Background document on

Immune-mediated inflammatory diseases (IMID)

Module 2

Vaccination in patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions

Document

prepared by Silja Bühler and Christoph Hatz on behalf of the Federal Advisory Commission on Immunisation and endorsed by the Swiss Society for Gastroenterology.

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Abbreviations

ADA	Adalimumab
AZA	Azathioprine
BCG	Bacillus Calmette–Guérin
CD	Crohn's Disease
CI	Confidence interval
GMT	Geometric mean titre
HBV	Hepatitis B Virus
HC	Healthy control
Hib	*Haemophilus influenzae* b
HPV	Human papillomavirus
HZ	Herpes zoster
IBD	Inflammatory Bowel Disease
IDSA	Infectious Diseases Society of America
IFX	Infliximab
MMR	Mumps, measles, rubella
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
RR	Risk ratio
SFOPH	Swiss Federal Office of Public Health
TBE	Tick-borne encephalitis
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative colitis
VZV	Varicella zoster virus
5-ASA	5-aminosalicylic acid
6-MP	6-Mercaptopurine
23-PPV	23-valent polysaccharide pneumococcal vaccine
13-PCV	13-valent pneumococcal conjugate vaccine

Search strategy

Published evidence was searched for in electronic databases (Cochrane, Medline, Pubmed, Embase). Unpublished (grey) literature (unpublished reports, conference abstracts) was retrieved through a targeted website search of relevant organisations and international conferences dealing with vaccination, infectious diseases and gastroenterology. Additional articles were identified through reference lists of selected papers.

The following search terms were used in combination:

Patients with inflammatory bowel diseases and other gastroenterological autoimmune conditions: “IBD”, “inflammatory bowel disease”, “autoimmune”, “immunocompromised”, “autoimmune inflammatory gastroenterologic disease”, “Crohn’s disease”, “Colitis ulcerosa”, “Collagenous colitis”, “autoimmune hepatitis”, “primary sclerosing cholangitis”, “autoimmune pancreatitis”, “primary biliary cirrhosis”, “coeliac disease”, “celiac disease”

Infections: “infection”, “risk of infection”, “tetanus”, “diphtheria”, “poliomyelitis”, “polio”, “pertussis”, “hepatitis A”, “hepatitis B”, “haemophilus influenza b”, “yellow fever”, “mumps”, “measles”, “rubella”, “varicella”, “herpes zoster” “rabies”, “tick borne encephalitis”, “TBE”, “Japanese encephalitis”, “cholera”, “human papillomavirus”, “HPV”, “typhoid fever”, “meningococcal” “pneumococcal”, “influenza”, “H1N1”, “tuberculosis”

Vaccines: “vaccination”, “vaccine”, “vaccination guideline”, “inactivated vaccin*”, “live vaccin*”, “conjugate vaccine*”, “polysaccharide vaccine*”, “tetanus vaccin*”, “diphtheria vaccin*”, “poliomyelitis vaccin*”, “polio vaccin*”, “pertussis vaccin*”, “hepatitis A vaccin*”, “hepatitis B vaccin*”, “haemophilus influenza b vaccin*”, “yellow fever vaccin*”, “mumps vaccin*”, “measles vaccin* ”, “rubella vaccin*”, “varicella vaccin*”, “herpes zoster vaccin*” “rabies vaccin*”, “tick borne encephalitis vaccin*”, “TBE vaccine*”, “Japanese encephalitis vaccin*”, “cholera vaccin*”, “human papillomavirus vaccin*”, “HPV vaccin*”, “typhoid fever vaccin*”, “meningococcal vaccin*” “pneumococc* vaccin*”, “influenza vaccin*”, “H1N1 vaccin*”, “tuberculosis vaccin*”, “BCG”

Mostly English and German articles were included. A summary of all relevant papers was produced. Data from meta-analyses, systematic reviews, randomized trials, and observational studies were taken into account. Case reports were only taken into account in specific situations when no other published evidence could be retrieved.

Table 1: Inflammatory bowel diseases and other gastroenterological (auto)immune conditions

Crohn's disease
Colitis ulcerosa
Collagenous colitis
Coeliac disease
Autoimmune pancreatitis
Autoimmune hepatitis
Primary sclerosing cholangitis
Primary biliary cirrhosis

Key messages

Please see specific sections for further details!

1. Vaccinations do not cause gastroenterological (auto)immune diseases (see list table 1), nor their exacerbations.
2. There are no specific contraindications for vaccination with inactivated and live vaccines in patients with inflammatory bowel diseases (IBD) and other gastroenterological (auto)immune conditions without immunosuppressive treatment.
3. The vaccination status of the patients should be assessed and documented at the earliest time point after the diagnosis of an (auto)immune disease and recommended vaccinations should be administered as soon as possible. Independent of history and vaccination status regarding measles and varicella, serologies should be performed to check whether the patient is protected.
4. Vaccination should preferentially be administered during stable disease because efficacy is highest.
5. If possible, vaccinate before initiation of immunosuppressive therapy. Inactivated vaccines can be given at any time. Live attenuated vaccines should be given at least 4 weeks before initiation of immunosuppressive treatment.
6. In already treated patients with IBD and other gastroenterological (auto)immune conditions, vaccines should ideally be administered when immunosuppressive therapy is at the lowest.
7. It is generally safe to administer inactivated vaccines to patients with IBD and other gastroenterological (auto)immune conditions under immunosuppressive treatment; the immunogenicity may be reduced.
8. The immune response to a booster vaccine administered during immunosuppressive treatment is considered to be less affected than a primary vaccine dose.
9. The administration of live vaccines to immunosuppressed patients bears the risk of replication of the attenuated microorganism and invasive infections. Live vaccines with a high potential of replication (e.g. yellow fever vaccine) should generally be avoided in patients with IBD and other (auto)immune gastroenterological conditions under treatments with a systemic immunosuppressive effect.
   However, specific exceptions apply: live vaccines may be used with caution in selected patients under immunosuppressive therapy (table 2).
10. Depending on the drug, different intervals for administration of a live vaccine after immunosuppressive treatment are advised (table 3).
11. Only use conjugate vaccines because they induce higher affinity antibody responses, longer lasting immune responses and memory responses as compared to polysaccharide vaccines.
12. General recommendations for basic vaccinations also apply to patients with IBD and other gastroenterological (auto)immune conditions.
13. Specific vaccinations are recommended for patients with IBD and other gastroenterological (auto)immune conditions as they may require a more comprehensive protection. These include:
    - the annual seasonal inactivated influenza vaccinations for all patients with gastroenterological (auto)immune conditions under immunosuppressive treatment (page 11)
    - pneumococcal vaccination with the 13-valent pneumococcal conjugate vaccine (Prevenar®) is recommended (page 12).
    - hepatitis B vaccination is recommended in all seronegative patients with gastroenterological (auto-)immune conditions (page 13)

- vaccination against human papillomavirus (HPV) is encouraged in all patients with IBD and other gastroenterological (auto)immune conditions aged 11-26 years (page 16).
- herpes zoster vaccination (Zostavax®) is recommended for future immunocompromised patients 50 to 79 years old, presenting without or with a “mild” (non-severe) immunodeficiency, which can be assumed to deteriorate to “severe” in the foreseeable future. The vaccine should ideally be administered at least 4 weeks before an assumed, anticipated or planned start of a severe immunosuppression (page 17).

14. Serology should be performed after a completed primary course of vaccination if the respective serology is available (see table 4) [1].

15. In a patient undergoing immunosuppressive therapy and in whom natural immunity or past vaccination towards measles and varicella are unknown, a specific serology should be performed. The same approach applies to yellow fever serology in a person under immunosuppressive therapy who intends to travel to a yellow fever endemic area and who received the yellow fever vaccination in the past (pages 18-20).

16. As the immunocompromised person may not be protected against diseases despite previous vaccination (e.g. against mumps, measles, rubella, varicella, influenza), insist on checking vaccinating status of household and other close contacts and vaccinate if indicated.

17. If the immunocompromised person is not protected against measles and/or varicella and has contact with an infected person: consider immunoglobulins/antivirals.

18. As a precaution, oral typhoid vaccination (Vivotif®) should generally be avoided in all patients with inflammatory bowel disease (expert opinion) and in patients with other gastroenterological (auto)immune conditions under immunosuppression. No published data on this topic however exists.

1 Increased risk of infection in patients with IBD and other gastroenterological (auto)immune conditions

Infections are a substantial cause of morbidity and mortality in patients with immune-mediated gastroenterological diseases [2,3]. Patients with chronic immune-mediated gastroenterological conditions are often treated with long-term immunosuppressive medications, thereby increasing their risk of acquiring an infection. It has been shown that the use of any immunosuppressive agent for the treatment of inflammatory bowel disease (IBD) patients increased the risk for opportunistic infections 3.9 fold (95% confidence interval (CI) 2.2-6.9). The use of one agent increased the risk 2.9 (1.5-5.3) fold and the use of 2 or 3 agents incremented the risk 14.5 (95%CI 4.9-43) fold [3]. The increased risk of infection does not only depend on the number of medications used, but also on the type of drug in use. The same study showed an increased risk for opportunistic infections for corticosteroids by 2.2 (95%CI 1.1-4.8), for azathioprine by 2.5 (95%CI 1.2-5.1), and for infliximab by 11.2 (95%CI 0.8-153). In a different study, the risk for serious infections was not increased for infliximab after adjusting for other medications (odds ratio (OR) 0.99; 95%CI 0.64-1.54), but corticosteroids remained independently associated with serious infections (OR 2.21, 95%CI 1.46-3.34) [4].

Especially the **risk of vaccine-preventable infections** is increased in patients with immune-mediated inflammatory diseases:

1.1 Influenza

Apart from one study, which showed that patients with ulcerative colitis with a low income to be at an increased risk of hospitalisation for influenza virus pneumonias [5], no data exist on the incidence of influenza infection in IBD patients [6]. However, therapy with immunosuppressants does generally enhance the risk of influenza infection.

1.2 Pneumococcal disease

IBD patients have been shown to have an increased risk of pneumonia compared to persons without IBD. The hazard ratio for patients with Crohn's disease (CD) was 1.71 (95%CI 1.62-1.80) and for patients with ulcerative colitis (UC) 1.41 (95%CI 1.34-1.48) [7]. Higher risks for pneumonia were independently associated with biologic medications, corticosteroids and thiopurine treatment.

Furthermore, patients with CD and primary biliary cirrhosis have been shown to have an elevated risk of being hospitalised for pneumococcal disease (Rate ratio 2.2, 95%CI 2.1-2.3 and 3.3, 95%CI 2.9-3.7, respectively) [8].

1.3 Hepatitis B

According to studies from Italy, France and Spain, the prevalence of hepatitis B infection in Western Europe seems to be similar in IBD patients compared to the general population [9–11].

Reactivation of hepatitis B virus is an important concern in IBD patients under immunosuppressive therapy; however, the rate to which reactivation occurs is unknown. Severe, and even fatal, cases of hepatitis B virus (HBV) reactivation in IBD patients under immunosuppressive therapy have been published in case reports or case series [12–15]. Reactivations have been described, both in HBsAg positive patients as well as rarely in patients that are only HBcAg positive [16,17]. In most cases, hepatitis flares occur at the time of tapering or stopping immunosuppressive therapy when an immune rebound occurs and virus-infected hepatocytes are destroyed [18]. This observation can be explained by a previous increased viral replication under the immunosuppressive therapy.

With higher levels of immunosuppression, the immune rebound is more pronounced and the risk of HBV reactivation is not only higher [19], but reactivation of the viral infection can also be more severe [20].

To our knowledge, it is unknown whether HBV infections of IBD patients under immunosuppressive become more often chronic than infections in healthy persons. However, increased carriage rates have been reported in other immunocompromised patients [21].

1.4 Human papillomavirus

Several studies have found an increased risk for abnormal Pap smears and higher-grade lesions in women with inflammatory bowel diseases [22,23]; however, this has not been universally confirmed [24,25]. It was also shown that the risk for a cervical abnormality amongst women with IBD is increased in those under immunosuppressive therapy [22,24], although also this finding was not confirmed in all studies [23,25]. The risk for cervical cancer among women with IBD has not been found to be elevated in one study [26], but a recent Danish population-based cohort study indicated that the risk for cervical dysplasia (incl. carcinoma in situ) may be 1.65 (95%CI 1.10-2.37) times higher in patients with Crohn's Disease [27], especially in smokers and patients under specific immunomodulatory/immunosuppressive treatments (5-aminosalicylic acid (5-ASA) or thiopurines).

1.5 Varicella/Herpes zoster

Varicella and herpes zoster infection may be severe and even fatal in IBD patients under tumor necrosis factor (TNF) blocking therapies [28–30] and the risk for herpes zoster (HZ) infections was shown to be elevated in IBD patients in large studies [31,32]. In a retrospective nested case-control study, the risk ratio (RR) for HZ was 1.21, 95%CI 1.05-1.40 and 1.61, 95%CI 1.35-1.92, respectively in patients with ulcerative colitis or Crohn's Disease [31]. Corticosteroid use and thiopurines were associated with an elevated HZ risk [31,33]. Also the use of TNF blockers and especially the combined use of TNF inhibitors (TNFi) and thiopurines seemed to elevate the HZ risk in IBD patients [32].

2 Vaccination coverage of patients with IBD and other gastroenterological (auto)immune conditions

Vaccines are often underutilised in patients with immune-mediated gastroenterological conditions [34] due to lack of awareness or concerns about vaccine safety [34,35]. Knowledge regarding vaccinations recommended in IBD patients and vaccines that should be avoided under immunosuppressive therapy has been shown to be inadequate among gastroenterologists and patients [36].

2.1 Influenza vaccine

In studies from Australia, Canada, Germany, Korea, Poland and the USA, regular or up-to date seasonal influenza vaccinations rates in IBD patients were poor and ranged between 7.8% and 37.5% [34,37–42]. Only two studies from the UK and the USA indicated vaccination coverage of more than 50% (59.5% and 54%, respectively) [43,44].

Coverage for H1N1 vaccine during the pandemic was reported to range between 16% and 41.6% in IBD patients [40,43,45].

2.2 Pneumococcal vaccine

Up to date vaccination coverage against pneumococcal disease was generally even lower and ranged between 5% - 31% [34,37,39,43,44]. In two studies in Germany, only 3% and 9% of IBD patients reported that they had ever received the pneumococcal vaccination, respectively [38,41].

2.3 Hepatitis B vaccine

A study in Northern France conducted between 2005 and 2009, revealed that only half of the patients with Crohn's Disease or Ulcerative Colitis were effectively vaccinated against hepatitis B [9]. Vaccination coverage was similar in a Korean study of IBD patients (53%) [39]. Contrarily, vaccination coverage was between 22-28% in studies from Germany and the USA [34,41] and even lower (12%) in a nationwide, multicentre study among IBD patients in Spain [10].

2.4 Human papillomavirus vaccine

Human papillomavirus (HPV) vaccination coverage has been assessed in a small study among women with IBD aged 18-26 years [46]. Only 17% had been counselled for HPV vaccination.

2.5 Tetanus vaccine

Coverage of tetanus vaccination (defined as last vaccination within previous 10 years) has been found to be between 15.6%-67% in studies form Korea, the USA and Germany [34,38,39].

2.6 Varicella vaccine

A survey among IBD patients in Israel showed that a negative history of varicella history is not a good indicator for a negative serology, and vice versa: among those with a positive varicella history, 7% were seronegative [47].

3 Immunogenicity and safety of vaccinations in patients with IBD and other gastroenterological (auto)immune conditions

3.1 Seasonal Influenza vaccine

Influenza vaccine has been reported to be safe and not associated with more vaccine-related adverse events compared to the general population nor with reactivation of disease in paediatric and adult IBD patients [48–51]. In general, antibody responses and seroprotection levels were similar in IBD with or without immunosuppressive therapy. Seroprotection levels against strain B appeared to be lower in IBD patients compared to healthy controls in some studies [52,53], and TNF blocking agents or TNF blockers in combination with other immunosuppressants (methotrexate (MTX), corticosteroids, 6-mercaptopurine (6-MP)) appeared to have a negative effect [48,50]. Other studies confirmed lower antibody rises and seroprotection levels against some vaccine strains in patients under TNF inhibitory therapy [54]. In two studies, antibody levels were lower in patients under TNF inhibitory therapy, but seroprotection levels were not significantly reduced [49,55]. However, persistence of seroprotection was shorter under TNFi therapy [55].

One study demonstrated that **timing of influenza vaccination** relatively to infliximab therapy (vaccination at time of infusion vs. midway between infusions) did not influence immunogenicity significantly in IBD patients [56].

The effect of a **booster influenza vaccine dose** administered three weeks after the first vaccine dose was examined in a Japanese study [57]. The vaccines were administered subcutaneously to IBD patients. A serology was performed before vaccination, 3 weeks after the first and the second vaccination (if applicable) as well as after influenza season. The immune responses did not shown any significant differences three weeks after the first *vs.* three weeks after the second dose.

One group compared the **split and whole virion influenza vaccine** in IBD patients [58]. In patients vaccinated with the split virion vaccine, antibody titres increased to a significantly larger degree than in the whole virion influenza group.

Recommendation

Annual vaccination with seasonal inactivated influenza vaccination is recommended in patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions under immunosuppressive therapy. Protection of immunosuppressed patients is reinforced by the immunisation of close contacts.

3.2 Pandemic H1N1 vaccine

H1N1 vaccination was safe in IBD patients and the risk of IBD flare was not increased after H1N1 vaccination [59,60].

In some studies, seroprotection was recorded in all patients under immunomodulatory and/or biological therapy after H1N1 vaccination [60,61], and in some seroprotection rates were lower than in the general population [62]. A general finding was that seroconversion rates were lower under combined TNFi/immunosuppressant (azathioprine (AZA); MTX, 6-MP, corticosteroids) therapy than under monotherapy immunosuppression [60,62,63].

Recommendation

In a pandemic situation, patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions should receive the influenza vaccine specific for the pandemic strain, if available. Immunogenicity may be reduced compared to the seasonal vaccine, as in a pandemic situation, the vaccine contains a new strain, and no booster effect can be expected. Contrarily, the annual influenza vaccine contains strains that are similar to previous years, and thus a “booster effect” will generally induce better antibody responses.

In a pandemic situation, immunosuppressed persons may thus benefit from additional vaccine doses for adequate protection. This will have to be defined on a case-based scenario.

3.3 Pneumococcal vaccine

Mostly studies on pneumococcal polysaccharide vaccination have been performed in IBD patients to date.

In all studies pneumococcal vaccination has been reported to be safe [64–66].

In a study by Gelinck et al., MTX therapy significantly decreased serological immune responses to 23-valent pneumococcal polysaccharide (23-PPV) vaccine in IBD patients; a combination therapy of anti-TNF plus MTX enhanced this effect even further [64]. TNF blocker therapy alone also inhibited antibody responses [64,66,67], but to a lesser extent than MTX alone [64,66]. A decreased immunogenicity under combination therapy with TNFi (infliximab (IFX) or adalimumab (ADA)) and either 6-MP, AZA or MTX was also demonstrated in two other studies [65–67]. Mesalamine [66,67] and AZA were shown to have no negative impact on vaccination responses [66].

One group studied the immunogenicity of 13-valent pneumococcal conjugate vaccine in paediatric IBD patients who were A) under no immunosuppressive therapy B) on TNFi or classical immunosuppressants (AZA, cyclosporine) or C) healthy controls [68]. Overall, vaccine responses were similar between patients and controls (90.4% *vs.* 96.5%, P=0.5281). Geometric mean titre increases, however, were lower in group B than in group A [68].

Recommendation

Vaccination against pneumococcal disease is recommended for all patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions. Ideally, the vaccination should be administered prior to the start of immunosuppressive therapy. If immunosuppressive therapy has already been started, the vaccination should be administered at a time point when level of immunosuppression is lowest (under maintenance therapy).

One dose of the 13-valent conjugate vaccine (Prevenar-13®, PCV13) should be administered according to the recommendations by the Swiss Federal Office of Public Health [69].

The conjugate vaccine should only be used (and no more the polysaccharide vaccine) as conjugate vaccines produce higher affinity antibody responses, longer lasting immune responses, and the production of memory B cells. Booster vaccinations after conjugate vaccinations are possible while in polysaccharide vaccines secondary vaccines may elicit only poor immune responses due to a lack of memory cells. The administration of plain polysaccharide vaccine may blunt the immune response to subsequent doses, such that the antibody levels following a second vaccination, and possibly the magnitude of clinical protection, may be lower than following a first vaccination. For this reason, a minimum time interval of 12 months should elapse since the last pneumococcal polysaccharide vaccination (Pneumovax®) before administration of the conjugate vaccine. For immunogenicity reasons, ideally, a time interval of 4 weeks to influenza vaccination should be maintained.

Booster vaccinations with the 23-valent polysaccharide vaccine are not recommended due to the potential induction of hyporesponsiveness. The current serotype distribution in Switzerland does not require coverage with the additional serotypes contained in the 23-valent vaccine. Whether and when booster vaccination may be needed following PCV13 priming remains to be defined.

3.4 Tetanus/diphtheria/polio vaccine

Tetanus vaccination has been reported to be safe in IBD patients.

In 10 IBD patients **without immunosuppressive therapy** and anti-tetanus antibody levels <0.1 IU/ml, immune responses to tetanus vaccination were not impaired in comparison with healthy controls [70].

In another study from 1985, immune responses were generally impaired in IBD patients compared to health controls (HCs), patients with systemic lupus erythematosus, and patients with other gastrointestinal diseases [71]. Corticosteroid treatment did not significantly influence vaccine responses. Another study from 1987 also demonstrated low immune responses upon tetanus vaccination; however medications were not reported [72].

One study on booster tetanus vaccination in IBD patients treated with various medications was published [73]. 98 patients were enrolled into the study and 84 completed it. Participants were stratified into five groups: A) no therapy or 5-ASA alone, B) TNFi therapy, C) immunomodulator

therapy (AZA, 6-MP, or MTX), D) TNFi plus immunomodulator, E) healthy controls. Tetanus response was defined as postvaccination antibody level ≥ 0.4 IU/ml in subjects with a baseline titre <0.1 IU/ml, or a > 4-fold rise in those with a baseline titre of ≥ 0.1 IU/ml. Immune responses were lowest in patients in group C (40%) and D (27%). Patients on sole TNFi therapy showed immune responses (56%) comparable to IBD patients without treatment (55%) and healthy controls (63%). Although all groups showed an antibody rise after vaccination, the absolute postvaccination geometric mean titre (GMT) was significantly lower in groups C and D.

Another study demonstrated that thiopurine treatment (AZA, 6-MP) did not hamper cellular and humoral immune response to tetanus vaccine [74]. However vaccination was administered just before treatment start.

Recommendation

As no evidence-based data on previously unvaccinated people are available and scarce information exists on subjects previously exposed, the experts suggest that after the primovaccination, booster doses of tetanus toxoid/diphtheria vaccine are indicated every 10 years in patients with IBD and other gastroenterological (auto)immune conditions.

3.5 Polio vaccine

There are no data on polio vaccination to date.

Recommendation

Parenteral polio vaccination should be administered according to the Swiss vaccination schedule of the Swiss Federal Office of Public Health (SFOPH).

3.6 Pertussis vaccine

One study on booster pertussis vaccination in IBD patients was published [73]. 98 patients were enrolled into the study and 84 completed it. Vaccination was safe. Participants were stratified into five groups: A) no therapy or 5-ASA alone, B) TNFi therapy, C) immunomodulator therapy (AZA, 6-MP, or MTX), D) TNFi plus immunomodulator, E) healthy controls. Booster response rates were defined as postvaccination antibody level ≥ 20 endotoxin units (EU)/ml in subjects with a baseline titre <5 EU/ml, a 4-fold rise in antibody titre in those with a baseline titre of 5-20 EU/ml, and a 2-fold rise in those with a baseline titre of ≥ 20 EU/ml. Immune responses were lowest in patients in group C and D. Patients on sole TNFi therapy showed immune responses comparable to healthy controls. However, all IBD groups showed postvaccination GMT increases between 3- to 9-fold for pertussis toxin and 4- to 7-fold for filamentous haemagglutinin (FHA).

Recommendation

Pertussis vaccination should be administered in the same time intervals and situations recommended in the Swiss vaccination schedule.

3.7 Hepatitis B vaccine

Hepatitis B vaccination has been reported to be safe in paediatric and adult patients with IBD or coeliac disease.

Antibody responses after hepatitis B vaccination have been shown to be lower in paediatric and adult IBD patients compared to HCs [75,76]. Immune responses were lower in patients under treatment with corticosteroids, azathioprine, and/or anti-TNF.

Rates of seroprotection (anti HBV >10 mIU/ml) after a standard hepatitis B vaccination scheme (0, 1 month, 6 months) ranged between 48%-80% for patients and 90-100% in HC [75–78]. Anti-Hbs ≥100 mIU/ml were achieved in 53% of IBD patients and 87% HC [76].

Risk factors associated with lower immune responses were higher age, as well as corticosteroid, azathioprine and TNFi therapy [76,77,79].

Cekic et al applied the standard 3-dose vaccination regimen to 125 seronegative IBD patients [80]. 56.8% had anti-HBs >10 IU/L after three vaccinations. For patients with immunosuppressive therapy (5-ASA, AZA, steroids, TNFi, AZA plus TNFi), only 40.7% achieved anti-HBs≥10 IU/L *vs.* 92.3% of untreated patients. Overall, 40% had titres >100 IU/L, 24.4% immunosuppressed and 74.4% non-immunosuppressed. In the multivariate model, higher age, vaccination during non-remission periods and immunosuppressive treatment predicted an unfavourable outcome.

One study by Gisbert et al demonstrated an improved immunogenicity when a double dosage vaccination (2 doses of Engerix-B® 20µg) was administered at time points 0, 1 and 2 months compared to the standard regimen with one dose Engerix-B 20µg at 0, 1 and 6 months (75% vs. 41% anti-HBs > 10 IU/l) [81]. 70% of patients were taking immunosuppressive medications: thiopurines only, TNFi only or both. The remaining 30% were not taking any immunosuppressive drugs or only medication not considered immunosuppressive (e.g. 5-aminosalicylates). Medications were not found to be associated with lower vaccine responses.

However, in another study reported by the same authors, the overall immunogenicity (anti-HBs > 10 IU/l) was only 59% (46% for patients receiving only TNF blocking therapy, 60% under anti-TNF and other immunosuppressants, 63% without immunosuppressants) when the double-dose scheme was followed [82]. Only 39% reached antibody levels of >100 IU/l. When the vaccination course was repeated (double dose at time point 0, 1 and 2 months) in 95 patients with an antibody titre <100 IU/l, 42% had a positive vaccine response (titre >100 IU/l; overall 65%). As expected, a higher response rate upon revaccination was achieved in patients with low, but measurable responses after the initial vaccination (76% in those with an initial response of 1-100 IU/l) compared to those with anti-HBs below detection after the initial doses (26%).

Another study by Gisbert et al examined the kinetics of anti-HBs titres after hepatitis B vaccination in IBD patients. In the Kaplan-Meier curve, a higher cumulative incidence of loss of anti-HBs titers was observed among those treated with TNFi. However, differences were not found depending on thiopurine treatment.18% of protective anti-HBs were lost per patient-year. Anti-TNF treatment was associated with an augmented risk of anti-HBs loss [83].

In a study by Chaparro and colleagues, 170 IBD patients were randomised to receive double Engerix-B® 20µg vaccination or the adjuvanted Fendrix® vaccine at time points 0, 1, 2 and 6 months [84]. Anti-HBs concentrations were measured at 4 and 8 months. Overall, 44% of patients had vaccine titres ≥100 IU/l after the 3rd dose and 71% after the 4th dose. The response rate was 67% for Engerix® and 76% for Fendrix® after the 4th dose (P=0.2). When using 10 IU/l as a threshold, the response rate was 73.6% for Engerix® and 87% for Fendrix® (P=0.04). In the multivariate analysis the following factors were associated with lower response rates: older age, immunosuppressive therapy or TNFi, but not the type of vaccine (Fendrix® single dose vs. Engerix® double dose). A 4th dose in this specific schedule appeared to increase vaccine responses by 27%.

In one study, 14 paediatric non-responders with IBD received a booster vaccine dose. After this 7/14 (50%) seroconverted. Overall, seroprotection of IBD patients was 85.1% after a full vaccination scheme plus a booster dose [75].

In a study by Moses et al, IBD patients under infliximab therapy with a previous full course of hepatitis B vaccinations (i.e. three doses or more) and who had a current titre < 10 IU/l, received a booster vaccination. 76% showed an anamnestic response [85].

In a study by Cossio-Gil et al, 172 susceptible IBD patients received a three-dose standard schedule of HBV vaccine (monovalent (Engerix® 20 or HBVAXPRO® 10) or combined hepatitis A and B (Twinrix® 720/20)) and non-responders were re-vaccinated with a second three-dose standard regimen [86]. After the first three vaccinations, 50.6% developed antibody titres ≥10 mIU/ml. Among those who received the combined hepatitis A and B vaccination, 58.4% developed titres ≥10mIU/ml *vs.* 44.2% of those who received the monovalent hepatitis B vaccination (P=0.064, OR 1.7, 95%CI 0.9–3.3). From the non-responders, 28/53 (52.8%) showed an adequate response after re-vaccination. Overall, 66.8% had achieved seroprotection at the end of the study. In the multivariate analysis, immunogenicity results did not differ significantly between patients without immunosuppressive treatment *vs.* with immunosuppressives *vs.* on biological therapy.

Opri et al conducted a systematic review and meta-analysis on hepatitis B vaccination in patients with coeliac disease under various treatments. They identified 12 controlled retrospective and four controlled prospective studies (partly one study included a retrospective and a prospective part) [87–100]. In the retrospective studies, the mean rate of protective antibody titres was 53.6% in patients *vs.* 82.1% in controls. In the prospective studies, the mean protection rate was 65.8% in patients *vs.* 89.7% in controls.

In a study by Urganci et al, vaccination responses were studied in 30 patients with coeliac disease compared to HC [100]. 70% of patients *vs.* 90% of controls achieved seroprotection, defined as anti-HBs ≥ 10mIU/ml. An additional hepatitis B dose was given to patients with anti-HBs <10mIU/ml after the standard 3-dose regimen; 3/9 (33.3%) responded after such a booster dose, i.e. overall, 80% achieved a titre ≥10mIU/ml.

One study has been published on hepatitis B vaccination in patients with autoimmune liver conditions [101]. 21 patients with autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis were vaccinated against hepatitis B. Out of these, eight were only vaccinated against hepatitis B, while 13 received a hepatitis A/hepatitis B combination vaccine. Five out of 21 patients (24%) were non-responders, eight (38%) developed anti-HBs antibodies ≥10 and < 100 UI/L ("low responders") and antibody levels >100 mIU were achieved in 8/21 (38%) patients with autoimmune liver diseases [101]. In non-responders, 4/5 (80%) received immunosuppressive therapy (azathioprine or prednisone or azathioprine/prednisone in combination); in low responders six out of eight (75%) were under immunosuppressive treatment (azathioprine/ prednisone or mycophenolate/prednisone). Amongst full responders, one patient was under low dose corticosteroid therapy and one received a combination therapy of azathioprine/low dose prednisone.

Recommendation

Screening: All IBD patients and patients with other gastroenterological (auto)immune conditions should be screened for hepatitis B infection and vaccination status via measurement of HBsAg, anti-HBs antibodies and anti-HBc antibodies. In patients with evidence for hepatitis B infection, HBeAg, anti-HBe, and HBV DNA should be determined.

Chronic HBsAg carriers: Prophylactic antiviral treatment with nucleoside/nucleotide analogues is recommended in chronic HBsAg carriers regardless of the degree of viraemia. Nucleoside/nucleotide treatment should be started at least two weeks before introduction of immunosuppressive/immunomodulatory therapy and continued for 12 months after their withdrawal. Entecavir and tenefovir are the currently preferred antivirals [102].

Patients with evidence of past infection (HBsAg-, anti-HBc+, anti-HBs- or +, undetectable HBV DNA): As reactivation of solely anti-HBc positive occult HBV infections does only occur in very rare cases, the Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in IBD patients does not recommend routine antiviral prophylaxis in these cases [102]. However, a routine monitoring of liver enzymes (ALT/AST) as well as of HBV serology and HBV DNA should be performed in IBD patients under immunosuppressive / immunomodulatory therapy [103].

Prophylaxis in seronegative patients: Because of potential severe disease, should hepatitis B virus (HBV) infection be acquired during immunosuppressive / immunomodulatory therapy, all seronegative (anti-HBc- and anti-HBs- negative) patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions should be vaccinated against hepatitis B according to the conventional scheme (0, 1, 6 months). If protection is needed more rapidly the accelerated scheme (1, 7, 21 days, 6-12 months) is indicated.

In patients who need to start treatment as soon as possible an accelerated scheme (0, 7 and 21 days) should be used before treatment start. If possible and indicated (no natural immunity against hepatitis A), the combined hepatitis A and B vaccine (Twinrix®) should be chosen as it is known to be more immunogenic than the monovalent hepatitis B vaccine. A fourth dose should be given after 6-12 months, at a time point when immunosuppressive treatment is relatively low. In immunosuppressed patients, antibody measurements should be performed 4-6 weeks after the 3rd vaccination (scheme 0, 1 and 6 months) and after the 4th dose if the scheme is 0, 7, 21 days and 6-12 months. Levels of anti-HBs >100 mIU/ml should be achieved. If necessary, booster doses should be administered.

Maintenance of HBs antibody should be monitored on a regular basis in immunosuppressed patients with significant exposure risks. A booster dose of hepatitis B vaccine should be given if anti-HBs fall below 10 IU/l.

3.8 Hepatitis A vaccine

Four studies of hepatitis A vaccination (Havrix®, 720 ELISA units) were identified in paediatric patients with gastroenterological autoimmune diseases. In all studies, vaccination against hepatitis A was safe.

In two studies in paediatric IBD patients, included subjects were under therapy with corticosteroids, AZA, mesalamine and/or 6-mercaptopurines.

In the first study, seroconversion (defined as ≥ 20 mIU/ml) was achieved in 39% of IBD patients compared to 64% of HCs after one vaccine dose. After the second dose, received after a 6-month interval, 100% of IBD patients and 100% of HC had seroconverted. Geometric mean titres were generally lower in IBD patients; AZA tended to have a smaller negative impact than corticosteroid treatment or combination therapy of corticosteroid and AZA/6-MP [104].

In the second study, seroconversion was defined as “having positive anti-HAV IgG” after vaccination. All HC and all IBD patients had become positive for anti-HAV antibodies one month after the second vaccine dose [75].

Seroconversion levels were lower in paediatric patients with coeliac disease; in a study by Urganci et al, only 75% of patients seroconverted after two vaccine doses [100].

Moses et al performed a study in 12 paediatric and adult IBD patients (age range 13-23 years) who received two doses of Havrix® (720 or 1440 ELISA units, according to age) on a 0 and 6-12 months schedule. All patients were under IFX therapy, two received concurrent MTX. 11/12 (92%) patients seroconverted four weeks after the second dose, the non-responder was only on IFX treatment [105]. Seroconversion after one vaccine dose as well as definition of seroconversion was not reported.

One study was identified on hepatitis A vaccination in 419 seronegative patients with IBD (n=355 Crohn’s Disease, n= 64 ulcerative colitis) [106]. Two doses of a virosome-formulated vaccine (Epaxal®) were administered at time points 0 and 6-12 months. A serology was performed before the first vaccination and 1-3 months after the second dose. The overall seroconversion rate was 97.6%. It was lower in patients on TNFi (IFX or ADA) than in those not treated (92.4% vs. 99.1%, P=0.001). Seroconversion rates were also lower in patients receiving ≥ 2 immunosuppressants compared to less than 2.

One study on hepatitis A vaccination was performed in 15 adult patients with autoimmune liver diseases (autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis and overlap syndromes). It was reported that all patients developed anti-HAV IgG after vaccination. However, patients were asked on whether they had been vaccinated against hepatitis A on the basis of the detection of positive anti-HAV IgG levels in the blood; i.e. patients without the development of anti-HAV IgG were not asked for their vaccination history [101]. Therefore, this study cannot be taken into consideration.

Recommendation

All patients with IBD should be immunised against hepatitis A before traveling to endemic areas. The normal two-dose schedule (0, 6 months) should be completed, preferably before travel. Response to hepatitis A immunisation in IBD patients on immunosuppressive / immunomodulatory treatment should be checked by a serological assay [102]. If only one (first time) vaccination against hepatitis A can be administered under immunosuppressive therapy before travel to an endemic area, a serology should be performed and/or further doses applied as an accelerated scheme. Two vaccine doses at the same time or at a one-month interval might be an option, but this approach has not been formally studied yet.

3.9 Human papillomavirus vaccine

In a prospective study of 37 female IBD patients, aged 9-26 years, the quadrivalent HPV (Gardasil®) was applied and no clinically relevant adverse events were detected [107]. 51% of the patients were on TNFi therapy, and the others on immunomodulating therapy. One month after vaccination, all

patients were seropositive for types 6, 11 and 16, and 96% for type 18. In a group of 15 previously vaccinated patients, antibody titres were measured 0.5-27 months after vaccination. In this group, only 40% were seropositive for type 18 measured by competitive Luminex immunoassay and 93% when measured by immunoglobulin G LIA. All were seropositive for the other types. Titres seemed to decrease with time since vaccination.

A second study demonstrated that the quadrivalent HPV vaccine was safe in 15 women with IBD [108]. Patients were aged between 12.8-24.6 years at time of first vaccination, three patients (20%) were on low-dose oral corticosteroid therapy, four on mesalamine (26.7%), two (13.3%) under thiopurine therapy, three (20%) received treatment with biologicals and three (20%) were under combined therapy. Out of 13 patients who completed the study, all seroconverted to HPV type 6, 11 and 16, and 84.6% to type 18. GMT for each HPV type were lower in IBD patients compared to historical controls. GMT were lower in patients under biological therapy or combination therapy compared to those under mesalamine treatment.

Recommendation

HPV vaccination is recommended in all patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions aged 11-26 years.

In line with the European Crohn's and Colitis Organisation (ECCO) recommendations, regular gynaecologic screening for cervical cancer is strongly recommended for women with IBD, especially if under treatment with immunosuppressive / immunomodulatory therapy. In patients with extensive cutaneous warts and / or condylomata, discontinuation of immunosuppressive / immunomodulatory therapy should be considered. Current or past infection with HPV is not a contraindication for immunomodulatory therapy [102].

3.10 *Haemophilus influenzae* b (Hib) vaccine

Therapy with azathioprine did not inhibit antibody responses to Hib vaccine [74].

Recommendation

Hib vaccination should be administered according to the Swiss vaccination schedule. Based on the current epidemiology, Hib immunisation is not recommended after the age of 5 years even in immunosuppressed patients.

3.11 Herpes zoster vaccine

In a retrospective study of data from a US nationwide health plan, 136 IBD patients aged 50 years and above were identified who received the herpes zoster vaccination [109]. HZ immmunisation was safe in all cases, also in patients under TNFi therapy.

A similar retrospective study used data from 463,541 Medicare beneficiaries with autoimmune diseases aged 60 years and above. Amongst these were 66,751 IBD patients; overall, 18,683 patients (4.0%) received the HZ vaccine. HZ vaccination was safe and HZ incidence was reduced amongst HZ vaccine recipients [110].

Recommendation

Herpes zoster vaccine is 14 times more potent than the live varicella vaccine, and in general, live viral vaccinations, such as herpes zoster vaccine, are contraindicated under immunosuppressive therapy.

Vaccination against HZ (Zostavax®) is recommended for future immunosuppressed patients 50 to 79 years old, presenting without or with a "mild" (non-severe) immunodeficiency, which can be assumed to deteriorate to "severe" in the foreseeable future. The vaccine should be administered at least 4 weeks before an assumed, anticipated or planned start of a severe immunosuppression. In future immunocompromised patients 18 to 49 years old HZ-vaccination is not recommended. However, patients with negative varicella history, vaccination status and / or VZV-serology should be protected according to current Swiss recommendations with 2 VZV-doses from varicella infection.

According to the US Centers for Disease Control and Prevention (CDC), HZ vaccination may be administered under low dose therapy with methotrexate (<0.4 mg/kg/week), azathioprine (<3.0

mg/kg/day), or 6-mercaptopurine (<1.5 mg/kg/day) [111]. These recommendations are in line with those published by the Infectious Diseases Society of America (IDSA), which recommend HZ vaccine in patients aged ≥ 60 years who receive a therapy with low level immunosuppression [112]. The American College of Rheumatology allows herpes zoster vaccination in immunocompromised patients under non-biological disease modifying antirheumatic drugs (DMARDs) [113]. The Swissmedic (Swiss safety monitoring board) states that herpes zoster vaccine is contraindicated in patients on methotrexate therapy (irrespective of dosage) [114].

Before vaccinating an immunocompromised patient against herpes zoster a serological antibody test is recommended. If the VZV-serology is negative, a herpes zoster vaccination is not indicated: (i) herpes zoster reactivation can only occur in case of previous VZV-infection, (ii) under immunosuppression herpes zoster vaccination has a higher potential of leading to a vaccine-strain-induced infection if no antibodies are present. In case of infection through the vaccine strain antiviral therapy can be used as “rescue therapy”.

For now, the vaccination schedule involves the administration of a single dose of Zostavax®. The expected introduction of an inactivated herpes zoster vaccination may render these cautious considerations unnecessary in the future.

Please consult table 2 for further details and exemptions and table 3 for time intervals between cessation or pausing of immunosuppressive therapy and administration of herpes zoster vaccine.

3.12 Varicella vaccine

On varicella vaccination in patients with IBD, only a case series of six children under various medications has been published [115]. In these cases, the vaccination was safe and immunogenic. In addition, data is accumulating in other immunosuppressed children [116].

Recommendation

After diagnosis of an inflammatory bowel disease or other gastroenterological (auto)immune condition, susceptibility to varicella infection should be assessed as soon as possible: all patients should be serologically tested for varicella zoster virus (VZV) antibodies. The serology should be sent to a „general laboratory“. If the results are equivocal or negative the serology should be retested in a reference laboratory. In this case, 50-100 µl serum could be sent to „Laboratoire de vaccinologie des Hôpitaux Universitaires de Genève“ where a more sensitive test can be performed.

Seronegative patients should be vaccinated before start of immunosuppressive / immunomodulatory therapy. Two vaccine doses, at least 1 month apart, should be administered and the last dose should be given ≥ 1 month before start of immunosuppressive therapy.

In general, live viral vaccinations, such as varicella vaccine, are contraindicated under immunosuppressive therapy. As the replication potential of varicella vaccine is low and antivirals are available, should vaccine infection require a treatment, varicella vaccine should be considered in any stable child under low dose therapy with methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6-mercaptopurine (<1.5 mg/kg/day). These recommendations are in line with those published by IDSA, which recommend varicella vaccination in patients without evidence of varicella immunity who receive a long-term therapy with low level immunosuppression [112]. Also in adults, varicella vaccination can be given in clinically stable cases during low dosage methotrexate therapy ≤0.4 mg/kg/week or ≤20 mg/week [117].

Above these thresholds, immunisation should only be considered on an individual patient basis, after expert advice. Please consult table 2 for further details and exemptions and table 3 for time intervals between cessation or pausing of immunosuppressive therapy and administration of varicella vaccine.

Insist on checking the history/vaccination status of household and other close contacts, and vaccinate them if indicated.

Post-exposure prophylaxis: In case of exposure to chickenpox or herpes zoster, an unimmunised, seronegative patient with IBD or other gastroenterological (auto)immune condition under immunosuppression should receive varicella zoster immunoglobulin within 10 days. After the receipt of immunoglobulins, the IBD patient should be observed for one month. In case of signs of varicella

infection, antiviral treatment should be given promptly without awaiting confirmatory laboratory results [102]. In some cases of severe infection, immunosuppressive / immunomodulatory treatment should be stopped. Therapy can be re-initiated after the lesions have crusted and fever has ceased.

If immunoglobulins did prevent the onset of chickenpox and the patient is seronegative, consideration should be given to perform varicella immunisation (see above).

3.13 MMR vaccine

To date, no studies on measles, mumps or rubella vaccination have been published in IBD patients. In one study, measles antibody measurements were performed in 19 children or adolescents with autoimmune hepatitis that were vaccinated before diagnosis. All had measurable antibodies (GMT 1.33 IU/ml (range 0.5-21.1 IU/ml) while under therapy with low dose corticosteroids or azathioprine [118].

Recommendation

After diagnosis of an inflammatory bowel disease or other gastroenterological (auto)immune condition the vaccination status/immune status should be assessed as soon as possible. All patients should be serologically tested for measles antibodies. The serology should be sent to a „general laboratory“. If measles results are equivocal or negative the serology should be retested in a reference laboratory. In this case, 50-100 µl serum could be sent to „Laboratoire de vaccinologie des Hôpitaux Universitaires de Genève“ where a more sensitive test can be performed.

Seronegative patients should be vaccinated before start of immunosuppressive / immunomodulatory therapy. Two vaccine doses, at least 1 month apart, should be administered and the last dose should be given ≥ 1 month before start of immunosuppressive therapy.

In general, live viral vaccinations, such as MMR vaccine, are contraindicated under immunosuppressive therapy. MMR vaccination can be given in clinically stable cases during low dosage methotrexate therapy ≤0.4 mg/kg/week or ≤20 mg/week [117]. Please consult table 2 for further details and exemptions and table 3 for time intervals between cessation or pausing of immunosuppressive therapy and administration of MMR vaccine.

Insist on checking the vaccination status of household and other close contacts, and vaccinate them if indicated. If a seronegative person under immunosuppressive therapy was in contact with a person with measles infection, the administration of immunoglobulins is recommended as soon as possible (within 72-96h).

3.14 Yellow fever vaccine

There are no data on yellow fever vaccination in patients with gastroenterological (auto)immune conditions under immunosuppressive therapy.

Recommendation

Yellow fever vaccination is generally contraindicated under immunosuppressive therapy. If a patient with a gastroenterological (auto)immune disease under immunosuppressive therapy intends to travel to a yellow fever endemic region and has been vaccinated against yellow fever in the past an antibody measurement should be performed[1]. The immunity against yellow fever should be checked irrespective of time point of vaccination, i.e. immunity should be checked if the vaccination was given ≤ 10 years ago as the immunosuppressive treatment may have reduced immunity. The immunity should also be checked if the vaccination was administered > 10 years ago as protection may last longer than 10 years and may still be present. Seropositivity (currently used surrogate of protection is >0.7 LNI corresponding to 0.5 IU/ml [119,120]), indicates past immunity and enables travel to yellow fever endemic areas regardless of time elapsed since immunisation.

[1] The yellow fever neutralization assay is not available in Switzerland to date. The neutralization assay can be performed at the Leiden University Hospital Centre, The Netherlands or at the Robert Koch Institut, Berlin, Germany.

Yellow fever vaccination can be given in clinically stable cases during low dosage methotrexate therapy ≤0.4 mg/kg/week or ≤20 mg/week [117]. Please consult table 2 for further details and exemptions and table 3 for time intervals between cessation or pausing of immunosuppressive therapy and administration of yellow fever vaccine.

3.15 Bacillus Calmette–Guérin (BCG) vaccine

Case reports on disseminated BCG infection have been reported in IBD patients under immunosuppressive therapy [121].

Recommendation

BCG vaccination is contraindicated in patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions.

4 Other vaccine-preventable diseases

In the literature, no data were found on the safety and immunogenicity of the inactivated vaccinations against rabies, Japanese encephalitis, meningococcal disease, tick-borne encephalitis (TBE) or typhoid fever in patients with gastroenterological (auto)immune conditions.

These vaccinations are indicated for specific risk groups or risk situations according to the annually published Swiss vaccination recommendations of the general population.

Rabies, Japanese encephalitis and parenteral typhoid vaccinations may be recommended before travelling to an endemic area. The indication should be discussed with a specialist for travel health before a planned international trip.

A vaccination against **tick-borne encephalitis** is recommended for persons with an increased risk of exposure. The map of areas with a TBE vaccination recommendation is updated annually by the Swiss Federal Office of Public Health.

For TBE, the usual course of vaccination should be followed (3 dose-scheme with a booster dose every 10 years). In immunosuppressed patients, a serology should be performed 4-6 weeks after the 3rd dose.

For all inactivated vaccinations with a lack of immunogenicity data, the usual recommended schedule should be followed until more data are available. For all primary vaccinations of immunosuppressed patients, e.g. a first course of vaccination against tick-borne encephalitis, the immunogenicity should be checked by a serology 4-6 weeks after the last dose of the course, if available. To find out whether a meaningful serological test is available, please consult table 4 [1].

Table 2: Immunosuppressants and vaccinations

Try to avoid vaccinations during the induction period of immunosuppressive treatment because i) during this period dosages of immunosuppressive therapies are generally highest and safety of live vaccines as well as immunogenicity of inactivated vaccines may be reduced ii) potential side effects may be misinterpreted during this unstable phase of disease.

	NO RESTRICTION	CONDITIONAL CONSTRAINT [6]	CONTRAINDICATION
INACTIVATED VACCINES	**All immunosuppressants** Immunogenicity may be reduced		**None**
LIVE VACCINES [1] MMR, Varicella, Yellow fever, Herpes zoster [2]	**Corticosteroids** [3] Systemic: only short-term or low dose Maintenance physiologic doses (replacement therapy) Non-systemic glucocorticoids **Balsalazide** **Budesonide** [4] **Mesalazine** **Olsalazine** **Sulfasalazine** **Vedolizumab** [5]	**Methotrexate** [7] **Azathioprine** [8] **6-Mercaptopurine** [9] **6-TGN (Lanvis®)** [10]	**Corticosteroids** [11] Systemic and high dosis and ≥2 weeks **Ciclosporine A** **Cyclophosphamide** **Leflunomide** **Mycophenolate** **Tacrolimus** **Adalimumab** **Certolizumab** **Golimumab** **Infliximab** **Ustekinumab**

1. As a precaution, oral typhoid vaccination (Vivotif®) should be avoided in patients with inflammatory bowel disease (expert opinion) and in patients with other gastroenterological (auto)immune conditions under immunosuppression.
2. The attenuated live vaccine against herpes zoster (Zostavax©) may not be administered to patients who have recently been treated or who are currently on treatment with immunosuppressants. This recommendation specifically applies if several immunosuppressants are used for treatment concomitantly. The vaccination is not contraindicated in patients who receive topical corticosteroids, inhalation therapy with corticosteroids, systemic low-dose corticosteroid or low-dose immunosuppressant therapy - with the exception of methotrexate. According to the Swiss Agency for Therapeutic Products (Swissmedic), methotrexate treatment is a contraindication for herpes zoster vaccination, independently of the taken dosage (114).
3. Short- or long-term daily or alternate-day therapy with <20 mg of prednisone or equivalent (adults) or 0.5 mg/kg/day of prednisone or equivalent in children. Maintenance physiologic doses (replacement therapy). Non systemic topical steroids (airways, skin, ears, or eyes) and injections (intraarticular, bursal, or tendon injection of steroids)
4. Budesonide at a dosage of ≤6 mg/day
5. Oral vaccinations (for example cholera vaccine) are not recommended under therapy with Vedolizumab or other α4β7 integrin inhibitors because they are not immunogenic [122].
6. This recommendation is provided for patients under a single immunosuppressant, not for a combination therapy. In case of a combination therapy the immunosuppressive effect can be enhanced and live vaccines may be contraindicated.
7. Live vaccinations generally contraindicated if methotrexate >0.4 mg/kg/week or >20 mg/week. For children, there are no data and the threshold is possibly different. MMR, varicella, yellow fever: in clinically stable cases, these live vaccines can be given during low dosage therapy: methotrexate ≤0.4 mg/kg/week or ≤20 mg/week [117]. This approach is based on expert opinion and requires future follow-up.
   Only varicella and herpes zoster: vaccination possible if azathioprine ≤3.0 mg/kg/day to prevent varicella infection or re-activation, above this threshold or other live vaccines: contraindicated [111,112]. For children, there are no data and the threshold is possibly different.
8. Only varicella and herpes zoster: vaccination possible if 6-mercaptopurine ≤1.5 mg/kg/day to prevent varicella infection or re-activation, above this threshold or other live vaccines: contraindicated [111,112]. For children, there are no data and the threshold is possibly different.
9. Used off-label in Switzerland. Specific threshold not yet defined
10. High-dose steroids: ≥20 mg per day of prednisone or equivalent in adults or ≥0.5 mg/kg/day of prednisone or equivalent in children.

Table 3: Time interval between cessation or pausing of an immunosuppressive agent and live vaccination (MMR, Varicella, Herpes zoster, Yellow fever)

MEDICATION	TIME INTERVAL
Corticosteroids [1)] Systemic: only short-term or low dose Maintenance physiologic doses (replacement therapy) Non-systemic glucocorticoids **Balsalazide** **Budesonide** [2)] **Mesalazine** **Olsalazine** **Sulfasalazine** **Vedolizumab**	Can always be given
Corticosteroids [3)] Systemic and high dosis and ≥2 weeks	1 month
Ciclosporine A **Cyclophosphamide** **Mycophenolate** **Tacrolimus**	3 months [5)]
Azathioprine **Methotrexate** **6-Mercaptopurine** **6-TGN (Lanvis®)**	3 months [5)], for exceptions, please see table 2
Adalimumab **Certolizumab** **Golimumab** **Infliximab** **Ustekinumab**	3 months [5)]
Leflunomide [4)]	2 years

1. Short- or long-term daily or alternate-day therapy with <20 mg of prednisone or equivalent (adults) or 0.5 mg/kg/day of prednisone or equivalent in children. Maintenance physiologic doses (replacement therapy). Non systemic topical steroids (airways, skin, ears, or eyes) and injections (intraarticular, bursal, or tendon injection of steroids)
2. Budesonide at a dosage of ≤6 mg/day
3. High-dose steroids: ≥20 mg per day of prednisone or equivalent in adults or ≥0.5 mg/kg/day of prednisone or equivalent in children
4. For safety reasons, live vaccines are contraindicated for at least 2 years after leflunomide therapy. But there is a specific wash-out option with inactivated carbon or colestyramin: According to Sanofi Pasteur a schedule similar to the one recommended for pregnancies under leflunomide can be followed before administration of a live vaccine: “after cessation of leflunomide therapy, ‘wash out’ with 8 g colestyramin 3 times daily over 11 days or 50 g activated carbon 4 times daily over 11 days. Independent of the wash-out method, the determination of the plasma level of leflunomide is necessary in two tests that are at least 14 days apart. After the first test with a plasma level below 0.02 mg/l it is necessary to wait for another 1.5 months before fertilisation is possible”
5. As currently no data are available, these recommendations are mostly based on expert opinion and medication half lives

Table 4: Correlates of protection for vaccine preventable diseases

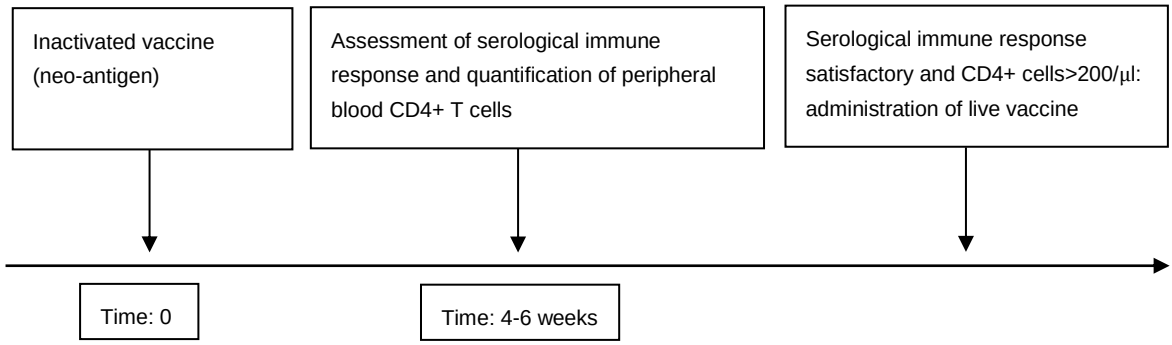
Source: [1]

VACCINATION	CORRELATES FOR PROTECTION				COMMENTS
	Units	Susceptible	Short-term protection	Long-term protection	
Diphtheria	IU/L	<100	100-999	≥1000	
Tetanus	IU/L	<100	100-999	≥1000	
Haemophilus influenzae type b (Hib)	mg/L	<0.15	0.15-0.99	≥1	
Hepatitis B	IU/L	<10	10-99	≥100	
Pneumococcal vaccination	mg/L	<0.3	0.3-0.9	≥1	Test available in „Laboratoire de vaccinologie des Hôpitaux Universitaires de Genève“
Tick-borne encephalitis (TBE) (Method Enzymgnost)	U/L	<6.98	≥10.32		
Tick-borne encephalitis (TBE) (Method VIE-ELISA)	VIEU/ml	<63	≥127		
Rabies	IU/ml	<0.5	≥0.5		
Hepatitis A	IU/L	<20	≥20		A positive result implies immunity. A negative result does not exclude immunity (routine tests not sufficiently sensitive)
Measles	IU/L	<250	≥500		
Rubella	IU/ml	<10	≥20		
Varicella (Method ELISA VZV gp)	IU/L	<50	50-200	>200	Test available in „Laboratoire de vaccinologie des Hôpitaux Universitaires de Genève“
Pertussis	Correlate for protection unknown or available routine tests not sufficiently sensitive				
Poliomyelitis					
Mumps					
Influenza					
Human papillomavirus					
Meningococci					
Yellow fever					

5 Specific procedure for the administration of live vaccinations in case of lack of data from the literature (in analogy with HIV)

If in doubt whether a live vaccine can be administered under immunosuppressive medication, **the specialist** can use the following approach: administer an inactivated vaccine (neo-antigen) and measure the humoral immune response after 4-6 weeks together with the number of CD4 positive cells. If the humoral immune response to the inactivated vaccine is satisfactory and the CD4+ cells are over a specific threshold (200 cells/µl in adults), a live vaccine can be administered (figure 1).

Figure 1: Scheme for the application of a live vaccine when the extent of the immunosuppressive treatment is unclear (in analogy with HIV)



References

[1] Bundesamt für Gesundheit (BAG) und Eidgenössische Kommission für Impffragen (EKIF). Empfehlungen zur Impfung von Empfängerinnen und Empfängern von Blut-Stammzellen. Bull BAG 2012;21:363–70.

[2] Hutfless SM, Weng X, Liu L, Allison J, Herrinton LJ. Mortality by medication use among patients with inflammatory bowel disease, 1996-2003. Gastroenterology 2007;133:1779–86.

[3] Toruner M, Loftus E V, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008;134:929–36.

[4] Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious Infections and Mortality in Association With Therapies for Crohn's Disease: TREAT Registry. Clin Gastroenterol Hepatol 2006;4:621–30.

[5] Stobaugh DJ, Deepak P, Ehrenpreis ED. Hospitalizations for vaccine preventable pneumonias in patients with inflammatory bowel disease: a 6-year analysis of the Nationwide Inpatient Sample. Clin Exp Gastroenterol 2013;6:43–9.

[6] Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2009;3:47–91.

[7] Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of pneumonia among patients with inflammatory bowel disease. Am J Gastroenterol 2013;108:240–8.

[8] Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. J Epidemiol Community Health 2012;66:1177–81.

[9] Chevaux J-B, Nani A, Oussalah A, Venard V, Bensenane M, Belle A, et al. Prevalence of hepatitis B and C and risk factors for nonvaccination in inflammatory bowel disease patients in Northeast France. Inflamm Bowel Dis 2010;16:916–24.

[10] Loras C, Saro C, Gonzalez-Huix F, Mínguez M, Merino O, Gisbert JP, et al. Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. Am J Gastroenterol 2009;104:57–63.

[11] Biancone L, Pavia M, Del Vecchio Blanco G, D'Incà R, Castiglione F, De Nigris F, et al. Hepatitis B and C virus infection in Crohn's disease. Inflamm Bowel Dis 2001;7:287–94.

[12] Michel M, Duvoux C, Hezode C, et al. Fulminant hepatitis after infliximab in a patien... [J Rheumatol. 2003] - PubMed - NCBI n.d.

[13] Millonig G, Kern M, Ludwiczek O. Subfulminant hepatitis B after inflixi... [World J Gastroenterol. 2006] - PubMed - NCBI n.d.

[14] Colbert C, Chavarria A, Berkelhammer C. Fulminant hepatic failure in chronic hepat... [Inflamm Bowel Dis. 2007] - PubMed - NCBI n.d.

[15] Esteve M, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. Gut 2004;53:1363–5.

[16] Morisco F, Castiglione F, Rispo A, Stroffolini T, Sansone S, Vitale R, et al. Effect of immunosuppressive therapy on patients with inflammatory bowel diseases and hepatitis B or C virus infection. J Viral Hepat 2013;20:200–8.

[17] Madonia S, Orlando A, Scimeca D, Olivo M, Rossi F, Cottone M. Occult hepatitis B and infliximab-induced HBV reactivation. Inflamm Bowel Dis 2007;13:508–9.

[18] Morisco F, Castiglione F, Rispo A, Stroffolini T, Vitale R, Sansone S, et al. Hepatitis B virus infection and immunosuppressive therapy in patients with inflammatory bowel disease. Dig Liver Dis 2011;43 Suppl 1:S40–8.

[19] López-Serrano P, Pérez-Calle JL, Sánchez-Tembleque MD. Hepatitis B and inflammatory bowel disease: role of antiviral prophylaxis. World J Gastroenterol 2013;19:1342–8.

[20] Chevaux J-B, Bigard M-A, Bensenane M, Oussalah A, Jarlot S, Belle A, et al. Inflammatory bowel disease and hepatitis B and C. Gastroentérologie Clin Biol 2009;33:1082–93.

[21] Horvath J, Raffanti SP. Clinical aspects of the interactions between human immunodeficiency virus and the hepatotropic viruses. Clin Infect Dis 1994;18:339–47.

[22] Kane S, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. Am J Gastroenterol 2008;103:631–6.

[23] Bhatia J, Bratcher J, Korelitz B, Vakher K, Mannor S, Shevchuk M, et al. Abnormalities of uterine cervix in women with inflammatory bowel disease. World J Gastroenterol 2006;12:6167–71.

[24] Singh H, Demers AA, Nugent Z, Mahmud SM, Kliewer E V, Bernstein CN. Risk of cervical abnormalities in women with inflammatory bowel disease: a population-based nested case-control study. Gastroenterology 2009;136:451–8.

[25] Lees CW, Critchley J, Chee N, Beez T, Gailer RE, Williams AR, et al. Lack of association between cervical dysplasia and IBD: a large case-control study. Inflamm Bowel Dis 2009;15:1621–9.

[26] Hutfless S, Fireman B, Kane S, Herrinton LJ. Screening differences and risk of cervical cancer in inflammatory bowel disease. Aliment Pharmacol Ther 2008;28:598–605.

[27] Jess T, Horváth-Puhó E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a danish population-based cohort study. Am J Gastroenterol 2013;108:1869–76.

[28] Leung VS, Nguyen MT, Bush TM. Disseminated primary varicella after initiation of infliximab for Crohn's disease. Am J Gastroenterol 2004;99:2503–4.

[29] Deutsch DE, Olson AD, Kraker S, Dickinson CJ. Overwhelming varicella pneumonia in a patient with Crohn's disease treated with 6-mercaptopurine. J Pediatr Gastroenterol Nutr 1995;20:351–3.

[30] Vergara M, Brullet E, Campo R, Calvet X, Blanch L. [Fulminant infection caused by varicella herpes zoster in patient with Crohn disease undergoing treatment with azathioprine]. Gastroenterol Hepatol 2001;24:47.

[31] Gupta G, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2006;4:1483–90.

[32] Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013;37:420–9.

[33] Naganuma M, Kunisaki R, Yoshimura N, Takeuchi Y, Watanabe M. A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. J Gastroenterol 2013;48:595–600.

[34] Melmed GY, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. Am J Gastroenterol 2006;101:1834–40.

[35] Wasan KS, Coukos J, Farraye FA. Gastroenterologist (GI) Knowledge and Behavior in Vaccinating the Inflammatory Bowel Disease (IBD) Patient. Gastroenterology 2010;138:534.

[36] Yeung JH, Goodman KJ, Fedorak RN. Inadequate knowledge of immunization guidelines: a missed opportunity for preventing infection in immunocompromised IBD patients. Inflamm Bowel Dis 2012;18:34–40.

[37] Crawford NW, Catto-Smith AG, Oliver MR, Cameron DJS, Buttery JP. An Australian audit of vaccination status in children and adolescents with inflammatory bowel disease. BMC Gastroenterol 2011;11:87.

[38] Teich N, Klugmann T, Tiedemann A, Holler B, Mössner J, Liebetrau A, et al. Vaccination coverage in immunosuppressed patients: results of a regional health services research study. Dtsch Arztebl Int 2011;108:105–11.

[39] Yun HS, Min YW, Chang DK, Rhee P-L, Kim JJ, Rhee JC, et al. Factors associated with vaccination among inflammatory bowel disease patients in Korea. Korean J Gastroenterol 2013;61:203–8.

[40] Narula N, Dhillon AS, Chauhan U, Marshall JK. An audit of influenza vaccination status in adults with inflammatory bowel disease. Can J Gastroenterol 2012;26:593–6.

[41] Wilckens V, Kannengiesser K, Hoxhold K, Frenkel C, Kucharzik T, Maaser C. The immunization status of patients with IBD is alarmingly poor before the introduction of specific guidelines. Scand J Gastroenterol 2011;46:855–61.

[42] Banaszkiewicz A, Klincewicz B, Lazowska-Przeorek I, Grzybowska-Chlebowczyk U, Kąkol P, Mytyk A, et al. Influenza vaccination coverage in children with inflammatory bowel disease. Influenza Other Respi Viruses 2014.

[43] Hanna M, Poullis A. Sub-optimal H1N1 vaccine uptake by immunocompromised inflammatory bowel disease patients. Clin Med 2011;11:301.

[44] Parker S, Chambers White L, Spangler C, Rosenblum J, Sweeney S, Homan E, et al. A quality improvement project significantly increased the vaccination rate for immunosuppressed patients with IBD. Inflamm Bowel Dis 2013;19:1809–14.

[45] Group GIS. [Adherence to the H1N1 vaccination recommendation in patients with Crohn's disease or ulcerative colitis]. Dtsch Med Wochenschr 2011;136:939–43.

[46] Al-Bawardy B, Fine S, Lafond J, Doran A, Borum ML. Missing cohort: Inflammatory bowel disease patients at increased risk for cervical dysplasia may be undervaccinated for HPV. Inflamm Bowel Dis 2012;18:797.

[47] Kopylov U, Levin A, Mendelson E, Dovrat S, Book M, Eliakim R, et al. Prior varicella zoster virus exposure in IBD patients treated by anti-TNFs and other immunomodulators: implications for serological testing and vaccination guidelines. Aliment Pharmacol Ther 2012;36:145–50.

[48] Lu Y, Jacobson DL, Ashworth LA, Grand RJ, Meyer AL, McNeal MM, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. Am J Gastroenterol 2009;104:444–53.

[49] Gelinck LB, van der Bijl AE, Beyer WE, Visser LG, Huizinga TW, van Hogezand RA, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis 2008;67:713–6.

[50] Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2007;5:851–6.

[51] Benchimol EI, Hawken S, Kwong JC, Wilson K. Safety and utilization of influenza immunization in children with inflammatory bowel disease. Pediatrics 2013;131:e1811–20.

[52] deBruyn JCC, Hilsden R, Fonseca K, Russell ML, Kaplan GG, Vanderkooi O, et al. Immunogenicity and safety of influenza vaccination in children with inflammatory bowel disease. Inflamm Bowel Dis 2012;18:25–33.

[53] Romanowska M, Banaszkiewicz A, Nowak I, Radzikowski A, Brydak LB. Immunization against influenza during the 2005/2006 epidemic season and the humoral response in children with diagnosed inflammatory bowel disease (IBD). Med Sci Monit 2010;16:CR433–9.

[54] Hagihara Y, Ohfuji S, Watanabe K, Yamagami H, Fukushima W, Maeda K, et al. Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. J Crohns Colitis 2014;8:223–33.

[55] Launay O, Abitbol V, Krivine A, Slama L Ben, Bourreille A, Dupas JL, et al. Immunogenicity and Safety of Influenza Vaccine in Inflammatory Bowel Disease Patients Treated or not with Immunomodulators and/or Biologics: A Two-year Prospective Study. J Crohns Colitis 2015;9:1096–107.

[56] deBruyn J, Fonseca K, Ghosh S, Panaccione R, Gasia MF, Ueno A, et al. Immunogenicity of Influenza Vaccine for Patients with Inflammatory Bowel Disease on Maintenance Infliximab Therapy: A Randomized Trial. Inflamm Bowel Dis 2016;22:638–47.

[57] Matsumoto H, Ohfuji S, Watanabe K, Yamagami H, Fukushima W, Maeda K, et al. Booster influenza vaccination does not improve immune response in adult inflammatory bowel disease patients treated with immunosuppressives: a randomized controlled trial. J Gastroenterol 2015;50:876–86.

[58] Bálint A, Farkas K, Éva P-K, Terhes G, Urbán E, Szucs M, et al. Antibody and cell-mediated immune response to whole virion and split virion influenza vaccine in patients with inflammatory bowel disease on maintenance immunosuppressive and biological therapy. Scand J Gastroenterol 2015;50:174–81.

[59] Rahier J-F, Papay P, Salleron J, Sebastian S, Marzo M, Peyrin-Biroulet L, et al. H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy. Gut 2011;60:456–62.

[60] Andrisani G, Frasca D, Romero M, Armuzzi A, Felice C, Marzo M, et al. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF-α agents: effects of combined therapy with immunosuppressants. J Crohns Colitis 2013;7:301–7.

[61] Molnár T, Farkas K, Jankovics I, Melles M, Nagy F, Szepes Z, et al. Appropriate response to influenza A (H1N1) virus vaccination in patients with inflammatory bowel disease on maintenance immunomodulator and/or biological therapy. Am J Gastroenterol 2011;106:370–2.

[62] Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. Gut 2012;61:385–91.

[63] Frasca D, Andrisani G, Diaz A, Felice C, Guidi L, Blomberg BB. AID in aging and autoimmune diseases. Autoimmunity 2013;46:168–75.

[64] Gelinck LB, van der Bijl AE, Visser LG, Huizinga TW, van Hogezand RA, Rijkers GT, et al. Synergistic immunosuppressive effect of anti-TNF combined with methotrexate on antibody responses to the 23 valent pneumococcal polysaccharide vaccine. Vaccine 2008;26:3528–33.

[65] Melmed GY, Agarwal N, Frenck RW, Ippoliti AF, Ibanez P, Papadakis KA, et al. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:148–54.

[66] Fiorino G, Peyrin-Biroulet L, Naccarato P, Szabò H, Sociale OR, Vetrano S, et al. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis

2012;18:1042–7.

[67] Lee CK, Kim H-S, Ye BD, Lee K-M, Kim YS, Rhee SY, et al. Patients with Crohn's disease on anti-tumor necrosis factor therapy are at significant risk of inadequate response to the 23-valent pneumococcal polysaccharide vaccine. J Crohns Colitis 2014;8:384–91.

[68] Banaszkiewicz A, Targońska B, Kowalska-Duplaga K, Karolewska-Bochenek K, Sieczkowska A, Gawrońska A, et al. Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine in Pediatric Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;21:1607–14.

[69] Bundesamt für Gesundheit (BAG). Pneumokokkenimpfung: Empfehlungen zur Verhinderung von invasiven Pneumokokkenerkrankungen bei Risikogruppen. Bull BAG 2014;8:129–41.

[70] Nielsen HJ, Mortensen T, Holten-Andersen M, Brünner N, Sørensen S, Rask-Madsen J. Increased levels of specific leukocyte- and platelet-derived substances during normal anti-tetanus antibody synthesis in patients with inactive Crohn disease. Scand J Gastroenterol 2001;36:265–9.

[71] Stevens R, Oliver M, Brogan M, Heiserodt J, Targan S. Defective generation of tetanus-specific antibody-producing B cells after in vivo immunization of Crohn's disease and ulcerative colitis patients. Gastroenterology 1985;88:1860–6.

[72] Brogan MD, Shanahan F, Oliver M, Stevens RH, Targan SR. Defective memory B cell formation in patients with inflammatory bowel disease following tetanus toxoid booster immunization. J Clin Lab Immunol 1987;24:69–74.

[73] Dezfoli S, Horton HA, Thepyasuwan N, Berel D, Targan SR, Vasiliauskas EA, et al. Combined Immunosuppression Impairs Immunogenicity to Tetanus and Pertussis Vaccination Among Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;21:1754–60.

[74] Dotan I, Werner L, Vigodman S, Agarwal S, Pfeffer J, Horowitz N, et al. Normal response to vaccines in inflammatory bowel disease patients treated with thiopurines. Inflamm Bowel Dis 2012;18:261–8.

[75] Urganci N, Kalyoncu D. Immunogenecity of hepatitis A and B vaccination in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013;56:412–5.

[76] Altunöz ME, Senateş E, Yeşil A, Calhan T, Ovünç AOK. Patients with inflammatory bowel disease have a lower response rate to HBV vaccination compared to controls. Dig Dis Sci 2012;57:1039–44.

[77] Sempere L, Almenta I, Barrenengoa J, Gutiérrez A, Villanueva CO, de-Madaria E, et al. Factors predicting response to hepatitis B vaccination in patients with inflammatory bowel disease. Vaccine 2013;31:3065–71.

[78] Belle A, Baumann C, Bigard M-A, Zallot C, Gizard E, Guéant J-L, et al. Impact of immunosuppressive therapy on hepatitis B vaccination in inflammatory bowel diseases. Eur J Gastroenterol Hepatol 2015;27:877–81.

[79] Andrade P, Santos-Antunes J, Rodrigues S, Lopes S, Macedo G. Treatment with infliximab or azathioprine negatively impact the efficacy of hepatitis B vaccine in inflammatory bowel disease patients. J Gastroenterol Hepatol 2015;30:1591–5.

[80] Cekic C, Aslan F, Krc A, Gümüs ZZ, Arabul M, Yüksel ES, et al. Evaluation of factors associated with response to hepatitis B vaccination in patients with inflammatory bowel disease. Medicine (Baltimore) 2015;94:e940.

[81] Gisbert JP, Menchén L, García-Sánchez V, Marín I, Villagrasa JR, Chaparro M. Comparison of the effectiveness of two protocols for vaccination (standard and double dosage) against hepatitis B virus in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2012;35:1379–85.

[82] Gisbert JP, Villagrasa JR, Rodríguez-Nogueiras A, Chaparro M. Efficacy of hepatitis B vaccination and revaccination and factors impacting on response in patients with inflammatory bowel disease. Am J Gastroenterol 2012;107:1460–6.

[83] Gisbert JP, Villagrasa JR, Rodríguez-Nogueiras A, Chaparro M. Kinetics of anti-hepatitis B surface antigen titers after hepatitis B vaccination in patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19:554–8.

[84] Chaparro M, Gordillo J, Domènech E, Esteve M, Barreiro-de Acosta M, Villoria A, et al. Prospective, randomized clinical trial comparing the efficacy of two vaccines against hepatitis B virus (HBV) in inflammatory bowel disease (IBD) patients. J Crohn's Colitis 2015;9:299.

[85] Moses J, Alkhouri N, Shannon A, Raig K, Lopez R, Danziger-Isakov L, et al. Hepatitis B immunity and response to booster vaccination in children with inflammatory bowel disease treated with infliximab. Am J Gastroenterol 2012;107:133–8.

[86] Cossio-Gil Y, Martínez-Gómez X, Campins-Martí M, Rodrigo-Pendás JÁ, Borruel-Sainz N, Rodríguez-Frías F, et al. Immunogenicity of hepatitis B vaccine in patients with inflammatory bowel disease and the benefits of revaccination. J Gastroenterol Hepatol 2015;30:92–8.

[87] Park S-D, Markowitz J, Pettei M, Weinstein T, Sison CP, Swiss SR, et al. Failure to respond to hepatitis B vaccine in

children with celiac disease. J Pediatr Gastroenterol Nutr 2007;44:431–5.

[88] Agostoni CV, Boccazzi A, Pontari S, Bedogni G, Prampolini L, Garotta M, et al. Inadequate seroconversion rates in celiac disease after 3 doses of hepatitis B vaccine, administered at 3,5 and 11 months of life. J Pediatr Infect Dis 2011:173–6.

[89] Balamtekın N, Uslu N, Baysoy G, Saltik-Temızel I, Demır H, Yüce A. Responsiveness of children with celiac disease to different hepatitis B vaccination protocols. Turk J Gastroenterol 2011;22:27–31.

[90] Ertekin V, Tosun MS, Selimoglu MA. Is there need for a new hepatitıs B vaccine schedule for children with celiac disease? Hepat Mon 2011;11:634–7.

[91] Ahishali E, Boztas G, Akyuz F, Ibrisim D, Poturoglu S, Pinarbasi B, et al. Response to hepatitis B vaccination in patients with celiac disease. Dig Dis Sci 2008;53:2156–9.

[92] Zanoni G, Contreas G, Valletta E, Gabrielli O, Mengoli C, Veneri D. Normal or defective immune response to Hepatitis B vaccine in patients with diabetes and celiac disease. Hum Vaccin Immunother 2015;11:58–62.

[93] Leonardi S, Longo R, Cotugno M, Tardino L, Spina M, Lionetti E, et al. [Vaccination and celiac disease: results of a retrospective study]. Minerva Pediatr 2011;63:363–7.

[94] Leonardi S, Praticò AD, Lionetti E, Spina M, Vitaliti G, La Rosa M. Intramuscular vs intradermal route for hepatitis B booster vaccine in celiac children. World J Gastroenterol 2012;18:5729–33.

[95] Walkiewicz-Jedrzejczak D, Egberg M, Nelson C, Eickoff J. Evaluation of the response to vaccination with hepatitis B vaccine in pediatric patients diagnosed with celiac disease. SAGE Open Med 2014;2:2050312114563346.

[96] Ertem D, Gonen I, Tanidir C, Ugras M, Yildiz A, Pehlivanoğlu E, et al. The response to hepatitis B vaccine: does it differ in celiac disease? Eur J Gastroenterol Hepatol 2010;22:787–93.

[97] Nemes E, Lefler E, Szegedi L, Kapitány A, Kovács JB, Balogh M, et al. Gluten intake interferes with the humoral immune response to recombinant hepatitis B vaccine in patients with celiac disease. Pediatrics 2008;121:e1570–6.

[98] Zingone F, Morisco F, Zanetti A, Romanò L, Portella G, Capone P, et al. Long-term antibody persistence and immune memory to hepatitis B virus in adult celiac patients vaccinated as adolescents. Vaccine 2011;29:1005–8.

[99] Zingone F, Capone P, Tortora R, Rispo A, Morisco F, Caporaso N, et al. Role of gluten intake at the time of hepatitis B virus vaccination in the immune response of celiac patients. Clin Vaccine Immunol 2013;20:660–2.

[100] Urganci N, Kalyoncu D. Response to hepatitis A and B vaccination in pediatric patients with celiac disease. J Pediatr Gastroenterol Nutr 2013;56:408–11.

[101] Wörns MA, Teufel A, Kanzler S, Shrestha A, Victor A, Otto G, et al. Incidence of HAV and HBV infections and vaccination rates in patients with autoimmune liver diseases. Am J Gastroenterol 2008;103:138–46.

[102] Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis 2014.

[103] EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–85.

[104] Radzikowski A, Banaszkiewicz A, Łazowska-Przeorek I, Grzybowska-Chlebowczyk U, Woś H, Pytrus T, et al. Immunogenecity of hepatitis A vaccine in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2011;17:1117–24.

[105] Moses J, Alkhouri N, Shannon A, Feldstein A, Carter-Kent C. Response to hepatitis A vaccine in children with inflammatory bowel disease receiving infliximab. Inflamm Bowel Dis 2011;17:E160.

[106] Park SH, Yang S-K, Park S-K, Kim JW, Yang D-H, Jung KW, et al. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. Inflamm Bowel Dis 2014;20:69–74.

[107] Jacobson DL, Bousvaros A, Ashworth L, Carey R, Shrier LA, Burchett SK, et al. Immunogenicity and tolerability to human papillomavirus-like particle vaccine in girls and young women with inflammatory bowel disease. Inflamm Bowel Dis 2013;19:1441–9.

[108] Tung J, Kane S, Enders FT, Jeavons EN. Hepatitis B vaccine in IBD. Am J Gastroenterol 2013;108:620–1.

[109] Zhang J, Delzell E, Xie F, Baddley JW, Spettell C, McMahan RM, et al. The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. Arthritis Res Ther 2011;13:R174.

[110] Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA

2012;308:43–9.

[111] Prevention of Herpes Zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57(RR-5): 1-30. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm (last accessed 12.11.2017)

[112] Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44–100.

[113] Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol (Hoboken, NJ) 2015;68:1–26.

[114] Swissmedic. Product information Zostavax. May 2017. http://www.swissmedicinfo.ch (last accessed 01.11.2017)

[115] Lu Y, Bousvaros A. Varicella vaccination in children with inflammatory bowel disease receiving immunosuppressive therapy. J Pediatr Gastroenterol Nutr 2010;50:562–5.

[116] Posfay-Barbe KM, Pittet LF, Sottas C, Grillet S, Wildhaber BE, Rodriguez M, et al. Varicella-zoster immunization in pediatric liver transplant recipients: safe and immunogenic. Am J Transplant 2012;12:2974–85.

[117] Eperon G, Vaudaux B. [Immunization for the immunosuppressed traveler]. Rev Med Suisse 2013;9:970–8.

[118] Szenborn L, Kacprzak-Bergman I, Zaleska I, Gruszka J. [Measles antibodies concentration in vaccinated children and adolescents with autoimmune hepatitis]. Pol Merkur Lekarski 2004;17:326–30.

[119] Plotkin SA, Orenstein WA, Offit PA. Vaccines. 6th ed. Philadelphia, Pennsylvania: Elsevier Saunders; 2012.

[120] Roukens AH, Vossen AC, van Dissel JT, Visser LG. Reduced intradermal test dose of yellow fever vaccine induces protective immunity in individuals with egg allergy. Vaccine 2009;27:2408–9.

[121] Enkai S, Miyakawa T, Kondou S, Kawasaki K, Seki M. [A case of disseminated BCG infection found during treatment of an infant with Crohn's disease]. Kekkaku 2009;84:597–603.

[122] Wyant T, Leach T, Sankoh S, Wang Y, Paolino J, Pasetti MF, et al. Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results. Gut 2014.