Vaccination Strategies for Patients with Inflammatory Bowel Disease on Immunomodulators and Biologics

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Abstract: The treatment of Crohn’s disease and ulcerative colitis frequently includes potent immunomodulator and biologic therapy to reduce intestinal inflammation, heal fistulae, limit complications, and improve quality of life. These medications may increase susceptibility to and severity of infections, many of which are preventable by preemptive immunizations. Conversely, live-virus vaccines are generally contraindicated in patients receiving immunosuppressive regimens due to risks of vaccine-associated infection. While most patients on immunosuppressive therapies develop immune responses after vaccinations, these may be impaired relative to their nonimmunosuppressed counterparts. This review discusses the rationale for currently recommended vaccinations, as well as issues pertaining to vaccine safety and immunogenicity in immunosuppressed patients with inflammatory bowel disease and their household contacts.

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Advances in the treatment of inflammatory bowel disease (IBD) with immunomodulators and antitumor necrosis alpha (TNF-α) biologic medications have significantly improved disease activity, reduced hospitalizations and surgery, and led to enhanced quality of life in many patients with ulcerative colitis and Crohn’s disease.1–3 Continued maintenance therapy with immunomodulators reduces the risk of relapse,4 and long-term benefits from continued anti-TNF therapy have been demonstrated.2 While the desired effect of these drugs is enabled by damping an overactive intestinal immune system, untoward effects of immune modification and suppression may result in increased susceptibility to acquiring and fighting various infections.5,6 Fulminant or fatal infections have been reported in patients with IBD on various immunosuppressive therapies, including 6-mercaptopurine, azathioprine, and anti-TNF agents.7–9 Many of these infections are preventable through preemptive vaccination and immunization strategies. However, there appears to be significant underutilization of recommended immunizations in the adult IBD population.10

Improved awareness of this increased risk in patients with IBD has resulted in efforts toward promoting prevention and prophylaxis against common and preventable infections. In 2004, guidelines were published specifically for vaccination and immunization of patients with IBD (Table 1).11 In addition to adherence to routine vaccination schedules, specific recommendations for those with IBD on immunosuppressive therapies include assessment of vaccine response when possible and general avoidance of live vaccines.11 Questions remain regarding the effectiveness, safety, and immunogenicity of common vaccines in at-risk populations including IBD and other immune-mediated conditions requiring the use of immunosuppressive medications. Effectiveness studies are largely lacking in the IBD population, although a study in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) found lower infection rates after influenza vaccination.12 Furthermore, large observational studies in the elderly have demonstrated the effectiveness of the influenza and pneumococcal vaccines for reduction of hospitalization and death.13,14 Vaccine safety and risk of vaccine-induced flares has not been directly assessed in the IBD population, but has been studied in other immune-mediated conditions; for example, in multiple sclerosis vaccines have been found to be safe, and not increase the risk of disease relapse.15 Recent investigations in subjects with IBD have examined vaccine-specific immunogenicity, particularly with influenza and pneumococcal vaccines. These studies are reviewed and an approach to vaccination of patients with IBD on immunosuppressive medications as well as household contacts of such individuals is presented.
TABLE 1. General Recommendations for Immunization of Patients with IBD

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

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INFLUENZA VACCINATION

Influenza infection resulted in an annual average of 36,000 deaths from primary influenza and secondary bacterial complications including pneumococcal pneumonia during the decade 1990–1999 in the United States.16 Currently available vaccines for those considered “at risk” include the trivalent inactivated vaccine and the live, attenuated intranasal vaccine. Immunization with inactivated vaccine is recommended for those receiving immunosuppressive therapy.17 However, despite recommendations, utilization of influenza vaccination across high-risk groups was only 22%–46% in all age groups in 2006–2007.17 Potentially modifiable patient-reported reasons for nonimmunization in an adult IBD clinic included lack of awareness, fear of side effects, and beliefs of vaccine inefficacy.10

Two published studies have assessed response rates in cohorts of children with IBD who were vaccinated with the inactivated trivalent influenza vaccine.18,19 Mamula et al18 compared 51 children with IBD and 29 healthy controls. Response (defined by postvaccination hemagglutinin inhibition titers ≥40) was less effective for 1 of 3 antigens among those with IBD as compared to controls, and those on anti-TNF medications in combination with immunomodulators showed impaired responses to 2 of 3 antigens. Another study assessed response rates in 146 consecutive children with IBD and found that vaccination responses were similar among all those with IBD, regardless of immunosuppressive status.19 However, subanalysis revealed impaired seroprotection against strain B specifically in those receiving anti-TNF medications. No patients in either study experienced a flare of disease after vaccination, and no serious adverse events were reported. Taken together, these studies show that vaccination against influenza in children with IBD is well tolerated and induces immune response in children with IBD, although anti-TNF medications may selectively impair response to specific serotypes. An unresolved question for which neither study was powered to address is whether impaired response is due to the anti-TNF therapy specifically or only when combined with an immunomodulator.

In the rheumatology literature, response rates to inactivated influenza vaccination in subjects treated with immunomodulators and anti-TNF therapy are somewhat conflicting. Several studies have assessed response to influenza vaccine in adult patients with RA and SLE on various disease-modifying antirheumatic drugs (DMARDS), and found no influence of immunosuppressive treatment, steroid use, or disease activity on immune response as compared to healthy controls.20–22 However, at least 2 controlled studies have shown azathioprine (but not methotrexate) associated with impaired response.23,24 Similarly, studies that have assessed the influence of anti-TNF therapy have yielded inconsistent results. In a double-blinded, randomized trial where RA patients received adalimumab or placebo, response rates to influenza and pneumococcal vaccines were assessed. Postvaccination influenza titers were similar in both adalimumab and placebo groups, and no significant effect of concomitant methotrexate use was noted.25 A study by Gelinck et al26 that included both rheumatology and gastroenterology patients found only slightly diminished responses in anti-TNF-treated patients. However, others have shown that anti-TNF treatment in combination
with methotrexate had less effective responses than those treated with methotrexate alone. The emerging conclusion from these studies may be that immunomodulators and anti-TNF agents diminish responses somewhat, but that overall the majority of patients develop protective titers after influenza vaccination irrespective of immunosuppression use.

Safety of Influenza Vaccines in Immunosuppressed Patients

Although no studies with IBD patients have directly addressed the safety of influenza vaccination, no serious adverse events were reported in the 2 published pediatric studies with influenza vaccine, which included a combined total of 197 children with IBD; specifically, there were no instances of disease flare as a result of vaccination noted at follow-up evaluations 4–8 weeks after vaccination. Two case reports described a relapse of ulcerative colitis following the influenza vaccine. However, these reports should be interpreted with caution; although no epidemiologic studies in IBD have been conducted to directly answer this question, rigorous studies in other immune-mediated conditions such as multiple sclerosis and RA have found a variety of vaccines to be safe and not increase the risk of disease flares.

PNEUMOCOCCAL VACCINATION

Indications for the 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23, Merck, Whitehouse Station, NJ) largely overlap with those considered “at risk” for influenza, including those on chronic immunosuppressive therapy. For patients in whom both influenza and pneumococcal vaccines are indicated, simultaneous administration is recommended in order to maximize vaccination opportunities.

The 23-valent pneumococcal polysaccharide vaccine (PPV23) appears to be immunogenic in immunosuppressed patients, although response rates may vary depending on the type of medication regimen, including anti-TNF-α therapy, immunomodulators, and combinations thereof. Efforts to compare studies are also confounded by the fact that the PPV23 comprises 23 antigens, only some of which are measured in individual studies. Furthermore, multiple and varying definitions of antigen-specific responses have been used in different studies. Therefore, results and conclusions across different studies may not be directly comparable.

Response rates to vaccination with PPV23 have been assessed in 2 IBD populations. Dotan et al evaluated the immune profiles of 36 patients with IBD initiating 6-mercaptopurine, and found normal vaccine response rates to PPV23, hepatitis B, tetanus, and influenza when compared with healthy controls. In another study, response rates to PPV23 were assessed in 21 adults with IBD on combination anti-TNF-α and immunomodulators, 25 nonimmunosuppressed patients with IBD, and 19 healthy controls. Immunosuppressed subjects had significantly impaired postvaccination titers, while those with IBD who were not immunosuppressed had response rates similar to healthy controls. Taken together, these studies suggest that neither the IBD disease state nor monotherapy with immunomodulators impair vaccine response, whereas the combined use of anti-TNF agents with immunomodulators may in fact dampen response to PPV23. Further studies of larger numbers of patients are needed to better understand which therapies or combinations thereof do in fact interfere with normal vaccine response.

It is unknown whether monotherapy with anti-TNF agents affects response rates to PPV23 vaccination in adults with IBD. In a study of 149 patients with RA, the response to PPV23 was enhanced among those treated with anti-TNF medications (infliximab or etanercept) alone as compared with either methotrexate alone or in combination with anti-TNF therapy. In this study, monotherapy with methotrexate showed the poorest response and was less effective than combination therapy with an anti-TNF agent and methotrexate. In a randomized controlled trial, Kaine et al showed that subjects with RA treated with adalimumab had similar response rates to those receiving placebo, suggesting that monotherapy with anti-TNF agents does not impair vaccine response rates. Others have also shown that those treated with combination anti-TNF therapy and methotrexate had lower response rates than those treated with methotrexate alone. From these studies it appears that response rates to vaccination in those on anti-TNF agents alone are normal, but are impaired in the setting of combination therapy with both anti-TNF therapy and immunomodulators.

HEPATITIS B VACCINATION

Hepatitis B (HBV) is a vaccine-preventable infection that can be reactivated in chronic HBV carriers receiving immunosuppressive therapy, including anti-TNF medications. In a European series of 80 consecutive patients treated with azathioprine and infliximab assessed for HBV, 3 patients were seropositive for chronic HBV, 2 of whom experienced fulminant hepatitis, resulting in 1 death. Routine screening for HBV in those at risk for HBV should be performed prior to initiation of anti-TNF therapy.

Vaccination against HBV involves a series of 3 injections of the inactivated recombinant HBSAg and is safe in immunosuppressed persons. In the IBD population, patients starting 6-mercaptopurine had normal response to HBV vaccination as compared to controls. In 22 patients with RA on various medication regimens, only 15 had an adequate response 1 month after completing the 3-injection HBV series. Consideration for vaccination against HBV
is therefore recommended in those with risk factors for HBV including intravenous drug use, travelers to endemic regions, high-risk sexual behavior, dialysis patients, healthcare providers, or any adult requesting protection against HBV.\textsuperscript{40}

**TETANUS**

Tetanus infection is extremely rare, but occurs almost exclusively in those not adequately vaccinated. Tetanus toxoid (Td) is recommended as part of the childhood DTaP series and a booster Td is recommended every 10 years after primary vaccination.\textsuperscript{42} One study demonstrated that vaccination with Td booster immunization was safe and effective in 10 patients with quiescent Crohn’s disease when compared with 12 healthy controls,\textsuperscript{43} although other studies have suggested an impaired antitetanus response.\textsuperscript{44} As Td is not infectious, it should be administered as scheduled in all adults regardless of immunosuppressive status.

**MENINGOCOCCAL VACCINE**

Although persons with compromised immunity are not considered at increased risk for meningococemia, some patients with IBD may meet other criteria for vaccination. In particular, first-year college students living in college dormitories should undergo vaccination with either the meningococcal conjugate or polysaccharide vaccines. Both vaccines are noninfectious and considered safe in persons with compromised immunity.\textsuperscript{31}

**HUMAN PAPILLOMA VIRUS (HPV)**

The HPV vaccine is a quadrivalent vaccine that targets the 4 HPV serotypes associated with highest risk of progression to cervical dysplasia and cancer. Immunity is achieved after 3 vaccinations over a 6-month period. Current guidelines recommend consideration of the HPV vaccine in all women between the ages of 9 and 26.\textsuperscript{45} The vaccine is noninfectious and considered safe in immunocompromised recipients, although no published studies have assessed immunogenicity or efficacy in immunocompromised women or men. Recent publications have shown that women with IBD have a higher risk for HPV and abnormal Pap smears.\textsuperscript{46,47} This association may be stronger in women who are receiving immunosuppressive therapy.\textsuperscript{47} Given these findings, it is reasonable to consider HPV vaccination in women with IBD, particularly among those contemplating or are already on immunosuppressive therapy.\textsuperscript{48}

**LIVE VIRUS VACCINES**

Live vaccines are considered contraindicated in patients with compromised immunity due to concern for vaccine-related infection (Table 2).

| TABLE 2. Live Vaccines, Generally Contraindicated in Patients Receiving Immune-Suppressive Therapy |
|---------------------------------|--------------------------------------------------|
| Anthrax vaccine                 | Intransanal influenza                             |
| Measles-mumps-rubella (MMR)     | Polio live oral vaccine (OPV)                     |
| Smallpox vaccine               | Tuberculosis BCG vaccine                         |
| Typhoid live oral vaccine      | Varicella*                                        |
| Varicella*                     | Yellow fever                                      |
| *See text for discussion on individuals at risk for infection. |

**Varicella**

Most adults will have acquired immunity to varicella through childhood infection or vaccination. However, a significant minority may not have been previously exposed, and are thus at risk for acquiring the infection. The varicella vaccine is a live-virus vaccine that is generally contraindicated in patients receiving immunosuppressive therapy. However, varicella infection is particularly aggressive in adults, with mortality rates of 20/100,000, and with disseminated disease in 30% of immunocompromised adults who acquire the infection.\textsuperscript{49} Therefore, it is of particular importance to identify those at risk for varicella prior to initiation of immunosuppressive therapy by asking about prior exposure (i.e., previous infection or vaccination). Although patient recall may be subject to bias, detection of varicella titers in a small sample of IBD adults correlated well with patient recall. While 25 of 25 adults reporting prior varicella exposure had detectable titers, only 4 of 7 who reported “no exposure” or “uncertain if exposed” had detectable titers.\textsuperscript{10} Therefore, if prior varicella exposure cannot be definitively recalled, confirmation of immunity with assessment of VZV serology should be performed.\textsuperscript{11}

The risk of varicella infection in the immunocompromised patient without prior immunity raises the challenging question of whether the benefit of vaccination outweighs its risk. In a study of children with leukemia in remission, live attenuated varicella vaccine was given after withholding maintenance steroids for 1 week. The vaccine was generally found to be safe, effective, and protective during a 3-year follow-up period.\textsuperscript{50} However, in the IBD patient on anti-TNF therapy, the approach of temporary withdrawal from immunosuppression may pose unacceptable risks of disease relapse. For those who may be at increased risk of occupational exposure to varicella (for example, an early childhood teacher or healthcare worker) without prior immunity, careful consideration of the risks of acquiring the infection need to be weighed against the potential risks and benefits.
benefits of vaccination.\textsuperscript{51} In cases of active varicella exposure in these patients, postexposure prophylaxis with VZIG is recommended.

Adults with IBD may be at increased risk for herpes zoster; in a nested, case–control study, both steroids and immunomodulators were associated with this increased risk.\textsuperscript{52} Reports have also described shingles in IBD after anti-TNF administration.\textsuperscript{53} Similar to varicella immunization, the varicella zoster vaccine is a live-virus vaccine that is generally contraindicated in immunosuppressed individuals.

**Yellow Fever**

Vaccination against yellow fever is recommended for travelers to endemic regions in Africa and South America. However, the live, attenuated yellow fever vaccine may potentially lead to severe and possibly lethal symptoms in immunosuppressed patients and is thus contraindicated. Immunosuppressed individuals are advised to avoid travel to endemic regions; if travel is unavoidable, travelers should be educated regarding the risks of such travel and instructed regarding prevention of mosquito transmission.\textsuperscript{54} Patients may require a letter of exemption from yellow fever vaccination based on their immunocompromised status.

**HOUSEHOLD CONTACTS AND HEALTHCARE WORKERS**

Annual influenza vaccination is recommended for household and other close contacts of those on immunosuppressive medications, including healthcare workers.\textsuperscript{55} While the inactivated vaccine poses no theoretical risk to immunocompromised contacts, the intranasal live attenuated influenza vaccine (LAIV) may shed vaccine-strain virus for up to 3 days in the healthy recipient. Secondary transmission is rare (less than 0.001%),\textsuperscript{55} and has not been reported in immunocompromised household contacts. However, theoretical risk for transmission exists and some advocate caution for administration of LAIV to household contacts of immunocompromised individuals.\textsuperscript{56} Most other live-virus vaccines can be safely administered to close contacts or healthcare workers of those on immunosuppressive regimens.\textsuperscript{56} Exceptions include live oral polio virus (OPV) and smallpox vaccine, which may result in infectious transmission to immunosuppressed contacts. Varicella transmission to household contacts is rare, and no special precautions are recommended unless the recipient develops a skin rash after vaccination (in which case direct contact should be avoided).\textsuperscript{57} With regard to rotavirus vaccination, fecal shedding may potentially occur after immunization. However, the benefit afforded to immunocompromised household contacts through herd immunity likely outweighs the theoretical risk of infection after vaccination.\textsuperscript{58} Rotavirus transmission can be minimized with handwashing for at least 1 week after diaper-changing a rotavirus-vaccinated infant.

**SUMMARY AND RECOMMENDATIONS**

Patients with IBD on immunomodulators and anti-TNF-\(\alpha\) agents are considered at risk for influenza and pneumococcal disease, and therefore should be appropriately immunized. Vaccination with inactivated influenza and pneumococcal polysaccharide vaccine in these patients is safe and most patients develop protective immune titers. However, some patients on these immunosuppressive therapies, especially those on anti-TNF agents with concomitant immunomodulators, may not respond as well to vaccination. Hepatitis B can be reactivated with anti-TNF therapy, and should be screened for in individuals with risk factors in whom immunosuppression is being considered; vaccination should be offered to at-risk nonimmune individuals. In addition, HPV vaccination in women on immunosuppressive therapy should be considered, due to increased frequency of abnormal Pap smears in women with IBD on immunosuppressive therapy. Other vaccinations should be administered based on recommended intervals and specific indications, but live-virus vaccines should be generally avoided in those receiving immunosuppressive therapies. However, an immunosuppressed adult who is not immune to varicella but occupationally at risk for the infection poses a challenge for which careful risk:benefit assessment for vaccination is required.

[Author’s opinion]: Given the significant but unpredictable likelihood of immunosuppression in patients with IBD, a proposed approach is to screen for vaccination history and risk at the time of the initial IBD consultation, and to offer influenza and pneumococcal vaccine to all patients, regardless of immunosuppression status. At the time of this initial visit, which is usually before initiation of immunosuppressive medications, appropriate counseling and education can be performed, including screening for prior varicella exposure, relevant travel history, and assessment of risk factors for viral hepatitis. When immune status is uncertain, assessment for titers at this time can preempt the need for future screening, which may otherwise occur when immunosuppressive therapy is urgently needed and opportunities for vaccination may be limited. Furthermore, routine follow-up visits present opportunities to reinforce these recommendations, including annual influenza immunization and boosters for other routine vaccinations. While additional controlled studies assessing vaccine response and effectiveness in IBD are needed, adherence to recommended guidelines will hopefully reduce morbidity and mortality associated with vaccine-preventable illnesses in immunosuppressed individuals.
REFERENCES


