

Vaccination for Inflammatory Bowel Disease Patients

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ABSTRACT

Inflammatory bowel disease (IBD) patients have an increased rate of some vaccine-preventable infection during their course of disease. However, the coverage of vaccination is still low. Many physicians often do not feel comfortable or confidence offering vaccination to IBD patients. Vaccine effectiveness can be altered by the immune dysregulation condition and immunosuppressive therapy that IBD patients use. There are also some concerns about IBD flare after vaccination and potential adverse events related to live vaccines. Nonetheless, offering vaccines and obtaining vaccination history is necessary for health care maintenance of IBD patients, especially those using immunosuppressive therapy.

Keywords: *vaccine, inflammatory bowel disease, vaccination, Crohn's disease, ulcerative colitis*

ABSTRAK

Pasien dengan inflammatory bowel disease (IBD) mempunyai risiko tinggi beberapa infeksi yang dapat dicegah dengan vaksin selama perjalanan penyakitnya. Namun demikian, cakupan vaksinasi umumnya masih kurang. Acapkali dokter tidak merasa nyaman atau yakin untuk menawarkan vaksinasi pada pasien dengan IBD. Efektivitas vaksin dapat berubah akibat kondisi disregulasi imun dan terapi immunosupresif yang digunakan pasien dengan IBD. Terdapat juga kekhawatiran terjadinya perburukan penyakit IBD setelah vaksinasi dan kemungkinan efek samping terhadap vaksin hidup. Namun demikian, menawarkan vaksin dan mendapatkan riwayat vaksinasi penting dalam mempertahankan kesehatan pasien IBD, terutama yang menggunakan terapi immunosupresif.

Keywords: *vaksin, inflammatory bowel disease, vaksinasi, penyakit Crohn, kolitis ulseratif*

INTRODUCTION

Inflammatory bowel disease (IBD) is immune-mediated inflammatory disease that refers to two main subtype, ulcerative colitis (UC) and Crohn's disease (CD). A cornerstone for IBD therapy are immunosuppressive therapy. IBD patients are at increased risk for many infections as a consequence of the disease and amplified by their immunosuppressive

treatments.¹ Some of the infections are vaccine-preventable diseases that we are going to discuss in this review.

RATE OF VACCINATION IN IBD PATIENTS

Historically, many countries reported that patients with IBD had lower rates of vaccination than the general population. Lack of knowledge and concern about

vaccine safety in IBD patients using immunosuppressive therapy were some of the reasons. Recent study before COVID-19 pandemic showed improving vaccination rate in IBD patients, and high uptake of COVID-19 vaccination in London.^{2,3} However, global data for vaccine uptake is still not available.

RISK OF VACCINE-PREVENTABLE DISEASE IN IBD PATIENTS

IBD patients are at increased risk for many vaccine-preventable diseases (VBD), such as influenza, pneumococcal, and herpes zoster compared to non-IBD population. Table 1 resume the risk of VBD in IBD patients. Moreover, a recent nationwide study in US revealed that VPDs represent an important cause of infectious disease-related admissions in patients with IBD. Those hospitalized for VPD have higher morbidity compared with patients with IBD and non-vaccine preventable infections.⁴

RISK OF RELAPSE AND ADVERSE EVENTS AFTER VACCINATION

Evidence on the safety of various vaccines in IBD patients is still limited.¹⁶ There is concern that COVID-19 vaccination would trigger IBD exacerbation. Immune activation triggered by COVID-19 vaccination may cause IBD exacerbations through an immune-mediated dysregulation of the mucosal immune system. Other than COVID-19 vaccine, there is no convicting evidence that vaccination will exacerbate IBD activity.¹⁷ Individuals with IBD were excluded from safety and efficacy phase III vaccine trials, as well as those being treated with immunosuppressive therapies.

Study by Cannatelli et al, in patients with IBD showed that the rate of reported adverse events (AEs) after COVID-19 vaccination are similar to the general population.¹⁸ About 81.4% patients were on remission. The patients got three different COVID-19

vaccines: BNT162b2 (Pfizer) 65.6%, RNA-1273 (Moderna) 30.7%, and Vaxzevria (AstraZeneca) 3.7%. AEs were reported by 46.7% patients. All cases were mild and self-limiting, and only one patient needed hospitalisation Systemic AE after the first dose was malaise (16.4%), headache (12.9%) and asthenia (10.5%). After the second dose, there were more systemic AEs, such as malaise (26.4%), fever (20.7%) and headache (19.7%). About 45.1% patients experienced pain at the site of injection after the first dose and 38.1% after second dose. Gastrointestinal symptoms were reported by 15.6% of patients at a mean of 3 days after the vaccine, with a minimum of 1 day and a maximum of 15 days. AEs are more common among younger patients, female, and with history of previous COVID-19 infection. Azathioprine was inversely correlated to the presence of any AEs. Patients with older age and disease remission showed lower risk of gastrointestinal symptoms after COVID-19 vaccination.

Another study by Garrido et al in IBD patients on biologic therapy [anti-tumour necrosis factor (TNF), ustekinumab and vedolizumab] showed that majority of AEs after COVID-19 vaccination were mild and lasted only a few days.¹⁹ Only four (1.7%) patients had IBD exacerbation after the vaccine. No serious AEs were reported and no patient was hospitalized. AEs was higher among patients younger than 50 years. This study included 239 patients vaccinated with PfizerBioNTech (59%), Moderna (20.5%), Janssen (14.2%), and AstraZeneca (6.3%). Biologic agents were 75.4%, 13.0% and 11.6%, respectively.

A study comparing 941 IBD patients who completed two doses of BNT162b2 with 1196 unvaccinated IBD controls also showed that no increased risk of severe disease flare-ups. No significant difference in unplanned IBD hospitalisation, all-cause hospitalisation or 28-day emergency department (ED) attendance.²⁰ Another study with BNT162b2 vaccine by Lev-Tzion, et al showed that no significant difference in the risk of

Table 1. Risk of vaccine-preventable disease in IBD patients

Infection	Risk in IBD patients	Author(s)
COVID-19	Do not appear to have higher risk	Wetwittayakhleng et al ⁵
Influenza	HR = 1.54 (95% CI: 1.49-1.63), and higher risk of hospitalization	Tinsley et al ⁶
Pneumococcal pneumonia	HR = 1.54 (95% CI: 1.49-1.60)	Long, et al. ⁷
Hepatitis B	Studies in Asia and endemic countries showed varied result. He, et al and Kim et al showed no significant difference, Huang et al showed higher prevalence in IBD. ^{8,9,10}	He et al ⁸ , Kim et al ⁹ , Huang et al ¹⁰
Herpes zoster (HZV)	HR = 1.42 (95% CI: 1.27-1.60) HR = 1.49 (95% CI: 1.42-1.57)	Tsai et al ¹¹ , Long et al ¹²
Meningococcal infection	No studies available, only case reports of functional hyposplenism in IBD patient and Crohn's disease patient after anti-TNF therapy	Shah and Lettieri ¹³ , Majumder and Kumar ¹⁴
Human papillomavirus (HPV)	Risk of developing cervical high-grade dysplasia/cancer OR = 1.34 (95% CI: 1.23-1.46)	Allegretti et al ¹⁵

exacerbation in the vaccinated patients compared with unvaccinated patients (29% vs. 26%, $p = 0.3$).¹⁷ Median follow-up were 14 weeks.

TIMING FOR VACCINATION

There is currently a scarcity of data on vaccination immunogenicity in IBD patients.¹⁶ Patients on low dose thiopurine or aminosallylates monotherapy can mount similar vaccine responses as healthy controls. According to Center for Disease Control (CDC), patients with IBD are considered severely immunocompromised if on: (1) prednisone ≥ 20 mg daily for at least 2 weeks; (2) thiopurines (≥ 1.5 mg/kg of 6-mercaptopurine or ≥ 3 mg/kg of azathioprine); (3) methotrexate ≥ 0.4 mg/kg/week.²¹ Studies on influenza, pneumococcal pneumonia, hepatitis B, and hepatitis A vaccines showed that IBD patients on anti-TNF drugs had reduced seroconversion rates compared to controls. The immunogenicity is lower in patients treated with thiopurines or methotrexate, alone or in combination with anti-TNF.^{22,23} New suppressive agent, vedolimumab, selectively inhibits the migration of memory T cells into the gastrointestinal mucosa. A small pilot study suggest that this drug has no effect on vaccine response.²⁴

Physicians should ask the patients about the vaccination history and think about the next vaccination plan at the time of IBD diagnosis. Whenever possible, it is recommended that vaccination is given before the immunosuppressive therapy. The recommended timing before initiating immunosuppressive therapy is at least 14 days for inactivated vaccines to get optimal immunogenicity, and at least 4 weeks for live vaccines. Live vaccines should not be administered for at least 3 months after immunosuppressive therapy.²¹ Immunogenicity of vaccine can be reduced significantly in IBD patients on high-dose systemic corticosteroid therapy. It is recommended that vaccine is administered after reducing the corticosteroids used to the lowest possible dose. However, IBD medication should not be delayed or stopped for vaccination. On the other hand, vaccination should not be delayed due to IBD medications. IBD patients being treated with biologic agents can be vaccinated irrespective of the timing of drug administration and dosage of the last biologic agent received. It is recommended that vaccination is given on a different day than the administration of the biological agent to monitor for adverse effects.²⁵

NON-LIVE VACCINES

COVID-19 vaccine

SARS-CoV-2 binds to their target cells via angiotensin-converting enzyme 2 (ACE2). ACE2 receptor overexpression in IBD patients may make patients more susceptible to COVID-19 infection across the intestinal mucosal barrier and increase the risk of cytokine release syndrome associated with lung injury and its severe consequences. Current data suggest that IBD patients do not appear to be at higher risk for COVID-19 infection than the general population. However, COVID-19 mortality in IBD patients shows a much broader range of variation (0% to 20.0%).¹⁵ A previous study also mentioned that the risk of severe COVID-19 was high in patients with UC and those treated with steroids or 5-aminosalicylate.²⁶

Similar to recommendations for the general population, COVID-19 vaccination is strongly recommended for IBD patients. The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) recommends that all IBD patients to receive non-live COVID-19 vaccination, while live vector or clonogenic vaccines that may be approved in the future are contraindicated.²⁵ Despite this recommendation, more than one-third of IBD patients expressed hesitation about getting COVID-19 vaccine, with vaccine safety and effectiveness being the most common reasons.²⁷

A meta-analysis also showed that the COVID-19 vaccine was effective and well tolerated in preventing COVID-19 infection in IBD patients. About 98% of patients had seroconversion after receiving two doses of COVID-19 vaccine, and the effect of biologics on vaccination was limited. The incidence of COVID-19 infection after COVID-19 vaccination was comparable between IBD and non-IBD patients and was higher in unvaccinated IBD patients than in vaccinated IBD patients.²⁶

A previous study with mRNA vaccines demonstrated that after receiving 2 doses of COVID-19 mRNA vaccination, there were significantly lesser proportion of patients with immune-mediated inflammatory diseases (IMIDs) (82.3%) that achieved a serological response compared with controls. Moreover, serological response after 1 dose (73.2%) appears to be lower than the reported rates in healthy controls.²⁸ Therefore, it is recommended that IMID patients should be fully immunized immediately. The weaker serological response to the 2-dose vaccination strategy for mRNA-

based vaccines also suggests that patients should be considered for a third dose of vaccine.^{28,29}

There is growing concern about whether IBD drugs will affect the effectiveness of the COVID-19 vaccine. A study showed that pooled seroconversion rates were numerically lower for patients receiving steroids and the association of anti-TNF with the immunomodulator. The patients receiving vedolizumab, ustekinumab, and JAK inhibitors were associated with good seroconversion rates after full immunization. In addition, patients receiving anti-TNF agents showed lower titers and the early decline in titers after COVID-19 vaccination. Interestingly, a study by Jena, et al did not show evidence of a reduction in seroconversion when the patient receive a combination of anti-TNF and an immunomodulator compared with receiving only anti-TNF.³⁰ A result of large cohort study on IBD in UK (impact of biologic therapy on COVID-19 infection and immunity, CLARITY) showed that patients receiving infliximab, and further in those treated in combination with anti-TNF drugs and immunomodulators shows less serologic response to COVID-19 vaccination.³¹

Despite the effects of medication on COVID-19 vaccination, patients with IBD who are treated with immunosuppressants are at increased risk of severe COVID-19, although studies have shown variety of results. Therefore, the recommendation of COVID-19 vaccination is reasonable to prevent severe cases of COVID-19 in IBD patients receiving immunotherapy. are being treated with high-dose systemic corticosteroids. Korean Association for the Study of the Intestinal Diseases (KASID) recommended the COVID-19 vaccine be administered after reducing the amount of corticosteroid used to the lowest possible dose.²⁵

A previous study showed that there was a high acceptance rate and a good safety profile for COVID-19 vaccination in IBD patients treated with biologic treatment. The adverse effects following vaccination are frequent but generally mild and transient. The two most common symptoms were local reaction at the

injection site and fatigue. Most AEs were mild and last only a few days. Only 1.7% of patients had an exacerbation of IBD after vaccination and no serious AEs were reported and no patients were hospitalized.¹⁹ In another study, the rates of adverse events, serious adverse events, and death after COVID-19 vaccination were 69%, 3%, and 0%, respectively.²⁶

Close observation should be conducted after COVID-19 vaccination due to the high risk of venous thromboembolism in IBD patients during active disease. However, there is no evidence that IBD patients have a higher risk of vaccine-induced thrombosis than the general population. Therefore, IBD patients should have the same level of caution after vaccination as the general population.²⁵

The Adult Immunization Task Force of the Indonesian Society of Internal Medicine at the end of 2021 has released recommendations for COVID-19 vaccine for moderate-severe immunocompromised patients, as shown in Table 2.³²

Influenza Vaccine

Influenza vaccine is highly recommended for IBD patients due to the higher risk of influenza compared to the overall population. Patients with IBD who are receiving immunomodulating treatment are at even higher risk for these infections.³³

It has been shown that the influenza vaccine gives high seroprotection level in adult patients with IBD.³³ It was presumed that IBD patients who had low seroprotective levels of antibody titer were susceptible to influenza infection due to high prevalence of influenza infection in subjects without seroprotective levels of antibody titer.²² In addition, it is important to note that seroprotection could decreased if the IBD patients receiving anti-TNF drugs or high-dose systemic corticosteroid.^{22,33}

It is important to remember that even the influenza virus can cause morbidity and mortality in young IBD patients.³⁴ Moreover, immunosuppressive therapy for IBD may further contribute to altered immune systems that increase the risk of these

Table 2. Recommendation for COVID-19 for moderate-severe immunocompromised patients in Indonesia

Type	Vaccine	Recommendation
Inactivated	Coronovac (Sinovac)	Same with others. No data on 3 rd dose for immunocompromised patients
	BBIBP (Sinopharm)	Same with others. No data on 3 rd dose for immunocompromised patients
mRNA	bNT162b2 (Pfizer-BionTech)	3 doses (3 rd dose: 28 days after 2 nd dose)
	mRNA-1273 (Moderna)	3 doses (3 rd dose: 28 days after 2 nd dose)
Viral vector	ChAdOx1 (Astra Zeneca)	Same with others. No data on 3 rd dose for immunocompromised patients
	Sputnik V (Gamaleya)	Same with others. No data on 3 rd dose for immunocompromised patients
	JNJ-78436735 (J&J)	1 dose. No data on 2 nd dose for immunocompromised patients
Subunit	NVX-CoV2372 (Novavax)	Same with others. No data on 3 rd dose for immunocompromised patients

vaccine preventable infections.³³ Patients undergoing immunosuppressive therapy with agents such as azathioprine, 6-mercaptopurine, and anti-TNF might have more severe influenza symptoms than those who have not received immunosuppressive therapy. Considering the benefit of influenza vaccine, IBD patients should receive an annual influenza vaccine, typically the inactivated form.²¹

Pneumococcal Vaccine

Compared to the general population, patients with IBD have a higher chance of acquiring pneumococcal pneumonia.⁷ The use of immunosuppressive therapy increased the risk of severe pneumococcal disease (SPD) in veterans with IBD, according to a study of 1798 cases of SPD in veterans with IBD. When compared to no vaccination, receiving PCV13 alone or in combination with PPSV23 predicted a 5-fold lower risk of SPD.³⁵

Patients should be vaccinated as soon as possible after being diagnosed with IBD, particularly before starting immunosuppression, to avoid a weakened immune vaccination response. Invasive pneumococcal disease was more common in nearly 75,000 IBD patients in recent Danish cohort research. The risk was especially high before and after the IBD diagnosis, implying that the rise in risk is linked to general changes in IBD patients' immune responses.^{36,37}

Melmed et al. found that only 9% of 169 IBD patients were immunized against pneumococcal illness in a study of 169 participants.³⁸ Furthermore, immune response rates were similar in people with IBD who were not on immunosuppressive therapy (80%) and in age-matched healthy controls (85%), but lower in patients receiving combination immunosuppressive therapy (45%).^{38,39}

According to previous studies, anti-TNF medication, alone or in combination with azathioprine, inhibits the response to pneumococcal immunization in individuals with IBD.⁴⁰ Meanwhile, a recent meta-analysis found that the rate of seroconversion after pneumococcal immunization was considerably lower in individuals receiving anti-TNF mono- or combination therapy.⁴¹ Nevertheless, regardless of the baseline treatment, PCV13 injection was highly immunogenic and well-tolerated, and it should be advocated in all individuals with IBD.⁴²

Currently, there are two pneumococcal vaccines: the pneumococcal conjugate vaccine PCV-13 and the pneumococcal polysaccharide PPSV23 vaccine, and

both can be given to patients with IBD regardless of immunosuppression status.

The Adult Immunization Task Force of the Indonesian Society of Internal Medicine recommends vaccinating all people 50 years of age and over with PCV13. If the patient has never received the pneumococcal vaccine, physicians can recommend PCV13 first then add PPSV23 with a gap of at least one year after PCV13 administration. PPSV23 is recommended to be given to all people aged 60 years and over regardless of immune status. If the patient has already received the PPSV23 vaccine, it is recommended to get PCV13 with a gap of at least one year after the administration of PPSV23.³² Physicians should recommend the pneumococcal vaccine to all IBD patients to increase the vaccine uptake.

Hepatitis B Vaccine

There is a high mortality rate associated with the advancement of hepatitis B virus (HBV)-related chronic liver disease in developing countries, including Indonesia.⁴³ Indonesia has a high endemicity of hepatitis B, the second-highest country in Southeast Asia after Myanmar. According to the findings of a study and blood screening of blood donors, 10 Indonesians out of 100 are infected with hepatitis B and C. Hepatitis B infection now affects an estimated 28 million Indonesians.^{44,45} Hepatitis B virus incidence in individuals with IBD in many countries is reported to closely reflecting the general public epidemiologic status.⁴⁶

HBV infection has been reported to cause fulminant or fatal hepatitis in IBD patients due to opportunistic infection or reactivation of HBV, but it is prevented with a vaccine.^{47,48} The nature of the disease, immunosuppressive medications such as biologics and immunomodulators, and procedures such as endoscopy, transfusion, and surgery, which are frequently necessary during treatment, all enhance the risk of infectious disease in patients with IBD.⁴⁸ Patients with IBD are at a higher risk of infection by the hepatitis B virus (HBV) as well as a reactivation of a latent HBV infection.⁴⁹

Previous research, however, has found that HBV vaccine compliance is low in IBD patients.¹⁶ Other authors have also observed low hepatitis B vaccine response rates in patients with IBD, particularly in those on immunosuppressive therapy and with active disease.^{16,50}

Patients newly diagnosed with IBD were found to be susceptible to HBV infection in a Korean study. Non-immunity was common, especially among

patients under the age of 20 and those who had been experiencing symptoms for a longer time before being diagnosed. As a result, individuals newly diagnosed with IBD should be screened for HBV serologic markers and given a thorough vaccination plan.⁵¹ In a study comparing single-dose versus double-dose hepatitis B virus vaccines for primo vaccination in IBD, researchers discovered that older age and treatment with steroids, immunomodulators, or anti-TNF were linked to a lower likelihood of immune response.⁵²

Furthermore, hepatitis B virus (HBV) reactivation is a severe complication of hepatitis B virus infection that causes changes in serum aminotransferase levels, fulminant hepatic failure, and death.⁵³ Nonetheless, due to concerns regarding the risk of HBV reactivation, all patients with IBD should be screened for prior HBV exposure. This should be done as soon as IBD is diagnosed, rather than waiting until the immunosuppressive medication is started.^{16,54}

The hepatitis B vaccines that are used in Indonesia are recombinant vaccines. Monovalent generic HBV vaccine (Bio Farma), Engerix B (GlaxoSmithKline Biologicals), Euvax B (Sanofi Pasteur), and Twinrix (GlaxoSmithKline Biologicals) are administered as a 3-dose series at 0, 1, and 6 months. Twinrix contains recombinant HBsAg and inactive hepatitis A virus.

The Adult Immunization Task Force of the Indonesian Society of Internal Medicine recommends hepatitis B vaccination of all adults without exception, and it is recommended to check HBsAg level first. Particular attention should be paid to high-risk groups: health care workers, drug users, people with multiple sexual partners, immunocompromised conditions, patients with chronic hepatic impairment, and patients with chronic kidney disorders, including those on hemodialysis. Post-vaccination anti-HBs antibody titer examination should be carried out periodically in immunocompromised individuals (booster should be given when the titer is 10 mIU/mL).³²

The hepatitis B vaccination can be safely administered in individuals with IBD utilizing a three-dose immunization schedule.³⁴ Multiple studies have found that immunosuppressed IBD patients have lower rates of HBV vaccine response than healthy controls or non-immunosuppressed IBD patients. Patients on immunomodulators or anti-TNF therapy were less likely to respond than those who were not immunosuppressed, according to a meta-analysis of these studies.^{50,55} As a result, serologic response testing should be done 1 to 3 months after the hepatitis B immunization.

The population of IBD patients has lower rates of HBV vaccination, so immunization initiatives should be supported and implemented effectively.¹⁶ A study of 310 IBD patients in Korea discovered inadequate vaccination uptake rates and low HBV seroprotection rates. This study also shows that physicians' vaccination recommendations and education can help IBD patients get the immunizations they need.⁵⁶

Human Papillomavirus (HPV) Vaccine

The human papillomavirus (HPV) is a common sexually transmitted infection. The vast majority of infections are asymptomatic and transient in nature. However, HPV is the leading cause of cervical cancer, dysplasia, and other premalignant and malignant vaginal, vulvar, and cervix disorders.⁵³

IBD is already considered an immunocompromised condition in and of itself.⁵⁷ Immunosuppression has been demonstrated to cause changes in immunological reconstitution, including dysregulation of the immune system, dysregulation of regulatory T-cell dysfunction, disordered antigen presentation of dendritic cells, and a switch from a Th2 to a Th1 phenotype. All of these processes may impair the immune system's ability to prevent HPV-related malignancies and mount an effective immunological response, resulting in a more aggressive phenotype than individuals who are not immunosuppressed.^{58,59}

The use of immune-altering medicines such as steroids, thiopurines, and biologics can enhance the prevalence of HPV-associated infections and hence potentially HPV-associated malignancies.⁵⁸ A meta-analysis of 77,116 patients indicated that IBD patients using immunosuppressive therapy had a greater incidence of high-grade cervical dysplasia and cancer than the general population.¹⁵ A cohort research also discovered a link between IBD and uterine cervix neoplastic lesions.⁶⁰ Another study discovered that IBD patients have a higher rate of abnormal cervical smears than healthy people. The distinction, however, is limited to patients with IBD who are receiving immunosuppressive medication.⁶¹

The nonavalent HPV vaccine (Gardasil 9, Merck Sharp & Dohme Limited), quadrivalent HPV vaccine (Gardasil, Merck Sharp & Dohme Limited), and bivalent HPV vaccine (Cervarix, GSK) are currently available. The human papillomavirus vaccine is a non-live vaccine aimed at young IBD patients. HPV vaccination is recommended to young patients (through 26 years) in most guidelines.^{23,34,62}

The HPV vaccination was reported to be immunogenic in a limited trial of immunocompromised female IBD patients aged 9-26 years old; however, it is uncertain if older immunocompromised IBD patients will have a similar reaction. After three treatments, 94 percent of the patients had seroconverted to the four HPV subtypes, with just 6 percent remaining seronegative to type HPV-18.^{53,63} This figure was similar to what was described in healthy people. Unfortunately, the study could not offer data on immunogenicity differences across groups receiving various IBD drugs because of the limited sample size.^{63,64}

The Adult Immunization Task Force of the Indonesian Society of Internal Medicine has released recommendations about adult vaccination schedules. It is suggested that three doses of bivalent or quadrivalent HPV vaccine are given for females aged 19-55. The vaccine can be given until 26 years of age in the immunocompromised population. In healthy or immunocompromised populations, it is recommended that three doses of the quadrivalent HPV vaccine are given for men aged 19-26.³²

Meningococcal Vaccine

Meningococcal disease is a rare but severe and life-threatening disease caused by *Neisseria meningitidis*. Meningococcal infection can cause sepsis and meningitis, leading to disability and death. The meningococcal vaccine includes serogroups A, C, W, and Y. There is no specific recommendation regarding the administration of the meningococcal vaccine in IBD patients.⁴

Advisory Committee on Immunization Practice (ACIP) recommends giving the meningococcal vaccine to at-risk individuals, such as students living in dormitories, soldiers, people traveling to certain countries, individuals with asplenia, etc. Patients with IBD are given meningococcal vaccination according to age and other conditions that put them at risk for developing invasive meningococcal disease.^{21,53}

LIVE VACCINES

Varicella and Herpes Zoster Vaccines

Primary varicella-zoster virus (VZV) infection tends to be more severe in older adults (over 50 years of age) than children. In contrast to primary VZV infection, reactivation of VZV tends to occur more frequently in older adults (over 50 years of age) and the

immunocompromised group. Among 20 patients with primary VZV infection reported in IBD patients on immunosuppressant therapy, five reported to be dead. A retrospective cross-sectional study also reported a strong association between hospitalizations due to primary VZV in pediatric IBD patients. The Canadian Association of Gastroenterology explains that the administration of varicella/herpes zoster vaccine can be given for adult patients who are at risk of being infected with varicella and suffering from IBD but are not on immunosuppressive therapy.^{4,65}

Meanwhile, the varicella vaccine is not recommended to give in adult IBD patients who are at risk of varicella infection and are on immunosuppressant treatment. From one study, herpes zoster was associated with mortality in IBD and higher costs with a longer length of stay than IBD alone. It shows the importance of vaccination in IBD patients.^{4,65}

Measles, Mumps, Rubella (MMR) Vaccine

In one systematic review study involving 2,852 patients with IBD on immunosuppressant therapy, when the antibody was compared between treated and untreated patients, the results were inconsistent, with some studies showing decreased serologic response and others not showing significant results.⁶⁶ The Centre for Disease Control and Prevention (CDC) recommends assessing the degree of immunosuppression in IBD patients before administering the MMR vaccine. CDC does not recommend administering live vaccines if the patient is receiving immunosuppressant therapy > 2 mg/kg/day or at least 20 mg/day after prednisone for 14 days.²¹

However, due to the difficult conditions to determine the level of immunosuppression in the field, the Canadian Association of gastroenterology explained that adult IBD patients who are at risk of MMR infection and on immunosuppressant treatment, it is not recommended to receive the MMR vaccine. Meanwhile, the MMR vaccine can be given to adult IBD patients who are not on immunosuppressant treatment.^{53,65}

VACCINATION SCHEDULE

Recently, The Adult Immunization Task Force of the Indonesian Society of Internal Medicine released a new recommendation for adult immunization in Indonesia, as shown in Table 3.³² IBD patients is considered as immunocompromised patients other than HIV.

Table 3. Recommendation for adult immunization other than COVID-19 vaccine for immunocompromised patients other than HIV in Indonesia

Vaccine	Dose and schedule
Non-live vaccines	
Influenza	1 dose every year
Tetanus, diphtheria, pertussis (Td/Tdap)	1 dose Tdap, 2 dose Td, followed by 1 dose booster Td/Tdap every 10 years
Human papillomavirus (female)	3 doses up to 55 years old (month 0, 1 or 2, and 6)
Human papillomavirus (male)	3 doses up to 26 years old (month 0, 1, and 6)
Pneumococcus, polysaccharide (PPSV23)/age \geq 60	1 or 2 doses
Pneumococcus, conjugate 13-valent/age \geq 50	1 dose
Meningococcus, polysaccharide	1 dose
Meningococcus, conjugate	1 dose
Hepatitis A	2 doses (month 0 and 6)
Hepatitis B	3 doses (month 0, 1, and 6)
Live vaccines	
Herpes zoster	Contraindicated
Mumps, measles, rubella (MMR)	Contraindicated
Varicella	Contraindicated

CONCLUSION

In conclusion, IBD patients have higher risk of some vaccine-preventable infection. Offering vaccines and obtaining vaccination history is necessary for health care maintenance of IBD patients, especially those using immunosuppressive therapy. Physicians managing IBD patients should be familiar with the vaccines recommended.

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