Mistakes in opportunistic infections and vaccinations in IBD and how to avoid them

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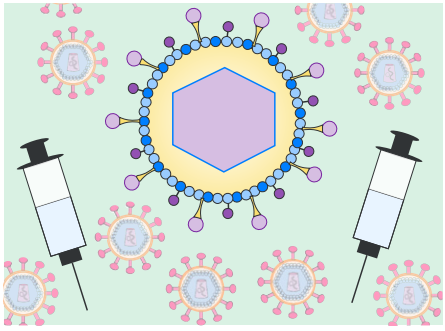
The introduction and general use of new immunosuppressive agents, including biologic agents and small molecules, has revolutionised the therapeutic management of inflammatory bowel disease (IBD). Such immunosuppression may expose patients to opportunistic infections, which can be challenging to recognise. These infections are crucial due to their association with morbidity or mortality and the challenges regarding effective treatment. New evidence in this field and vaccination strategies for immunosuppressed IBD patients led to updated European Crohn's and Colitis Organization (ECCO) guidelines in 2021.

Here we discuss the errors to avoid when managing the risk of opportunistic infections in IBD patients. The discussion is based on evidence, whenever possible, and our clinical experience.



Mistake 1 Not screening for viral infections at IBD diagnosis

Serologic screening for Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Human Immunodeficiency Virus (HIV), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) is recommended in all patients with IBD during the diagnosis. Serologic screening for Varicella zoster (VZV) and Measles virus is only recommended in the absence of past infection or vaccination documentation. Serologic screening at an early stage of the disease allows for a vaccination strategy before exposure to immunosuppressive therapy, which has been associated with suboptimal serological responses to various vaccines (see Table 1).[1]

Vaccine strategy	
General population vaccines	Follow a routine vaccination program including age-specific vaccines (i.e., Influenza, Zoster) according to country specific guidelines
At diagnosis of IBD	VZV vaccine (if no history of chickenpox and negative VZV serology, contraindicated during immunosuppressive therapy) Hepatitis B (if hepatitis B virus serology is negative) Influenza (trivalent inactivated) Human papilloma virus
Before advanced therapies	Pneumococcal vaccines
Annually	Influenza (trivalent, inactivated) Booster Pneumococcal polysaccharide vaccine (5 years)
Discretionary travel vaccines	Live vaccines (e.g., Yellow fever, oral Poliomyelitis) are contraindicated during immunosuppressive therapy

Table 1 | Vaccination strategy in patients With IBD

Mistake 2 Not vaccinating patients for pneumococcal disease and influenza

Pneumococcal vaccination should be recommended for all patients with IBD before immunosuppressive therapy since IBD has been associated with an increased risk of pneumococcal infection. Pneumococcal vaccines with both the 13-valent Pneumococcal Conjugate Vaccine (PCV13) and the 23-valent Pneumococcal Polysaccharide Vaccine (PPSV23) are also recommended, with a single revaccination after five years for the polysaccharide vaccine. Annual Influenza vaccination should be administered to patients under immunosuppressive therapy according to national guidelines.[2]

Mistake 3 Not checking for Tuberculosis infection before advanced therapies

Among advanced therapies (biologics and small molecules), anti-TNF agents and Janus kinase (JAK) inhibitors have been found to make more patients susceptible to tuberculosis infection. The accuracy of interferon-gamma release assays (IGRAs) and tuberculin skin tests in diagnosing latent tuberculosis in immunocompromised IBD patients, notably patients exposed to corticosteroids, is lower than in immunocompetent adults. For this reason, testing should be ideally performed at the time of diagnosis. IGRAs should be preferred over tuberculin skin tests (TSTs), as there is no cross-reactivity with the Bacillus Calmette-Guerin vaccine and IGRAs are more likely to be positive in case of recent tuberculosis infection compared to TSTs.[3]

Patients at risk for tuberculosis infection, notably those living or travelling in intermediate or high tuberculosis incidence areas, should be re-screened before initiation of advanced therapy as latent TB might have been acquired. A chest X-ray must also be performed. Anti-TNF therapy should be postponed, and antituberculosis treatment should be given according to national guidelines whenever latent or active tuberculosis is suspected.

Intestinal tuberculosis and Crohn's disease can have similar clinical and endoscopic presentations. In countries where tuberculosis is endemic, tuberculosis infection must be ruled

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Checks before advanced therapy initiation	
Detailed medical history	Previous bacterial, viral, and fungal infections (particularly TB, HSV, VZV, HIV, Hepatitis A, B, and C)
History of travel, living abroad, or both	Particularly areas with endemic infections (TB, Yellow fever, Strongyloides) plus intention to travel to areas with endemic infections
Immunization status	All recommended immunizations should be checked (Diphtheria, Tetanus, Poliomyelitis, Pertussis, MMR, HPV, Hepatitis B). In addition, immunization status for patients with chronic diseases should be assessed as they are recommended in IBD patients e.g., yearly Influenza, Pneumococcal vaccines
Laboratory values to assess for concomitant immunodeficiency or infection	Full blood count including neutrophil and lymphocyte counts, C-reactive protein, urine analysis (if symptoms indicate), Hepatitis B and C serologies, CMV and EBV serologies, HIV testing after previous counselling, TB screening (TST $^{+/-}$ IGRA $^{+/-}$ chest X-ray) If history or vaccination status for MMR and VZV is unknown, serology is recommended, and vaccination should be performed accordingly if there is no contraindication to live vaccines
Physical examination	HPV screening

Abbreviations: TB: Mycobacterium tuberculosis, HSV: Herpes simplex virus, VZV : Varicella zoster virus, HIV : Human immunodeficiency virus, HPV : Human papilloma virus, MMR : Measles-Mumps-Rubeola, CMV : Cytomegalovirus, EBV : Epstein Barr Virus, TST : tuberculin skin testing : IGRA : interferon gamma release assays, IBD : inflammatory bowel diseases

Table 2 | Recommended checks before advanced therapy initiation

out in patients suspected of Crohn's disease, especially in those with the ileal or perineal disease.

Healthcare workers are particularly at risk of tuberculosis infection, which implies regular testing when workers are under treatment with advanced therapies (see Table 2).

Mistake 4 Underestimating the risk of Herpes zoster and Varicella

IBD itself and specific IBD treatment have been associated with an increased risk of Herpes zoster infection (shingles), mainly when the patient receives thiopurines or JAK inhibitors. Based on data from randomised clinical trials of tofacitinib in ulcerative colitis, the absolute risk of Herpes zoster in patients older than 65 years is approximately 100 events per 1000 person-years. Patients should be informed of the risk of zoster before starting JAK inhibitors. Antiviral medicines should be started within 72 hours after rash onset to decrease the duration and severity of pain.[4]

The varicella vaccines should be considered in patients with no history of Chickenpox or Shingles, no prior immunisation, and negative serology for Varicella zoster. The varicella vaccine is a live attenuated vaccine contraindicated in patients receiving immunosuppressive drugs. A 2-dose vaccination schedule (with four weeks between doses) is recommended for adults. For the prevention of Herpes zoster, two vaccines are available in some countries, a live attenuated vaccine, and a non-live recombinant vaccine. The latter is preferred notably in immunocompromised patients and is recommended in any patient aged 50 years and older in the United States, regardless of their immunocompromising status.[5]

Frequent and/or severe recurrences of the Herpes simplex virus can be prevented when this is indicated with daily therapy with oral acyclovir or valaciclovir.

Mistake 5 Not considering EBV status before thiopurines use

EBV naïve men or women exposed to thiopurines are at increased risk of severe EBV primoinfection, potentially leading to hemophagocytic lymphohistiocytosis (HLH). The risk of post-mononucleosis lymphoma is also increased, particularly in young men. Alternatives to prolonged use of thiopurines should be considered in EBV naïve patients, except in cases with severe uncontrolled IBD and no alternative to combination therapy.[6]

Mistake 6 Neglecting life-threatening complications (hemophagocytic lymphohistiocytosis)

HLH is a rare but deadly complication. The diagnosis must be discussed in case of fever/prolonged fever, splenomegaly, lymph nodes, cytopenia, high liver enzymes, and high levels of ferritin and triglycerides. A myelogram is not mandatory if clinical and biological criteria are present.[7]

Infections, especially from viruses (EBV and CMV), in patients with IBD represent the most causes. Special attention is required for patients receiving thiopurines. It may also reveal lymphoma or leukaemia. In the case of recurrent HLH in patients with IBD, X-linked inhibitor of apoptosis (XIAP) deficiency must be considered, and an appropriate investigation carried out.

Mistake 7 Not considering HPV vaccination

IBD is also associated with an increased risk of human papillomavirus (HPV) related to cervical neoplasia and anal squamous cell carcinomas. Among treatments usually used in IBD, thiopurines may contribute to an increased risk.[8]

According to national guidelines, routine prophylactic HPV vaccination is recommended for young female and young male patients with IBD. Immunosuppressed women with IBD should undergo annual cervical cancer screening.

Mistake 8 Prescribing concomitant immunosuppressants without prophylaxis for pneumocystis pneumonia

Primary prophylaxis for *Pneumocystis jiroveci* pneumonia should be given to patients receiving triple immunosuppressive therapy, with one of these being a calcineurin inhibitor or anti-TNF agent. Standard prophylaxis with cotrimoxazole is recommended (double strength tablet 160–800 mg three times/week). Trimethoprim/sulfamethoxazole is the drug of choice for therapy in the absence of allergies or contraindication (notably in patients treated with methotrexate). Treatment alternatives are aerosolised pentamidine or atovaquone. Prophylaxis for *Pneumocystis jiroveci* pneumonia should also be considered in patients with low lymphocyte count when treated with immunosuppressive therapy.[2]

Mistake 9 Assuming that all patients have a similar risk of opportunistic infections

Age is a critical factor in the incidence and mortality of infection. The incidence rates of serious infections are two- to three-fold greater, with higher mortality rates (10%) in patients aged 65 and older compared to younger patients. Patients with specific conditions such as HIV, diabetes mellitus, malnutrition, and intravascular devices are at risk of invasive infections, especially bacterial and fungal. Native country and specific travels must be considered. Severe Strongyloidiasis may occur in patients who have lived or travelled in endemic countries for 30 years before onset.[9] Serologic testing should be performed, and systemic hypereosinophilia should be assessed. Patients with positive screening tests and/or unexplained hypereosinophilia and a history of travel or residence indicative of exposure to Strongyloides stercoralis should be treated empirically before starting immunosuppressive therapy.[2]

Mistake 10 Administrating live vaccines in immunocompromised patients

There is a risk of disseminated infection associated with live vaccines in immunocompromised patients. The most commonly used live vaccines are measles-mumps-rubella, yellow fever, and Varicella zoster. Live-attenuated vaccines are contraindicated in IBD patients exposed to immunosuppressive therapies. In patients already under immunosuppressive treatment, the drug's half-life and time to recover from the immunosuppressive effect should be considered to determine the safest timepoint for vaccination in patients treated with immunosuppressants. A usual and arbitrary threshold of three months after immunosuppressant withdrawal was considered to administer live-attenuated vaccines. However, this period may be shortened in clinical practice. Notably, the American College of Rheumatology has recently provided guidelines for vaccinations in patients with rheumatic and musculoskeletal diseases. [10] In these guidelines, holding anti-TNFs for one dosing interval before and four weeks after live-attenuated virus vaccination is recommended.

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Your opportunistic infections and vaccination in IBD briefing

UEG Week

- 'Opportunistic infections in IBD, case closed? Live expert lunch' session at UEG Week Virtual 2021 [https://ueg.eu/library/opportunistic-infections-in-ibd/248526]
- 'Where to place novel JAK inhibitors' session at UEG Week Virtual 2021 [https://ueg.eu/library/where-to-place-novel-jak-inhibitors/247959]
- 'Herpes Zoster infection in patients with ulcerative colitis receiving Tofacitinib: results from the phase 2 and phase 3 clinical programs' session at UEG Week Virtual 2021 [https://ueg.eu/library/herpes-zoster-infection-in-patients-with-ulcerative-colitis-receiving-tofacitinib-results-from-the-phase-2-and-phase-3-clinical-programmes/248464]

Standards and Guidelines

- Stallmach, Andreas et al. 'Addendum to S3-Guidelines Crohn's disease and ulcerative colitis: Management of Patients with Inflammatory Bowel Disease in the COVID-19 Pandemic - open questions and answers. *Zeitschrift fur Gastroenterologie* vol. 58,10 (2020): 982-1002. [https://ueg.eu/library/addendum-to-s3-guidelines-crohn-s-disease-and-ulcerative-colitis-management-of-patients-with-inflammatory-bowel-disease-in-the-covid-19-pandemic-open-questions-and-answers/234076]