Risk of Infection and Prevention in Pediatric Patients With IBD: ESPGHAN IBD Porto Group Commentary

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ABSTRACT

Combined immunosuppression by immunomodulators and biological therapy has become standard in the medical management of moderate-to-severe inflammatory bowel disease (IBD) because of clearly demonstrated efficacy. Clinical studies, registries, and case reports warn of the increased risk of infections, particularly opportunistic infections; however, already in the steroid monotherapy era, patients are at risk because it is accepted that a patient should be considered immunosuppressed when receiving a daily dose of 20 mg of prednisone for 2 weeks. Prescriptions increasingly involve azathioprine, methotrexate, and various biological agents. The TREAT registry evaluated safety in >6000 adult patients, half of them treated with infliximab (IFX) for about 1.9 years. IFX-treated patients had an increased risk of infections and this was associated with disease severity and concomitant prednisone use. The REACH study, evaluating the efficacy of IFX in children with moderate-to-severe Crohn disease, refractory to immunomodulatory treatment, reports serious infections as the major adverse events and their frequency is higher with shorter treatment intervals. The combination of immunosuppressive medications is a risk factor for opportunistic infections. Exhaustive guidelines on prophylaxis, diagnosis, and management of opportunistic infections in adult patients with IBD have been published by a European Crohn's and Colitis Organization working group, including clear evidence-based statements. We have reviewed the literature on infections in pediatric IBD as well as the European Crohn's and Colitis Organization guidelines to present a commentary on infection prophylaxis for the pediatric age group.

Key Words: biological therapy, ECCO statements, guidelines, IBD, immunization, opportunistic infections, pediatrics, vaccination

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Given present treatment recommendations, the majority of treated pediatric patients with Crohn disease (CD) receive maintenance treatment that induces immunosuppression. It is the combination of classical immunomodulatory therapy with biological agents that has prompted the medical community to recognize patients with inflammatory bowel disease (IBD) as immunosuppressed and to focus on the risk for opportunistic infections.

Corticosteroids have been the hallmark of IBD therapy for years and a patient receiving a daily dose of ≥20 mg of prednisone for 14 days should also be considered immunosuppressed (1). Azathioprine or 6-mercaptopurine has become standard therapy in most centers for the maintenance treatment of pediatric CD. Following the successful use of biologics for IBD in adults, an even superior efficacy was demonstrated in children (2). Double-blind randomized controlled pediatric trials have been performed with infliximab (IFX) and adalimumab as both induction and maintenance therapy of moderate-to-severe CD (2,3). Several databases for short- and long-term safety monitoring have been initiated to address concerns regarding the potential adverse effects of immunosuppressive therapy, combined with biologics.

Although malignancy is the most dreaded complication, it clearly appears that opportunistic infections are the main risk for immunosuppressed patients with IBD (4). Postmarketing surveillance indicates that opportunistic infections occur in 1.81 of 1000 patients (data from Janssen Biotech, Horsham, PA). The European Crohn's and Colitis Organization (ECCO) undertook extensive work in reviewing the evidence and providing guidelines for prevention of infection in adult patients with IBD. The present article focuses on the risk and prevention of opportunistic infections due to immunosuppression in pediatric IBD.

Overall, the guidelines that are formulated by ECCO are applicable to the pediatric population. They are not repeated here and the reader is referred to the exhaustive document published by Rahier et al (5) on behalf of the ECCO Working Group. The pediatric literature on opportunistic infections in IBD is scarce (6). There is an urgent need for prospective studies to improve our guidelines and practices. Nonenteric infections do not appear to be a risk factor for relapse in adult CD (7), but there are no comparable data in children. Antibiotic prophylaxis is generally not recommended but can be used in special situations such as surgery (8).

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Available data and recommendations for treatment or prevention are reviewed per infectious agent. In addition, particular pediatric issues are addressed. One issue that concerns children in particular is the increased risk of developing IBD in the presence of a congenital immunodeficiency disorder (9). Another important pediatric aspect is faltering growth and malnutrition. Pediatric IBD, especially CD, compromises the child's nutritional status and as a consequence impairs the immune response. Lastly, the schedule of recommended childhood immunizations (10) should be adapted to suit the needs of compromised patients with IBD and a strategy at diagnosis is proposed.

REVIEW OF OPPORTUNISTIC INFECTIONS IN PATIENTS WITH IBD

Pediatric Literature

The REACH (Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Infliximab in Pediatric Patients with Moderate to Severe Crohn Disease) study demonstrated higher efficacy of maintenance therapy with IFX when given every 8 weeks compared with every 12 weeks. The incidence of infections, however, clearly increased in cases of shorter drug-free interval: they occurred in 73.6% of children treated every 8 weeks compared with 38% of those treated every 12 weeks; however, most of these infections were mild. Severe infections, that is, requiring hospitalization, were present in 5.7% of the every 8-weeks group and in 8% of the every 12-weeks group (being, respectively, 3/52 and 4/51 patients) (2). During the 36 months of follow-up in the REACH open-label extension study, the most prevalent adverse events were respiratory infections. Of the 60 patients completing the follow-up, 6 (10%) had a severe respiratory infection (3). A recent review of children in the United Kingdom who had received adalimumab identified 2 deaths, both related to sepsis. In both cases, the children were receiving other immunosuppressive treatments (in 1 case multiple therapies) and had central venous catheters in situ (11).

Herpes zoster and *Listeria monocytogenes* infections have been reported in pediatric patients with IBD receiving IFX (12–14). Three patients developed herpes zoster and 1 developed *L monocytogenes* meningitis in a series of 82 pediatric patients with CD treated with IFX (13). Epstein-Barr virus (EBV) polymerase chain reaction values increased (>100-fold) in 8 of 21 children with severe CD who were treated with IFX (15). A case report relates the disease course of a 16-year-old girl with CD and Wilson disease who developed lymphoproliferative disease as a result of a primary EBV infection. The patient had been treated with azathioprine and IFX for 6 months (16). Histoplasmosis and *Pneumocystis* pneumonia were reported in a child treated with IFX (17). Databases with long-term follow-up of pediatric patients with IBD are ongoing. The industry-sponsored US-European 20-year follow-up registry, DEVELOP, initiated in 2008 monitors the safety of 5000 pediatric patients with IBD, half of them treated with IFX.

Adult Literature

The TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry reported on long-term safety in 6290 adult patients with IBD under IFX and other therapies. IFX was not an independent predictor of serious infections in contrast to prednisone, narcotic analgesics, and disease activity (4). Another study with 100 IBD-matched controlled cases confirmed the risk of combined immunosuppressive medication and added older age (>60 years) as a significant factor (18). The most frequently occurring infectious agents in 100 patients were herpes zoster (n = 28), *Candida albicans* (n = 26), herpes simplex virus (HSV) (n = 18), cytomegalovirus (CMV) (n = 12), and EBV (n = 8). A recent long-term follow-up study of 734 IFX-treated patients with IBD showed no increased incidence of infections compared with a control group. For the IFX-treated cases presenting with infections, corticosteroid treatment was an independent risk factor (19).

Latent tuberculosis (TB) can be reactivated with antitumor necrosis factor therapy (20). It should be noted, however, that due to corticosteroid use, the incidence of TB was higher in patients with IBD compared with the general population also in the pre-IFX era (21).

The use of an otherwise effective agent, natalizumab, which is a humanized monoclonal antibody directed against the cellular adhesion molecule α4-integrin, was suspended for IBD treatment in 2005 because of reactivation of latent human Jakob-Creutzfeldt (JC) virus, leading to progressive multifocal leukoencephalopathy (Van Assche, 2005 #40).

At least 6 case reports have been published on *Listeria* meningitis or meningoencephalitis in adult patients with CD receiving combined immunosuppressive therapy with IFX (22–27).

SPECIFIC PEDIATRIC ISSUES

Primary Immune Deficiencies in Early-onset IBD

Severe forms of IBD presenting in early life are distinct clinical entities (28,29). In some cases, specific immune defects have been identified such as interleukin-10 receptor defects (9,30), altered regulatory T cell function, and decreased FOXp3 protein levels (31,32). Different therapeutic strategies, including bone marrow transplantation, apply to these patients. They are known to develop severe complications such as EBV-induced lymphoproliferative disorder (33).

Consequences of Malnutrition

Malnutrition is a most prominent feature of pediatric IBD, characterized by weight loss in up to 70% of children with CD and in 34% with ulcerative colitis, growth failure, and micronutrient depletion (34). Disease-related malnutrition and weight loss may be present at any stage of the disease course (35). The causes of a poor nutritional status are multiple, including active inflammation (36), impaired nutrient digestion and absorption, enteric loss of nutrients during periods of both disease activity and remission (37), as well as increased nutrient requirements (35). Malnutrition, with or without concomitant disease, is associated with poor linear growth and impaired muscle, respiratory, and immune function (35). Malnutrition downregulates immune function (38) and reduces resistance to infection (39) by several mechanisms: a negative impact on the barrier protection (40), atrophy of the thymus and lymphoid tissues, reduced B-cell activation and complement formation affecting both innate and acquired immunity, leptin deficiency, and low macro- and micronutrient levels, especially vitamin D (41). Conversely, infections deteriorate the nutritional status by reducing dietary intake and intestinal absorption, increasing catabolism and sequestration of nutrients (40). Unfortunately, studies on the relation between pediatric IBD, malnutrition, and infections are lacking.

PREVENTION IN PEDIATRICS: COMMENTARY ON THE ECCO STATEMENTS

At present, there is no formal evidence that children with IBD treated with biologics and other concomitant immunosuppressives and/or immunomodulators such as corticosteroids, azathioprine, or

methotrexate are at increased risk for severe infections. Clearly, physicians should be vigilant while awaiting pediatric data from the many ongoing registries. Based on the adult literature, the risk is real, but the role of age and disease duration is unclear at present. Prevention is possible on various levels: high suspicion mandating careful and regular clinical follow-up, patient information and education, screening for latent diseases whenever possible, a complete immunization program, avoidance of live vaccines, hygienic measures in general and especially when traveling, and dietary precautions to avoid potentially contaminated foods. Generally speaking, there is no basis for modifying the ECCO statements for the pediatric population.

The authors of the ECCO Working Group have addressed bacterial infections including TB, viral, and parasitic infections and special situations such as travel and vaccination (5). The following sections are commentaries on specific pediatric aspects.

Pediatric Commentaries on Infections

Hepatitis Viruses

There is no published experience of coexistence of hepatitis B and IBD in children. Therefore, general principles may be derived from cases in adults. There are case reports in the literature on relapse of hepatitis B infection following treatment with IFX and other immunomodulators. Thus, great care must be taken to assess immunological status before antitumor necrosis factor is started. In adults, it is strongly recommended to use preemptive therapy with antiviral drugs before starting immunomodulators and/or biologics in patients with past infection with hepatitis B virus; however, until now, the safety of this protocol has not been demonstrated in children. Specific pediatric studies should address this issue to provide evidence for specific recommendations.

There seems to be no increased risk of coexistence of hepatitis C and IBD despite some conflicting results in adults, as reviewed by Horn et al (42). Although patients with CD have a higher probability of needing surgery, safety measures and screening tests should protect them from being infected. There is no vaccination against hepatitis C infection, and therefore protective measures rely on standard practices for cross-infection. The evidence on increased risk from the coexistence of the 2 conditions is scarce in adults and absent in children. The available evidence from small studies in adults suggests that there is no increased risk in treating both diseases but close monitoring is recommended (42). The absence of published pediatric experience renders it impossible to issue specific guidelines for children or adolescents.

Herpesviruses

The seroprevalence for varicella zoster virus (VZV) and CMV has been rising during the last 40 years, as shown in a Swedish pediatric cohort (43). Serum samples from 819 Swedish children from 4 cohorts, 9 to 12 years old in 1967–1968, in 1977–1978 (2 cohorts), and in 1997, respectively, were examined for these viruses. The seropositivity for VZV for 9-to 12-year-old children was 50% in 1967–1968, 74% to 82% in 1977–1978, and 98% in 1997 (significant increment). The corresponding figures were 31%, 53%, 50%, and 58% for CMV (significant increment); 35%, 35%, 32%, and 38% for HSV; 64% in 1967–1968 and in 1977–1978 (both cohorts), and 62% in 1997 for EBV.

We could not find any literature on VZV primo infection in pediatric patients with IBD, especially when immunosuppressed. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) IBD Working Group shared 1 case: a 15-year-old girl with pancolitis on 6-mercaptopurine developed varicella. She lacked previous exposure or vaccination, was treated with acyclovir, whereas 6-mercaptopurine was interrupted for 1 week. The varicella course was mild and uncomplicated (personal communication Dr A. Levine). In the transplant literature, severe, fatal, and disseminated cases have been reported, and it is generally accepted that varicella zoster immunoglobulins and antiviral treatment should be initiated in an exposed seronegative patient (44). The detailed recommendations from ECCO are not evidence based for pediatric IBD but are in line with practices in other immunosuppressed pediatric groups: passive immunization with a high-titer preparation of VZV IgG antibodies within 96 hours of exposure (125 U/10 kg to a maximum 625 U) and close observation for 28 days (5).

There are only a few case reports on the prevalence of CMV infection in adult patients with IBD and 1 pediatric case report (16,45,46). Data on immunosuppressed patients are described in the transplantation literature. A retrospective study described experience with a hybrid prevention strategy combining short-course antiviral prophylaxis (14 days of ganciclovir) and preemptive CMV polymerase chain reaction monitoring every 4 weeks. A total of 39% of subjects were spared antiviral medications beyond their initial postoperative prophylaxis. The authors concluded that a hybrid preventive approach for CMV is a reasonable alternative to prolonged antiviral prophylaxis and may reduce unnecessary exposure to antiviral therapy (47). Similarly, the experience with VZV in pediatric liver transplant recipients is reported. A total of 556 pediatric patients received liver transplantations (1985–2001). Twenty-two of them had varicella. On admission, 5 of 22 patients (23%) had received varicella zoster immunoglobulin within 96 hours of exposure. All of the immunosuppression dosages were reduced during the admissions. None of the patients had been treated with high-dose corticosteroids for acute rejection before the onset of the varicella infection. Patients were treated until defervescence with intravenous acyclovir and until their varicella lesions crusted. Patients were discharged with oral acyclovir to complete a 10-day course (including the intravenous treatment). No patients had complications from the varicella infection (48).

Screening for JC virus may be possible, but the general seroprevalence is high (65%) and the viral load is higher in patients with CD (49). JC virus reactivation has been demonstrated in children with severe CD, but none developed progressive multifocal leukoencephalopathy (50).

Parasitic and Fungal Infections

Children with immunodeficiency are at risk for gastrointestinal bacterial, fungal, and parasitic infections that may mimic IBD. As an example, a 14-year-old girl with hyperimmunoglobulin E (Job) syndrome presenting with fatigue, abdominal pain, fever, and weight loss had intracellular yeast forms compatible with *Histoplasma capsulatum* in terminal ileum biopsies. The patient was treated with oral itraconazole and had a rapid and complete response (51).

The ECCO statements (5) for chemoprophylaxis are applicable to children. The adapted drug dosages are given in Table 1 (4,52).

For *Pneumocystis jiroveci*, co-trimoxazole prophylaxis is advised in children with triple immunosuppressive therapy, in malnourished children with dual immunosuppressive therapy including IFX or calcineurin inhibitors, and in children younger than 6 years with severe manifestation of IBD, in whom a primary immunodeficiency disorder is likely or cannot be excluded. There is no evidence-based recommendation for treatment of *Strongyloides stercoralis* infections.

TABLE 1. Recommended pediatric dosages for chemoprophylaxis and treatment of parasitic and fungal infections (4)

Pneumocystis jiroveci
- Prophylaxis: 150 mg TMP/m^2/day + 750 mg SMX/m^2/day in 2 doses orally 3 times per week
- Second-line prophylaxis: atovaquone 30 mg/kg BW/day in 1 dose
- Treatment: TMP 15–20 mg/kg BW/day and SMX 75–100 mg/kg BW/day in 3–4 divided doses IV
- Second-line treatment: pentamidine in children 4 mg/kg BW/day in 1 once daily IV after clinical improvement therapy can be switched after 7–10 days to oral therapy with atovaquone 30–40 mg/kg BW/day in 2 doses orally (with fatty meal)
- Or: trimetrexate 45 mg/m^2 body surface once daily IV + folic acid 20 mg/m^2 BS IV or orally every 6 h for 24 days.

Strongyloides stercoralis
- Treatment: ivermectin 200 μg/kg BW/day for 2 days
- Second-line treatment: albendazole 15 mg/kg BW/day in 2 divided doses for 5–10 days

Toxoplasma gondii
- Prophylaxis: hygiene and co-trimoxazole as for *P jeroveci* prophylaxis
- Treatment: sulfadiazine (50)–100 mg/kg BW/day in 4 doses (max 6 g/day) + pyrimethamine 1 mg/kg BW/day in 1 dose + folinic acid 5 (–10) mg 2–7 times per week (depending on age)

Invasive candidiasis
- Fluconazole 6 mg/kg BW/day in 1 dose for at least 14 days
- Amphotericin B deoxycholate 0.5–1.0 mg/kg BW/day in 1 doses for at least 14 days
- Liposomal amphotericin B (Ambisome): 1–3 mg/kg BW/day IV in 1 dose
- Caspofungin first day 70 mg/m^2/day, from 2nd day on 5 0 mg/m^2/day IV in 1 dose

Invasive aspergillosis
- First-line treatment and in case of CNS involvement:
  - Voriconazole
    - 2–11 years of age: 14 mg/kg BW in 2 divided doses without loading dose
    - ≥12 years: 8 mg/kg BW in 2 doses after a loading dose of 12 mg/kg BW in 2 doses
- Second-line treatment:
  - Liposomal amphotericin B (Ambisome): 3 (–5) mg/kg BW/day IV in 1 dose (if non-CNS involvement)
  - Caspofungin first-day loading dose of 70 mg/m^2/day, from 2nd day on 50 mg/m^2/day IV in 1 dose

Histoplasma capsulatum
- Liposomal amphotericin B (Ambisome): 3 (–5) mg/kg BW/day IV in 1 dose for 14–21 days

Cryptococcus neoformans
- Amphotericin B deoxycholate 0.5–1.0 mg/kg BW/day in 1 dose for at least 14 days
- Liposomal amphotericin B (Ambisome): 1–3 mg/kg BW/day IV in 1 dose

BS = body surface; BW = body weight; CNS = central nervous system; SMX = sulfamethoxazole; TMP = trimethoprim.

TB

Approximately 10% of all new cases with TB detected worldwide are children younger than 15 years (53). In the literature, there is 1 report on the development of active TB in a child with RA treated with IFX (54). The ESPGHAN IBD Working Group shared 2 personal experiences on the development of active TB in children with IBD (1 case from Rome, Italy, 1 case from Rotterdam, the Netherlands), but so far, none have been published.

Screening for TB is recommended as common practice when considering therapy with biological agents; however, skin tests are unreliable because of a high incidence of anergy in patients with IBD. Therefore, careful clinical history including a travel history and inquiry for possible TB contacts, physical examination, and a high level of suspicion should be maintained, which may involve obtaining chest radiography.

Bacterial Infections

Streptococcus pneumoniae. Children with chronic diseases and children with immunodeficiencies are more susceptible to invasive pneumococcal diseases (55), but there is no specific information on patients with IBD.

Legionella pneumophila. *L pneumophila* pneumonia occurs rarely in healthy children; however, in immunocompromised children, the occurrence of *L pneumophila* pneumonia has been described, although there are no reports in pediatric patients with IBD. Children with IBD treated with immunomodulatory therapy and developing pneumonia should not routinely be tested for *L pneumophila* but only if not responding to the routine antibiotic treatment.

Salmonella Species. Patients receiving immunomodulators are at risk for developing more severe infections with *Salmonella enteritidis* and *S typhimurium*. Pediatric patients may be less susceptible to nontyphoid *Salmonella* bacteremia than adults, and their infections are less severe (56).

Listeria monocytogenes and Nocardia Species. Data in the pediatric population on these agents are scarce. There is no basis for modifying the ECCO statements.

Clostridium difficile. Patients with colitis are particularly susceptible to *C difficile* infection. This was confirmed for the pediatric population (57). *C difficile* screening should therefore be performed in pediatric patients with IBD during every flare of

colonic disease and should include the detection of cytotoxin A and B.

Screening is possible and should be performed for other latent infections such as leishmaniasis, histoplasmosis, and coccidioidomycosis (58). Chemopropylaxis is possible for TB (INH and rifampicin) and HSV (acyclovir) (59).

Pediatric Commentaries on Immunizations

Recommendations for immunization of adult patients are available (60,61). Pediatricians are familiar with immunization schedules and follow the recommendations by the American Academy of Pediatrics (10) or local guidelines. Special consideration should be given to the immunization of healthy infants whose mother experiences IBD and receives biological treatments during pregnancy. A recent study reports that adalimumab crosses the placental barrier and that significant levels can be found in cord blood and in the infant's serum (62). Pediatricians should therefore be extremely cautious regarding the administration of live vaccines to such infants during the first 6 months of life.

A good collaboration means that pediatric gastroenterologists provide precise immunization records when transitioning a patient to adult care. Ideally, a newly diagnosed patient with IBD should receive live attenuated vaccines, such as measles, mumps, rubella and chickenpox (HZV) before initiating immunosuppressive therapy. Therefore, if there is no clear disease history, for example, for varicella, antibody status should be evaluated. Immunosuppressive therapy should be withheld for 3 weeks after administration of a live vaccine. Once immunosuppressive therapy has been initiated, live vaccines are contraindicated until 3 months after terminating therapy (Fig. 1). Obviously, it is difficult to administer live vaccines to our patients under the present treatment practices (63).

In pediatrics, exclusive enteral nutrition (EEN) is considered a valuable alternative for induction therapy (64). Interestingly, mucosal healing has been demonstrated with EEN in children as well as in adults (Beattie RM, 1994 #103; Fell JM, 2000 #97). In a recent prospective randomized controlled trial in children with active CD, a polymeric diet for 10 weeks was markedly superior to corticosteroids in promoting healing of inflammatory lesions of the gut (65). A strategy using enteral feeding therapy to create a window for immunization should therefore strongly be considered. At diagnosis, the initiation of EEN would allow time for assessing

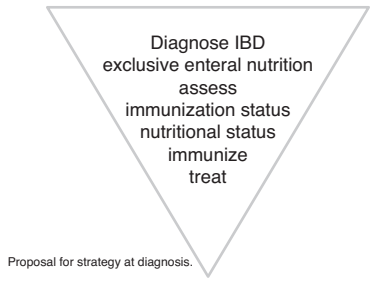

FIGURE 2. Proposal for strategy at diagnosis. IBD = inflammatory bowel disease.

the patient's nutritional and immunization status and for completing immunizations, including live vaccines (measles, mumps, rubella, HZV) while the patient receives an effective and risk-free therapy (Fig. 2). After a minimum of 3 weeks of nutritional therapy, conventional therapy could be initiated if the patient did not respond well to EEN. Alternatively, the patient could continue EEN for 6 weeks. The feasibility and efficacy of these recommendations need to be validated in practice.

Nonlive vaccines such as influenza are to be recommended yearly. Lower (66) as well as adequate serologic responses (67) have been reported in pediatric patients with IBD receiving IFX and immunomodulatory therapy. The significance and potential risk associated with this altered responsiveness in IBD as such and in association with immunosuppression are unclear at present and deserve to be studied.

A special situation is travel to countries requiring vaccinations. Common sense dictates that the adult guidelines (5,61) apply and that country-specific requirements need to be taken into account. For a pediatric patient with IBD treated with immunomodulators, live vaccines are contraindicated. The same windows before and after immunosuppression apply as at diagnosis (Fig. 1). Furthermore, the vaccination status of first-degree relatives of a patient with CD should be optimized, but there are no data on the impact of household infections.

Food-borne Risk Avoidance

Salmonella and *Listeria* are notoriously acquired through food (eg, eggs, seafood, nonpasteurized cheeses). Caregivers and

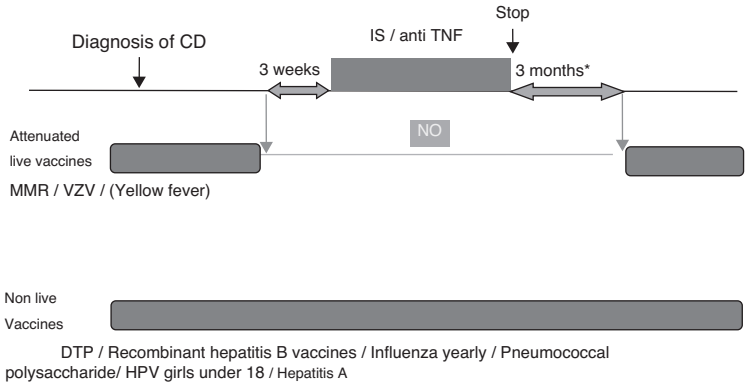

FIGURE 1. Immunization schedule at diagnosis. DTP = diphtheria, tetanus, pertussis; IBD = inflammatory bowel disease; MMR = measles, mumps, rubella; TNF = tumor necrosis factor; VZV = varicella zoster virus.

TABLE 2. Potential food contaminants and symptoms

Agent	Food	Symptoms
Salmonella	Meat and meat products, poultry, eggs, shrimp, frog's legs	Gastroenteritis
Yersinia enterocolitica	Pork, tofu, mussels, oysters	Gastroenteritis (2- to 4-day incubation)
Vibrio cholerae	Soiled (feces) water	Profuse watery diarrhea (incubation 6 h–5 days)
Vibrio parahaemolyticus	Seafood	Mild gastroenteritis (incubation 1 day)
Campylobacter	Raw chicken, seafood, unpasteurized milk, soiled water	Gastroenteritis (2- to 10-day incubation), muscle pain
Listeria monocytogenes	Raw milk and milk products (cheeses), processed meat (paté), raw vegetables	Flu-like symptoms, meningitis, maternofetal transmission
Escherichia coli	Meat, poultry, diary, raw vegetables, fast food, soiled water	Gastroenteritis
Shigella	Milk, salad, shrimp	Dysentery: bloody diarrhea (incubation 12–50 h)

children should be informed about these risks and about possible alternatives in the kitchen (eg, egg replacements for desserts). Dieticians should instruct parents about basic hygienic measures in the kitchen and provide lists of avoidable foods (Table 2).

CONCLUSIONS

At present, the literature on opportunistic infections in pediatric patients with IBD is scarce. The available evidence shows that immunosuppression increases the risk for infections, but these infections usually seem mild. In contrast, several fatal cases in adults older than 60 years have been published. Pediatric registries have just been initiated and will generate the information needed to issue evidence-based guidelines.

Patients with early-onset IBD may be suffering from monogenic immunodeficiencies, which should be identified and treated appropriately. Malnourished children are at greater risk for infections and may present a more severe disease course. The impact of nutritional status on the incidence of opportunistic infections in malnourished pediatric patients with IBD should be studied. Nutritional rehabilitation is crucial in the care of pediatric patients with IBD.

TABLE 3. Specific pediatric recommendations for the prevention of opportunistic infections in IBD

1. Assess and correct nutritional status
2. Consider EEN as bridge to immunosuppression
3. Update recommended immunization schedule before immunosuppression
4. Immunize against HZV (unless there is a history of chickenpox or seropositivity)
5. Screen for TB before prescribing biologicals
6. Prescribe yearly immunizations against influenza
7. Provide information on food safety
8. Be aware of risks involved in traveling: warn against live attenuated vaccines while immunosuppressed
9. Provide complete immunization information in transition file
10. Adhere to ECCO statements regarding prevention, diagnosis, and management of opportunistic infections

ECCO = European Crohn's and Colitis Organization; EEN = exclusive enteral nutrition; IBD = inflammatory bowel disease; HZV = herpes zoster virus; TB = tuberculosis.

The IBD Working Group of ESPGHAN recommends vigilance regarding immunizations at diagnosis and proposes a strategy that requires future validation (Table 3). Physicians caring for young children and adolescents should maintain a high level of suspicion for opportunistic infections. Assessing and correcting the patient's nutritional status is a crucial part of the practice of a pediatric gastroenterologist. Common sense dictates that immunizations in children and adolescents be optimized before initiating immunosuppressive agents. Immunization history should be included in every transition file. It is necessary to instruct caregivers and young patients to avoid food that carries the risk of contamination and to provide valuable alternatives. Furthermore, we recommend adherence to all of the ECCO statements regarding the prevention, diagnosis, and management of opportunistic infections (5) in pediatric IBD.

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