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IMMUNIZATION IN INFLAMMATORY BOWEL DISEASES: RECOMMENDATIONS ON THE ADMINISTRATION OF VACCINES

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Immunization in patients with inflammatory bowel disease (IBC) has certain specificities associated with etiopathogenesis and treatment modalities of the underlying disease. Modern principles of IBC treatment are characterized by the frequent application of immunomodulatory therapy, which is most often introduced in early stages of treatment, which is one of the main reasons for the strong predisposition of patients with IBC for the development of infection. Vaccination of patients with IBC is necessary in order to reduce infectious complications, especially those that could be prevented by vaccination. It is therefore very important to establish recommendations on the basis of which the immunization of IBC patients would become an integral part of their treatment. The planning and implementation of vaccination in patients with IBC depend on the assessment of the immune response status of each patient at a given moment. This review work presents an overview of the current views on the time of administration of vaccines in patients with IBC, the type of vaccine that can be applied as well as their effect on the course of the disease, the complications and outcome of the treatment. Also, the results of studies that examined the efficacy and safety of vaccines for influenza, varicella zoster, pneumococcal infections, human papillomavirus, hepatitis B and C viruses in IBC patients are presented. Recommendations on vaccinations in case of travel are also given.

Key words: vaccination, IBC, immunosuppression.

Imunizacija kod pacijenata sa inflamacijskim bolestima creva (IBC) ima određene specifičnosti koje su povezane sa etiopatogenezom i modalitetima lečenja osnovne bolesti. Savremene principe lečenja IBC obeležava česta primena imunomodulatorne terapije koja se najčešće uvodi već u ranim fazama lečenja, što je jedan od osnovnih razloga izražene predispozicije pacijenata sa IBC za razvoj infekcije. Vakcinacija pacijenata sa IBC je neophodna u cilju smanjenja infektivnih komplikacija, posebno onih koje bi mogle da se spreče vakcinacijom. Zbog toga je veoma važno ustanoviti preporuke na osnovu kojih bi
Imunizacija obolelih od IBC postala sastavni deo njihovog lečenja. Planiranje i sprovođenje vakcinacije kod pacijenata sa IBC zavise od procene statusa imunskog odgovora svakog pacijenta u datom momentu. U ovom preglednom radu dat je prikaz aktuelnih stavova o vremenu primene vakcina kod pacijenata sa IBC, tipu vakcina koji se može primeniti kao i njihovom delovanju na tok bolesti, komplikacije i ishod lečenja. Takođe, prikazani su i rezultati studija koje su ispitivale efikasnost i bezbednost primene vakcina protiv gripa, varičele-zoster, pneumokoknih infekcija, humanog papiloma virusa, virusa hepatitis B i C kod pacijenata sa IBC. Date su i preporuke o vakcinacijama u slučaju putovanja.

**Ključne reči:**

vakcinacija, IBC, imunosupresija.

**Introduction**

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

This opinion is the result of the following findings: the majority of patients with IBC will be treated with immunosuppressive therapy during the illness; a large number of IBC 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 IBC. The possible more favourable relationship between the cost of treatment of infectious complications and the resulting hospitalization and the costs of vaccination of these patients should not be neglected either.

The immunization of patients with IBC has certain specificities due to the fact that 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, type of vaccine, as well as 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 IBC. Namely, the implication of compulsory vaccinations, which have been conducted in most patients and prior to the diagnosis of IBC, 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 ways of vaccination of patients with IBC, establish recommendations on the basis of which the immunization of IBC patients will become an integral part of their treatment and an important segment in the prevention of infectious complications of these patients.

_Predisposition for the development of complications from infectious diseases of ibc patients_

Infections that complicate IBC 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).

Patients who are immunocompromised have altered, cellular and / or humoral immunity, which increases the risk of opportunistic and infections in general. In patients with IBC, 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). Also, in patients with IBC, the activity of the acquired (adaptive) immunity cells is also changed. In Crohn's disease, for example, there is a description of an 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 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. Also, T lymphocytes of patients with ulcerative colitis have a slower cell cycle and are more susceptible to the programmed cell death (apoptosis) compared to control cells (4). Bearing in mind all the above findings, it is clear that the intestinal lesion in IBC 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 IBC can be considered immunocompromised (5). Although there is no clear definition of the immunocompromised condition in the IBC, IBC patients are considered immunocompromised if treated with: corticosteroids for two weeks and longer or repeated within three months, with azathioprine (or 6 mercaptopurine), methotrexate, anti-TNF agents as well as patients with high protein-caloric malnutrition.

Table 1.

Some causes of the state of deficiency of the immune system (according to the Center for Disease Control, ACIP - US Advisory Committee on Vaccination)

<table>
<thead>
<tr>
<th>1. People who are in severe immunodeficiency which is not the result of 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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. People with HIV infection</td>
</tr>
<tr>
<td>3. People with conditions that cause a limited deficit of the immune system (eg, hyposplenism, renal insufficiency, etc.)</td>
</tr>
</tbody>
</table>

Modern principles of treatment of IBC are characterized by the frequent application of immunomodulatory and immunosuppressive therapy (corticosteroids, azathioprine, methotrexate, calcineurin inhibitors, anti-TNF agents, and other biological agents) which is most commonly introduced in early stages of treatment. This is one of the main reasons for the high predisposition of patients with IBC for the development of infection. The aforementioned immunosuppressive agents used in the treatment of IBC, in achieving the
therapeutic effect, act on different levels, including the modulation of the functions and activities of the components of the immune system.

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. Azathioprine and 6 mercaptopurine (AZA, 6MP), in the form of nucleotides, have been shown to lead to apoptosis of T lymphocytes. Methotrexate (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 the IBC is TNF. The biological agents, antibodies that bind TNF (anti-TNF antibodies), except that they can inactivate the effect of TNF, can also induce monocyte apoptosis and thus suppress the inflammatory process in the IBC.

Application of 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, elderly age, co-morbidity, 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, are associated with high morbidity and mortality because they are potentially serious and less responsive to effective treatment. Within a number of clinical studies, an increased incidence of opportunistic infections in IBC patients has been observed, including the occurrence of opportunistic infections associated with the use of immunosuppressive therapy in the treatment of patients with IBC.(5,6,7,8)
Table 2.

Opportunistic infections associated with the use of immunosuppressive therapy in the treatment of IBC (7)

<table>
<thead>
<tr>
<th>VIRAL INFECTIONS</th>
<th>Virus Varicella zoster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Virus Herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Epstein Barr virus</td>
</tr>
<tr>
<td></td>
<td>Human papilloma virus</td>
</tr>
<tr>
<td>BACTERIAL INFECTIONS</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td></td>
<td>Salmonella spp.</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td></td>
<td>Clostridium difficile</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus spp.</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Legionella pneumophila</td>
</tr>
<tr>
<td></td>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium avium spp.</td>
</tr>
<tr>
<td></td>
<td>Nocardia</td>
</tr>
<tr>
<td>FUNGAL AND PARASITIC INFECTIONS</td>
<td>Candida spp.</td>
</tr>
<tr>
<td></td>
<td>Pneumocystis carinii</td>
</tr>
<tr>
<td></td>
<td>Aspergillus spp.</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Cryptococcus spp.</td>
</tr>
<tr>
<td></td>
<td>Coccidoides immitis</td>
</tr>
<tr>
<td></td>
<td>Blastomycosis</td>
</tr>
<tr>
<td></td>
<td>Leishmania donovani</td>
</tr>
</tbody>
</table>
**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 illness. The principles of childhood immunization are based on the above.

**Table 3.**

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

<table>
<thead>
<tr>
<th>Age</th>
<th>BCG</th>
<th>HB</th>
<th>DTP</th>
<th>OPV</th>
<th>MMR</th>
<th>Hib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st month (birth)</td>
<td></td>
<td></td>
<td>I dosage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd month</td>
<td></td>
<td>II dosage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd month</td>
<td></td>
<td>I dosage</td>
<td>I dosage</td>
<td></td>
<td>I dosage</td>
<td></td>
</tr>
<tr>
<td>3 and a half months</td>
<td></td>
<td>II dosage</td>
<td>II dosage</td>
<td></td>
<td>II dosage</td>
<td></td>
</tr>
<tr>
<td>By 6. month</td>
<td></td>
<td>III dosage</td>
<td>III dosage</td>
<td></td>
<td>III dosage</td>
<td></td>
</tr>
<tr>
<td>From 12 to 15. month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vaccination</td>
<td></td>
</tr>
<tr>
<td>From 17th to 24th month</td>
<td></td>
<td>DTP Revaccination I</td>
<td>Revaccination I</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7 years of age (before going to school) | DT Revaccination II | Revaccination II | Revaccination II
---|---|---|---
12 years | 3 dosage* |  |  |
14 years of age | DT Revaccination III | Revaccination III |  

*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 new-born babies of mothers who are HBsAg positive).

Since most IBC patients were vaccinated prior to diagnosis of IBC, when their immune response was not changed due to illness, and according to the mandatory vaccination plan (Table 3), the specific effect of administered vaccines in patients with IBC does not differ significantly from their effect in non-IBC 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 IBC population is negligible. Recommendations for the immunization of patients with IBC (immediately after diagnosis of IBC) are based on the assumption that compulsory vaccines have been previously used, which requires adequate evidence.

HB - hepatitis B vaccine, contains purified 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 - poliomyelitis vaccine, contains live, attenuated, 2 types of polio virus; Hib - conjugated vaccine against Hemophilus influenza type B.
Table 4

General Recommendations for Immunization of Patients with IBD (9)

1. Standard recommended immunization schedules for children and adults should be generally adhered to.

2. At diagnosis, children and adults should have 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. Non-immune individuals should receive varicella vaccine. Children who are not immune by vaccination or acquired immunity through infection should receive varicella vaccine.

4. Live bacterial or viral vaccines should be avoided in immune-compromised children and adults with IBD. This includes: 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 of stopping). ii. Treatment with effective doses of 6-mercaptopurine/azathioprine (effect on safety not established) and within 3 months of stopping. iii. Treatment with methotrexate (effect on safety not established) and within 3 months of stopping. iv. Treatment with infliximab (effect on safety not established) and within 3 months of 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 immune-suppressed. Repeat dosing may be considered when immune response to immunization is insufficient.

Planning and implementation of vaccination in patients with IBD is part of the infection prevention process. Infections can complicate IBD during 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.

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 on the basis of which it is possible to assess the clinical response to the immunological changes caused by vaccination in the IBC patients. The results of studies investigating the effects of immunization of immunocompromised patients or the immunization of patients suffering from immunosuppressive therapy (SLE, RA) have shown that these patients create an adequate humoral immune response (specific antibodies have been detected). Also, 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, 16, 17,18).

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 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 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 titre of the antibodies produced. Titre 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 titre in seronegative persons (who did not have a measurable antibody titre prior to vaccination), which makes them seropositive. In the seroconversion process, a minimum titre of an anti-infection antibody
(wild type) is required, and the achievement of said level or greater titre defines the so-called seroprotection - the expected protection (4).

**Time of vaccine administration**

In conditions of immunosuppression, and therefore in patients with IBC, 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 infectious disease.

*Table 5.*

**Live Vaccines, Generally Contraindicated in Patients Receiving Immune-Suppressive Therapy (9)**

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

The IBC 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 vaccine administered.
As part of the above, it is recommended that the appropriate vaccines be administered within 3 weeks of starting of the immunosuppressive therapy, and the possible application, if the treatment with immunosuppressants is in progress, is recommended after 3 months of discontinuation of these drugs.

The specific situation is vaccination of new-borns of mothers who are treated with anti-TNF agents. According to recent recommendations, the first vaccination should be administered from the 6th month of life, since after this period, the anti-TNF antibodies, which the mother received as a therapy, transferred to the child transplanted, have withdrawn from the bloodstream of the child.

Specificity of vaccination of IBC patients

The most important infectious diseases of adult patients with IBC that can be prevented (mitigated) by vaccines and in which it is the most effective prevention are influenza, varicella, pneumococcal infections. Additionally, the recommendations for vaccination include specific situations that include vaccination against viral infections such as hepatitis B virus, HPV (human papillomavirus) infection in women, and the need for vaccination in case of travel 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 IBC after administration of the vaccine. In
several studies, where patients with IBC and patients with other immunologically mediated diseases were examined, vaccination efficacy was assessed based on the change in antibody titre after administration of the vaccine. Data on the safety and tolerance of influenza vaccines are also limited, but generally show that this vaccine is well tolerated and safe to use (20).

As noted earlier, the application of a live, attenuated influenza vaccine is contraindicated in patients on immunosuppressive therapy. In this group of IBC patients, the use of trivalent influenza vaccine (TIV) is recommended, which is a type of inactivated vaccine. 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 IBC activity. It has also been confirmed that seroconversion has not been reduced and altered in patients on steroid, methotrexate 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. A routine check of a serological response in these cases is not necessary in view of 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 IBC. 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, 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 IBC patients.

If the previous medical history of varicella and/or herpes zoster treatment is negative and if the patient is not vaccinated in childhood, the VZV vaccine should be administered
immediately after diagnosis of the IBC or at least three weeks before initiating immunosuppressive therapy. If there is no vaccination or infection information, serological analyses - IgG VZV antibody titres 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 discontinuation of 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 daily).(9,10,11)

Table 6.

Levels of Immunosuppression Based Upon Strength of Immunosuppressive Medication(10)

<table>
<thead>
<tr>
<th>High-Level Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with glucocorticoids (prednisone &gt;20 mg/day for ≥2 weeks and within 3 months of stopping therapy)</td>
</tr>
<tr>
<td>Treatment with effective doses of 6-mercaptopurine, azathioprine, or methotrexate compared with those with low-level immunosuppression (described below) or discontinuation within 3 months</td>
</tr>
<tr>
<td>Treatment with adalimumab, certolizumab pegol, golimumab, infliximab, natalizumab, or vedolizumab, or recent discontinuation within 3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low-Level Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>


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)

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 a 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 VZV vaccine, as well as all other vaccines, should be assessed individually in each IBC 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.

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 IBC within this), chronic illness and older age. Severe, invasive forms of pneumococcal infections - pneumonia and meningitis (with or without bacteraemia) are followed by higher mortality. In patients with IBC who are on immunomodulatory therapy, bacterial pneumonia caused by pneumococcal is one of the most common opportunistic infections.

Vaccination against pneumococcus should be performed in all patients with risk factors (older age, associated chronic illness, immunosuppression, splenectomized patients, immunosuppressive therapy patients). Three types of vaccines are available: 23-valent polysaccharide (PPV23) that provides protection against the action of 80-90% of strains responsible for severe infections; 13-valent pneumococcal conjugated (PCV13) and 7-
valent pneumococcal conjugated vaccine (PCV7). Patient with IBD should be vaccinated with pneumococcal vaccine according to recommendations (Table 8).

IBC 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).

Specific situations

*Human papillomavirus (hpv)*

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 condition the reactivation of HPV infection. Study data indicate an increased percentage of abnormal PAPA 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).
Comparison of abnormality of PAPA findings in patients with IBC and control group

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with IBC</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of abnormal PAPA findings</td>
<td>% of abnormal PAPA findings</td>
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<tr>
<td>Kane, 2008</td>
<td>42.5</td>
<td>7</td>
</tr>
<tr>
<td>Tamas, 2002</td>
<td>47</td>
<td>15</td>
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<tr>
<td>Bhatia, 2006</td>
<td>18</td>
<td>5</td>
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</table>

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. It is recommended to use in young women of the female sex with IBC (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 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 in patients with IBC is no different from that in the general population (21). No direct connection was established between the application of immunosuppressive therapy in the treatment of IBC and the course and outcome of chronic viral infection of the liver.

In each patient with IBC, screening for the presence of hepatitis B and C viruses should be done immediately after diagnosis. It has been shown that, in patients with IBC, 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 IBC patients should be used with caution, depending on the severity of the IBC and the degree of damage to the liver. The application of immunosuppressive therapy does not affect the course of HCV infection, 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 the prevention of HCV infection.

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

In all IBC patients, a serological analysis of HBV antigen (HbsAg) and anti-HBs and anti-HBc antibodies is performed. In HBsAg positive patients, the viral DNA concentration is checked using a PCR method. In seronegative patients, vaccination is carried out. In most cases, the standard protocol for the administration of the vaccine (0, 1, 6 months) will not provide seroprotection, so 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 IBC, decreased serum albumin level at the start of the vaccine protocol, administration of corticosteroids in more than one vaccination term (26). If the "accelerated" regime is insufficient for protection as well, it is recommended to perform revaccination according to the same application scheme. Serological testing is performed at 1-2 months from 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 IBC in immunosuppressive therapy. Nucleotide / nucleoside analogues (Ribavirin, Tenefovir) are applied before, during and 12 months after interruption of immunosuppressive therapy. If the use of antiviral drugs was not effective, in 50% of cases, the reactivation of HB infection was described.
In patients who are HBsAg negative, and HBcAb positive (occult infection) virus reactivation occurs rarely during immunosuppressive therapy (5). In these patients, virus activity should be monitored for 2-3 months, with DNA virus detection, using the PCR method, and in case of positivity (HBV-DNA detection), antiviral drugs should be applied according to the above protocol.

### Table 8.

**Inactivated Vaccines for Patients With 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.

BSG Vaccine

BCG is still one of the most commonly used childhood vaccinations worldwide, with more than 1 billion recipients. The WHO recommends vaccination as soon as possible after birth to babies who are more likely to come into contact with someone with TB.

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 vaccine given, with a 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 recognised 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 active disease could have just a harmful consequence on pregnancy outcome.

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

Only few studies have assessed effects of vaccination with BCG on subsequent risk of IBD (Leigh 1980, Gilat 1987, Baron 2005). Danish prospective and population-based case–cohort study conducted at 47622 participants showed that BCG vaccination do not affect later risk of developing CD and UC (Villumsen 2013).

**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 infectious endemic disease. In these cases, consultations with a doctor prior to travel are required, especially for those patients who are 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 travel to endemic regions; if travel is unavoidable, travelers should be educated regarding the risks of such travel and instructed regarding 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, rabies. In the case of travel to countries with endemic diseases that are prevented by live vaccines, a risk assessment of the onset of infection for each patient individually and good information about preventive measures is necessary (9, 10).

Preparation of patients with ibc for the application of immunosuppressive therapy

The majority of patients with IBC will be treated with immunosuppressive therapy (80% corticosteroids, 40% immunomodulators and 20% biological therapy) during the course of the disease. Infectious complications are most common complications of IBC and are responsible for increased mortality in IBC 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 the IBC, 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, TIV

In addition to the planning of vaccination, the preparation of patients for the application of immunosuppressive therapy also implies:

- 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 PPD, Quantiferon (test for interferon-gamma production in response to Mycobacterium tuberculosis antigens)

• Laboratory tests: detection of titer and antibody class against viruses EBV, 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 PVU carcinoma

The results of testing the modality of administration and effect of vaccines in patients with IBC are still not at the highest level (20). Gastroenterologists who treat patients with IBC best know 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 IBC patients to applied vaccines, or to define clear recommendations for the vaccination of these patients. All this is necessary in order to improve and treat patients with IBC, 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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