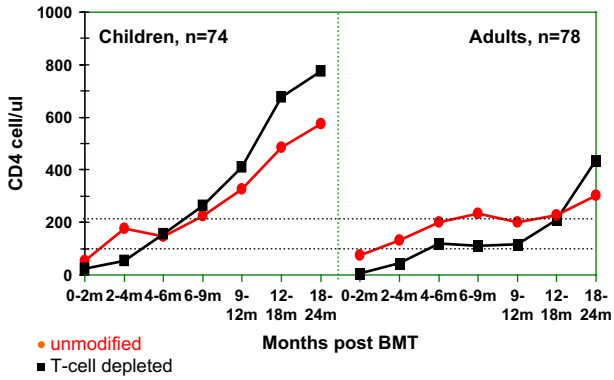

Figure 3. Median CD4+ cell count/ul following T cell depleted or T-replete Unrelated BMT: Children Versus Adults.

to IPV whether randomized to vaccination with IPV at 6, 8, and 14 months (n = 23) or at 18, 20, and 26 months (n = 22). In our center [30], 210 of 219 recipients of an alloHCT responded to a series of 3 IPV when administered following acquisition of minimal milestones of immune competence (CD4 >200/μL, PHA within 10% of normal). The range of responses observed in these 3 studies (50%-100%) may reflect in part variable levels of immune competence at the time of revaccination.

Pure polysaccharide antigens, including the 23-valent pneumococcal vaccine Pneumovax (PPV23), are poor immunogens in healthy infants (reviewed in [9]) and HCT recipients [31-35], populations at risk for severe invasive pneumococcal and H flu infections. Guinan et al [31] demonstrated a <20% response to PPV administered as a single dose at 24 months or in a 2-dose regimen at 12 and 24 months post-HCT. At our center, <25% of 156 patients responded to >3 pneumococcal serotypes following immunization with PPV [33]. Response was poor in all age groups, whether vaccinated early (<24 months) or later post-HCT. In a study of 53 pediatric recipients of an autologous or allogeneic HCT, Avanzini et al [34] reported that all children vaccinated more than 2 years after transplantation responded to PPV, whereas responses were observed in only 20%-30% and 50% of those immunized with PPV at 0.5-1.0 year or 1-2 years post-HCT, respectively. In univariate analysis, the interval between BMT to vaccination, presence of chronic graft-versus-host disease (cGVHD), and female sex influenced the response rate. In multivariate analysis, only time between marrow transplant and immunization predicted response. These data suggest a deficiency of critical B cell and/or antigen presenting cells necessary to respond to the T cell-independent pneumococcal polysaccharide antigens during the first 2 years post-HCT. During the first year post-HCT, the circulating B cells of patients following an autologous or allogeneic HLA matched T cell-depleted or unmodified BMT express an immature phenotype