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Immune response to vaccines in children with celiac disease

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Abstract

Celiac disease (CD) is an immune-mediated systemic condition evoked by ingestion of gluten and related prolamines in genetically susceptible subjects. The disease is featured by a variable combination of clinical signs, specific antibodies, HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. Vaccination is the most potent intervention for infectious disease prevention. Several factors including age, gender, ethnicity, quality and quantity of vaccine antigen, doses, and route of administration can influence immune response to vaccination, although the main cause of variation in the responsiveness among vaccine recipients is host genetic variability. The HLA system has a fundamental role in identifying the antigens introduced into the host with the vaccines and in the development of specific antibodies, and some HLA phenotypes have been associated with a less effective immunological response. The available literature indicates that the immunological response to vaccines in CD children does not differ markedly from that of general population and antibody titres are high enough to provide long-term protection, except for hepatitis B virus vaccine. In this article, we review and discuss the scarce literature in this field in order to provide clinical practice guidelines to achieve the most efficient monitoring of the response to vaccines in pediatric CD patients.

Key words: Celiac disease; Children; Infection; Vaccines; Hepatitis B vaccine; HLA; Gluten free diet

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Core tip: The available literature indicates that the immunological response to vaccines in children with celiac disease (CD) does not differ markedly from that of general population and antibody titres are high enough to provide long-term protection, except for hepatitis B virus (HBV) vaccine. Because the majority of persons with CD has the HLA-DQ2 haplotype, it

has been hypothesized that such genetic profile could have an important part in predisposing CD subjects to a less degree of immunity following HBV vaccination. New vaccination strategies have been proposed to give protection to all of these CD patients.

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INTRODUCTION

Celiac disease (CD) is an immune-mediated systemic condition evoked by ingestion of gluten and related prolamines in genetically susceptible subjects. The disease is featured by a variable combination of clinical signs and symptoms, specific antibodies, HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. Genetic, immunological and environmental factors therefore appear to be accountable for the disorder. CD is strongly associated with HLA-DQ2 and HLA-DQ8. HLA-DQ2 is found in 90% to 95% of CD individuals, HLA-DQ8 haplotype in 5%, and at least one of the two DQ2 alleles in 5% of them^[1,2].

Vaccines have been, and continue to be, among the greatest public health achievement in history, and they are the most powerful measure for the prevention of infectious diseases^[3]. They have lowered both morbidity and mortality from severe global infections such as diphtheria, pertussis, tetanus, measles, mumps, rubella, hepatitis B and others^[4]. Several factors such as age, gender, ethnicity, quality and quantity of vaccine antigen, doses, and route of administration^[5], can influence immune response to vaccine, although the main cause of variation in the responsiveness among vaccine recipients is host genetic variation^[6]. Single nucleotide polymorphisms (SNPs) in human leukocyte antigen (HLA) class I and II, cytokine and their receptors, and innate immunity (*i.e.*, toll-like receptor) genes have been hypothesized as responsible for the variability among individuals in protective immunity induced by vaccines, including neutralizing antibodies^[7]. In particular, the HLA system has a fundamental role in identifying the antigens introduced into the host with the vaccines and in the development of specific antibodies^[8,9] and some HLA phenotypes have been associated with a less effective immunological response^[10]. The available literature indicates that the immunological response to vaccines in children with CD does not differ markedly from that of general population and antibodies titres are high enough to provide long-term protection, except for hepatitis B virus (HBV)^[11-24]. Although the

mechanism for HBV vaccination failure in subjects with CD is unknown, a few hypotheses have been made. There has been advocated that HLA genotype DQ2 may predispose CD subjects to a lesser degree of immunization to recombinant HBV vaccine^[11,25-27]. HLA-DQ2 haplotype may be responsible for lack of induction of the Th2 response that is necessary for B cell differentiation and formation of memory B cells. Other authors have suggested that the response to HBV vaccination in individuals affected by CD may depend on disease activity and compliance to a gluten free diet (GFD)^[12,13,15,18]. Indeed, gluten consumption at the time of vaccination has been hypothesized as a cause of failure of immunity. Gluten may be implicated since both HBV surface antigen (HbsAg) protein fractions and gliadin peptides fasten to HLA-DQ2 particles and activate proliferation of T lymphocytes^[12]. Contention between the proteins might lead to impaired antibody synthesis. In this article, we review and discuss the scarce literature on this field in order to provide clinical practice guidelines to achieve the most efficient monitoring of the response to vaccines in pediatric CD patients.

CELIAC DISEASE AND THE RISK OF INFECTIONS

Several respiratory infections have been associated with CD in adults, such as invasive pneumococcal disease (*i.e.*, pneumonia)^[28-30], sepsis^[31], incident tuberculosis^[32], and death resulting from tuberculosis^[33]. In addition, children with CD have a higher risk of influenza infection and secondary hospital admission^[21]. The increased infection risk in CD patients is probably due to several factors. Malnutrition or increased intestinal permeability associated with CD could be one of them. Defective nutritional status, that is frequent both in CD and in patients with subclinical disease as well as following the start of GFD^[34], can result in lack of folate, vitamin B12, and in poor vitamin D status. Deficiency of folate and vitamin B12 are correlated with a decrease in immune-competence^[35] and a higher burden of respiratory infections (including influenza)^[36,37], while poor vitamin D status^[38] may result in the impairment of the defense mechanisms against respiratory pathogens and predispose to respiratory infections such as influenza and tuberculosis^[39]. CD patients have increased intestinal mucosal permeability, but not only^[40]: respiratory mucosal permeability is also increased^[41], and this may facilitate the entry of influenza virus. Hyposplenism also occurs in CD, although this condition seems to be important only in adult cases of CD^[42].

Thus, it is essential to implement a comprehensive vaccination program for CD patients with the available vaccines and to evaluate immunological response to these vaccines in CD patients.

RESPONSES TO VACCINATIONS IN CHILDREN WITH CELIAC DISEASE

There are few studies on the antibody response to vaccines of patients with CD. The majority relate to HBV, while very few reports are available on the immunological response to other vaccinations.

Some reports imply that celiac patients may have a low level of protective antibodies after HBV vaccination. The lack of response among CD subjects to HBV vaccination is important for public health policies because these non-responders may be a reservoir for HBV^[43]. The published studies on the association between CD and HBV vaccination in children are presented in Table 1^[11-21,24]. In the earliest report, involving 26 celiac patients aged 9.2 ± 4.6 years and 18 age-matched controls, receiving the full complement of childhood vaccination (HBV, tetanus, rubella, *Haemophilus influenzae* type b), Park *et al.*^[11] showed that a significantly greater percentage of children with CD did not respond to HBV vaccination in comparison with controls (53.9% vs 11.1%, $P < 0.05$). However, all of the children responded to other vaccinations. These results led the authors to consider the importance of HLA haplotypes in the development of immunity to HBV vaccine. Nemes *et al.*^[12] evaluated HBV vaccine response in CD children in relation to disease activity, assessed by measuring serum antibody concentrations to transglutaminase, and dietary gluten in the failure to reach protective antibody titers. The authors studied 128 biopsy-proven CD children and adolescents and 113 age-matched controls: 22 patients with CD on GFD were prospectively given a recombinant HBV vaccine, while the remaining 106 CD patients received a recombinant HBV vaccine which was not related to the diagnosis of CD or compliance to GFD. They found that the rate of seroconversion for anti-HBs was 95.5% (95%CI: 78.25%-99.2%) in the patients prospectively immunized. However, for the other patients the response rate was 50.9% and was related to gluten consumption (youths on gluten-containing diet, 25.9%; patients non-compliant to GFD, 44.4%; patients on strict GFD, 61.4%). These results would suggest the importance of disease activity in vaccination failure rather than specific HLA alleles^[12]. Subsequently, Ertem *et al.*^[13], evaluated serologically the anti-HBs status of 63 biopsy-proven CD patients on a strict GFD and 54 healthy children. CD youths with negative anti-HBs antibodies at baseline were reevaluated after full vaccination. The authors demonstrated that the seroconversion rate to HBV vaccine in CD patients was 96.9%, the same as that observed in the healthy population. It was concluded that GFD and compliance to diet, rather than the specific HLA alleles may increase the immune response to HBV vaccination in CD patients^[13]. Balamtekin *et al.*^[14] compared the rates of seroconversion to HBV vaccine in the

first year of life, utilizing two different immunization schedules. The entire study population consisted of 64 CD children (group 1 who received HBV vaccination at birth, at 2 mo and at 9-12 mo of life and group 2, at birth, 1 mo and 6 mo of life), and 49 healthy controls. The response rate to HBV vaccination as well as anti-HBs levels in CD children who completed the HBV vaccination were significantly lower than that of healthy controls, whereas no statistically significant difference was observed between the two different HBV vaccination schedules^[14]. Similarly, Ertekin *et al.*^[15] evaluated the response to HBV vaccination in youths affected by CD compared to healthy children and examined the association between the patients' responses, the clinical signs of the disease, and compliance to GFD. They evaluated the production of specific anti-HBs surface antigen antibodies in 52 CD children and 20 controls matched for age and gender who received standard HBV vaccination. The authors found that 32 (61%) of CD patients had positive anti-HBs titers, while 18 (90%) of control subjects had positive anti-HBs titers. Among youths affected by CD, they also showed statistically significant differences between responders and non-responders with respect to clinical signs of the disease, and compliance to GFD ($P < 0.05$). Thus, they concluded that, in children with CD, the immune response to HBV vaccination may be improved by compliance to GFD^[15]. Leonardi *et al.*^[16] in a retrospective report confirmed that fewer CD patients respond to HBV vaccination than healthy subjects. Among 60 CD patients, they found that 30 (50%) were non-responders to HBV vaccination while 7 of 60 controls (11.6%) were non-responders. They also demonstrated that a significantly greater proportion of non-responders were adolescents older than 14 years, and concluded that very early diagnosis of CD increases the response rate to HBV vaccination. A short period of exposure to gluten appears, therefore, to have a favorable effect on the antibody memory^[16]. In a subsequent retrospective study^[17], the immunologic response against obligatory vaccination (HBV, diphtheria and tetanus component and Bordetella pertussis) and against recommended vaccination (measles virus, paramyxoviridae and rubella virus) were compared in 66 CD patients and 50 healthy children. The authors found that the two groups responded similarly to obligatory and to recommended vaccines, except for HBV vaccine. Moreover, they compared children with a diagnosis of CD before and after 18 mo of age, and found that an early or a delayed diagnosis does not change the immunological response to vaccines, with the exception of HBV vaccination. Thus, the immunologic response would not appear to be affected by the natural history of CD^[17]. Urgancy and Kalyoncu^[18] determined the response rate to hepatitis A (HAV) and HBV vaccination, persistence of protection against HAV and HBV, and the occurrence of acute HAV or HBV infections during a period of follow-up in 30 children

Table 1 Immune response to vaccinations in youths with celiac disease

Ref.	Year	Country	Study design	Patients population and sample size	Vaccine	Non responders	HLA
Park <i>et al</i> ^[11]	2007	Japan	Prospective	26 (mean age ± SD, 9.2 ± 4.6 yr) untreated CD vs 18 (10.4 ± 3.8) controls	HBV	53.90% <i>vs</i> 11.1%, <i>P</i> < 0.05	NA
					RUBELLA	0% <i>vs</i> 0%	
					TETANUS	3.90% <i>vs</i> 0%, <i>P</i> = 1.0	
					HIB	33% <i>vs</i> 44.4%, <i>P</i> = 0.53	
Nemes <i>et al</i> ^[12]	2008	Finland	Prospective	22 (mean age, 8.8 yr) treated CD prospectively immunized; 27 (16.7 yr) untreated CD; 79 (16.7 yr) treated CD vs 113 (16.1 yr) controls	HBV	0.50% 74.00% 38.60% <i>vs</i> 24.8%, <i>P</i> < 0.001, <i>P</i> < 0.001, <i>P</i> = 0.102	Group 1 (22 treated CD): HLA DQ2 Group 2 (53/106 treated and untreated CD): 51: HLA DQ2 2: HLA DQ8
Leonardi <i>et al</i> ^[16]	2009	Italy	Retrospective	60 (mean age, 9.32 yr) treated CD vs 60 (10.1 yr) controls	HBV	50% <i>vs</i> 11.6%, <i>P</i> < 0.0001	15/60: 13 HLA-DQ2 2 HLA-DQ8
Ertem <i>et al</i> ^[13]	2010	Turkey	Retrospective	40 vaccinated (mean age ± SD, 12.4 ± 5.4 yr) treated CD vs 54 (9.8 ± 3.6 yr) controls	HBV	32.50% <i>vs</i> 14.8%, <i>P</i> < 0.05	37.5% CD 23.8% controls: HLA DRB1*03 21% CD
			Prospective	28 prospectively vaccinated treated CD			
Ertekin <i>et al</i> ^[15]	2011	Turkey	Retrospective	52 (mean age ± SD, 10.7 ± 4 yr) CD; vs 20 (10.7 ± 4 yr) controls	HBV	38.50% <i>vs</i> 10%, <i>P</i> < 0.05	NA
Balamtekin <i>et al</i> ^[14]	2011	Turkey	Retrospective	64 (mean age ± SD, 4.69 ± 2.31 yr) treated and untreated CD vs 49 (mean age 5.45 ± 2.92 yr) controls	HBV	21.90% <i>vs</i> 4.1%, <i>P</i> = 0.001	NA
Urganci and Kalyoncu ^[18]	2013	Turkey	Prospective	30 (mean age ± SD, 6.15 ± 4.1 yr) treated and untreated CD vs 50 (8.13 ± 1.7 yr) controls	HBV	30% <i>vs</i> 10%, <i>P</i> = 0.03	NA
Leonardi <i>et al</i> ^[17]	2011	Italy	Retrospective	66 (mean age ± SD, 8.34 ± 3.47 yr) CD, vs 50 (7.58 ± 3.51 yr) controls	HBV	53% <i>vs</i> 16%, <i>P</i> < 0.0001	NA
					POLIO	100% <i>vs</i> 100%, <i>P</i> = NS	
					DIPHThERIA	100% <i>vs</i> 100%, <i>P</i> = NS	
					TETANUS	100% <i>vs</i> 100%, <i>P</i> = NS	
					MEASLE	72% <i>vs</i> 82%, <i>P</i> < 0.0001	
					PAROTITIS	81% <i>vs</i> 92%, <i>P</i> = NS	
					RUBELLA	81% <i>vs</i> 80%, <i>P</i> = NS	
					PERTUSSIS	54% <i>vs</i> 54%, <i>P</i> = NS	

Leonardi <i>et al</i> ^[19]	2015	Italy	Prospective	30 (mean age, 6 yr) CD/DMT1 vs 100 (13.6 yr) DMT1 vs 60 (8.6 yr) CD	HBV	53.3% vs 38.2% vs 50%, <i>P</i> > 0.02	NA
Sari <i>et al</i> ^[20]	2011	Turkey	Prospective	33 (mean age ± SD, 8.4 ± 3.6 yr) CD vs 62 (8.9 ± 3.6 yr) controls	HAV	21.2% (after 1 mo) vs 3% (after 7 mo) vs 22.6% (after 1 mo) vs 1.6% (after 7 mo)	62.1% CD 21.8% controls: HLA-DQ2 34.8% CD 9.7% controls: HLA-DR3 13.6% CD 4.8% controls HLA-DR7 50% CD: HLA DQ2 heterozygous 50% CD: HLA DQ2 homozygous 23.50% HLA DQ2 Omozygous 13.70% HLA DQ2/DQ8
Schäppi <i>et al</i> ^[21]	2012	Switzerland	Prospective	14 (mean age 12.9 yr) treated CD vs 14 (12.9 yr) controls	Influenza A/H1N1/09	0 vs 0	50% CD: HLA DQ2 heterozygous 50% CD: HLA DQ2 homozygous 23.50% HLA DQ2 Omozygous 13.70% HLA DQ2/DQ8
Filippelli <i>et al</i> ^[24]	2016	Italy	Prospective	51 CD children at diagnosis	HBV	30.60%	HLA DQ2/DQ8

HBV: Hepatitis B virus; CD: Celiac disease; HLA: Human leukocyte antigen; NA: Non available; DMT1: Diabetes mellitus type 1; NS: Not statistically significant; HAV: Hepatitis A virus; SD: Standard deviation.

affected by CD in comparison with 50 healthy controls matched for age, sex, and body mass index^[18]. They found natural immunity for HAV in 14 (46%) out 30 CD patients and 15 (30%) of the 50 controls, whereas none of the patients and controls showed evidence of earlier exposure to HBV. Sixteen of the patients and 35 of the controls were vaccinated with HAV; 12 of the sixteen patients and all the controls (75% vs 100%) developed anti-HAV antibodies. All of the 30 youths affected by CD and all of the 50 controls were vaccinated with HBV vaccine; 21 (70%) of the patients and 45 (90%) of the controls reached seroprotection. It was concluded that CD patients achieve a lower seroconversion rate to HBV and HAV vaccines than controls. Of note, there was a difference in GFD compliance between responders and nonresponders, though it was not statistically significant.

Zingone *et al*^[22] evaluated the response to HBV vaccine in relation to gluten consumption in three groups of patients with CD and in a control group: group A, adolescents on gluten-containing diet vaccinated at age 12 years in whom CD was diagnosed after vaccination; group B, adolescents vaccinated when 12-years old who were on GFD at the time of vaccination; and group C, patients who received HBV vaccine at birth; and group D, healthy subjects. An insufficient response to HBV immunization was observed in 43.9%, 34.8%, and 58.3% of CD patients in group A, B, and C, respectively, vs 8.3% of subjects in group D. Thus, the authors suggested that the immune response to HBV vaccine is independent of gluten exposure and that the human leukocyte antigen possibly act as the principal immunological determinant of poor responses to HBV vaccine in CD patients. Zingone *et al*^[23] also investigated the duration

of anti-HBs 11 years following primary vaccination and immune memory to HBV in adult individuals with CD who had been vaccinated when adolescents. They showed that the proportion of vaccinated persons with antibody titres ≥ 10 mIU/mL was less among CD patients than among controls. Finally, in a very recent paper Leonardi *et al*^[19] comparing a group of patients affected by diabetes mellitus type 1 (DMT1) and CD and a group affected by DMT1 without CD (the HLA haplotype was similar in both groups), demonstrated a higher (though non-significant) proportion of non-responders, 53.3%, in the DMT1/CD group than in the DMT1 group, 38.2%; comparing the DMT1/CD group with CD group the authors found a similar percentage (53.3% vs 50%) of non-responders and this result supports the hypothesis that the efficacy of HBV vaccine can be further decreased by gluten, beyond the HLA system^[19].

The effect of HAV vaccine in children with CD was studied by Sari *et al*^[20]. After administration of inactivated HAV vaccine intramuscularly in a 2-dose schedule at 0 and 6 mo to 33 CD patients and healthy controls, the authors found that seroconversion rates at 1 mo were 78.8% and 77.4%, respectively; by 7 mo the rates were 97.0% and 98.4%. Therefore, they concluded that in children with CD, HAV vaccine produces a good immune response, almost the same as healthy controls, and that the routine HAV immunization protocol for healthy children may be utilized with success in these patients. A prospective investigation by Schäppi *et al*^[21] about vaccine response in 14 pediatric patients with CD and controls matched for age and gender demonstrated that CD children achieved protective antibody titers comparable with the control group.

ROLE OF HLA IN IMMUNE RESPONSE

Immune response to vaccines has been found to be affected by several factors, but host genetic variations are thought to be the main cause for variable vaccine responsiveness^[6]. The HLA alleles, holding in one of the most gene-dense, but most variable regions of human genome, namely the major histocompatibility complex region^[44], are essential for determining the specificity of an individual's immune response^[6].

As HLA molecules are part of the structural component for immune recognition by T-lymphocytes, polymorphisms in these molecules were expected to modulate antibody responses to vaccination^[45]. The HLA are coded by the major histocompatibility complex group of genes located on chromosome six in the human genome and they are essential for determining the specificity of an individual's immune response^[6]. There are three classes of HLA: HLA class I, class II and class III. Among them, HLA class II molecules have the task of presenting antigens to the T-lymphocytes from outside the cell. Antibody-producing B-cells are then stimulated to produce specific antibodies by these antigens^[46]. HLA-DQ2 haplotype may be responsible for lack of induction of the Th2 response necessary for the promotion of the differentiation of B cells and the formation of memory B cells. HLA is believed to contribute significantly to the genetic susceptibility immune response variations to the vaccine^[25]. Poor or non-responsiveness to HBV vaccine has been related to HLA DQ2, DR3, and DR7 alleles that are also linked to CD^[25-27]. In particular, HLA genotype DQ2, present in 90%-95% of individuals with CD, may have a fundamental part in the predisposition to a weaker response to recombinant HBV vaccine. Inadequate or scarce HBsAg-specific T-helper cells, defective T-helper 1 and T-helper 2 cytokine release^[7,44-48], or reduced expression of cell-contact signal between activated T and B cells, such as CD40L^[49] may also be responsible for the lack of response to HBsAg^[50,51]. Interleukin genotype (IL10, IL12, IL18) was related to the development of anti-HBs antibodies in response to HBsAg in hemodialysis patients^[52,53]. Chen *et al.*^[54] in 2011 found that anti-HBsAg response to HBV vaccination in healthy persons was closely related to 4 specific SNPs in the IL4, IL4RA, IL13 and toll-like receptor (TLR2) genes and suggested that variation in these structures may influence the persistence and degree of HBV vaccine-induced immune response^[54].

Other studies suggested that compliance with a GFD is responsible for the effect of HBV vaccine in patients with CD^[12]. Indeed, it has been hypothesized that gluten intake may be the cause of failed immunity after vaccination. Gluten may be responsible since both HBsAg protein fragments and gliadin peptides bind to HLA-DQ2 molecules inducing proliferation of T lymphocytes. Defective antibody production may result

from competition between the proteins^[48].

NEW STRATEGIES FOR HEPATITIS B VACCINATION IN CHILDREN WITH CELIAC DISEASE

Inadequate effect of HBV immunization in youths affected by CD is a public health concern because those who fail to respond may become a reservoir of HBV infection. Thus, immune response to HBV vaccine needs to be studied in these patients. In order to prevent HBV infection in these patients and to achieve universal protection, new immunization strategies were proposed for patients with CD: the first is to administer booster HBV vaccine and/or higher doses given intramuscularly, the second is to use the intradermal route. The studies that have addressed these new immunization strategies in subjects with CD are summarized in Table 2^[12,13,55,56]. Nemes *et al.*^[12] administered intramuscularly 20 µg of recombinant HBV vaccine as a booster to 37 non-responder CD children on GFD, and found that 36 out of 37 (97.3%) had seroconversion 4 wk after vaccination. However, success with the booster vaccination after controlled GFD suggests that vaccination failure may be affected by disease activity. Few studies exist about HBV vaccine administered by intradermal route in patients with CD who do not respond to intramuscular recombinant vaccine. Leonardi *et al.*^[55] re-vaccinated 20 children and adolescents with CD using a 2 µg dose of recombinant intradermal HBV vaccine. At 4 wk, they found that 15 out of 20 patients (75%) showed a protective titer of anti-HBs. Subsequently Leonardi *et al.*^[56] conducted a prospective, randomized study involving 58 CD patients, who had been vaccinated in infancy, but without protective HBV antibodies as demonstrated by blood analysis. They randomly administered a 2 µg booster dose of recombinant HBV vaccine by the intradermal route in 30 of these children, and a 10 µg dose of the same vaccine by the intramuscular route in 28 of them. Four weeks after the third booster dose, 90% of patients received the vaccine by the intradermal route and 96.4% of subjects received it by the intramuscular route showed a protective anti HBs titer. The authors concluded that both routes are effective in revaccinating CD patients, although the intradermal route may yield a significantly higher proportion of higher responders.

The intradermal route may offer greater immunogenicity due to the straight contact between antigen and the immune system of the skin, also if smaller amounts of antigen are used^[53]. Furthermore, determination of a skin reaction at the place of the intradermal injection might be a more economic policy to detect anti-HBs antibodies following the booster vaccine^[54]. Economic studies suggest that substantial cost-saving benefits could be achieved employing a fraction of the intramuscular dose through the

Table 2 Seroconversion rate in children and adolescents with celiac disease after intramuscular or intradermal hepatitis B virus vaccination

Ref.	Year	Country	Study design	Patients population and sample size	VAC Ag	Type of vaccine	Route	Number of booster doses	Seroconversion
Nemes <i>et al</i> ^[12]	2008	Finland	Prospective	37 (mean age, 16.7 yr) non responders CD on GFD	HBV	Recombinant	IM	1	97.30%
Ertem <i>et al</i> ^[13]	2010	Turkey	Prospective	28 (mean age \pm SD, 12.4 \pm 5.4 yr) non responders CD	HBV	Recombinant	IM	3 doses of HBV vaccine	96.40%
Leonardi <i>et al</i> ^[55]	2010	Italy	Prospective	20 non responders CD to IM vaccination	HBV	Recombinant	ID	4	90%
Leonardi <i>et al</i> ^[56]	2012	Italy	Prospective	58 (mean age \pm SD 9.8 \pm 6.2 yr) non responders CD	HBV	Recombinant	30 ID vs 28 IM	3	After first dose: ID: 76.7% vs IM: 78.6% After third dose: ID: 90% vs IM: 96.4% High responders (anti-HBs > 1000 IU/L): ID: 40% IM: 7%, $P < 0.01$

IM: Intramuscular; ID: Intradermal; VAC: Vaccine; Ag: Antigen; GFD: Gluten free diet; HBV: Hepatitis B virus; anti-HBs: Anti-hepatitis B surface.

intradermal administration^[57,58].

CONCLUSION

Present evidence supports the good immunogenicity of vaccines in children affected by CD with the exception of HBV. The available literature shows that HBV vaccine response is lower in subjects with CD. Some Authors hypothesize that the lack of response to HBV vaccination is related to specific HLA association while others argue that exposure to gluten at the time of vaccine administration may be responsible. Nonetheless, non-responsiveness to HBV vaccination in CD subjects is a serious public health problem because of the wide diffusion of CD, which affects about 1% of the European population. Consequently, new vaccination strategies have been proposed in order to reach complete protection, including administration of booster shots of HBV vaccine by the intramuscular or the intradermal *via*. An evaluation of the response to HBV vaccine should be implemented as a routine assessment in youths newly diagnosed CD who were previously vaccinated for HBV. When unresponsiveness occurs, revaccination utilizing the intradermal route determines a potentially higher immune response than the intramuscular route, even employing smaller doses, owing to the direct delivery of antigen to the skin immune system. Moreover, revaccination needs to be done following the decline of specific antibodies, which commonly emerges after approximately 1 year of GFD.

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