Immunizations in Patients with Inflammatory Bowel Disease

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Abstract: Patients receiving immunosuppressive therapies may be at increased risk for complications of vaccine preventable diseases, including influenza, varicella, and pneumococcus. However, studies suggest that patients with chronic illness may be inadequately immunized. In part, this is because of a paucity of formal vaccine studies in immune compromised populations. This review discusses the methods one uses to assess vaccine efficacy and provides an update on currently known data on the vaccine antibody responses in immune compromised hosts. Currently published studies suggest that influenza vaccine can be safely administered to patients with IBD on immunosuppression, and is effective in the majority of patients. Further formal studies with other inactivated vaccines (e.g., pneumococcal vaccine, meningitis vaccine) should be conducted. While some studies in immune compromised hosts suggest the live attenuated varicella vaccine can be given without adverse events, administration of this vaccine in patients on immunosuppression remains controversial.

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Key Words: Crohn’s disease, ulcerative colitis, inflammatory bowel disease, vaccine, immunization, opportunistic infection, immunosuppression, tumor necrosis factor inhibitor, 6-mercaptopurine, azathioprine, infliximab

Evidence is mounting that patients with Crohn’s disease (CD) and ulcerative colitis (UC) have subtle alterations in immunity, and that the medications used to treat these conditions may increase the risk of infection. Genetic mutations that are associated with changes in innate immunity (including NOD2 and IL23R) have been found in inflammatory bowel disease (IBD) patients.1–4 Functional assays also suggest that adaptive immunity is altered in CD and UC. In CD, there is evidence of an exaggerated Th1 inflammatory response, including increased production of interferon-γ by intestinal CD4+ T-cells, and increased IL-12 and IL-18 by mucosal macrophages. In contrast, UC is generally characterized by an excessive Th2 T-helper response. T-cells from UC patients produce a larger amount of IL-13 and IL-5, have a slower cell cycle, and are more prone to undergo apoptosis than control cells.5

In order to control intestinal inflammation, physicians often treat IBD patients with immunosuppressive therapies (corticosteroids, immunomodulators, calcineurin inhibitors, and tumor necrosis factor [TNF] inhibitors).6 Immunosuppressive medications can be further categorized by their mechanism of action. Corticosteroids operate by various mechanisms, such as altering gene transcription in various cells involved in immune response to ultimately reduce inflammation. Azathioprine, 6-mercaptopurine, and methotrexate all inhibit DNA synthesis, resulting in decreased lymphocyte number and function. Cyclosporine and tacrolimus are calcineurin inhibitors that prevent transcription of IL-2 to hinder T-cell activation. Infliximab and adalimumab are monoclonal antibodies used to bind TNF-α, and can also induce monocyte apoptosis.6 Thus, the degree of immunosuppression in IBD patients may vary by type of therapy they receive.

IBD patients may be at risk for infections due to underlying disease, malnutrition, surgery, or immunosuppressive therapy.7,8 Table 1 lists opportunistic infections that have been observed in IBD patients, as well as preventive mechanisms and screening tests for these infections. Some studies have looked at infection rates in IBD patients overall and others have focused on patients receiving immunosuppressive medications. In one study, there was a higher prevalence of Clostridium difficile among IBD patients compared to gastrointestinal patients without IBD and general medical patients.9 Another study found that 15.8% of IBD patients were infected with cytomegalovirus (CMV).10 In addition, data have shown that women with IBD are at a higher risk for abnormal Pap smears (18%–42.5%) compared to healthy age-matched controls (5%–7%).11,12 In a number of case studies or case series, various opportunistic infections were observed in IBD patients on immunosuppressive therapies, including corticosteroids, 6-mercaptopurine, azathioprine, cyclosporine, or infliximab. These infections include cytomegalovirus (CMV colitis, pneumonitis, mononucleosis),13 Epstein–Barr virus (resulting in death from multiorgan failure),14 herpes simplex...
virus (leading to pneumonia and acute respiratory distress syndrome), varicella (varicella pneumonia, shingles), tuberculosis, histoplasmosis, and Pneumocystis jiroveci (carinii) pneumonia.

Because of the potential susceptibility of IBD patients to infection, immunization may play a critical role in preventing illness. However, there are a paucity of data that evaluate the immune response to routine vaccinations in IBD patients. This article reviews the currently available recommendations, as well as the few formal vaccine studies that evaluate the immune response to immunizations in IBD patients receiving immunosuppressive therapy. Based on the current data, further recommendations for research are proposed.

**ASSESSING THE EFFICACY OF IMMUNIZATIONS**

The immune system recognizes and responds to antigens through the production of antibodies and/or activated immune cells. Vaccines contain live or killed microorganisms or synthesized particles. The body mounts an immune response to the vaccine antigens that results in memory cells that are prepared to respond to future exposure to wildtype organisms. Antibody levels to vaccine antigens are measured to determine the degree of immunologic response to the vaccine. Investigators studying vaccine efficacy typically draw antibody levels before immunization and at a fixed timepoint after immunization (e.g., 4 weeks after the final immunization in a series). By comparing the antibody titer before and after immunization, a vaccine’s immunogenicity can be determined.

Various terms are utilized in the immunization literature to describe vaccine immunogenicity. **Seroconversion** to vaccination is defined as the development of antibodies (seropositive) after immunization in a person without a detectable titer before vaccination (seronegative). A patient who seroconverts must develop a minimum antibody titer to be protected against wildtype infection. Thus, when the antibody titer to the vaccine antigens reaches or exceeds this threshold, a patient is **seroprotected**. The average titer in a group of patients that has been immunized is called the **geometric mean titer** (GMT).

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**TABLE 1. Common Opportunistic Infections in IBD Patients**

<table>
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<tr>
<th>Infection</th>
<th>References</th>
<th>Preventative Mechanism</th>
<th>Screening Test</th>
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<tr>
<td><strong>Viral</strong></td>
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<tr>
<td>Cytomegalovirus</td>
<td>7, 8, 10, 13, 53</td>
<td>Handwashing</td>
<td>Serology, CMV antigenemia, culture, CMV DNA by PCR, biopsy</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>7, 8, 14, 54, 55</td>
<td>Avoid exposure</td>
<td>Serology, monospot, culture, PCR</td>
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<tr>
<td>Hepatitis B</td>
<td>8, 56</td>
<td>Vaccine, hepatitis B immune globulin</td>
<td>HBsAg, HbeAg, anti-HBs, anti-HBc, anti-HBe, HBV DNA/PCR</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>7, 8, 15, 57</td>
<td>Avoid exposure</td>
<td>Culture, serology, biopsy</td>
</tr>
<tr>
<td>Influenza</td>
<td>8, 58, 59</td>
<td>Vaccine, oseltamivir, zanamivir</td>
<td>Serology, viral culture, rapid antigen testing, PCR, immunofluorescence assays</td>
</tr>
<tr>
<td>Varicella</td>
<td>7, 8, 16, 17, 60</td>
<td>Vaccine zoster immune globulin</td>
<td>Serology, Tzanck smear, viral culture, PCR, direct fluorescence antibody, biopsy</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>7, 8, 11, 12, 61, 62</td>
<td>Vaccine, sexual abstinence, barrier contraception</td>
<td>Serology, Pap smear, pelvic exam, HPV DNA test</td>
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<tr>
<td><strong>Bacterial</strong></td>
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<tr>
<td>Clostridium difficile</td>
<td>7–9, 63</td>
<td>Gown and gloves, soap and handwashing, proper handling of contaminated waste, disinfect fomites, limit antibiotic use</td>
<td>Stool test (toxin A and B), colonoscopy</td>
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<tr>
<td>Tuberculosis</td>
<td>7, 8, 18, 64</td>
<td>Isoniazid</td>
<td>PPD, chest x-ray, <em>Mycobacterium tuberculosis</em> culture, acid-fast bacillus smear, biopsy</td>
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<td><strong>Fungal</strong></td>
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<td>Histoplasmosis</td>
<td>7, 8, 19, 20, 65</td>
<td>Avoid exposure to contaminated soil and dust</td>
<td>Serology, CXR, culture, stains, titers, <em>H. capsulatum</em> polysaccharide antigen, lung biopsy</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em> (carinii) pneumonia</td>
<td>7, 8, 21, 22, 66</td>
<td>Trimethoprim/ sulfamethoxazole, atovaquone</td>
<td>Chest x-ray, lung biopsy, staining of respiratory tract secretions</td>
</tr>
</tbody>
</table>

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IMMUNIZATION STUDIES IN ADULTS AND CHILDREN WITH CHRONIC ILLNESSES OTHER THAN IBD

Children with Non-IBD Chronic Illness May Have Decreased Rates of Immunization and Decreased Immune Response

Immunizations are especially important in patients with chronic illnesses or in immunocompromised patients because the hosts are more susceptible to infection. However, data have shown that such patients tend to be underimmunized or have inadequate levels of seroprotection after immunization. Zignol et al evaluated titers to various childhood vaccines (hepatitis B, measles, mumps, rubella, tetanus, polio) in children with malignancies before and after they received chemotherapy. The percentage that lost seroprotective antibodies to the above vaccines ranged from 8% for polio to 52% for hepatitis B. Fortunately, subjects in this group who were given a booster vaccination had an overall response rate of 93%.

Another study found that only 4% of pediatric renal transplant patients received all necessary vaccinations before and after transplantation.

Prior Studies on Immune Response to Vaccines in Immunocompromised Children

Immunocompromised children have varying degrees of immune response to vaccination. The immune response to vaccination was adequate in 2 studies of HIV-infected infants. In a randomized trial conducted by the Pediatric AIDS Clinical Trials Group, infants with HIV were immunized with doses of heptavalent pneumococcal conjugate vaccine in a 2:1 placebo-controlled randomized trial. The baseline median CD4 cell count between the vaccine and placebo groups was similar (2457 cells/mm3 in the vaccine arm, 1870 cells/mm3 in the placebo arm, P = 0.44). The HIV-positive infants produced a good immune response after receiving the primary series and booster vaccines for the heptavalent vaccine. However, patients with symptomatic HIV had a slightly higher incidence of adverse events (including extremity induration and fever). A similar study of Haemophilus influenzae type b conjugate vaccine once again demonstrated a similar antibody response (titer >0.15 mg/L) in HIV-infected infants compared to HIV-uninfected infants after receiving the primary series and booster doses. The mean CD4 cell count differed between these 2 groups (1803/µL in the HIV-infected group, 3327/µL in the HIV-exposed group, P < 0.001).

In contrast to children with HIV infection, children who are treated with chemotherapeutic agents for cancer may have a suboptimal serologic response to vaccines. One study vaccinated pediatric oncology patients with 2 doses of influenza vaccine and found that unprimed subjects had a 40%–65% seroconversion rate (≥4 increase in hemagglu-
However, another small study showed that patients on dialysis who were vaccinated with measles-mumps-rubella vaccine had a lower serologic response to all 3 (30%) compared to healthy children (91%). No clinical symptoms of measles, mumps, or rubella infection were noted after vaccination.33

Prior Studies on Immune Response to Vaccines in Immunocompromised Adult Patients

Vaccine studies in patients with chronic illness suggest there are varying degrees of serologic response to vaccination in adults. Several studies have shown that adult patients with rheumatoid arthritis (RA) have similar antibody titer levels to influenza vaccine compared to controls.34,35 However, Fomin et al16 showed that the postvaccination GMT and response rate (defined as a ≥4-fold increase in titers) in RA patients receiving immunosuppressive therapy were lower for 1 of 3 vaccine strains compared to healthy controls.

Patients with systemic lupus erythematosus (SLE) have a decreased response to pneumococcus,37,38 tetanus,39 and influenza40,41 vaccines compared to controls. One study showed a protective response to H. influenzae type b vaccine in most SLE patients studied, but it had no control group for comparison.42 Vaccination did not appear to increase disease activity or the likelihood of a disease exacerbation in SLE patients.41,42

Immunosuppressive medications may dampen the immune response to vaccination and the response may vary with the type of vaccine. Kapetanovic et al43,44 conducted a study to evaluate the antibody response in RA patients to influenza and pneumococcal vaccine. RA patients treated with methotrexate without TNF-α inhibitors produced a better antibody response to influenza vaccination compared to subjects treated with TNF-α inhibitors alone or in combination with methotrexate and/or other disease-modifying antirheumatic drugs.43 However, RA patients receiving TNF-α inhibitors without methotrexate mounted a higher antibody response after pneumococcal vaccination compared to subjects receiving methotrexate (with or without TNF-α inhibitors).44

EVIDENCE SUPPORTING CURRENT IMMUNIZATION GUIDELINES IN IBD PATIENTS IS INCOMPLETE

In 2004, a committee formed by the Crohn’s and Colitis Foundation of America provided a consensus statement on immunizations in IBD patients.45 The consensus article reviewed the immunologic alterations in patients with IBD and routine immunization schedules (e.g., pneumococcal vaccination) and those for travel to high-risk areas (e.g., yellow fever and typhoid). While the consensus statement reflected a recommendation by a well-respected group of experts, the article only identified a few formal vaccine studies performed in immunocompromised populations. They noted case reports of complications after measles virus vaccination, and a study in which patients with leukemia on long-term 6-mercaptopurine therapy tolerated the varicella vaccine. At the time the authors wrote their guidelines, there was little published literature on immunizing transplant patients with live vaccines.31,32 Although the panel stated that most patients would benefit from immunization with these live vaccines without complications, the experts still recommended against the use of live vaccines in IBD patients on immunosuppressive therapy given the possibility of vaccine-associated disease. The panel did recommend the use of inactivated vaccines (including pneumococcal and influenza vaccine) whether or not IBD patients were on immunosuppressive therapy.45 The paucity of formal evidence in the 2004 IBD Immunization Guideline emphasizes the need for additional studies.

IBD Patients are Underimmunized

Similar to pediatric patients with chronic illnesses, data have shown that IBD patients tend to be underimmunized. Melmed et al46 conducted a study where IBD patients completed a questionnaire to assess their immunization history and exposure risk to influenza, pneumococcus, tetanus, varicella, and viral hepatitis. Serology to hepatitis A, hepatitis B, and varicella were evaluated in 41 of these subjects who voluntarily gave a blood sample. Of 169 patients who completed the questionnaires, 28% received regular influenza immunizations, 9% received a pneumococcal vaccination, and 45% received a tetanus vaccination within the past 10 years. Among reasons for not getting the influenza vaccine, patients cited that they were unaware they needed it, afraid of adverse events, or believed the vaccine would not be efficacious.

Eleven percent of subjects in the study by Melmed et al46 were considered at risk for varicella because they did not have a history of varicella infection or vaccination. Of the patients who had varicella zoster virus antibody titers evaluated, 96% (24/25) of patients with a history of varicella infection or immunization were immune, compared to 25% (1/4) of those who had no history of infection or immunization. This finding emphasizes that a patient’s history of varicella infection or immunization is a good predictor of immunity or lack thereof.

Melmed et al46 also found that 44% of patients in the study had at least 1 risk factor for hepatitis B (e.g., had a blood transfusion or tattoos). However, only 28% of all patients (47/169) had been vaccinated. Of this subgroup that was immunized, 33% (3/9) had detectable hepatitis B surface antibody titers.
Prior Studies Involving Influenza Vaccination in Pediatric IBD Patients

Studies conducted in children with IBD have involved the influenza vaccine and shown that it is generally immunogenic and safe in this patient population. Mamula et al. prospectively evaluated serologic responses to the 2002–2004 inactivated influenza vaccines in 51 pediatric IBD patients and 29 healthy children. The study demonstrated that children with IBD had a lower seroconversion rate to 1 of 3 influenza strains in the vaccine compared to healthy controls (89% versus 62%). In addition, patients receiving both infliximab and immunomodulators were less likely to seroconvert 2 vaccine strains compared to healthy controls (63% versus 95% for strain A/New Caledonia, 33% versus 89% for strain B/Hong Kong). There were no serious adverse events related to the vaccine. Vaccination did not worsen clinical activity of IBD.

We recently conducted a prospective, open label study to evaluate the safety and immunogenicity of inactivated influenza vaccine in 137 pediatric IBD patients during the 2007–2008 influenza season. The study suggested that the influenza vaccine was safe and immunogenic in children with IBD. The vaccine was well tolerated, with few side effects. There were no serious vaccine-associated adverse events. Immunization did not have an effect on severity of disease activity. A high proportion of patients were seroprotected regardless of immunosuppression status, especially to A strains (79%–100% for A strains, 21%–80% for B strain). However, in the subset of patients who were not seroprotected prior to vaccination, patients receiving anti-TNF therapy were less likely to be seroprotected against influenza strain B after vaccination (14%) compared to patients on other types of IBD therapy (32%–75%).

In the same study, we also compared the proportion of patients who were seroprotected after vaccination to a cohort of pediatric historical healthy controls (n = 76) who were immunized with the same influenza strains as IBD patients in the study during the same influenza season (2007–2008). The proportion of patients who were seroprotected against the 2 influenza A strains was high, and similar between historical controls (84%–85%) and IBD patients (79%–100%) in our study. However, the lower seroprotection rate for strain B in healthy controls suggested that this strain was less immunogenic in general (57%).

Prior Studies Involving Vaccination in Adult IBD Patients

One early study by Stevens et al. showed that adults with IBD who received a booster immunization with tetanus and diphtheria toxoids produced inadequate levels of antibody titers after vaccination. Specifically, patients with CD and UC who were immunized with a tetanus toxoid booster had lower antibody levels in vitro and produced a suboptimal serum tetanus IgG response compared to controls with systemic lupus erythematosus or gastrointestinal disease. Many of the IBD patients who produced an inadequate IgG antibody response to tetanus also had a suboptimal IgG antibody response to diphtheria vaccination.

Other studies found that the immune response to vaccinations in IBD patients may depend on the type of immunosuppressive therapy they receive, especially if they receive anti-TNF therapy. For example, Gelinck et al. studied the serologic response to influenza vaccine in 112 patients who were treated with TNF-α inhibitor for autoimmune diseases, including 22 patients with IBD and 90 patients with rheumatologic disease. The percentage of subjects who had a seroprotective titer was high (80%–94%) and there was no difference among patients who were treated with TNF-α inhibitor, patients who were treated with another immunosuppressive medication, and healthy controls. However, postvaccination GMT against 2 strains was significantly lower in subjects treated with TNF-α inhibitor compared to the other 2 groups. In addition, seroconversion rate to all 3 strains was lower in patients receiving TNF-α inhibitor compared to patients not receiving TNF-α inhibitor. No major side effects or worsening of underlying disease in patients were reported.

Another study by Melmed evaluated the immunogenicity to 23-valent pneumococcal polysaccharide vaccine in IBD patients receiving both anti-TNF and immunomodulator therapy, IBD patients not receiving any immunosuppressive therapy, and in healthy controls. IBD patients who received combination immunosuppressive therapy mounted a lower immune response compared to IBD patients who received nonimmunosuppressive therapy and to controls. These 2 latter groups exhibited a similar response.

SUMMARY

In conclusion, there is a need for more data on the immune response to vaccinations in patients with IBD and other chronic illnesses. Research on patients with chronic illnesses or who are immunocompromised suggest that there are varying degrees of antibody titers that develop after vaccinations. Population studies and questionnaires conducted on adult patients with IBD suggest this population may not be receiving routine vaccines, and may not be seroprotected against various vaccine-preventable infections. The currently available data suggest a good immune response to influenza vaccine, even if IBD patients are receiving systemic immunosuppression. However, some studies have suggested that patients on TNF-α inhibitors may have a slightly decreased immune response; this subpopulation may benefit from booster shots, but formal
studies of this strategy have not been published. Whichever therapy is used, there do not appear to be any significant adverse events from inactivated vaccines.

It is important to conduct further research to evaluate the immune response in IBD patients to various types of vaccines (such as meningitis and human papillomavirus vaccines). If there is evidence that patients do not form an adequate immune response after vaccination, then perhaps clinical guidelines should suggest booster doses. In addition, patients and physicians may falsely assume that these patients will form antibodies and be adequately protected long-term. This latter point argues for further research to examine the sustainability of titers. Even if patients initially form adequate antibody titers after vaccination, these titers may wane and leave patients unknowingly susceptible to infection.

Current guidelines suggest against immunizing IBD patients on immunosuppressive therapy with live vaccines such as varicella. However, data from transplant patients suggest that such immunization may be safe. In addition, the immunocompromised state of IBD patients on immuno-suppression increases their risk of complications from wild-type varicella, making it even more crucial that these patients be protected against varicella infection. Therefore, the efficacy and safety of varicella vaccine in patients receiving immunomodulators is a much needed area of research. In the meantime, for immunocompromised children who are at risk for repeated exposure to varicella in school or daycare, physicians should consider performing a varicella titer and being aware of their immune status.

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