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Immunization in inflammatory bowel diseases: recommendations on vaccines administration

Imunizacija kod inflamatornih bolesti creva: preporuke za primenu vakcina

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Introduction

The planning and implementation of immunization in patients with inflammatory bowel diseases (IBD) is just a necessary step in treating and monitoring the underlying disease, especially in preparing a patient for the introduction and application of immunosuppressive therapy.

This opinion is the result of the following findings: the majority of patients with IBD will be treated with immunosuppressive therapy during the illness; a large number of IBD patients are immunocompromised due to the nature and the course of the underlying disease; vaccination is the only form of prevention in certain infectious diseases that can complicate the condition of patients with IBD. The possible, more favourable relationship between the cost of the treatment of the infectious complications, the resulting hospitalization, and the costs of vaccination of these patients should not be neglected either.

The immunization of patients with IBD has certain specificities since the immune system and the immune response of the patients have been altered under the influence of etiopathogenesis, clinical course characteristics, and the treatment of the underlying disease. Due to all this, adequate vaccination planning is needed – the time of vaccine use, the type of vaccine, as well as the knowledge of safe and effective application, possible interactions with immunosuppressive drugs, and the effect of immunization on the immune response.

In routine clinical practice, special attention is rarely given to immunization data and its implementation in patients with IBD. Namely, the implication of compulsory vaccinations, which have been conducted in most patients and prior to the diagnosis of IBD, separates the clinician from the idea of the necessity of using vaccines during the treatment of these patients. It is, therefore, very important to define methods of vaccination of IBD patients, establish recommendations based on which the immunization of IBD patients will become an integral part of their treatment and an important segment in preventing infectious complications of these patients.

Predisposition for developing complications from infectious diseases in IBD patients

Infections that complicate IBD are on the rise. They are the basis of the highest percentage of complications and the need for hospital treatment of these patients. Among them, opportunistic infections, but also infectious diseases that can be prevented by immunization, are particularly important.

Opportunistic infections are defined as serious, usually progressive, infections caused by microorganisms that have limited pathogenic or even non-pathogenic capacity in people with uncompromised immune system. The same microorganisms can cause severe illnesses in the conditions of the predisposing effect of another associated disease or its treatment [1].

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Table 1

Some causes of the state of deficiency of the immune system (according to the Center for Disease Control, The Unites States Advisory Committee on Immunization Practices – US ACIP)

People who are in severe immunodeficiency which is not the result of human immunodeficiency virus (HIV) infection (congenital immunodeficiency, leukaemia, lymphoma, malignancy or application of therapy – alkylating agents, antimetabolites, radiation, high doses of corticosteroids – 2 mg/kg/bw or more than 20 mg of prednisone daily);
People with HIV infection;
People with conditions that cause a limited deficit of the immune system (e.g. hyposplenism, renal insufficiency, etc.).

Patients who are immunocompromised have altered cellular and/or humoral immunity, which increases the risk of opportunistic infections and infections in general. In patients with IBD, gene mutations for molecules that play an important role in innate immunity have been described, such as receptors for molecular patterns of pathogens and damaged cells (NOD2) or cytokine receptors (IL23R). These mutations are responsible for the changed functional capacity of innate immunity [2, 3]. Moreover, the activity of the acquired (adaptive) immunity cells in patients with IBD is also changed. In Crohn's disease, for instance, there is a description of increased activity of Th1 subpopulation of helper lymphocytes (CD4+ T lymphocytes) manifested by increased production of interferon gamma (INF-γ), as well as increased production of cytokines IL-12 and IL-18 by macrophages of the mucosa. In contrast to Crohn's disease, in ulcerative colitis, there is primarily an over-response of Th2 subpopulation of helper lymphocytes characterized by increased production of cytokines IL-13 and IL-5. Furthermore, T lymphocytes of patients with ulcerative colitis have a slower cell cycle and are more susceptible to programmed cell death (apoptosis) compared to control cells [4]. Bearing in mind all the above findings, it is clear that the intestinal lesion in IBD patients is completely under the influence of different "branches" of the immune system.

Despite the deficiencies described in the function of innate immunity and the changed immune function of the cells of the acquired immunity, not all patients with IBD can be considered immunocompromised [5]. Although there is no clear definition of the immunocompromised condition in the IBD, IBD patients are considered immunocompromised if treated with the following: corticosteroids for two weeks and longer or repeated within three months, with azathioprine (AZA) or 6-mercaptopurine (6MP), methotrexate (MTX), anti-tumor necrosis factor (TNF) agents, as well as patients with high protein-caloric malnutrition (Table 1).

Corticosteroids reduce the synthesis of cytokines with pro-inflammatory activity by inhibiting the transcription of the gene for these cytokines. This results in a decrease in the activity of various immune system cells, including inhibition of leukocyte migration, inhibition of the function of phagocytes (neutrophils and monocytes), and the function of T lymphocytes. AZA and 6MP, in the form of nucleotides, have been shown to lead to apoptosis of T lymphocytes. MTX, as a folic acid antagonist, inhibits the synthesis of purine, DNA and RNA structures, consequently inhibiting the S phase of the cell cycle. Cyclosporin, as the most commonly used calcineurin inhibitor, reduces the production of cytokine (IL-2, IL-3, IL-4, IL-5, TNF-α, TNF-β, INF-γ) by T helper lymphocytes. One of the main activators of the inflammatory process in IBD is TNF. The biological agents, antibodies that bind TNF (anti-TNF antibodies), except that they can inactivate the effect of TNF, induce monocyte apoptosis, and thus suppress the inflammatory process in IBD.

Applying the combination of immunosuppressants in therapy thus modulates the immune system at multiple levels.

Other risk factors for the development of infections, which also intensify the degree of immunosuppression, are malnutrition, surgical interventions, old age, co-morbidities, and leukopenia within the immunosuppressant application [6].

The occurrence of opportunistic infections is a problem for clinicians. These infections are often more difficult to recognize and diagnose, and are associated with high morbidity and mortality because they are potentially serious and less responsive to effective treatment (Table 2). Within a number of clinical studies, an increased incidence of opportunistic infections in IBD patients has been observed, including the occurrence of opportunistic infections associated with the use of immunosuppressive therapy in the treatment of patients with IBD [5–9].

Table 2

Opportunistic infections associated with the use of immunosuppressive therapy in the treatment of inflammatory bowel diseases (IBD) [7]

Causes of opportunistic infections
Viral infections
Varicella zoster virus
Herpes simplex virus
Cytomegalovirus
Epstein Barr virus
Human papillomavirus
Bacterial infections
Escherichia coli
Salmonella spp.
Streptococcus pneumoniae
Clostridium difficile
Staphylococcus spp.
Mycobacterium tuberculosis
Legionella pneumophila
Listeria monocytogenes
Mycobacterium avium spp.
Nocardia spp.
Fungal and parasitic infections
Candida spp.
Pneumocystis carinii
Aspergillus spp.
Histoplasmosis
Cryptococcus spp.
Coccidioides immitis
Blastomycosis

Vaccination

Vaccines are used to achieve a qualitatively and quantitatively appropriate (adequate) immune response from a recipient that ensures the usefulness of the applied protection. The time of immunization should be such as to provide a balance between the desire to achieve an optimal immune response and the practical need to achieve protection against an illness. The principles of childhood immunization are based on the above.

Since most IBD patients were vaccinated prior to the diagnosis of IBD, when their immune response was not changed due to the illness, and according to the mandatory vaccination plan (Table 3), the specific effect of administered vaccines in patients with IBD does not differ significantly from their effect in the non-IBD population. Therefore, although no precise data are available, it is considered that the incidence of the disease against which early immunization was carried out (diphtheria, pertussis, polio, measles, rubeola, tetanus) in the IBD population is negligible. Recommendations for immunizing patients with IBD (immediately after the diagnosis of IBD) are based on the assumption that compulsory vaccines have been previously used, which requires adequate evidence.

Planning and implementation of vaccination in patients with IBD is part of the infection prevention process (Table 4). Infections can complicate IBD during the application of immunosuppressive therapy, like in immunocompromised patients in general. This plan and its implementation depend on the assessment of the immune response status of each patient individually at a given moment.

Table 3

Calendar of compulsory vaccinations in Serbia, according to age (Institute of Public Health of Serbia "Dr Milan Jovanović Batut")

Age	BCG	HB	DTP	OPV	MMR	Hib
1st month (birth)	Vaccination	I dosage				
2nd month		II dosage				
3rd month			I dosage	I dosage		I dosage
3 and a half months			II dosage	II dosage		II dosage
By 6th month		III dosage	III dosage	III dosage		III dosage
From 12th to 15th month					Vaccination	
From 17th to 24th month			DTP Revaccination I	Revaccination I		
7 years of age (before going to school)			DT Revaccination II	Revaccination II	Revaccination	
12 years		3 doses*				
14 years of age			DT Revaccination III	Revaccination III		

HB – hepatitis B vaccine, contains purified hepatitis B surface antigen (HbsAg); DTP – diphtheria, pertussis, and tetanus vaccine, contains diphtheria toxoid, tetanus, and inactivated corpuscle *B. pertussis*; DT – adult vaccine, contains diphtheria toxoid and tetanus; MMR – vaccine against measles, mumps, and rubella, contains live, attenuated viruses; OPV – oral poliomyelitis vaccine, contains live, attenuated, 2 types of poliovirus; Hib – a conjugated vaccine against *Haemophilus influenzae* type B.

***children who have not been vaccinated by 12 years of age with three doses of vaccine by the scheme of 0, 1, 6 months.**

The calendar also includes the use of a tetanus vaccine (toxoid) that is applied after 30 years of age, every ten years, as well as the use of hepatitis B immunoglobulins (applied in newborn babies of mothers who are HBsAg positive).

Table 4

General recommendations for immunization of patients with inflammatory bowel diseases (IBD) [9]

1. Standard recommended immunization schedules for children and adults should be generally adhered to.
2. Upon diagnosis, children and adults should have a complete review of immunization history for completeness. All patients with incomplete series should commence catch-up vaccination.
3. Adults who cannot provide a clear history of chickenpox should have serologic testing for varicella. Nonimmune individuals should receive the varicella vaccine. Children who are not immune by vaccination or have not acquired immunity through infection should receive the varicella vaccine.
4. Live bacterial or viral vaccines should be avoided in immunocompromised children and adults with IBD. This includes the following: i) Treatment with glucocorticoids (prednisone 20 mg/d equivalent, or 2 mg/kg/d if less than 10 kg, for 2 weeks or more, and within 3 months upon stopping); ii) Treatment with effective doses of 6-mercaptopurine/azathioprine (effect on safety not established) and within 3 months upon stopping; iii) Treatment with methotrexate (effect on safety not established) and within 3 months upon stopping; iv) Treatment with infliximab (effect on safety not established) and within 3 months upon stopping; v) Significant protein-calorie malnutrition.
5. Whenever possible, adequate immune response (as reflected by serologic response) should be ascertained for individuals who have required immunization while immunosuppressed. Repeat dosing may be considered when the immune response to immunization is insufficient.

The effect of vaccination depends on the quality of the immune response and the compromising effect of immunomodulatory therapy on this response. There is still insufficient data based on which it is possible to assess the clinical response to the immunological changes caused by vaccination in IBD patients. The results of studies investigating the effects of immunization of immunocompromised patients or the immunization of patients suffering from immunosuppressive therapy [systemic lupus erythematosus (SLE), reumatoid arthritis (RA)] have shown that these patients create an adequate humoral immune response (specific antibodies have been detected). Moreover, these patients did not exhibit an increase in the activity of the underlying disease as a result of the response of their immune system to the use of vaccines [10, 15–18].

Vaccines can be classified into several categories, depending on the characteristics (forms) of the antigens used for their making. They may contain live (attenuated, avirulent) infectious agents (live vaccines), or they may be dead vaccines containing inactivated infectious agents of preserved immunogenicity. The immune system recognizes and responds to antigens by activating B lymphocytes (antibody production) and activating T lymphocytes. From activated T and B lymphocytes, in the process of developing the immune response to the pathogen, memory lymphocytes are created with mechanisms of even faster response in each future exposure to a given pathogen. By measuring the level of production of a specific antibody after immunization, as well as by comparing the antibody level before and after immunization, it is possible to estimate the degree of the immune response or the immunogenicity of the applied vaccine.

The immunogenicity of the vaccine (potential to produce an adequate immune response) can be determined in several ways and is usually estimated based on the titer of the antibodies produced. The titer of antibodies is determined before immunization and at a certain time interval after vaccination (usually four weeks after immunization). The process of seroconversion involves the formation of a specific antibody titer in seronegative persons (who did not have a measurable antibody titer prior to vaccination), which makes them seropositive. In the seroconversion process, a minimum titer of an anti-infection antibody (wild type) is required, and the achievement of said level or greater titer defines the so-called seroprotection – the expected protection [4].

Time of vaccine administration

In conditions of immunosuppression and, therefore, in patients with IBD, the use of live, attenuated vaccines is contraindicated since the entry of a causative agent in the condition of a compromised immune system can lead to the occurrence of an infectious disease (Table 5).

IBD patients need adequate access to the administration of vaccines with the knowledge of all of the aforementioned characteristics that relate to the changed immune system of the recipient and the application of immunosuppressive therapy. Bearing in mind the specificity of the recipient's immune response caused by the disease and/or the applied therapy that could affect the immunogenicity of the vaccine and the process of seroconversion, it is necessary to assess with great care the safety and efficacy of the administered vaccine.

Table 5

Live vaccines, generally contraindicated in patients receiving immunosuppressive therapy [9]

Anthrax vaccine
Intranasal influenza
Measles-mumps-rubella (MMR)
Oral polio live vaccine (OPV)
Smallpox vaccine
Tuberculosis BCG vaccine
Typhoid live oral vaccine
Varicella
Yellow fever

As part of the above, it is recommended that the appropriate vaccines be administered within 3 weeks upon starting the immunosuppressive therapy. Furthermore, if the treatment with immunosuppressants is in progress, the possible application is recommended 3 months after discontinued use of these drugs.

Vaccinating newborns of mothers treated with anti-TNF agents is a specific situation. According to the recent recommendations, the first vaccination should be administered from the 6th month of life. This is due to the fact that after this period, the anti-TNF antibodies, which the mother received as therapy and which were thus transferred to the child, have withdrawn from the child's bloodstream.

Specificity of vaccination of IBD patients

The most important infectious diseases of adult patients with IBD that can be prevented (mitigated) by vaccines and in which prevention is the most effective are influenza, varicella, and pneumococcal infections. Additionally, the recommendations for vaccination include specific situations that include vaccination against viral infections such as hepatitis B virus, human papillomavirus (HPV) infection in women, and the need for vaccination in case of traveling to certain parts of the world.

Influenza virus (flu)

Infection with the influenza virus has an annual epidemic character. Vaccines are formed each year according to the frequency of antigen properties of virus strains (type A, with H1N1 and H3N2 subtypes having global distribution and type B). In 2009, the World Health Organization (WHO) defined H1N1 as a pandemic strain, and since 2010, this strain is compulsorily contained in all vaccines produced for a given year.

Morbidity and mortality in influenza virus infections are increasing in immunocompromised patients. Thus, the current recommendations for vaccination are directed towards this population.

There are still insufficient results based on which it would be possible to evaluate clinical protection against influenza in patients with IBD after the vaccine administration. In several studies, where patients with IBD and patients with other immunologically mediated diseases were examined, vaccination efficacy was assessed based on the change in antibody titer after the vaccine administration. Data on the safety and tolerance of influenza vaccines are also limited, but they generally show that this vaccine is well tolerated and safe to use [19, 20].

As noted earlier, the application of a live, attenuated influenza vaccine is contraindicated in patients on immunosuppressive therapy. In this group of IBD patients, the use of trivalent influenza vaccine (TIV), a type of inactivated vaccine, is recommended. It is administered once a year (usually before the onset of influenza and in accordance with the recommended vaccine administration time). It has been shown that administration of the vaccine has no effect on IBD activity. It has also been confirmed that seroconversion has not been reduced and altered in patients on steroids, MTX, and anti-TNF agents, or dual therapy with these drugs. At the same time, the administration of thiopurine and cyclosporine affects the reduction in the percentage of seroconversion [21]. A routine check of a serological response in these cases is not necessary, given the above-mentioned existing knowledge [5].

Varicella–zoster virus (VZV)

VZV causes varicella and herpes zoster (after reactivating a latent VZV infection from the dorsal ganglia). Studies have shown that this is the most common herpes-viral infection in immunocompromised patients with IBD. Immunosuppression increases the incidence of herpes zoster (mainly in patients older than 50 years of age) and the risk of disseminated and complicated forms of illness (pneumonia, meningoencephalitis, and haemostasis disorders).

Primary prevention of varicella by vaccination is routinely recommended according to the calendar of vaccinations in childhood, in immunocompetent children (after the first year of life and in the period from 4 to 6 years of life-booster dose). This vaccination is not mandatory in our country. Given that these vaccines (against varicella and zoster) belong to the category of live, attenuated vaccines, the question arises as to the justification and risk of their use in immunocompromised IBD patients.

If the previous medical history of varicella and/or herpes zoster treatment is negative and if a patient is not vaccinated in childhood, the VZV vaccine should be administered immediately after the diagnosis of IBD or at least three weeks before initiating immunosuppressive therapy. If there is no vaccination or infection information, serological analyses – IgG VZV antibody titers should be done. Vaccination is performed in all seronegative patients. Two doses of live vaccine are administered, at a minimum interval of one month. If immunosuppressive therapy is discontinued, the vaccine should be administered no earlier than 3 months after the discontinuation of the therapy. The use of a vaccine is considered safe in patients with lower doses of immunosuppressive therapy (less than 20 mg of prednisone daily) or higher doses for less than two weeks, or AZA less than 3 mg/kg a day [9–11].

The levels of immunosupression are given in Table 6.

Previously treated VZV infection is not a contraindication for the use of immunosuppressive therapy but should not be initiated in the event of an acute infection. In the case of the VZV infection in the course of immunosuppressive therapy, antiviral drugs (acyclovir) should be used, and the immunosuppression should be stopped, especially in more complicated cases [13], and immunosuppressive therapy should be reintroduced after febrile and vesicle regression [14].

The need for the VZV vaccine, as well as all other vaccines, should be assessed individually in each IBD patient, depending on the application of immunosuppressive therapy, dose, and duration of treatment, as well as the assessment of the risk-benefit ratio of the above.

Table 6

Levels of immunosuppression based upon strength of immunosuppressive medication [10]

High-level immunosuppression
Treatment with glucocorticoids (prednisone >20 mg/day for ≥2 weeks and within 3 months of stopping therapy);
Treatment with effective doses of 6-mercaptopurine, azathioprine, or methotrexate compared with those with low-level immunosuppression (described below) or discontinuation within 3 months;
Treatment with adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, or vedolizumab, or recent discontinuation within 3 months.
Low-level immunosuppression
Treatment with effective doses of 6-mercaptopurine, azathioprine, or methotrexate compared with those with low-level immunosuppression (described below) or discontinuation within 3 months;
Treatment with lower total daily doses of corticosteroids compared with those with high-level immunosuppression for more than 14 days;
Patients receiving methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or mercaptopurine (<1.5 mg/kg/day).

Pneumococcal infections

Streptococcus pneumoniae-induced infections cause more deaths than other vaccine-preventable bacterial infections. Risk factors for the emergence of these infections are chronic immunosuppressive therapy (we see patients with IBD within this), chronic illness, and old age. Severe, invasive forms of pneumococcal infections – pneumonia and meningitis (with or without bacteraemia) are followed by higher mortality. In patients with IBD who are on immunomodulatory therapy, bacterial pneumonia caused by *pneumococcus* is one of the most common opportunistic infections.

Vaccination against *pneumococcus* should be performed in all patients with risk factors (old age, associated chronic illness, immunosuppression, splenectomized patients, and immunosuppressive therapy patients). Three types of vaccines are available, and they are the following: 23-valent polysaccharide (PPV23) that provides protection against the action of 80–90% of strains responsible for severe infections; 13-valent pneumococcal conjugate (PCV13), and 7-valent pneumococcal conjugate vaccine (PCV7). A patient with IBD should be vaccinated with pneumococcal vaccine according to recommendations.

IBD patients should be administered with pneumococcal vaccine prior to the introduction of immunosuppressive therapy (at least two weeks before). Combined immunosuppressive therapy has been shown to significantly reduce the immunogenic response to this vaccine (in particular, the combination of immunomodulators and anti-TNF agents), while monotherapy with immunomodulators (AZA) has no effect on the reduction of immunogenicity.

In the case of an active pneumococcal infection, the use of immunosuppressive therapy should be suspended until the infection is resolved. Any pneumonia in IBD patients should be treated with antibiotics acting on *pneumococcus* (penicillin, cephalosporins II and III generations) [9, 10].

Human papillomavirus

In all patients with IBD, regular gynaecological examinations and screening for cervical cancer should be performed. In particular, this refers to patients receiving immunosuppressive therapy and implies a compulsory prerequisite for the decision to include this therapy.

HPV is the most common sexually transmitted infection. Approximately 40 types of this virus are divided into those with low risk – skin and anogenital warts (condyloma) and those with high risk (high-grade dysplasia) – causing carcinoma of the cervix or anus (types 16 and 18).

The use of immunomodulatory therapy can cause the reactivation of HPV infection. Study data indicate an increased percentage of abnormal Papanicolaou (PAP) smear test findings in patients receiving immunosuppression (Table 7), an increased risk of cervical dysplasia, and a higher number of patients with persistent HPV infection [22–24].

Table 7

Comparison of abnormality of Papanicolaou (PAP) test findings in patients with inflammatory bowel diseases (IBD) and control group

Author	% of abnormal PAP test findings	
	Patients with IBD	Control group
Kane et al, 2008 [22]	42.5	7
Tamas et al, 2002 [23]	47	15
Bhatia et al, 2006 [24]	18	5

When it comes to HPV infection, especially infection with high-risk viral types, the best preventive measure is vaccination. The use of 4-valent (containing types 6, 11, 16, and 18) Gardasil vaccine, belonging to the type of inactivated vaccines, is recommended. It is effective, safe, and provides long-lasting immunity. Vaccination is recommended in young women with IBD (up to 26 years of age), as well as in men of the same age (especially those who practice homosexual relationships). Routine administration in the general population is recommended at the age before starting sexual intercourse (for the female sex, from 11 to 14 years of age).

The use of immunomodulatory therapy has no effect on the administration and effectiveness of this vaccine. In the case of a clinically high infection (extensive skin changes or genital warts), discontinuation of immunosuppressive therapy should be considered until the changes are cured.

Hepatitis B and C

The prevalence of infection with hepatitis B and C viruses (HBV and HCV, respectively) in patients with IBD is no different from that in the general population [21]. No direct connection was established between the application of immunosuppressive therapy in treating IBD and the course and outcome of chronic viral infection of the liver.

In each patient with IBD, screening for the presence of hepatitis B and C viruses should be done immediately after diagnosis. It has been shown that, in patients with IBD, impairment of liver function is significantly higher in patients with chronic hepatitis B virus infection than hepatitis C virus infection. In the case of hepatitis C infection, immunosuppressive therapy may worsen liver function, especially in the case of associated infection with another virus or hepatotoxic effect of drugs. Namely, this infection has increased prevalence of existence and associated, hidden, hepatitis B infection. Immunosuppressive therapy in chronic hepatitis C infection in IBD patients should be used with caution, depending on the severity of the IBD and the degree of damage to the liver. The application of immunosuppressive therapy does not affect the course of HCV infection, and progression to cirrhosis of the liver is the same as in the general population. The use of interferon in the treatment of HCV infection is contraindicated in Crohn's disease. There is no vaccine for preventing HCV infection.

Vaccination against hepatitis B is carried out by mandatory immunization schedule (after birth, and after 1 and 6 months), and efficacy is checked serologically. Provided it has not been conducted at the specified age, it is applied at the age of 12 in three doses (0, 1, and 6 weeks).

In all IBD patients, serological analysis of HBV surface antigen (HbsAg) and anti-HBs and anti-HBc antibodies is performed. In HBsAg positive patients, the viral DNA concentration is checked using a polymerase chain reaction (PCR) method. In seronegative patients, vaccination is carried out. In most cases, the standard protocol for the vaccine administration (0, 1, 6 months) will not provide seroprotection. Therefore, an accelerated protocol that implies a double dose of the vaccine and a schedule application of 0, 1, 2 months, with a mandatory serological conversion check, is recommended. Possible causative factors of reduced response include longer duration of IBD, decreased serum albumin level at the start of the vaccine protocol, administration of corticosteroids in more than one vaccination term [25, 26]. If the "accelerated" regime is insufficient for protection as well, performing revaccination according to the same application scheme is recommended. Serological testing is performed 1–2 months after administrating the last dose of the vaccine. It is believed that the concentration of anti-HBs antibodies greater than 100 mIU/L provides high protection [9, 10].

In HBsAg-positive patients, the use of antiviral drugs is required if they are within the immunosuppressive therapy in IBD. Nucleotide/nucleoside analogues (ribavirin, tenofovir) are applied before, during, and 12 months after the interruption of the immunosuppressive therapy. If the use of antiviral drugs was not effective, the reactivation of HB infection was described in 50% of cases.

In patients who are HBsAg negative and HBcAb positive (occult infection), virus reactivation rarely occurs during immunosuppressive therapy [5]. In these patients, virus activity should be monitored for 2–3 months, with DNA virus detection, using a PCR method, and in case of positivity (HBV-DNA detection), antiviral drugs should be applied according to the above protocol.

Recommendations for the use of inactiveated vaccines in patients with IBD are given in Table 8.

Bacillus Calmette–Guérin (BSG) vaccine

BCG vaccine is still one of the most commonly used childhood vaccines worldwide, with more than 1 billion recipients. The WHO recommends vaccinating babies, who are more likely to come in contact with someone with tuberculosis, as soon as possible after birth.

The BCG vaccine contains a live, attenuated form of *Mycobacterium bovis*, whose antigenic profile is akin to *Mycobacterium tuberculosis*.

In a child with a normal immune system, a granulomatous skin reaction develops only at the site of BCG vaccination. If an individual has an underlying immunodeficiency, this can lead to dissemination of the bacteria followed by widespread granulomatous inflammation. Disseminated BCG infection has an incidence of 1–20 per 10 million doses of the vaccine given, with mortality of 50–80%. The incubation period varies from 1 to 5 months, and children are usually reported as healthy prior to vaccination.

The majority of cases of disseminated BCG have been reported in immunocompromised hosts, particularly those infected with HIV.

There are no previous case reports of disseminated BCG following vaccination of individuals or infants born to mothers taking anti-TNF therapies. However, it is well

Table 8
Inactivated vaccines for patients with inflammatory bowel diseases (IBD) [10]

Influenza: All patients with IBD should be vaccinated seasonally with the intramuscular/intradermal inactivated influenza vaccine prior to starting immunosuppressive therapy.
Pneumococcal pneumonia: All patients with IBD should be vaccinated once with the PCV13 followed by the PPSV23 (first dose after 8 weeks if immunocompromised, or after ≥1 year if immunocompetent; second dose after 5 years; and third dose after 65 years of age). If previously vaccinated with the PPSV23, then the PCV13 should be administered at least 1 year after the PPSV23 in both immunocompromised and immunocompetent adults.
Hepatitis A: Check hepatitis A immune status at the patient's initial visit. If nonimmune to hepatitis A, vaccinate the patient with a 2-dose series (0 months and 6-12 months).
Hepatitis B: Check hepatitis B immune status at the patient's initial visit. If nonimmune to hepatitis B, vaccinate the patient with a 3-dose series (0 months, and 1 and 6 months after first dose) and recheck titers 1 to 2 months after last vaccination. If the patient remains nonimmune, offer booster with a double dose of hepatitis B vaccine or offer combined hepatitis A/B vaccination.
Human papilloma virus: All male and female IBD patients between the ages of 11 and 26 years should be vaccinated with the human papilloma virus vaccine.
Meningococcal disease: Patients with IBD should be vaccinated with the meningococcal vaccine according to standard ACIP recommendations for the general population.
Tetanus, diphtheria, and pertussis: All patients with IBD should be vaccinated with Td every 10 years. Tdap should be substituted once for the Td vaccine to provide additional coverage for pertussis.

PCV – preumococcal conjugate vaccine; PPSV – pneumococcal polysaccharide vaccine; ACIP – Advisory Committee on Immunization Practices; Td – tetanus, diphtheria; Tdap – tetanus, diphtheria, accelular pertussis

recognized that TNF-alpha is crucial to granuloma formation and anti-tuberculous immunity.

Infliximab is an IgG1 antibody that does not cross the placenta in the first trimester, thereby reducing exposure to the foetus during the period of organogenesis. The evidence suggests that the rates of miscarriage, prematurity, and congenital malformations in women exposed to infliximab are not different from non-exposed pregnancies. However, in the third trimester, it readily crosses the placenta, remaining detectable in the infant's serum for up to 7 months after birth.

When possible, infliximab should be stopped in the 3rd trimester. However, the decision must be made on a case-by-case basis when the active disease could have just as harmful consequence on the pregnancy outcome.

If BCG vaccination is accidentally given to an infant born to a mother on infliximab (avoid until 12th month of life), imperial mycobacterium prophylaxis may reduce the chances of dissemination infection [27–31].

Only a few studies have assessed the effects of vaccination with BCG on the subsequent risk of IBD [29–31]. A Danish prospective and population-based case-cohort study conducted on 47,622 participants showed that BCG vaccination does not have an effect on the later risk of developing Crohn's disease and ulcerative colitis [28].

Vaccination in case of travel

Patients with IBD do not have special restrictions on travel to developing countries or countries with endemic diseases. The specificities of these trips are reflected in the possibility of a relapse of the basic disease and the disease from the infectious endemic disease. In these cases, consultations with a doctor prior to travel are required, especially for those patients on immunosuppressive therapy. Vaccination before traveling to the mentioned areas is carried out according to the same recommendations as in the general population. The hepatitis A vaccine is administered in one or two doses before traveling to the endemic areas. Yellow fever vaccination against yellow fever is recommended for travelers to endemic regions in Africa and South America. However, the live, attenuated yellow fever vaccine may potentially lead to severe and possibly lethal symptoms in immunosuppressed patients and is thus contraindicated. Immunosuppressed individuals are advised to avoid traveling to endemic regions; if travel is unavoidable, travelers should be educated regarding the risks of such travels and instructed regarding the prevention of mosquito transmission. Vaccine use is only permitted in patients who have been treated with low doses of steroids (20 mg prednisone, shorter than two weeks) for a short period of time. Other vaccines that can be safely administered are the vaccine against Japanese encephalitis and rabies. In case of traveling to the countries with endemic diseases that are prevented by live vaccines, risk assessment of the onset of infection for each patient individually and good information about preventive measures are necessary [9, 10].

Preparation of patients with IBD for the application of immunosuppressive therapy

The majority of patients with IBD will be treated with immunosuppressive therapy (80% corticosteroids, 40% immunomodulators, and 20% biological therapy) during the course of the disease. Infectious complications are the most common complications of IBD and are responsible for increased mortality in IBD and increased hospitalization, and immunosuppression is the most important factor that suits the above. Measures to prevent opportunistic infections and infections in general in these patients involve the adequate preparation of patients for the introduction of immunosuppressive therapy, which reduces the risk of infection and allows, if necessary, appropriate treatment before the introduction of therapy. Immunization as a preventive measure of infection, which is prevented in this way, is only one part of the patient's preparation. The status of immunization that was previously performed is mandatory checked when diagnosing IBD, and then vaccination is planned regarding the specificity of the application of immunosuppressive therapy: routine applied vaccines – cardboard vaccination (diphtheria, tetanus, pertussis, polio, HPV vaccine); when diagnosing – HB and VZV vaccines; before introducing immunosuppressive therapy – PCV13, PPSV23, and TIV.

In addition to the planning of vaccination, the preparation of patients for the application of immunosuppressive therapy also implies the following: anamnestic data on treated bacterial, viral, fungal, and parasitic infections, treatment of tuberculosis, environmental factors (contact with tuberculosis, conditions of life), travel to endemic areas; physical examination; screening for tuberculosis: lung Rtg, reaction to a purified protein derivative (PPD), Quantiferon (test for interferon-gamma production in response to *Mycobacterium tuberculosis* antigens); laboratory tests: detection of titer and antibody class against viruses – EBV, hepatitis A virus (HAV), HCV, HIV, VZV, HBV, HbsAg virus antigens in the serum, examination of urine and stools on *Clostridium difficile*; patient education – hygienic diet regime during travel, travel consultations, screening on *portio vaginalis uteri* (PVU) carcinoma.

Conclusion

The results of testing the modality of administration and effect of vaccines in patients with IBD are still not at the highest level. Gastroenterologists who treat patients with IBD know best the current status of each patient. Therefore, they can and should be responsible for deciding when to use the most appropriate immunosuppressive therapy. For the same reasons, they can also assess the response capacity of IBD patients to applied vaccines or to define clear recommendations for vaccinating these patients. All this is necessary in order to improve and treat patients with IBD, as this could reduce the prevalence and incidence of infectious complications in these patients, in particular, complications that could be prevented by vaccination.

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