Taylor & Francis
Taylor & Francis Group

Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: http://www.tandfonline.com/loi/ierh20

Pharmacological treatments and infectious diseases in pediatric inflammatory bowel disease

Valeria Dipasquale & Claudio Romano

To cite this article: Valeria Dipasquale & Claudio Romano (2017): Pharmacological treatments and infectious diseases in pediatric inflammatory bowel disease, Expert Review of Gastroenterology & Hepatology, DOI: 10.1080/17474124.2018.1391091

To link to this article: http://dx.doi.org/10.1080/17474124.2018.1391091

Accepted author version posted online: 10 Oct 2017.

Publisher: Taylor & Francis

Journal: *Expert Review of Gastroenterology & Hepatology*

DOI: 10.1080/17474124.2018.1391091

Review

Pharmacological treatments and infectious diseases in pediatric inflammatory bowel disease

Valeria Dipasquale and Claudio Romano

Department of Human Pathology in Adulthood and Childhood, University of Messina, Messina, Italy

Correspondence:

Claudio Romano

University of Messina, Department of Human Pathology in Adulthood and Childhood "G. Barresi", Via Consolare Valeria, 1, Messina, Italy 98125

E-mail: romanoc@unime.it

Abstract

Introduction: The incidence of pediatric inflammatory bowel disease (IBD) is rising, as is the employment of immunosuppressive and biological drugs. Most patients with IBD receive immunosuppressive therapies during the course of the disease. These molecules are a double-edged sword; while they can help control disease activity, they also increase the risk of infections. Therefore, it is important that pediatricians involved in primary care, pediatric gastroenterologists, and infectious disease physicians have a thorough knowledge of the infections that can affect patients with IBD.

Areas covered: Abroad review of the major infectious diseases that have been reported in children and adolescents with IBD was performed, and information regarding surveillance, diagnosis and management were updated. The possible correlations with IBD pharmacological tools are discussed.

Expert commentary: Opportunistic infections are possible in pediatric IBD, and immunosuppressive and immunomodulator therapy seems to play a causative role. Heightened awareness and vigilant surveillance leading to prompt diagnosis and treatment are important for optimal management.

Keywords: biological therapy, child, infection, inflammatory bowel disease, immunomodulators

1. Introduction

Inflammatory bowel diseases (IBDs) encompass Crohn's disease (CD), ulcerative colitis (UC) and IBD-unclassified (IBD-U) according to the classification of Paris [1]. The Paris classification for CD includes classifying age at diagnosis as A1a (0 to <10 years), A1b (10 to <17 years), A2 (17 to 40 years), and A3 (>40 years); the disease location as L1 (distal 1/3 of the small intestine with limited or no cecal disease), L2 (colonic), L3 (ileocolonic) and L4a and b (above the distal ileum, proximal and distal to ligament of Treitz respectively); disease behavior as B1 (non-stricturing, non-penetrating), B2-B3 (both penetrating and stricturing), p (perianal disease modifier). Growth failure at diagnosis is also documented at any time as G_1 versus G_0 (no growth failure). The Paris Classification for UC [1] defines disease extent as E1 (proctitis), E2 (left-sided), E3 (extensive) and E4 (pancolitis), andseverity (never or ever severe, respectively S0 and S1), according to the Pediatric Ulcerative Colitis Activity Index (PUCAI) [2]. IBDs are characterized by chronic idiopathic intestinal inflammation that commonly begins during adolescence and young adulthood. The prevalence of pediatric IBD is 100–200 per 100,000 children in the United States and is rising, particularly in children younger than 10 years [3,4]. Corticosteroids are effective for inducing clinical remission in pediatric CD and UC. Aminosalicylates exert a topical anti-inflammatory effect on the intestinal mucosa, with fewer collateral effects than corticosteroids. Immunomodulators are effective for maintaining steroid-induced remission [5], conferring a steroid-sparing effect in IBD adults and children. The most used drugs of this class are methotrexate and thiopurines (including azathioprine sodium and its active metabolite,6-mercaptopurine or 6-MP).Biological therapies, such as tumor necrosis factor-alpha (TNF-α)-blocking agents, induce and maintain remission in patients with moderate or severe IBD [6,7].

Clinical studies, registries, and case reports have highlighted the increased risk of infection, particularly opportunistic infections, in young and adult patients with IBD. An opportunistic infection is a serious infection caused by microorganisms that have limited virulence, but can cause serious disease when the patient has a predisposing pathologic condition or is receiving certain therapies [8]. Nutritional deficiency impairs immune system function and represents a major risk factor for opportunistic infection worldwide [9-14]. Bacterial, viral and fungal infections have all been associated with IBD treatment-related immunomodulation [9]. Furthermore, many immunomodulators may be prescribed together to treat IBD, and such a combination amplifies infective risk [5-9,15]. IBD can also be caused, in the pediatric population, by monogenic diseases, such as primary immunodeficiencies (PID) [16]. Many PID show an increased susceptibility for severe, prolonged, opportunistic or recurrent infections and fever [16,17]. While standard IBDs are common (prevalence 1:500), monogenic disorders are very rare (prevalence <1:10,000) [18]. More than 50 monogenic defects have been associated to IBD-like phenotype etiology [18]. Among these,interleukin-10 (IL-10) signaling defects, chronic granulomatous disease (CGD), X-linked inhibitor of apoptosis (XIAP) deficiency and immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome with FOXP3 mutations may present with classical IBD phenotype and may occur early in life [16,18,19].

Vaccination has shown to be one of the most successful strategies against the spread of several infectious diseases. Children with IBD can follow the same routine immunization schedule as healthy children, avoiding live vaccines during immunosuppressive therapy [9]. The Infectious Disease Society of America [20] recommends administering live vaccines before the start of immunosuppressive therapy — at least 4 weeks before starting treatment in the case of the varicella vaccine, and 6 weeks before treatment

begins in the case of the measles, mumps, and rubella (MMR) vaccine. If immunosuppressive therapy has already begun, guidelines recommend administering live vaccines after discontinuation for at least 3 months (only 1 month if corticosteroid monotherapy is being used). The immunization status of the patient should be primarily checked at the time of IBD diagnosis for routinely administered vaccines, such as tetanus, diphtheria, poliomyelitis [9], especially if there is no clear history of vaccination or wild-type infection [21].Before the start of immunosuppressive therapy, it is important to check whether patients are seronegative for HBV infection [22].

Consensus meetings of the European Crohn's and Colitis Organization (ECCO) in 2009 [23] and 2014 [9] established guidelines on the diagnosis, management, and prevention of opportunistic infections in patients with IBD, through a systematic review of the existing evidence. Currently, there is not adequate up-to-date documentation on risk of infection in children with IBD. In addition, there is a lack of instructions for adequate surveillance and prevention. In the present manuscript, we provide an upgraded review of literature regarding the risk of infection in children with IBD, and correlation with pharmacological therapies. Appraisal of published literature was carried out, categorizing type into bacterial, viral, mycobacterial or fungal infection. The section concerning biologic drugs is more thorough than those concerning both steroids and immunosuppressants, due to greater availability of literature data.

2. Steroids

Steroids alone or in combination seem to be correlated with a high risk of infection in IBD patients, above all at mucosal surfaces, such as candidiasis [5]. *A list of the main studies investigating the relationship between infectious diseases and corticosteroid therapies in pediatric IBD is reported in Table 1.* Steroids may affect post-operative wound infection in pediatric patients with UC: a 10-year retrospective review of children with UC,

who had been surgically treated, first demonstrated that pre-operative steroids, when combined with other pre-operative factors, such as hypoalbuminemia and anemia, are associated with higher rates of post-operative infection [14]. Moreover, steroid therapy is a risk factor for catheter-related bloodstream infection in early-onset CD [24].

2.1. Viral infections

Primary EBV infection with subsequent development of HLH was described in five pediatric patients with IBD who had been treated with systemic steroids and thiopurines [25].

2.2. Parasitic infections

Over the past 25 years, 24 cases, including three pediatric cases, of severe and fulminant amebic colitis have occurred in patients who had been treated with high dose systemic corticosteroids, mainly for misdiagnosed IBD [26]. However, patients with IBD may also have amebiasis, and this is a diagnostic dilemma in endemic countries, as many of the symptoms of amebic colitis overlap with IBD symptoms [26]. In endemic areas or if there is an appropriate travel history, all patients with a new diagnosis of IBD should be screened for amebiasis with a stool study for fecal antigen testing or serum for amebic serology, especially prior to steroid administration [26].

2.3. Bacterial, mycobacterial, and fungal infections

To date, there are no data on the correlation between steroid monotherapy and bacterial, mycobacterial or fungal infections in children with IBD.

3. Immunosuppressors

Thiopurines are maintenance medications initially introduced as steroid-sparing agents, in order to reduce IBD flares. In the past two decades, the use of

immunomodulators for pediatric IBD has increased, and the overall therapeutic approach has shifted toward early introduction of maintenance immunosuppression and immunomodulation. For instance, steroids have been the mainstay in managing pediatric acute severe disease, but the severe onset of disease may indicate early introduction of maintenance therapy with immunosuppressors [27]. Among immunomodulators, azathioprine is most often used, while the use of methotrexate has been limited. In the early stages of IBD, there areno clear, specific guidelines for when to introduce azathioprine, even if steroid-dependency is the main indication in the case of early stage UC [28,29]. In 2008, the Japanese Society for Pediatric Inflammatory Bowel Disease carried out a retrospective questionnaire survey involving 35 patients with UC who had received azathioprine or 6-MP [30]. The median age at the start of azathioprine/6-MP therapy was 13. According to the medication regimen of each institute, azathioprine and 6-MP had been prescribed at a wide range of doses: 1.39±0.53 mg/dg/day for azathioprine (n=27), and 1.06±0.37 mg/kg/day for 6-MP (n=8). The patients were followed up for an average of 20 months(range: 1–98 months) after the start of therapy. Forty percent of the patients experienced adverse effects, mainly myelosuppression; no opportunistic infections were detected. No further specific data on the infection risk related to 6-MP have been reported in pediatric IBD. With regard to methotrexate, studies report the infection risk of methotrexate in combination with other IBD therapies, such as biological therapy. *In Table 2, the main studies on the relationship between infectious disease and immunomodulatory therapy in pediatric IBD are summarized.*

3.1. Viral infections

Thiopurines mainly predispose patients to viral infections [5]. Primary EBV infection with associated HLH and lymphoproliferative disorder (LPD) isa rare complication of thiopurine therapy in pediatric IBD patients [25, 31-33]. Fitzgerald et al. [33] reported the case of a

14-year-old girl with CD who developed EBV-associated HLH after azathioprine therapy. Similarly, Ross et al. [31] described the development of EBV-associated LPD in a 10-year-old boy with CD who was being treated with azathioprine. Therefore, before azathioprine treatment is started, clinicians should consider screening for EBV infection [9]. Few data regarding the prevalence of EBV in serum exist on children with IBD [34]. The first report of the prevalence of EBV seropositivity (40%) was in a letter by Love et al. [35] pertaining to a group of newly diagnosed IBD adolescent patients. In a recent cross-sectional study by Hradsky et al. [36] involving 106 children with IBD, 64% were seropositive for EBV, with a similar median age at determination (14 years). Furthermore, azathioprine was significantly associated with EBV seropositivity, especially in patients aged > 10 years old.

3.2. Bacterial infections

Regarding bacterial infections, only one pediatric case of disseminated nocardiosis has been reported; the patient was an adolescent with CD who was receiving 6-MP and steroids [37].

3.3. Mycobacterial and fungal infections

There are currently no studies on the risk of infection in IBD children treated with immunosuppressive monotherapy.

4. Biological Therapies

4.1. Anti-TNF-α drugs

Many pediatric patients with IBD are candidates for anti-TNF-α drugs, such as infliximab and adalimumab, whose role in the management of pediatric IBD has recently been updated in the Consensus guidelines of ECCO/ESPGHAN [28,29]. They are effective in inducing and maintaining remission in patients with moderately to severely active CD,

including fistulizing, perianal, and steroid-unresponsive disease and in patients with steroid-dependent, severe, or refractory UC. The goals of therapy with anti-TNF α agents are mucosal healing, prevention of long-term end organ damage, and delay in growth and development. Anti-TNF-α drugs are a unique challenge to healthcare providers in terms of infection risk, but pediatric-specific data are lacking in current literature. *In Table 3, the main studies on the relationship between infectious disease and biological therapy in pediatric IBD are summarized*. Some of the first pediatric data on the risk of infection in IBD patients come from pharmaco-epidemiological and registry studies evaluating the safety and efficacy of both infliximab and adalimumab. In the **R**andomized, multicentre, open-label study to **E**valuate the safety and efficacy of **A**nti-TNF-α **C**himeric monoclonal antibody in pediatric subjects with moderate to severe Cro**h**n's disease (REACH) study [6], the incidence of mild infections was found to be higher than that of serious infections, and the infection risk was higher among patients with a shorter drug-free interval (for mild infections, 73.6% vs. 38% respectively in the group treated every 8 and 12 weeks; 5.7% vs. 8% respectively in the group treated every 8 and 12 weeks for serious infections).A recent meta-analysis of 65 pediatric studies reports that the rate of serious infections was lower among pediatric IBD patients receiving anti-TNF-α agents than among adult patients on the same treatment. In addition, the pediatric rate was similar to the expected rate among pediatric patients receiving immunomodulator monotherapy, and significantly lower than the expected rate among children receiving steroids [38]. Similarly, a systematic literature review reported that the incidence of infections among pediatric IBD patients receiving anti-TNF-α was low (0%–10%), but that various serious infections occurred, including disseminated varicella, *Listeria meningitides* infection, histoplasmosis, disseminated CMV, bacterial sepsis, *Pneumocystis jirovecii* pneumonia (PCP), and systemic non-tuberculous mycobacterial infection, with a predominance of viral respiratory infections [39]. Adalimumab is an anti-TNF-α fully human monoclonal antibody usually

started in IBD patients as a second-line therapy after infliximab failure, with higher efficacy in CD than UC pediatric patients, and in those who have lost response to infliximab rather than infliximab non-responders. One of the first reports of infection risk during adalimumab therapy came from the 2009 **R**etrospective **E**valuation of the **S**afety and **E**ffect of **A**dalimumab **T**herapy (RESEAT) study, which reported neither serious nor opportunistic infections among 115 CD children on adalimumab; only 2 infectious complications were registered, -sinusitis and colonic abscess [40]. The 2012 IMAgINE 1 study (NCT00409682), a 52-week multicenter, randomized, trial assessing safety and efficacy of adalimumab among 152 children with moderate to severe CD, reported a rate of 67% (N=129) infectious complications, of which 6.3% (N=12) were serious and 1.3% (N=2) opportunistic [41]. Patients who completed IMAgINE 1 were enrolled, in 2017, in the IMAgINE 2 extension study, which did not identify new safety signals in terms of infectious complications [42]. The trend is an increase in the number of infections in IBD patients on anti TNF-α therapy in combination with other immunosuppressive agents (most commonly methotrexate and prednisone) [15]. The Porto Pediatric IBD working group of ESPGHAN conducted a multinational-based survey among pediatric gastroenterologists who suggested that combination therapy (2 or more immunosuppressive agents) is related to a higher risk of severe infections and malignancies [43]. The combinations are at least as immunosuppressive as the most immunosuppressive drug combined. The infection risk also depends on the duration of exposure to anti TNF-α therapy, with higher risk occurring shortly after starting anti TNF-α therapy (within 3-6 months) [15]. In the following sections, a comprehensive report of all invasive and unusual infections which have occurred to date in IBD children and adolescents on anti-TNF-α therapy is presented. The data have been divided by type into bacterial, viral, mycobacterial or fungal infection.

4.1.1. Bacterial infections

TNF-α is critical in the T-lymphocyte-mediated immune response to intracellular pathogens and invasive bacterial infections. Sporadic cases of bacteremia and sepsis by *Staphylococcus aureus*, coagulase-negative staphylococci, and *Escherichia coli* have been reported in children with IBD on anti-TNF-α agents; occasionally, such infections have been associated with central venous catheters[39]. Cases of *Listeria monocytogenes* bacteremia and meningitis - the most common clinical syndromes of invasive listeriosis in immunocompromised patients [44] – have been reported early (3–12 days) during infliximab therapy [44-47]. *Listeria monocytogenes* is an intracellular gram-positive microorganism that is transmitted via ingestion of contaminated foods. Another serious complication of TNF-α blockers use is nocardiosis: Verma et al. [37] reported the first pediatric case of pulmonary nocardiosis, - the most common localization [15] – in a 16-year-old boy with CD during the course of treatment with infliximab, 6-MP, and steroids. *Nocardia* spp are slow-growing, gram-positive rods that are ubiquitous in soil, organic matter, and water. Patients must be advised to clean open wounds after contact with soil and avoid soil-contaminated dust [15].

4.1.2. Viral infections

The true incidence and burden of viral infections in all pediatric patients with IBD, and in those receiving TNF-α antagonists, is unknown. TNF-α inhibits CMV replication and dissemination; therefore, anti-TNF–α agents increase the risk of CMV reactivation, once latent infection is established in hematopoietic cells [15]. Primary CMV infection is more likely in children than in adults, but a few pediatric cases have been reported in literature [48,49]. A fatal case of disseminated CMV in a child with CD receiving infliximab and 6-MP has been described [50]. Screening for CMV before the start of anti-TNF-α therapy is not routinely recommended [15]. Another complication of long-term TNF-α antagonist therapy

is VZV infection—both primary and zoster [39]. The overall incidence of primary varicella infection in children has been reduced since the licensure of the Varicella-zoster two-dose vaccine in 1995 [51].TNF-α blockers confer a high risk of severe primary infection with VZV, as TNF-α blockade suppresses T-cell immunity and promotes the replication and dissemination of the virus in the early stages of infection. Kunz and Rajnik [52] reported two pediatric cases of disseminated cutaneous VZV infection as a complication of a 2-year course of infliximab therapy. In immunocompromised hosts, serology is not reliable in confirming acute infection. Nonetheless, it should be performed as initial screening and to document immunity before the start of immunosuppressive therapeutic regimens, especially if the patient has not been vaccinated [15]. There is no clear evidence for increased EBV infection rates during anti-TNF-α monotherapy [15,36]. In a recent systematic review, the risk of infection or lymphoma was no greater among children with IBD who had received anti-TNF-α agents than among those who had been treated using other means [38].

4.1.3. Mycobacterial infections

The incidence of *Mycobacterium tuberculosis* (MTB)-related disease is low in pediatric IBD patients on anti-TNF-α drugs, probably due to the global lower incidence of MTB infection in children[15]. Clinicians have been advised to screen patients for such infections before starting immunosuppressive therapy. If MTB disease occurs, the disseminated - or extra-pulmonary - form is more frequent [39]. Until 2015, there had been nine publishedcases of MTB disease in patients aged <18 years who had been treated using anti-TNF-α agents for different chronic inflammatory diseases [53,54]. In 2015, a study with the largest (in terms of both number of children [614] and length of follow-up, median time 2.3 years per patient)cohort of patients aged <18 years who had received anti-TNF-α agents for chronic inflammatory diseases, including IBD (20.8%) was published

[54]. The authors reported no incident cases of MTB disease after 1 year of follow-up and a1.4% (n = 3) prevalence of latent tuberculosis infection (LTBI), which is comparable to that reported in the healthy pediatric population (0.9%) [55]. Similar incidences from both Turkey and England have been published [39,54]. All patients with LTBI in these studies received chemoprophylaxis before biological therapy, and few cases of TB were reported [55]. In low-burden TB settings, immunodiagnostic screening for TB is recommended in all IBD pediatric patients at the time of IBD diagnosis and prior to starting anti-TNF-α therapy, and consists of a dual testing strategy that involves the tuberculin skin test, and an interferon-gamma release assay (IGRA)test (Quantiferon-TB Gold test) [54-56]. If either test is positive, a chest radiograph is recommended to check for MTB disease. A positive immunodiagnostic result in an asymptomatic patient with negative imaging leads to a diagnosis of LTBI. The patient should be treated using LTBI chemoprophylaxis for at least 2 months before anti-TNF-α treatment is begun; the total duration of LTBI chemoprophylaxis should be 9 months in the case of isoniazid monotherapy [9], or 3 months if isoniazid is combined with rifampicin [54]. Clinicians should check proper compliance to anti-mycobacterial drugs before starting anti-TNF-α therapy. Furthermore, all patients receiving anti-TNF-α therapy should be screened annually. With regard to non-TB mycobacteria infections, the risk is higher in adult IBD patients who are receiving anti-TNF-α agents, but it has not yet been precisely calculated in children with IBD. An 11-year-old girl with CD developed a systemic, complex *Mycobacterium avium* infection, with generalized lymphadenopathy, after receiving infliximab followed by adalimumab [57]. Notably, in one boy born to a woman with CD, intrauterine infliximab exposure led to fatal disseminated disease after the bacillus Calmette-Guérin (BCG) vaccination, which was performed when he was 3 months old [58].

4.1.4. Fungal infections

TNF-α ensures an appropriate cell-mediated immune response to fungal infection, including granuloma formation. For this reason, TNF-α inhibition can lead to weak immune responses to new exposure, and reactivation of previously controlled fungal agents. Histoplasmosis is the most frequent invasive fungal infection in patients receiving TNF-α blockers [15]; it has also been described in the pediatric population [59]. The infection is transmitted via the inhalation of microconidia after soil disruption. The most common symptomatic manifestation is acute pneumonia, which is often indistinguishable from a community-acquired pneumonia. The largest case series of histoplasmosis in pediatric IBD patients on TNF-α antagonists involved 5 CD patients (median age:14 years). They had received 2–13 doses of infliximab or adalimumab, combined with an immunomodulator (6-MP or methotrexate), and had beenfree from steroids for at least 2 months [60]. All the patients were successfully treated using antifungal therapy; however, after 2 years, only two of them had successfully restarted anti-TNF-α therapy. A diagnosis of active histoplasmosis is an indication for antifungal therapy; the treatment should be started at least 3 months before the start of anti-TNF-α therapy, and should continue for at least 1 year if anti-TNF-α must be maintained. Itraconazole prophylaxis is not routinely recommended in patients who are on biological treatment and live in endemic areas, but it may be considered in outbreak situations and in patients who have had active histoplasmosis in the 2 years prior to anti-TNF-α therapy [61]. *Aspergillus* spp. are ubiquitous environmental fungi, mostly transmitted via inhalation from soil and rotting vegetation, with a high proclivity for vascular invasion that favors disseminated infections, especially in immunocompromised patients. Warris et al. [62] described the first case of *Aspergillus fumigates* pneumonia in a 25-year-old man with CD; the patient developed the infection 5 days after receiving his first dose of infliximab. Ten years later, a pediatric case

was described: that of a 15-year-old boy with CD who developed invasive pulmonary aspergillosis after receiving 20 doses of adalimumab and methotrexate [63]. Candidemia associated with central venous catheters, invasive systemic diseases and osteomyelitis has been reported in children receiving anti-TNF-α drugs [39,64]. Most infections due to *Candida* spp. result from endogenous invasion, although other risk factors include long-term placement of central venous catheters, abdominal surgery, intravenous alimentation, or broad-spectrum antibiotics [15]. Anti-TNF-α agents also increase the risk of PCP. Tschudyet al. [59] described the first pediatric case of PCP in an 8-year-old child with CD who had been treated with infliximab for 15 months. Another adolescent girl with CD developed PCP after 2months of infliximab therapy, combined with prednisone, methotrexate, and mycophenolate mofetil [65]. European Consensus guidelines recommend PCP prophylaxis for IBD adults who are receiving an anti-TNF-α drug either as part of a triple immunomodulation regimen or in combination with a calcineurin inhibitor[9]. Similar PCP prophylaxis recommendations pertain to IBD children receiving combination immunosuppression; however, clinicians must also consider severity of disease, the presence of co-morbidities such as malnutrition, and the age of the child, particularly if <6 years old [66].

4.2. Anti-integrin drugs

Pediatric patients with CD with anti TNF-α therapy failure to treatment may respond to anti-integrin biologics, such as natalizumab and vedolizumab. Natalizumab appeared safe in a small cohort of9 CD pediatric patients, as no infusion reactions, serious adverse events or infections occurred [67]. The major concern with the use of natalizumab is the association with the development of JC-related progressive multifocal leukoencephalopathy (PML), a rare opportunistic infection that is typically fatal. Exposure to JC virus can be assessed by testing for JCV antibody status; an anti-JCV index has

been developed for actual quantification [68,69], with a higher anti-JCV index correlating with an increased risk of PML. JVC antibody status and/or anti-JCV index determination could be performed before and during natalizumab treatment. Vedolizumab seems to be the preferred molecule in the anti-integrin class of therapy, since it has a similar mechanism of action targeting the gastrointestinal tract, but does not interfere with immune surveillance in the central nervous system,and therefore, does not seem to increase the risk of PML. Two case series on vedolizumab from North America have recently concluded that vedolizumab is safe in pediatric IBD patients. Singh et al. [70] reported no infectious complications among 52 IBD children after at least 6 weeks of therapy; Conrad et al. [71] reported upper respiratory tract infections (n=5), nasopharyngitis (n=2), skin infections (n=2) and sinusitis (n=1) among 21 IBD children, but they may not be directly related to vedolizumab. Similar results have been found in a retrospective multi-center experience on 64 IBD children on vedolizumab [72]. Controlled clinical trial data are warranted.

5. Clostridium difficile

Children with IBD are susceptible to recurrent *Clostridium difficile* infection (CDI) [73,74]. *Clostridium difficile* is a gram-positive, anaerobic, spore-producing bacterium that primarily infects the colon and can produce 2 exotoxins, A and B; it is acquired from the environment or via the fecal-oral route from direct contact with another colonized or infected patient or by indirect contact via carriage on the hands of healthcare personnel [15]. The spectrum of disease caused by *C. difficile* varies from mild or moderate gastrointestinal illness characterized by watery diarrhea and mild abdominal pain to severe colitis and toxic megacolon. Clinicians should only test for *Clostridium difficile* when it is clinically appropriate and the patient is symptomatic [75]. From Centers for Disease Control and Prevention criteria, this requires 3 or more loose stools in 24 hours. In the setting of IBD it can mean a change in baseline clinical status, as in the initial work-up of

acute severe colitis (ASC). A combination of nucleic acid amplification testing and cell cytotoxin immunoassay provides accurate screening of *Clostridium difficile.* Even though endoscopy is rarely performed to diagnose CDI in children, it is notable that the classic pseudomembranes of non-IBD-associated CDI are rarely reported in IBD [76]. No guidelines recommend screening for *Clostridium difficile* before the start of IBD therapies, including biological ones [15]. An Italian retrospective, case-control study evaluated hospitalizations with an admitting diagnosis of diarrhea, and reported a higher prevalence of CDI in pediatric patients with IBD than in those without IBD (24.7% vs. 8.9%) [77]. In addition to symptomatic CDI, there is a growing rate of asymptomatic colonization of *Clostridium difficile* in pediatric IBD patients [78]. In adults with IBD, immunomodulators and steroids have been associated with a heightened risk of CDI [79,80]. In the pediatric population with IBD, no increased risk of symptomatic CDI or *Clostridium difficile* colonization has been associated to type of IBD therapy, including the major immunosuppressant agents of glucocorticoids and biological treatments [77,78,81,82], even though CDI is generally more common in the immunosuppressed pediatric population [83]. However, no studies have been designed to address this issue specifically, and thus the true prevalence may have been underestimated [81]. Similarly, antibiotics and gastric acid suppressants seem not to increase the risk of symptomatic CDI in children with IBD [77,78,82]. *The main literature data on CDI in pediatric IBD patients are reported in Table 4.*

6. Conclusions

Nearly one-quarter of patients with IBD are younger than 20 years of age at diagnosis; pediatric IBD is an aggressive disease that requires early steroid and immunomodulatory therapies. The data found in children have shown that these drugs are safe and effective. Biological drugs seem to be safer than steroids or immunosuppressive

drugs in the pediatric IBD population. Clinicians should carefully monitor the risk of opportunistic infections at the time of diagnosis of IBD and before starting any treatment. The immunization status of children with IBD should be checked, and immunization with routinely administered vaccines should be considered. One important aim in the management of pediatric IBD is to improve the nutritional status, in order to reduce infection risks. In general, IBD therapy should be discontinued during any severe infection. Uniform recommendations regarding if and when to resume IBD therapy, especially anti-TNF—α drugs-based regimen, following resolution of an infection cannot be made, since it depends on various factors (such as host factors, pathogen characteristics, severity of infection and underlying disease). A case-by-case evaluation is needed. Recurrent or unusual infectious diseases are one of the important aspects of the medical history of a child with IBD, when dealing with possible PID; immunological dysregulation results in higher susceptibility to infection in this group of patients. Heightened awareness and vigilant surveillance leading to prompt diagnosis and treatment are imperative for optimal outcomes in children with IBD.

7. Expert commentary

The results of this study have confirmed that IBD patients have an increased risk of opportunistic infections, but data on pediatric populations are not relevant when compared with adult populations. Steroids alone or in combination carry higher risk of infection in children, and the risk is proportional to the dose and duration of treatment. The correlation between the increased risk of infection and the use of immunomodulatory drugs has not yet been fully quantified in pediatric populations, despite a more frequent, early use. Biological therapy has only recently been introduced in the management and there are no long-term surveillance data. A very important data that can be extrapolated is the relative safety of biological drugs in the pediatric population compared with steroids or

immunosuppressive drugs. However, a risk/benefit evaluation should be carried out in each patient before the start of anti-TNF-α therapy, and infections should be monitored or screened. The infection risk is higher in the case of combination therapy with other immunosuppressive agents. Baseline tests that include neutrophil and lymphocyte cell count, VZV and HBV serology, eosinophil cell count and serum immunoglobulin dosages may help to identify those patients with higher risk of infection if immunomodulatory therapies are started. Anemia, hypoalbuminemia and malnutrition can be considered additional risk factors for opportunistic infections and should be corrected before starting immunomodulatory drugs. The weakness of this study is that data reported are extracted from published studies and not from National IBD Registries, with probable underestimated incidence. The most important goal is to achieve higher sensitivity in pediatric and adult physicians in monitoring and prevention of opportunistic infections at the time of diagnosis and after starting therapy. This monitoring should also be conducted versus lesser known infectious agents such as *Listeria monocytogenes, Nocardia* spp and microconidia. Research and knowledge in this field should be oriented to the identification of some disease-related factors (age of diagnosis, extension, complications, genetics) that could increase the risk of opportunistic infections beyond the use of drugs. A small number of monogenic mutations have been identified in children with early IBD onset with associated primary immunodeficiencies. The very young age and the complicated disease should lead tomore careful monitoring of the infectious risk and adequate prophylaxis. Vaccinations are also needed to induce the most importantpreventive strategies and prophylaxis. The limited pediatric data available should stimulate new epidemiological studies to assess true incidence, microbiologic features and severity of infections. Further studies are warranted to define the role of IBD treatment-related immunomodulation in the development of infections. The care of children with IBD is being advanced by new drug development, such as antibodies against α4β7 integrin that inhibits lymphocyte migration.

The efficacy of this strategy is confirmed in adult populations but no data have been established regarding the safety and infection risk in a pediatric population. New collaborative research networks targeted toward the discovery of new pediatric IBD risk genes, and insights into the microbiome and molecular pathogenesis may allow the identification a subset of patients with increased susceptibility to infections.

8. Five-year view

In recent years, increasing interest has been shown in the diagnosis, management, and prevention of opportunistic infections in patients with IBD. However, specific data on the pediatric population are lacking, above all on steroid and immunomodulator safety, while more attention has been paid to the risk associated to the use of biological therapies. The main information comes from epidemiological and registry studies evaluating the efficacy and safety of these molecules, with the support of case reports and series: extension to larger-scale and specifically-addressed studies is strongly recommended. In the upcoming years, studies will define specific screening and surveillance programs for IBD pediatric patients, before and during immunosuppressive and biological therapy. In clinical practice, it is recommended that greater focus be placed in the execution of screening tests and vaccinations at the time of diagnosis of disease. Future studies are also needed to quantify the role of IBD drugs in the development of infections in pediatric patients, through long-term follow-up data. A primitive immunodeficiency should be excluded in early-onset IBD due to higher risk of drug-related infections and adverse events. Primary EBV infection is considered the most important risk factor to induce lymphoproliferative disorder and lymphoma in immunocompromised pediatric patients. The screening for latent or subclinical EBV infection and chemoprophylaxis before onset of immunomodulator therapy can be considered in pediatric population.

Key issues

- Opportunistic infections are possible complications in pediatric IBD
- Potential risks can be related to the disease or the use of steroids, immunosuppressants and biological therapies
- The risk of infection associated with the use of steroids is proportional to the dose and duration of treatment. Despite a more frequent, early use of methotrexate, thiopurines and biological therapies, the increased risk of infections has not yet been fully quantified in pediatric populations
- No long-term surveillance data are available on use of biological therapies in pediatric population
- Immunocompetence and assessment of the immune and serological status should be evaluated before the start of anti-TNF-α therapy
- The infection risk seems to be higher in the case of combined therapies (biological and thiopurine)
- Screening tests and vaccinations at disease diagnosis remain the most important ways of a proper prevention
- Anti-TNF-α therapy should be discontinued in the case of severe infection. After resolution, timing and modalities of anti-TNF-α therapy resumption remains to be defined

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

Papers of special note have been highlighted as:

* of interest

** of considerable interest

[1] 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;17:1314-21.

[2] 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;133:423–32.

[3] Abramson O,DurantM,Mow W,et al. Incidence, prevalence, and time trends of pediatric inflammatory bowel disease in Northern California, 1996 to 2006.J Pediatr. 2010;157:233-239.e1.

[4] Peloquin JM, GoelG, Villablanca EJ, et al. Mechanisms of pediatric inflammatory bowel Disease. Annu Rev Immunol. 2016;34:31-64.

[5] Nuti F, Civitelli F, Cucchiara S.Long-term safety of immunomodulators in pediatric inflammatory diseases.Paediatr Drugs. 2014;16:343-52.

[6] Hyams J,CrandallW,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.

[7] Hyams J, Damaraju L, Blank M, et al; T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:391-399.e1.

[8] Symmers WS. Opportunistic infections. The concept of 'opportunistic infections'. Proc R Soc Med. 1965;58:341-6.

[9] ** **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 CrohnsColitis.2014;8:443-68.** ***Most recent guidelines of European Crohn's and Colitis Organisation (ECCO) on the diagnosis, management, and prevention of opportunistic infections in patients with IBD.***

[10] Krok KL, Lichtenstein GR. Nutrition in Crohn disease. Current opinion in gastroenterology 2003;19:148 – 53.

[11] Ainley C, Cason J, Slavin BM, et al. The influence of zinc status and malnutrition on immunological function in Crohn's disease. Gastroenterology1991;100:1616-25.

[12] Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. Dis Colon Rectum 2000;43:1141 – 5.

[13] Kudsk KA, Tolley EA, DeWitt RC, Janu PG, Blackwell AP, Yeary S, et al. Preoperative albumin and surgical site identify surgical risk for major postoperative complications. JPEN2003;27:1-9.

[14] Markel TA, Lou DC, Pfefferkorn M, et al. Steroids and poor nutrition are associated with infectious wound complications in children undergoing first stage procedures for ulcerative colitis. Surgery 2008;144:540-5.

[15] ****Ardura MI, Toussi SS, Siegel JD, et al. NASPGHAN Clinical Report: Surveillance, Diagnosis, and Prevention of Infectious Diseases in Pediatric Patients with Inflammatory Bowel Disease Receiving Tumor Necrosis Factor-α Inhibitors. J Pediatr Gastroenterol Nutr. 2016 Jul;63:130-55.*Provide up-to-date data regarding infections in pediatric patients with IBD receiving anti-TNF-a therapies.***

[16] Tegtmeyer D, Seidl M, Gerner P, Baumann U, Klemann C. Inflammatory bowel disease caused by primary immunodeficiencies-Clinical presentations, review of literature, and proposal of a rational diagnostic algorithm.Pediatr Allergy Immunol. 2017;28:412-29.

[17] Uhlig HH, Schwerd T, Koletzko S et al. The Diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology 2014;147:990–1007.e3.

[18] Uhlig HH, Schwerd T. From genes to mechanisms: the expanding spectrum of monogenic disorders associated with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22:202 – 12.

[19] Capriati T, Cardile S, Papadatou B, et al. Pediatric inflammatory bowel disease: specificity of very early onset. Expert Rev ClinImmunol2016;12:963-72.

[20] Rubin LG,Levin MJ, Ljungman P, et al. 2013IDSAclinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:309-18.

[21] Lu Y, Bousvaros A. Immunizations in children with inflammatory bowel disease treated with immunosuppressive therapy. Gastroenterol Hepatol (N Y). 2014;10:355-63.

[22] Urganci N, Kalyoncu D. Immunogenecity of hepatitis A and B vaccination in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2013;56:412-15.

[23] 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 Crohn's Colitis.2009;3:47-91.

[24] Koike Y,UchidaK,Inoue M, et al. Infantile Crohn's disease is one of the risk factors for catheter-related bloodstream infection. Pediat rInt. 2014;56:364-8.

[25] Biank VF, Sheth MK, Talano J, et al. Association of Crohn's disease, thiopurines, and primary epstein-barr virus infection with hemophagocytic lymphohistiocytosis. J Pediatr. 2011;159:808–12.

[26] Shirley DA, Moonah S. Fulminant Amebic Colitis after Corticosteroid Therapy: A Systematic Review. PLoSNegl Trop Dis. 2016;10:e0004879.

[27] Kolho KL, Ainamo A.Progress in the Treatment and Outcome of Pediatric Inflammatory Bowel Disease Patients. Expert Rev Clin Immunol. 2016;12:1337-45.

[28] Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55:340–61.

[29] Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohn's Colitis. 2014;8:1179–207.

[30] Tajiri H, Tomomasa T, Yoden A, et al. Japanese Society for Pediatric Inflammatory Bowel Disease. Efficacy and safety of azathioprine and 6-mercaptopurine in Japanese pediatric patients with ulcerative colitis: a survey of the Japanese Society for Pediatric Inflammatory Bowel Disease. Digestion 2008;77:150-4.

[31] Ross S,RajwalSK,Sugarman I, et al. Epstein-Barr virus-associated lymphoproliferative disorder in Crohn disease treated with azathioprine. J Pediatr Gastroenterol Nutr. 2010;51:229–31.

[32] Gidrewicz D, Lehman D, Rabizadeh S, et al. Primary EBV infection resulting in lymphoproliferative disease in a teenager with Crohn disease. J Pediatr Gastroenterol Nutr. 2011;52:103-5.

[33] Fitzgerald MP, Armstrong L, Hague R, et al. A case of EBV driven haemophagocytic lymphohistiocytosis complicating a teenage Crohn's disease patient on azathioprine, successfully treated with rituximab. J Crohns Colitis. 2013;7:314-7.

[34] Comar M,DelbueS,Lepore L, et al. Latent viral infections in young patients with inflammatory diseases treated with biological agents: prevalence of JC virus genotype 2.J Med Virol. 2013;85:716-22.

[35] Love KA, Henderson P, Garrick V, et al. Letter: Epstein-Barr virus status may be especially important in paediatric IBD populations. Aliment Pharmacol Ther. 2014;39:231-2.

[36] Hradsky O, Copova I, Zarubova K, et al. Seroprevalence of Epstein-Barr Virus, Cytomegalovirus, and Polyomaviruses in Children with Inflammatory Bowel Disease. Dig Dis Sci. 2015;60:3399-407.

[37] Verma R, Walia R, Sondike SB, et al. Pulmonary nocardiosis in an adolescent patient with Crohn's disease treated with infliximab: a serious complication of TNF-alpha blockers. W V Med J. 2015;111:36–9.

[38] Dulai PS, Thompson KD, Blunt HB, et al. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clin Gastroenterol Hepatol. 2014;12:1443-51.

[39] Toussi SS, Pan N, Walters HM, et al. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor-α inhibitors: systematic review of the literature. Clin Infect Dis. 2013;57:1318-30.

[40] Rosh JR, Lerer T, Markowitz J, et al. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease. Am J Gastroenterol.2009;104:3042-9.

[41] Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology 2012;143:365-74.e2.

[42] Faubion WA, Dubinsky M, Ruemmele FM, et al. Long-term efficacy and safety of adalimumab in pediatric patients with Crohn's disease. Inflamm Bowel Dis. 2017;23:453-60.

[43] De Ridder L, Turner D, Wilson DC, et al. Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the Porto pediatric IBD group. Inflamm Bowel Dis. 2014;20:291–300.

[44] Silk BJ, Date KA, Jackson KA, et al. Invasive listeriosis in the Foodborne Diseases Active Surveillance Network (FoodNet), 2004-2009: further targeted prevention needed for higher-risk groups. Clin Infect Dis. 2012;54Suppl 5:S396-404.

[45] Kamath BM, Mamula P, Baldassano RN, et al. Listeria meningitis after treatment with infliximab.JPediatrGastroenterolNutr. 2002;34:410-2.

[46] Chuang MH, Singh J, Ashouri N, et al. Listeria meningitis after infliximab treatment of ulcerative colitis. J Pediatr Gastroenterol Nutr. 2010;50:337-9.

[47] Miranda-Bautista J, Padilla-Suárez C, Bouza E, et al. Listeria monocytogenes infection in inflammatory bowel disease patients: case series and review of the literature. Eur J Gastroenterol Hepatol. 2014;26:1247-52.

[48] Chirumamilla SR, He C,RacusenLC, et al. Acute kidney injury in a girl with ulcerative colitis and cytomegalovirus-induced focal segmental glomerular sclerosis. World J Pediatr. 2013;9:84-6.

[49] Ghidini B, Bellaiche M, Berrebi D, et al. Cytomegalovirus colitis in children with inflammatory bowel disease. Gut 2006;55:582-3.

[50] Pickering O, Weinstein T, Rubin LG. Fatal disseminated cytomegalovirus infection associated with infliximab and6-mercaptopurine therapy in a child with Crohndisease.Pediatr Infect Dis J. 2009;28:556.

[51] Marin M,ZhangJX,Seward JF. Near elimination of varicella deaths in the US after implementation of the vaccination program. Pediatrics 2011;128:214-20.

[52] Kunz AN,Rajnik M. Disseminated cutaneous varicella zoster virus infections during infliximab therapy for Crohn's disease: case report of two pediatric patients at one institution. ClinPediatr (Phila)2011;50:559-61.

[53] Cruz AT,KaramLB,Orth RC, et al. Disseminated tuberculosis in 2 children with inflammatory bowel disease receiving infliximab. Pediatr Infect Dis J.2014;33:779-81.

[54] Calzada-Hernández J,Anton-LópezJ,Bou-Torrent R, et al. Tuberculosis in pediatric patients treated with anti-TNF-α drugs: a cohort study. PediatrRheumatol Online J. 2015;13:54.

[55] SacristánMartín AM, Casares Alonso I, LageGarcía MJ. Prevalencia de infección tuberculosa en adolescentes de 11 a 14 años en Palencia. Rev Pediatr Aten Primaria.2004;6:9-17.

[56] Starke JR; Committee on Infectious Diseases. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. Pediatrics 2014;134:e1763-73.

[57] Jordan N, Waghmare A, Abi-Ghanem AS, et al. Systemic Mycobacterium avium complex infection during antitumor necrosis factor-α therapy in pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2012;54:294-6.

[58] Cheent K, Nolan J, Shariq S, et al. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohn's Colitis. 2010;4:603-5.

[59] Tschudy J, Michail S. Disseminated histoplasmosis and pneumocystis pneumonia in a child with Crohn disease receiving infliximab. J PediatrGastroenterolNutr.2010;51:221-2.

[60] Dotson JL, Crandall W, Mousa H, et al. Presentation and outcome of histoplasmosis in pediatric inflammatory bowel disease patients treated with antitumor necrosis factor alpha therapy: a case series. Inflamm Bowel Dis. 2011;17:56-61.

[61] Wheat LJ, Freifeld AG, Kleiman MB, et al.; Infectious Diseases Society of America. Clinical practice guidelines for the management of patients with histoplasmosis:2007update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45:807-25.

[62] Warris A, Bjørneklett A, Gaustad P. Invasive pulmonary aspergillosis associated with infliximab therapy. New Engl J Med. 2001;344:1099-100.

[63] Russell RK, Wilson ML, Loganathan S, et al. A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease. Aliment Pharmacol Ther. 2011;33:946-53.

[64] Huang A, Huang C, Kugathasan S. Vertebral osteomyelitis due to Candida parapsilosis in a child with Crohn disease while receiving anti-TNF therapy. J Pediatr Gastroenterol Nutr. 2013;56:e23-6.

[65] Lawrance IC, Radford-Smith GL, Bampton PA, et al. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. J Gastroenterol Hepatol. 2010;25:1732-8.

[66] Veereman-Wauters G, deRidder 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;54:830-7.

[67] Singh N, Deshpande R, Rabizadeh S, et al. Real world experience with natalizumab at a tertiary Care pediatric IBD center. J Pediatr Gastroenterol Nutr. 2016;62:863 – 6.

[68] Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. Ann Neurol2010;68:295–303.

[69] Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol 2014;76: 802–12.

[70] Singh N, et al. Multi-center experience of vedolizumab effectiveness in pediatric inflammatory bowel disease. Inflamm Bowel Dis 2016;22:2121-6.

[71] Conrad MA, Stein RE, Maxwell EC, et al. Vedolizumab therapy in severe pediatric inflammatory bowel disease. Inflamm Bowel Dis 2016;22:2425-31.

[72] Ledder et al. Vedolizumab in pediatric inflammatory bowel disease: a retrospective multi-center experience from the Paediatric IBD Porto group of ESPGHAN. J Crohns Colitis. 2017 Jun 9. [Epub ahead of print]

[73] Sandberg KC, Davis MM, Gebremariam A, et al. Disproportionate rise in Clostridium difficile-associated hospitalizations among US youth with inflammatory bowel disease, 1997-2011. J Pediatr Gastroenterol Nutr. 2015;60:486-92.

[74] Kelsen JR, Kim J, Latta D, et al. Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17:50-5.

[75] Schutze GE, Willoughby RE; Committee on Infectious Diseases; American Academy of Pediatrics. Clostridium difficile infection in infants and children. Pediatrics. 2013;131:196-200.

[76] Ben-Horin S, Margalit M, Bossuyt P, et al; European Crohn's and Colitis Organization (ECCO).Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and Clostridium difficile infection. J Crohn's Colitis. 2010;4:194-8.

[77] Pascarella F, Martinelli M, Miele E, et al. Impact of Clostridium difficile infection on pediatric inflammatory bowel disease. J Pediatr. 2009;154:854-8.

[78] Hourigan SK, Chirumamilla SR, Ross T, et al. Clostridium difficile carriage and serum antitoxin responses in children with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:2744-52.

[79] Schneeweiss S,KorzenikJ, Solomon DH, et al. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. Aliment Pharmacol Ther. 2009;30:253-64.

[80] Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5:345 – 51.

[81] ***Hourigan SK, Sears CL, Oliva-Hemker M. Clostridium difficile Infection in Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22:1020-5.*** ***Provide up-to-date data regarding Clostridium difficile infections in pediatric patients with IBD and review of current evidence about its association with IBD therapy.***

[82] Martinelli M, Strisciuglio C, Veres G, et al; Porto IBD Working Group of European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Clostridium difficile and pediatric inflammatory bowel disease: a prospective, comparative, multicenter, ESPGHAN study. Inflamm Bowel Dis. 2014;20:2219-25.

[83] Hojsak I, Ferenc T, Bojani K, et al. Incidence of Clostridium difficile infection in children with inflammatory bowel disease compared to oncology and immunocompetent patients. Digestion. 2012;86:6 – 11.

Table 1. Infectious disease and corticosteroid therapy

Authors	Type of Study	Results
Markel TA et al. [14]	Retrospective	Higher post-operative wound infection rate among UC pediatric patients on pre-operative steroid treatment
Koike Y et al. [24]	Retrospective	Immunosuppressants (including steroids) (P = 0.043) are independent risk factors for catheter-related bloodstream infections
Shirley DA et al. [26]	Systematic review	High risk of developing fulminant amebic colitis for patients on steroid therapy

UC ulcerative colitis, CD Crohn's disease, IBD inflammatory bowel disease

Table 2. Infectious disease and immunomodulatory therapy: original articles

Authors	Type of Study	Results
Biank VF et al. [25]	Retrospective	Primary EBV infection and thiopurines are possible risk factors for HLH
Love KA et al. [35]	Prospective	High prevalence (40%) of EBV seropositivity in a newly diagnosed pediatric IBD population Association with IBD therapy not found
Hradsky et al. [36]	Cross-sectional	High prevalence (64%) of EBV seropositivity in IBD pediatric population Azathioprine therapy is possible risk factor for early EBV seropositivity in IBD children

IBD inflammatory bowel disease, HLH haemophagocytic lymphohistiocytosis, EBV Epstein Barr Virus

Table 3. Infectious disease and biological therapy

Authors	Type of Study	Type of drug	Results
Hyams J et al. [6]	Randomized, multicenter, open-label	Anti-TNF-α	Higher risk of infections during infliximab shortened drug-free interval (every 8 weeks versus every 12 weeks) Higher incidence of mild rather than serious infections
Toussi SS et al. [39]	Systematic review	Anti-TNF-α	Low incidence of both mild and serious infections among pediatric IBD patients treated with either adalimumab or infliximab
Dulai PS et al. [38]	Systematic review/ Meta-analysis	Anti-TNF-α	Lower rate of serious infection among pediatric patients with IBD on anti-TNF-α agents than those treated with steroids Similar rate to those on immunomodulators
Calzada-Hernández et al. [54]	Retrospective and observational	Anti-TNF-α	No incident cases of MTB disease after a year follow-up among 127 IBD pediatric patients treated with anti-TNF-α agents in a low-incidence context LTBI prevalence rate of 1.4% (n=3)
Singh et al. [67]	Retrospective	Anti-integrins	No serious infections (including PML) reported among 9 CD children on natalizumab
Singh et al. [70]	Retrospective	Anti-integrins	No serious infections (including PML) among 52 IBD children on vedolizumab
Conrad et al. [71]	Prospective and observational	Anti-integrins	Upper respiratory tract infection (n=5), nasopharyngitis(n=2), skin infections (n=2), sinusitis (n=1) among 21 IBD children on vedolizumab; no certain correlation to the drug has

			been proved
Ledder et al. [72]	Retrospective	Anti-integrins	Otitis media (n=1) among 64 IBD children on vedolizumab; no certain correlation to the drug has been proved

CD Crohn's disease, IBD inflammatory bowel disease, TNF Tumor Necrosis Factor, MTB Mycobacterium tuberculosis, LTBI latent tuberculosis infection, PML progressive multifocal leukoencephalopathy

Table 4. Clostridium difficile infections

Authors	Type of Study	Results
Pascarella F et al. [77]	Retrospective and case-control	Higher prevalence of CDI in children with IBD than in the control population without IBD Type of IBD therapy does not impact on CDI rate
Kelsen JR et al. [74]	Retrospective and case-control	Higher rate of both recurrence and exacerbation of symptoms of CDI in children with IBD than in the control population with CDI but without IBD
Hourigan SK et al. [78]	Prospective and case-control	Greater symptomatic Clostridium difficile carriage in IBD pediatric patients than controls Type of IBD therapy does not impact on CDI rate
Hourigan SK et al. [81]	Retrospective	Higher rate of CDI in IBD than non-IBD hospitalized children
Martinelli M et al. [82]	Prospective and case control	Higher prevalence of active disease in IBD children with CDI than in IBD children without CDI Type of IBD therapy does not impact on CDI rate
Sandberg KC et al. [73]	Retrospective	5-fold increase in IBD hospitalizations with CDI from 1997 to 2011in the United States versus 2-fold increase without CDI. Association with IBD therapy not found

CDI Clostridium difficile infection, IBD inflammatory bowel disease