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Vaccine Immunity and Immune Reconstitution in Children After Hematopoietic Stem Cell Transplantation: A Retrospective Single-center Study

To the Editor:

Infections by vaccine-preventable diseases constitute a threat for children after hematopoietic stem cell transplant (HSCT) due to a loss of specific immunity.[1,2] Revaccination is an important strategy to improve survival in this population.[3] Current guidelines of the European Conference on Infections in Leukaemia,[4] the Infectious Diseases Society of America[5] and, in Switzerland, the Federal Office of Public Health[6] recommend vaccinations at fixed time-points beginning 3 to 6 months after HSCT.

Our study, conducted at the Children's Hospital of Geneva after ethics approval (CCER 2020-01581) between January 2015 and December 2019, retrospectively assessed antigen-specific vaccine seroprotection and lymphocyte subpopulation recovery post-HSCT, aiming to optimize post-transplant vaccination schedules. We included children 0 to 18 years of age at the time of HSCT.

On the basis of the Swiss recommendations,[6] our center has developed a revaccination protocol postpediatric HSCT. This includes vaccinations against *Streptococcus pneumoniae*, diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* type b (Hib) (for children below 5 years), and hepatitis B at 3 months post-HSCT, followed by regular (at least at 6 and 12 months) vaccine serology for pneumococcus, tetanus, diphtheria, Hib for children below 5 years, and booster doses according to serology results. Vaccinations against measles and varicella are initiated at 24 months post-HSCT if there is no contraindication (such as graft versus host disease [GVHD]), in case of negative serology, and if CD4 cell levels > 700/μL, followed by a booster dose 1 month later. Meningococcal, human papillomavirus and tick-borne

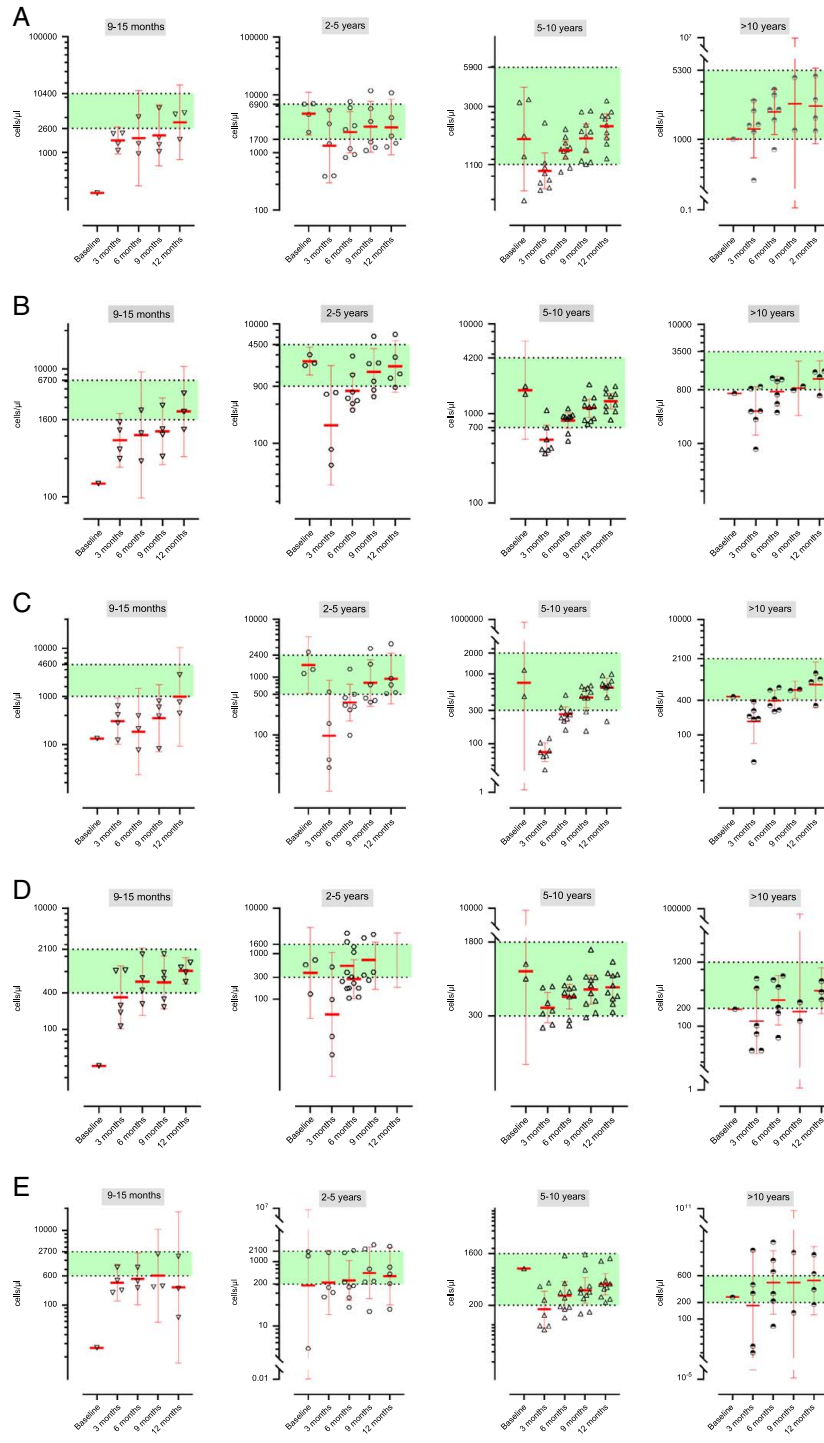

FIGURE 1. Concentrations of immune cells at baseline and 3, 6, 9, 12 months post-HSCT in pediatric patients, stratified by age groups according to age-based normal reference ranges[7] (in green). (A) total lymphocytes, (B) total T cells, (C) CD4+ T cells, (D) CD8+ T cells, and (E) CD19 B cell. HSCT indicates hematopoietic stem cell transplant. full color online

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encephalitis vaccines are administered 12 months post-HSCT.

We analyzed 28 transplantations, with a median age of 5 years at transplant. The predominant stem cell source was bone marrow, with most patients receiving allogenic stem cells from HLA-matched unrelated donors. The majority underwent myeloablative conditioning, with a significant proportion experiencing acute (32%) and chronic GVHD (25%).

The kinetics of the immune reconstitution showed varying trends depending on age (Fig. 1). All children achieved normal levels of B and T cells within 12 months after the transplantation. During the first year post-HSCT, vaccine-induced protection remained robust for tetanus and Hib. However, the level of protection against pneumococcus was insufficient, with rates ranging from 54% at 3 months to 70% at 12 months post-HSCT. Furthermore, the study revealed a decline in seroprotection against varicella and measles at 12 months post-HSCT, with rates dropping to 73% and 44%, respectively. These findings suggest that current vaccination guidelines may need revision to diminish the risk of invasive pneumococcal disease, as well as varicella and measles, in the year following HSCT.

Further studies should assess the safety and effectiveness of earlier administration of live-attenuated vaccines, possibly around 12 months post-HSCT, in the absence of contra-indications such as GVHD.

We recommend pre-HSCT vaccine-specific serology assessments, administering PCV13 pre-HSCT if necessary, followed by systematic post-HSCT doses and booster doses based on serology. The combined DTPa-IPV ± Hib ± HBV vaccine should be given at 6 and 8 months post-HSCT, with further vaccinations guided by 12-month serology results.

Larger prospective studies are needed to explore individualized vaccination programs based on post-HSCT vaccine serology to enhance vaccine protection in this at-risk population.

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Olanzapine for Chemotherapy-induced Nausea and Vomiting Pediatric Population: Take Home Message?

To the Editor:

We read the article "Efficacy and Safety of Olanzapine for the Prevention of Chemotherapy-induced Nausea and Vomiting in Children: A Systematic Review and Meta-analysis of Randomized Controlled Trials" published in your reputed journal.[1] The authors attempted to establish the role of olanzapine in preventing chemotherapy-induced nausea and vomiting in the pediatric population. This SRMA was registered in PROSPERO, which improved the credentials. Upon reading the article, many questions arose that required clarification. It appears that the authors performed a search nonchalantly as it shows very few results, and the authors included Google Scholar as well for searching the trials, but forgot to discuss about their search strategy in the supplementary file. Further, no information about results obtained from the individual database search has been provided. The authors chose the primary end point for this SRMA as no episode of vomiting and no need for rescue therapy.[1] However, the complete response (CR) has a very variable definition in all the included trials. One of the trials defined complete control of CIV as no vomiting or need for rescue medications.[2] In another study, complete response was defined as no vomiting, no need for rescue therapy, and lack of nausea up to 3 days after completion of chemotherapy.[3] In addition, the child was considered to have CR when there was no episode of vomiting and no use of rescue medication.[4] It appears dubious as to how the authors were able to club this data for generating a result. Moreover, to define the heterogeneity, $P > 0.05$ was considered significant by the review authors, which does not correlate with the Cochrane guidelines (indicates P should be <0.10).[5] The authors have mentioned that they analyzed the risk of bias as per the RoB2 tool, claiming that every study is at low risk, yet we observed that 2 of them do not comply well with the D1 domain of the RoB2 tool.[3,4] Likewise, the analysis of data on reportedly any adverse event is also not congruent with the data provided in individual studies; rather, the data on somnolence from each trial have been analyzed under the said subhead. The authors have also created a forest plot with a single study for few outcomes, which is unacceptable. Finally, information about the certainty of the evidence needs to be included. We do appreciate the authors' objective and effort in deliberating the data about the use of olanzapine among pediatric patients as a prophylaxis for chemotherapy-induced nausea and vomiting, but the methodology implemented for generating evidence on the same requires considerable refinements.

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