

Vaccination in children with chronic severe neutropenia – review of recommendations and a practical approach

SZYMON JANCZAR¹, BEATA ZALEWSKA-SZEWCZYK¹, KATARZYNA BAŁOL-POKORA¹, JAROSŁAW PAŚNIK², KRZYSZTOF ZEMAN², WOJCIECH MŁYNARSKI¹

¹Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Poland

²Department of Pediatrics, Immunology and Nephrology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland

Abstract

While the management of childhood neutropenia associated with a modifiable factor should be appropriate for the primary cause, there are misconceptions regarding the management of severe congenital neutropenia, immune neutropenia and cases classified as “idiopathic”. Antibiotic prophylaxis or granulocyte-colony stimulating factor (G-CSF) are prescribed by specialists in pediatric hematology or immunology, whereas immunization may be conducted by primary care physicians should clear recommendations be provided. There is a belief that severe neutropenia, as an immunodeficiency, is associated with compromised effectiveness and increased rate of complications of immunization. The immunization might be delayed or omitted, increasing the risk of unnecessary infection. We discuss the available data and recommendations regarding vaccination of children with chronic severe neutropenia. While there are virtually no studies addressing the safety and effectiveness of vaccination in neutropenia, expert opinions provide information on immunization policy in “phagocytic cells defects” or explicitly neutropenia. There are no contraindications for inactivated vaccines in neutropenia. Live bacterial vaccines are contraindicated. While in general the vaccination with live viral vaccines is encouraged, occasionally neutropenia might be associated with defects of adaptive immunity, which would preclude the administration of such vaccines. Although this should be easily phenotypically identified, we propose assessing immunoglobulin levels and performing a low-cost flow cytometry test for major lymphocyte subpopulations to exclude significant defects in adaptive immunity before administration of live viral vaccines to such patients. This can improve the adherence of patients' guardians and physicians to proposed vaccination policy and the professional and legal safety associated with the procedure.

Key words: immunodeficiency, vaccine, immunization, severe neutropenia.

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Introduction

Chronic neutropenia is a persistent abnormally low level of neutrophils in peripheral blood of varied etiology. The awareness of medical practitioners of neutropenia and associated morbidity in children is growing. While antibiotic prophylaxis or the use of G-CSF are usually prescribed by pediatric hematology or immunology specialists in a tertiary center, immunization may be effectively conducted by primary care physicians should clear recommendation for a particular patient be provided. Unfortunately, there is a frequent belief that severe neutropenia, as an immunodeficiency, is associated with compromised effectiveness and increased rate of complications of vaccination. Consequently, the immunization of children with neutropenia might be delayed or omitted, increasing the risk of

unnecessary infection. Here we discuss the available data and recommendations regarding vaccination of children with chronic severe neutropenia. Neutropenia is classified as mild (absolute neutrophil count below 1500/ μ l), moderate (below 1000/ μ l) and severe (below 500/ μ l) [1]. We do not discuss mild and moderate neutropenia in the context of vaccination as these are not associated with compromised response to vaccine antigens or increased risk of adverse effects, and unless there are other relevant associated phenotypes or morbidity, should not differ from general population regarding vaccination policy. We concentrate on chronic neutropenia in children that cannot be attributed to a modifiable factor. These include severe congenital neutropenia, immune neutropenia and cases classified as “idiopathic neutropenia”. The latter are likely,

Correspondence: Szymon Janczar MD, PhD, Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, 36/38 Sporna St., 91-738 Lodz, Poland, e-mail: szymon.janczar@umed.lodz.pl
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in this age group other, unrecognized or underdiagnosed forms of neutropenia (in particular autoimmune neutropenia), but we attempt to review data and recommendations regarding immunization irrespective of such dilemma or applied nomenclature. The management of neutropenia (including immunization) attributed to a modifiable factor (infection-related, drug-induced, associated with bone marrow failure, rheumatic disease, hypersplenism) should be guided by its etiology and disease-specific, and is not discussed here [1-6]. Occasionally, neutropenia could be a part of larger phenotypes or be also associated with adaptive immunity defects [1, 4, 6-8].

There is a lack of studies addressing the optimal vaccination policy in children with chronic severe neutropenia, which is at least partly explained by the low frequency of severe neutropenia, doubts regarding the classification (diagnosis) of particular patients and very varied diagnostic strategies and efforts associated with this disease. We present and discuss the available studies and expert opinions and propose a practical approach to vaccination of children with severe chronic neutropenia. While there are virtually no studies addressing the safety and effectiveness of vaccination in neutropenia, several expert opinions provide information on vaccination policy in “phagocytic cells defects” or explicitly neutropenia, however these are usually classified as “weak recommendation, low-quality evidence” [9-12].

Review of recommendations

Inactivated vaccines

No killed inactivated vaccines are contraindicated in severe neutropenia. These include routine immunization and also vaccines, which are not included in national vaccination programs in some countries. Inactivated vaccines are nowadays a backbone of all immunization schedules worldwide and cover a variety of viral and bacterial contagious diseases. The use of some of these vaccines is highly encouraged considering the increased risk of infections in children with severe neutropenia. These include in particular pneumococcal (PCV, PPSV23) and meningococcal (A, B, C, W135, Y) if not covered in national immunization schemes, as well as seasonal influenza vaccine, hepatitis B vaccine considering that they can prevent respective hospital-acquired infections [1, 9-12].

Live bacterial vaccines

All live bacterial vaccines are contraindicated in severe neutropenia (BCG, live typhoid vaccine, other in development). It must be though acknowledged that there are very few live bacterial vaccines available on the market and in clinical practice. What is more, in several countries newborns are universally vaccinated with BCG in the first

days of live, which obviously precedes any suspicion of the diagnosis of severe neutropenia. There are very few reports of BCG-related complications in infants later found to suffer from severe neutropenia, still the recommendation against their use is extrapolated from phagocytic cell defects, especially that their effectiveness (e.g. BCG) is limited [1, 9-12].

Live viral vaccines

Live viral vaccines are generally more effective and provide more sustained effect than inactivated vaccines and are currently the only available immunization option for several viral diseases (especially mumps, measles and rubella). In general live viral vaccines are not contraindicated in severe neutropenia but we believe defects in adaptive immunity on this group of patients should be considered before their administration for the reasons discussed below as though rare they are much more common than in general population [1, 9-12]. Table 1 presents the associations with adaptive immunity defects of major well-described types of severe congenital neutropenia and other conditions potentially complicated with neutropenia. The safety of live vaccine immunization in all populations may probably be improved by newborn immunodeficiency screening. Specific live viral vaccines are discussed below.

Rotavirus

This is very likely that most children with severe neutropenia will receive rotavirus immunization before the realization of this hematologic abnormality and will not have complications. On the other hand severe neutropenia determined in the first weeks of life might be a component of a syndrome associated with adaptive immunity defects. Adaptive immunity defects, and some syndromic phenotypes that could be associated with them, are very difficult to exclude at this early age. Therefore we discourage the administration of rotavirus vaccine in children with severe neutropenia. Should the first dose of the vaccine be administered before neutropenia was suspected with no complications, this is probably safe to continue the vaccination. There are no studies assessing the safety of rotavirus vaccines in children with immunodeficiency [9].

Oral polio vaccine, live attenuated influenza vaccine, yellow fever vaccine

Oral polio vaccine (OPV) is generally contraindicated in all primary immunodeficiencies and there is no rationale for the use of OPV in severe neutropenia, considering the availability of inactivated polio vaccine (IPV). Similarly, there is no justification for the use of live attenuated influenza vaccine (if available) considering the availability of seasonal killed vaccine [9-12]. We also argue live viral

Table 1. Major recognized forms of severe congenital neutropenia and other conditions potentially associated with neutropenia and their associations with adaptive immunity defects ([1-6, 8])

Disease	Affected gene	Adaptive immunity defects
Cyclic neutropenia	<i>ELANE</i>	No
SCN- <i>ELANE</i>	<i>ELANE</i>	No
SCN- <i>GFI</i>	<i>GFI</i>	Yes
SCN- <i>WAS</i>	<i>WAS</i>	Yes
SCN- <i>HAX1</i>	<i>HAX1</i>	No
Reticular dysgenesis	<i>AK2</i>	Yes
GATA2 deficiency	<i>GATA2</i>	Yes
Glycogenosis type Ib	<i>SLC37A4</i>	No
G6PC3 deficiency	<i>G6PC3</i>	No
Barth syndrome	<i>TAZ</i>	No
Schwachman-Diamond syndrome	<i>SBDS</i>	No
Chediak-Higashi syndrome	<i>LYST</i>	Yes
Griscelli syndrom	<i>RAB27A</i>	Yes
Hermansky-Pudlak syndrome type 2	<i>AP3B1</i>	Yes
VPS45 deficiency	<i>VPS45</i>	Yes
Cohen syndrome	<i>COH1</i>	No
Poikiloderma with neutropenia	<i>C16ORF57</i>	No
Charcot-Marie-Tooth disease	<i>DNM2</i>	No
P14 deficiency	<i>MAPBP1P</i>	Yes
Cartilage-Hair hypoplasia	<i>RMRP</i>	Yes
WHIM syndrome	<i>CXCR4</i>	Yes
Hiper-IgM	<i>CD40L</i>	Yes
NK cell deficiency with neutropenia	Not determined	Yes
X-linked agammaglobulinemia	<i>BTK</i>	Yes
22q11 deletion syndrome	Contiguous 22q11 deletion	Yes

WHIM – warts-hypogammaglobulinemia-infections-myleokathexis syndrome, SCN – severe congenital neutropenia

yellow fever vaccine is contraindicated due to limited use and lack of safety data in the context of immunodeficiency.

Immunization against mumps, measles, rubella and varicella-zoster viruses

In general terms, these vaccines are not contraindicated in patients with severe neutropenia, however their use is most commonly associated with doubts of the guardians

and primary care physicians [1, 9-12]. The most comprehensive recommendations for active immunization in immunodeficiency are provided in a document entitled Infectious Disease Society of America Clinical Practice Guideline for Vaccination of the Immunocompromised Host. This document states that “live viral vaccines should be administered to patients with CGD and to those with congenital or cyclical neutropenia”, however this is quoted as “weak recommendation, low-quality evidence” [9]. Considering the strength of these recommendations and the fact that severe neutropenia can be a component of broader syndromes (though unlikely not to be recognized considering the expected clinical symptoms) or associated with a deficit of adaptive immunity it could become a safe practice to formally exclude significant adaptive immunodeficiency in patients with severe neutropenia before administration of live vaccines. This is applicable especially to immunization against mumps, measles, rubella and varicella-zoster (VZV) viruses as other live viral vaccines can either be replaced with inactivated vaccines or are of limited use. This would provide an enhanced legal and professional security for the medical practitioner and better acceptance of the vaccination approach of the guardians of children with neutropenia and of the primary care physician, considering that any immunization might be associated with adverse events in any child (and might be more frequent in immunodeficient patients [13]) and the activity of anti-vaccination movements [14]. We propose a low-cost flow cytometry screen for the major T-, B-, and NK-cells markers (CD3, CD4, CD8, CD19, CD16, CD56 – after applying elliptical gate to the side scatter vs. forward scatter dot plot to identify the lymphoid population) and immunoglobulins G, A and M. Abnormalities in these parameters in children with severe neutropenia would necessitate specialist immunologist consultation before vaccination with live viral vaccines.

Vaccination in relatives and contacts of patients with neutropenia

Full routine vaccination is recommended in relatives and close contacts of individuals with severe neutropenia. This should include seasonal vaccination against influenza and vaccination against VZV in contacts without VZV immunity. OPV is contraindicated, while the risk of viral shedding in other live viral vaccines is considered unlikely [9-12].

Conclusions

This must be indicated that the strength of available recommendations and consensus statements is low. Consequently we propose an approach that increases the legal and professional security for the medical practitioner and the acceptance of the vaccination approach of the guardians

of children with neutropenia and of the primary care physician. In general, active immunization appears safe and beneficial in the setting of pediatric severe chronic neutropenia with the exception of otherwise rarely used live bacterial vaccines. The children with chronic neutropenia should receive all routine inactivated vaccines covered by a particular national scheme. Because of the susceptibility to bacterial infection and the risk of hospital-acquired infection they should also receive, if not covered by national programs, pneumococcal and meningococcal vaccines as well as seasonal influenza vaccine and hepatitis B vaccine. Live viral vaccines are likely safe and active and in our opinion should be administered, unless an inactivated vaccine against the particular disease is available, after negative basic screening for adaptive immunity defects.

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