Vaccinations and Immunization Status in Pediatric Inflammatory Bowel Disease: A Multicenter Study From the Pediatric IBD Porto Group of the ESPGHAN

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Background: Vaccine-preventable diseases and opportunistic infections in pediatric inflammatory bowel disease (IBD) are increasingly recognized issues. The aims of this study were to evaluate vaccinations, immunization status, and consequent therapeutic management in children with IBD and to analyze the differences among patients diagnosed before (Group 1) and after June 2012 (Group 2).

Methods: This was a multicenter, retrospective cohort investigation. Between July 2016 and July 2017, 430 children with IBD were enrolled in 13 centers. Diagnosis, therapeutic history, vaccinations, and immunization status screening at diagnosis and at immunosuppressant (IM)/biologic initiation and reasons for incomplete immunization were retrieved.

Results: Vaccination rates at diagnosis were unsatisfactory for measles, mumps, and rubella (89.3%), *Haemophilus influenzae* (81.9%), meningococcus C (23.5%), chickenpox (18.4%), pneumococcus (18.6%), papillomavirus (5.9%), and rotavirus (1.9%). Complete immunization was recorded in 38/430 (8.8%) children, but specific vaccines were recommended in 79/430 patients (18.6%), without differences between the 2 groups. At IM start, 22% of children were tested for Epstein-Barr virus (EBV) status, with 96.2% of EBV-naïve patients starting azathioprine, without differences between Groups 1 and 2. Screening for latent tuberculosis (TB) before start of biologics was performed in 175/190 (92.1%), with up to 9 different screening strategies and numerous inconsistencies.

Conclusions: We demonstrated a poor immunization status at diagnosis in children with IBD, which was not followed by proper vaccination catch-up. EBV status before IM initiation and latent TB before biologics were not adequately assessed. Thus, the overall impact of the current guidelines seems unsatisfactory.

Key Words: inflammatory bowel disease, pediatrics, vaccinations

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INTRODUCTION

Although the incidence and prevalence of inflammatory bowel diseases (IBDs) differ among countries, the general trend highlights an overall increase over the past few decades, especially in adolescence and young adulthood.[1, 2] It is well known that pediatric IBD is characterized by a more extensive involvement and severe course when compared with adults, including a higher need of immunosuppressive and biological therapies.[3–5] Due to the underlying disease, poor nutritional status, and early aggressive immunomodulatory treatments, the risk of opportunistic infections and their prevention in children with IBD are increasingly recognized issues.[6, 7] Attention to this topic has progressively grown after the widespread use of biologics. The first reported pediatric data on opportunistic infections in IBD came from the REACH study.[8] Of all the infections, 6.8% were classified as severe and included sepsis, pneumonia, herpes zoster and abscesses.[8] In 2009, the European Crohn's and Colitis Organization (ECCO) published the first evidence-based guidelines on the management of opportunistic infections in IBD patients.[9] As these guidelines were not specifically conceived for the pediatric population, in June 2012 the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published a commentary on the risk and the prevention of infections in children with IBD, with the main objective of adapting the ECCO guidelines to the pediatric scenario.[10] With regards to prevention, the following points were recommended: immunization history should be obtained at the time of IBD diagnosis; children with IBD should receive inactivated vaccines following the routine childhood immunization schedule; attenuated live vaccines are contraindicated in patients treated with immunosuppressive drugs.[10] In addition to these recommendations, the 2014 ECCO guidelines were updated, emphasizing essential topics, such as the need for testing for Epstein-Barr virus (EBV) before starting azathioprine (AZA) and the importance of tuberculosis (TB) screening before initiating biologic treatment.[11] Despite this growing body of literature, few data have been published in children, and pediatric gastroenterologists (GIs) seem not to perceive the importance of this issue, which is frequently overlooked.[12–14] Therefore, the primary aims of this study were to evaluate the vaccinations, immunization status, and management of immunoregulatory therapies in a cohort of children with IBD; the secondary aims were to assess the impact of the ESPGHAN commentary,[10] analyzing the differences among patients diagnosed before and after June 2012.

METHODS

The Vaccinations and Immunization status in Pediatric IBD (VIP-IBD) study was a multicenter, retrospective cohort investigation conducted between July 2016 and July 2017 including 13 different ESPGHAN IBD referral centers. Participating centers were required to select a representative sample of children newly diagnosed with IBD before June 2012 (Group 1) and after June 2012 (Group 2) and to retrospectively collect their data. Each center had to enroll at least the first 5 consecutive patients diagnosed in each of the 3 years before and after June 2012. The inclusion criteria were a confirmed diagnosis of IBD, age at diagnosis ≤18 years, and clinical follow-up of at least 12 months. Diagnosis of IBD was established on the basis of clinical, endoscopic, radiological, and histological criteria according to the Porto criteria.[15] The distribution of the enrolled children among the different centers is shown in Table 1. Each participating center was required to complete a structured 28-item questionnaire form (Supplementary Table 1) for each enrolled patient. The form was designed to measure adherence to the ESPGHAN commentary on the risk and prevention of infections in children with IBD.[10] In addition, some of the topics were derived from the most recent ECCO evidence-based guidelines on the management of opportunistic infections in IBD patients.[11] The questionnaire included all the following items: demographic data (age, sex, parental education); diagnostic characteristics (type, age at diagnosis, disease activity and extent at diagnosis, extra-intestinal manifestations, comorbidities); therapeutic history; evaluation of the recommended routine childhood vaccinations (diphtheria, tetanus, and poliomyelitis [DTP], pertussis, haemophilus influenzae, hepatitis B, pneumococcus, meningococcus C, measles, mumps, and rubella [MMR], chickenpox, papillomavirus, rotavirus); annual influenza vaccination at diagnosis and during follow-up; serological titer assessment for the recommended infectious agents (hepatitis A, B, and C, EBV, rubella, herpes simplex virus [HSV], chickenpox, HIV, TB) at diagnosis, at initiation of immunosuppressant and biological therapies, and at follow-up; tests to detect latent TB (tuberculin skin test [TST], quantiferon TB gold [QFT], Elispot, chest x-ray); reasons for

TABLE 1. Distribution of Enrolled Children Among the 13 Different Centers

Center	Group 1, No. (%) (n = 218)	Group 2, No. (%) (n = 212)
Budapest, Hungary	15 (6.9)	15 (7.1)
Cluj-Napoca, Romania	19 (8.7)	24 (11.3)
Kaunas, Lithuania	6 (2.8)	9 (4.2)
Krakow, Poland	15 (6.9)	15 (7.1)
Málaga, Spain	15 (6.9)	15 (7.1)
Messina, Italy	15 (6.9)	15 (7.1)
Naples, Italy	26 (11.9)	29 (13.7)
Petach Tikva, Israel	15 (6.9)	15 (7.1)
Prague, Czech Republic	15 (6.9)	15 (7.1)
Rome, Italy	15 (6.9)	14 (6.6)
Vilnius, Lithuania	30 (13.8)	15 (7.1)
Warsaw, Poland	17 (7.8)	16 (7.5)
Zagreb, Croatia	15 (6.9)	15 (7.1)

incomplete immunization and decision-making regarding immunoregulatory therapies on the basis of immunological status. A complete immunization status at diagnosis was defined when a patient was vaccinated and/or showed positive titers for the following pathogens: DTP, poliomyelitis, haemophilus influenzae, hepatitis B, MMR, pneumococcus, meningococcus C, and chickenpox.[10, 11] Disease extent was characterized according to the Paris classification,[16] whereas disease activity was reported using the Pediatric Ulcerative Colitis Activity Index (PUCAI)[17] and the Pediatric Crohn's Disease Activity Index (PCDAI).[18]

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of the University of Naples "Federico II" with the protocol registration number 175/16. Subsequently, all the remaining enrolling units obtained specific approval from their local IRBs.

Statistical Analysis

Variables were screened for their distribution, and appropriate parametric or nonparametric tests were adopted as necessary. Percentages were rounded to the nearest whole numbers. The Student *t* test and Mann-Whitney test for continuous variables and the χ^2 and Fisher exact tests for categorical variables were used where appropriate. Statistical significance was predetermined as $P < 0.05$. SPSS, version 20 (SPSS Inc, Chicago, IL, USA), was used for all the analyses.

RESULTS

Baseline Characteristics

Four hundred thirty patients met the inclusion criteria and were enrolled between July 2016 and July 2017 (CD: 254, 59.1%; UC: 164, 38.1%; IBD-U: 12, 2.8%; median age at diagnosis [range], 12 [1–18] years; M/F: 236/194). Among the 430 patients, 218 were diagnosed before June 2012 (Group 1: 50.7%) and 212 after June 2012 (Group 2: 49.3%). Baseline characteristics of the 2 groups of children are presented in Table 2.

Vaccinations and Serological Evaluation at Diagnosis

The rates of vaccination at diagnosis were: diphtheria, tetanus, and pertussis (DTP; 427/430, 99.3%), poliomyelitis (426/430, 99.1%), hepatitis B (418/430, 97.2%), MMR (384/430, 89.3%), *Haemophilus influenzae* (352/430, 81.9%), meningococcus C (101/430, 23.5%), chickenpox (79/430, 18.4%), pneumococcus (80/430, 18.6%), papillomavirus (22/430, 5.9%), and rotavirus (8/430, 1.9%). When comparing children diagnosed before and after June 2012, no significant differences were observed for all the vaccines, except for meningococcus C, pneumococcus, chickenpox, and papillomavirus, which were significantly increased in Group 2 (18.8% vs 28.3%; $P = 0.01$; 14.7% vs 22.6%; $P = 0.02$; 14.7% vs 22.2%; $P = 0.03$; 2.8% vs 7.5%; $P = 0.02$, respectively). The rates of vaccination coverage for each pathogen before and after 2012 and the differences among each enrolling country are presented in Figure 1 and Supplementary Figure 1, respectively. The rates of assessment at diagnosis for each pathogen were TB (226/430, 52.5%), EBV (164/430, 38.1%), hepatitis B (161/430, 37.4%), hepatitis C (127/430, 29.5%), HSV (71/430, 16.5%), hepatitis A (54/430, 12.5%), rubella (51/430, 11.8%), chickenpox (70/430, 16.2%), and HIV (53/430, 12.3%). When comparing Group 1 and Group 2, we observed a statistically significant increase in the evaluation of the following pathogens: hepatitis A (10.6% vs 14%; $P = 0.01$), hepatitis B (28% vs 47.2%; $P < 0.001$), hepatitis C (20.2% vs 39.2%; $P < 0.001$), EBV (27.5% vs 47.7%; $P < 0.001$), HIV (9.2% vs 15.1%, $P = 0.04$), rubella (8.3% vs 15.6%; $P = 0.01$), and TB (46.8% vs 58.5%; $P = 0.01$).

Vaccine Catch-up

A complete immunization status was recorded in 38/430 patients (8.8%). An increase in the rate of complete immunization was observed in Group 2, even if this was not statistically significant (Group 1: 16/218, 7.3%; vs Group 2: 22/212, 10.3%; $P = 0.1$). None of the variables were significantly associated with a complete immunization rate. Among the 392 children with incomplete immunization, specific vaccinations were recommended in 79 patients (20.1%), without differences between Group 1 and Group 2 (46/202, 22.7%, vs 33/190, 17.3%; $P = 0.1$). The following vaccines were caught-up: pneumococcus (78/79, 98.7%), meningococcus C (57/79, 72.1%), chickenpox (55/79, 69.6%), hepatitis B (40/79, 50.6%), MMR (29/392, 36.7%), papillomavirus (20/79, 25.3%), rotavirus (5/79, 6.3%), DTP (1/79, 1.2%), and poliomyelitis (1/79, 1.2%). In the remaining children, the reasons for not being vaccinated were need for immediate IM therapies (87/313, 27.8%), parental refusal (24/313, 7.7%), vaccination costs (4/313, 1.6%), and unknown (154/313, 49.2%).

Influenza

One hundred twenty-three children out of 430 (28.6%) underwent yearly influenza vaccination, whereas 276 (64.2%) were not routinely exposed to the vaccine; in 31 (7.2%) cases, the status of influenza vaccination was not known. An increase of influenza vaccination was observed in Group 2 when compared with Group 1 (70/212, 35.4%, vs 53/218, 24.3%; $P = 0.03$). A higher number of children exposed to immunosuppressive and/or biologic therapy underwent annual influenza vaccination when compared with the remaining patients (60/80, 75%, vs 20, 25%; $P < 0.001$).

Screening Before Immunosuppressive Therapy

Two hundred fifty-one (58.3%) out of 430 children started IM (AZA: 238, 94.8%; methotrexate [MTX]: 13, 5.2%). Group 2 children started IM significantly earlier than

TABLE 2. Baseline Characteristics of the Enrolled Patients

Characteristics	Group 1 (n = 218)	Group 2 (n = 212)	P^a
Median age at diagnosis (range), y	12 (1–18)	12.3 (2–18)	0.2
Sex, No. (%)			
Male	113 (51.8)	123 (58)	0.1
Diagnosis, No. (%)			0.8
CD	132 (60.6)	122 (57.5)	
UC	80 (36.7)	84 (39.6)	
IBD-U	6 (2.8)	6 (2.8)	
Median PCDAI at diagnosis (range)	35 (5–70)	32 (7.5–65)	0.7
Median PUCAI at diagnosis (range)	45 (11–85)	45 (15–75)	0.4
Disease location at diagnosis, No. (%)			
CD			
Ileum only (L1)	18 (13.6)	30 (24.5)	0.03
Colon only (L2)	27 (20.4)	26 (21.3)	0.8
Ileum and colon (L3)	83 (62.8)	62 (50.7)	0.06
Upper gastrointestinal tract (L4)	44 (20.1)	50 (23.5)	0.2
Perianal disease	15 (11.2)	13 (10.6)	1
UC			
Ulcerative proctitis (E1)	12 (15)	8 (9.6)	0.3
Left-sided colitis (E2)	12 (15)	16 (19)	0.5
Extensive colitis (E3)	6 (7.5)	11 (13)	0.3
Pancolitis (E4)	50 (62.5)	49 (58.4)	0.6
Induction therapy at diagnosis, No. (%)			
CD			
EEN	36 (27.3)	55 (45.1)	<0.001
Steroids	71 (53.8)	39 (32)	<0.001
Biologics	3 (2.3)	10 (8.2)	0.04
EEN+steroids	7 (5.3)	11 (9)	0.3
Mesalazine	14 (10.6)	6 (4.9)	0.1
Surgery	1 (0.7)	1 (0.8)	1
UC			
Steroids	34 (42.5)	50 (59.5)	0.04
Mesalazine	45 (56.2)	29 (34.5)	<0.001
Biologics	1 (1.3)	5 (6)	0.2
IBD-U			
EEN	1 (16.6)	2 (33.4)	1
Steroids	5 (83.4)	3 (50)	0.5
Mesalazine	0	1 (16.6)	1

Group 1: patients diagnosed before June 2012; Group 2: patients diagnosed after June 2012.
[a]Fisher exact test or Mann-Whitney test was used for categorical and continues variables, respectively.

patients in Group 1 (median time [range], 1 [0–24] months vs 2 [0–108] months; $P < 0.001$). The number of children starting immunosuppressive therapy was significantly decreased in Group 2 when compared with Group 1 (115/212, 54.2%, vs 136/218, 62.3%; $P = 0.03$). Before starting IM, we observed a significant increase in the percentage of subjects tested for HIV (2/136, 1.5%, vs 9/115, 7.8%; $P = 0.01$). There were no statistical differences when comparing the 2 groups with regards to hepatitis A, B, and C (17.9% vs 28.1%; $P = 0.5$; 17.4% vs 19%; $P = 0.2$; 13.9% vs 20.6%; $P = 0.7$, respectively; HSV: 13.9% vs 11.1%; $P = 0.4$; chickenpox: 9% vs 9.6; $P = 0.7$; rubella: 14.6% vs 12.8%; $P = 0.2$), or for the percentage of patients tested for latent TB (19.9% vs 25.2%; $P = 0.2$).

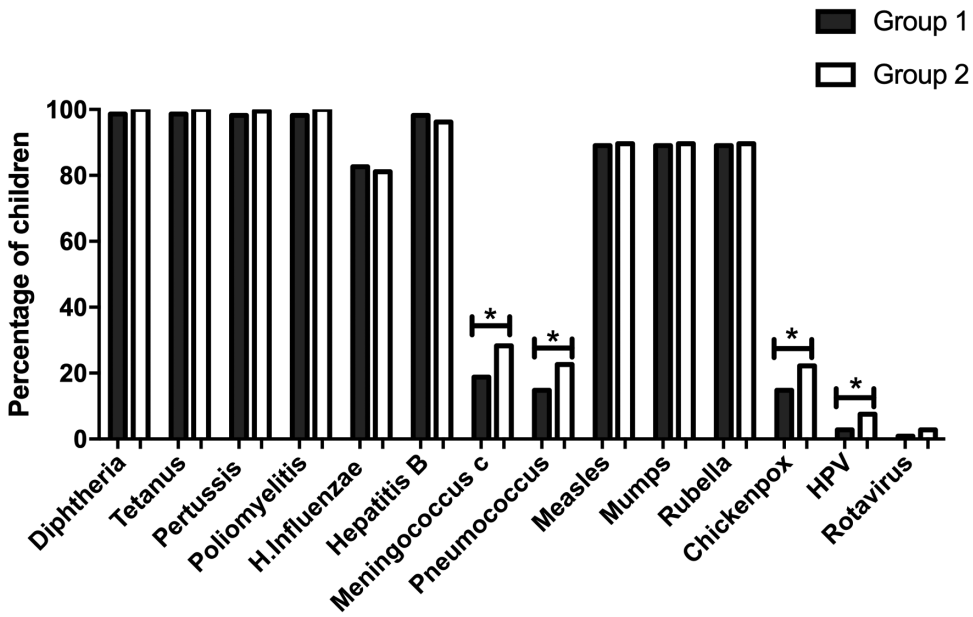

FIGURE 1. Rates of vaccination coverage at diagnosis before (Group 1) and after June 2012 (Group 2). *$P < 0.05$, Fisher exact test.

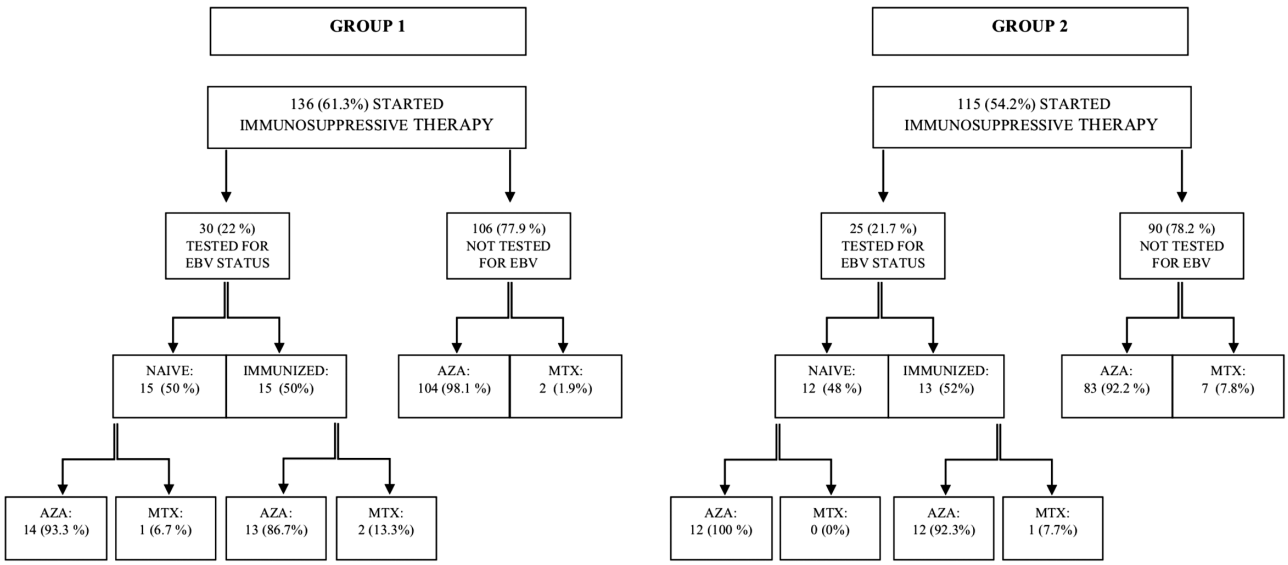

FIGURE 2. Flow diagram of EBV screening before starting immunosuppressive therapy in children diagnosed before (Group 1) and after June 2012 (Group 2).

EBV Status

Fifty-five children (22%) out of 250 children were tested for EBV status before starting IM, with 28 (50.9%) immunized for EBV and 27 (49.1%) EBV naïve. Among those who were EBV naïve, 26/27 started AZA (96.2%), whereas only 1 patient (3.7%) started MTX. There was no statistical difference between Groups 1 and 2 in the percentage of patients tested for EBV before starting AZA ($P = 0.5$); no difference was detected between the 2 groups in the percentage of patients who started AZA being EBV naïve ($P = 1$). The percentage of male sex in EBV-naïve children starting AZA did not differ between Group 1 and Group 2 (8/14, 57.1, vs 5/12, 41.7%; $P = 0.3$). A flow diagram of EBV status and consequent therapeutic management is shown in Figure 2.

Screening Before Biologics

Biologics were started in 190 (44.2%) out of 430 children (infliximab: 152/190, 80.2%; adalimumab [ADA]: 38/190, 20%). The median time to start biologics among the entire population (range) was 12 (0–108) months. Group 2 children

tended to start biologic therapy significantly earlier than patients in Group 1 (median time [range], 10 [0–82] months vs 18 [0–108] months; $P < 0.001$). In Group 1, biologic therapy was started in 98 out of 218 patients (45%), compared with 92/212 patients (43.4%) in Group 2 ($P = 0.4$). Infliximab was started in a significantly higher percentage of patients in Group 1 compared with Group 2 (87/218, 39.9%, vs 65/212, 30.7%, respectively; $P = 0.03$), whereas ADA therapy was started in a major number of patients in Group 2 compared with Group 1 (27/212, 12.7%, vs 11/218, 5%, respectively; $P = 0.004$). There was no statistically significant difference between the 2 groups in the percentages of patients tested for hepatitis A, B, and C (21.8% vs 21.6%; $P = 1$; 54.6% vs 48.3%; $P = 0.1$; 49.6% vs 48.3%; $P = 0.5$, respectively), EBV (47% vs 47.5%; $P = 1$), HSV (31.1% vs 26.7%; $P = 0.3$), HIV (16% vs 20%; $P = 0.2$), chickenpox (23.5% vs 16.6%; $P = 0.1$), and rubella (11.7% vs 15%; $P = 0.2$). After starting, a significantly higher number of children continued to be monitored for serological titers in Group 2 when compared with Group 1 (78/92, 84.8%, vs 65/98, 66.3%; $P = 0.003$). Serological titers during the course of biologic therapy were checked with the following frequencies: every year (45/65, 69.2%, vs 53/78, 66.7%; $P = 0.4$), every 6 months (2/65, 3.1%, vs 2/78, 2.6%; $P = 0.6$), and every other administration (10/65, 15.4%, vs 7/78, 9%; $P = 0.1$).

Latent Tuberculosis

Screening for latent TB before starting biologics was performed in 175/190 (92.1%), without significant differences when comparing children from both groups (Group 1: 93/98, 94.9%; vs Group 2: 82/92, 89.1%; $P = 0.1$). The 4 available exams—TST, QFT, Elispot, and chest x-ray—were used with 7 and 9 different diagnostic strategies in Group 1 and Group 2, respectively (Fig. 3). No significant differences were observed regarding the use of each specific combination and single test. A huge variation in TB screening modalities was observed among the different enrolling centers (Table 3).

DISCUSSION

To the best of our knowledge, the VIP-IBD study is the largest multicenter survey to evaluate vaccinations, immunization status, and subsequent therapeutic management in pediatric IBD. Our data highlight that children with IBD show insufficient immunization coverage at diagnosis and that vaccination

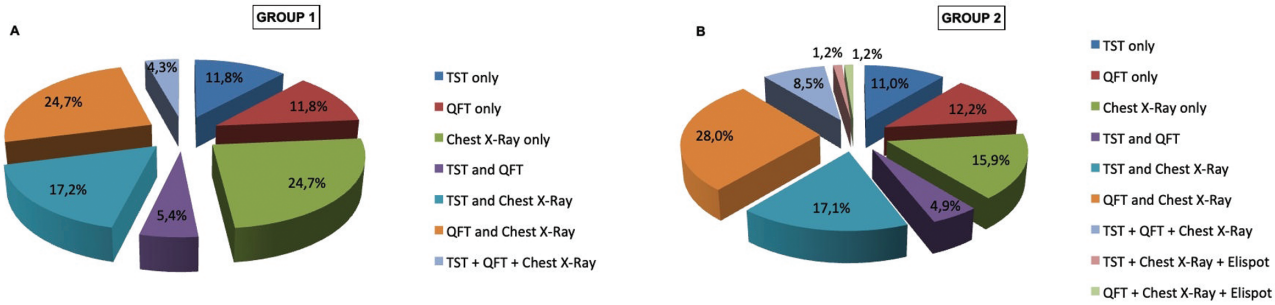

FIGURE 3. Diagnostic strategies to screen latent TB before starting biologics in children diagnosed before (Group 1) (A) and after June 2012 (Group 2) (B).

TABLE 3. Different Diagnostic Strategies to Screen Latent Tuberculosis Before Starting Biologics

Screening Strategy	Croatia (n = 4), No. (%)	Czech Rep. (n = 16), No. (%)	Hungary (n = 27), No. (%)	Israel (n = 18), No. (%)	Italy (n = 53), No. (%)	Lithuania (n = 10), No. (%)	Poland (n = 30), No. (%)	Romania (n = 3), No. (%)	Spain (n = 14), No. (%)
TST only	-	-	-	2 (11.1)	14 (26.4)	-	-	-	4 (28.6)
QFT only	4 (100)	-	-	-	17 (32)	-	-	-	-
X-ray only	-	7 (43.7)	27 (100)		-	2 (20)	-	-	-
TST + QFT	-	-	-	-	1 (1.9)	-	-	-	8 (57.1)
TST + x-ray	-	-	-	16 (88.9)	6 (11.3)	7 (70)	1 (3.3)	-	-
QFT + x-ray		8 (50)	-	-	10 (18.9)	-	28 (93.4)	-	-
TST + QFT + x-ray	-	-	-	-	4 (7.6)	1 (10)	1 (3.3)	3 (100)	2 (14.3)
QFT + Elispot + x-ray	-	1 (6.3)	-	-	-	-	-	-	-
TST + Elispot + x-ray	-	-	-	-	1 (1.9)	-	-	-	-

catch-up is not adequately performed. We also demonstrated an unsatisfactory awareness of 2 hot topics of IBD preventive care: EBV status at the start of AZA therapy and screening for latent TB before anti–tumor necrosis factor (anti-TNF) agents. Overall, the majority of the analyzed variables were modestly impacted by the ESPGHAN recommendations.

Inflammatory bowel disease is considered a condition at high risk of opportunistic infections, particularly in childhood.[19, 20] Strategies that can be used to decrease the hazard of opportunistic infections include screening, chemoprophylaxis, and vaccination.[7] In line with the literature, which reports nonsatisfactory immunization coverage in Europe and North America,[21, 22] our cohort shows insufficient rates for MMR, *Haemophilus influenzae*, meningococcus C, pneumococcus, chickenpox, papillomavirus, and rotavirus. As a consequence of this overall tendency, only 8.8% of children showed complete immunization at diagnosis. These alarming findings once more point out the essential role of the IBD practitioner, who should promptly test immunization for the most notable vaccine-preventable diseases. Indeed, the period from diagnosis to the initiation of immunosuppressive therapy should be considered a crucial window of opportunity for appropriate vaccination before the initiation of immunosuppressive therapy. In 2015, Lester et al. surveyed 178 North American pediatric GIs, demonstrating that at diagnosis only half of them asked verbally about immunization status, 31% obtained records, and only 9% required specific serologies.[13] More recently, deBruyn and colleagues reported that despite adequate vaccination coverage, a high percentage of the children with IBD showed low serologic protection against the main vaccine-preventable childhood infections.[23] In our cohort, we observed a significant increase of serological titer evaluation after the publication of a paper by Veereman et al.[10] Nevertheless, proving incomplete immunization status did not necessarily translate into active vaccination catch-up, which was performed only in 18.6% of children. When analyzing the reasons for not performing vaccine catch-up, we found that only in about 27.8% of children was there an immediate need to start IM therapy, whereas in the remaining cases parental refusal, vaccination costs, and unknown causes were reported. These factors can be certainly improved with a major commitment of pediatric GIs and with an increase in educational efforts. Actually, different studies demonstrated that specific campaigns are able to revert this tendency.[24–26] Fleurier and colleagues reported a significant increase in vaccination coverage in 92 French children with IBD after an awareness campaign on the risk of infection.[26] Most of these efforts are currently being perpetuated for annual influenza vaccination. In 2015, Huth and colleagues reported the successful results of 2-year prospective study.[27] The authors used 2 different strategies: the administration of an educational module with or without vaccine access in the clinic. Both strategies led to significant increases in the vaccination rate, from 34% at baseline to 75% and 89.5%, respectively.[27] In our multicenter study, we observed a significant increase in the influenza vaccination rate from 24.3% to 33% after 2012. Although significant, this result cannot be considered satisfactory, and it still confirms that the publication of guidelines needs to be followed by specific strategies for their widespread implementation.

Over the last 2 decades, pediatric IBD therapeutic strategies have profoundly evolved, leading to an increasing use of more aggressive "top-down" approaches with the early introduction of biologics.[28, 29] Our study gives a clear overview of this tendency, as demonstrated by the significant rise of biologics as firstline therapy and the decreased use of conventional immunosuppressants in children diagnosed after 2012. Despite this trend, our data show that >50% of children are still exposed to AZA, which remains one of the mainstays of pediatric IBD. This finding is particularly remarkable if we take into account the recent controversial warning on thiopurines' use, due to their potential relationship with EBV infection and the risk of lymphoproliferative disorders.[31, 31] These potential risks led the ECCO to state in 2014 that EBV IgG screening should always be considered before initiation of immunomodulatory treatment and that anti-TNFs are preferred in seronegative children.[11] Despite these recommendations, in our cohort only 21.9% of children starting AZA were checked for EBV status, and among those tested, AZA was started in almost all the cases of seronegative EBV patients, irrespective of sex.

The above-mentioned increase of anti-TNF agents' use, together with the recrudescence of TB-multiresistant strains in Europe, has also raised new concerns regarding biologics' safety.[32] It is well elucidated that anti-TNFs increase the risk of TB, particularly the reactivation of latent TB, and that when TB occurs in children on biologics therapy it is more commonly atypical, extrapulmonary, and disseminated.[33, 34] According to the ECCO guidelines, latent TB should be diagnosed by a combination of patient history, chest x-ray, TST, and interferon-gamma release assays (IGRA) according to local prevalence and national recommendations.[6] Our results demonstrate that a considerable inconsistency in TB screening remains in children with IBD starting biologics. Indeed, we observed a lack of standardization, with 9 different diagnostic strategies, and a huge variation among different countries. In some cases, we also observed a high percentage of inappropriateness: an example is represented by the 30% rate of chest x-ray performed as the only screening test before June 2012, without TST or IGRA. This approach, which obviously lacks the proper sensitivity to exclude latent TB, was decreased in the children in Group 2, but was still performed in 15% of the children.

The present study is not without limitations. The main drawback is obviously related to the retrospective nature, which may have resulted in missing data, especially clinical and microbiological findings. In addition, the concrete possibility of recall biases needs to be taken into account. Otherwise, the main strength of the study lies in the large sample size, well distributed among 13 different ESPGHAN tertiary centers, which

gives us a very precise picture of the application of the recommendations in Europe and Israel.

In conclusion, the VIP-IBD study demonstrated poor immunization status at diagnosis in children with IBD, which is frequently not followed by proper vaccination catch-up. Moreover, pediatric GIs seem not to perceive the risks of thiopurines in relation to EBV status and frequently do not adequately screen children with IBD for latent TB before starting anti-TNFs. On the basis of these findings, the overall impact of the current guidelines on vaccination and immunization status in children with IBD appears unsatisfactory, highlighting an urgent need for further educational efforts to disseminate the available recommendations and to promote their correct application.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

REFERENCES

1. Benchimol EI, Fortinsky KJ, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis.* 2011;17:423–439.
2. Virta LJ, Saarinen MM, Kolho KL. Inflammatory bowel disease incidence is on the continuous rise among all paediatric patients except for the very young: a nationwide registry-based study on 28-year follow-up. *J Crohns Colitis.* 2017;11:150–156.
3. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology.* 2008;135:1114–1122.
4. Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology.* 2008;135:1106–1113.
5. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol.* 2009;104:2080–2088.
6. De Greef E, Vandenplas Y, Veereman-Wauters G. Opportunistic infections in paediatric inflammatory bowel disease patients. *Arch Dis Child.* 2012;97:5–7.
7. Gisbert JP, Chaparro M. Vaccination strategies in patients with IBD. *Nat Rev Gastroenterol Hepatol.* 2013;10:277–285.
8. Hyams J, Crandall W, Kugathasan S, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology.* 2007;132:863–73; quiz 1165.
9. Rahier JF, Ben-Horin S, Chowers Y, et al; European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2009;3:47–91.
10. Veereman-Wauters G, de Ridder L, Veres G, et al; ESPGHAN IBD Porto Group. Risk of infection and prevention in pediatric patients with IBD: ESPGHAN IBD Porto Group commentary. *J Pediatr Gastroenterol Nutr.* 2012;54:830–837.
11. Rahier JF, Magro F, Abreu C, et al; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2014;8:443–468.
12. Crawford NW, Catto-Smith AG, Oliver MR, et al. An Australian audit of vaccination status in children and adolescents with inflammatory bowel disease. *BMC Gastroenterol.* 2011;11:87.
13. Lester R, Lu Y, Tung J. Survey of immunization practices in patients with inflammatory bowel disease among pediatric gastroenterologists. *J Pediatr Gastroenterol Nutr.* 2015;61:47–51.
14. Pham HV, Hasan I, Udaltsova N, et al. Rates and predictors of vaccinations among inflammatory bowel disease patients receiving anti-tumor necrosis factor agents. *Dig Dis Sci.* 2018;63:209–217.
15. Levine A, Koletzko S, Turner D, et al; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr.* 2014;58:795–806.
16. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis.* 2011;17:1314–1321.
17. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology.* 2007;133:423–432.
18. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr.* 1991;12:439–447.
19. Lu Y, Jacobson D, Bousvaros A. Immunizations in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2009;15:1417–1423.
20. Long MD, Gulati A, Wohl D, et al. Immunizations in pediatric and adult patients with inflammatory bowel disease: a practical case-based approach. *Inflamm Bowel Dis.* 2015;21:1993–2003.
21. de Figueiredo A, Johnston IG, Smith DM, et al. Forecasted trends in vaccination coverage and correlations with socioeconomic factors: a global time-series analysis over 30 years. *Lancet Glob Health.* 2016;4:e726–e735.
22. World Health Organization. *Global Vaccine Action Plan 2011–2020*. Geneva: World Health Organization; 2013.
23. deBruyn JCC, Soon IS, Fonseca K, et al. Serologic status of routine childhood vaccines, cytomegalovirus, and Epstein-Barr virus in children with inflammatory bowel disease. *Inflamm Bowel Dis.* 2019;25:1218–1226.
24. Walsh AJ, Weltman M, Burger D, et al. Implementing guidelines on the prevention of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2013;7:e449–e456.
25. Parker S, Chambers White L, Spangler C, et al. A quality improvement project significantly increased the vaccination rate for immunosuppressed patients with IBD. *Inflamm Bowel Dis.* 2013;19:1809–1814.
26. Fleurier A, Pelatan C, Willot S, et al. Vaccination coverage of children with inflammatory bowel disease after an awareness campaign on the risk of infection. *Dig Liver Dis.* 2015;47:460–464.
27. Huth K, Benchimol EI, Aglipay M, et al. Strategies to improve influenza vaccination in pediatric inflammatory bowel disease through education and access. *Inflamm Bowel Dis.* 2015;21:1761–1768.
28. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110:1324–1338.
29. Lee WJ, Briars L, Lee TA, et al. Top-down versus step-up prescribing strategies for tumor necrosis factor alpha inhibitors in children and young adults with inflammatory bowel disease. *Inflamm Bowel Dis.* 2016;22:2410–2417.
30. Hyams JS, Dubinsky MC, Baldassano RN, et al. Infliximab is not associated with increased risk of malignancy or hemophagocytic lymphohistiocytosis in pediatric patients with inflammatory bowel disease. *Gastroenterology.* 2017;152:1901–1914.e3.
31. Beaugerie L, Brousse N, Bouvier AM, et al; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet.* 2009;374:1617–1625.
32. Dye C, Watt CJ, Bleed DM, et al. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA.* 2005;293:2767–2775.
33. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* 2001;345:1098–1104.
34. Abitbol Y, Laharie D, Cosnes J, et al; GETAID. Negative screening does not rule out the risk of tuberculosis in patients with inflammatory bowel disease undergoing anti-TNF treatment: a descriptive study on the GETAID cohort. *J Crohns Colitis.* 2016;10:1179–1185.