



## Updates in vaccination: Recommendations for adult inflammatory bowel disease patients

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### Abstract

Treatment regimens for inflammatory bowel disease (IBD) incorporate the use of a variety of immunosuppressive agents that increase the risk of infections. Prevention of many of these infections can be achieved by the timely and judicious use of vaccinations. IBD patients tend to be under-immunized. Some of the contributing factors are lack of awareness regarding the significance of vaccinating IBD patients, misperception about safety of vaccinations in immunocompromised patients, ambiguity about the perceived role of the gastroenterologist in contrast to the primary care physician and unavailability of vaccination guidelines focused on IBD population. In general, immunocompetent IBD patients can be vaccinated using standard vaccination recommendations. However there are special considerations for IBD patients receiving immunosuppressive therapy, IBD travelers and pregnant women with IBD. This review discusses current vaccination recommendations with updates for adult IBD patients. Centers for Disease Control and Prevention 2013 vaccination guidelines with 2014 updates and the Advisory Committee on Immunization Practices recommendations have been highlighted as a primary source of recommendations.

**Key words:** Inflammatory bowel disease; Vaccination; Immunocompromised; Influenza; Pneumococcal; Centers for Disease Control and Prevention

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**Core tip:** Patients with inflammatory bowel disease (IBD) are at increased risk of infection because of use of immunosuppressive agents for treatment in many of them. While immunocompetent IBD patients can be vaccinated using standard vaccination schedule, special guidelines need to be followed for IBD patients getting immunosuppressive therapy. In this review article the focus is on current vaccination recommendations for adult IBD patients. This is a much needed dis-

cussion as lack of awareness and misperceptions about vaccination safety is a major cause of under immunization in IBD patients.

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## INTRODUCTION

Inflammatory bowel disease (IBD) is an immunologically mediated disease often necessitating the use of immunosuppressive therapies as treatment. Maintenance therapy can involve long term use of immunomodulators, biologic agents or the combination of both. Immunosuppression leads to increased susceptibility to many infectious diseases as hepatitis B, pneumococcal sepsis and disseminated zoster. Several of these infections are preventable with the timely and diligent use of vaccination<sup>[1,2]</sup>. There has been a longstanding debate about the ability of immunosuppressed patients to mount an adequate antibody response to vaccinations. Currently available knowledge has led to the general consensus that IBD patients including those on immunosuppressive therapy will likely respond adequately to vaccinations<sup>[3]</sup>. However, even if the response is suboptimal in some cases, it may still be sufficient to render immunity. Studies evaluating the safety profile and impact of vaccinations on disease activity have shown reassuring results even in immunocompromised patients. Table 1 demonstrates a widely accepted expert consensus statement that defines an immunocompromised IBD patient. IBD patients can be vaccinated following the standard guidelines applicable to general population. Routine vaccination schedules are recommended to be followed for most IBD patients. Live vaccinations are contraindicated in immunocompromised patients. An approach to vaccination of adult IBD patients including those on immunosuppressive medications is presented in this review article.

## PNEUMOCOCCAL VACCINE

### *Pneumococcal Infection*

*Streptococcus pneumoniae* (pneumococcus) remains a leading cause of serious illness, including bacteremia, meningitis, and pneumonia among adults in the United States<sup>[4]</sup>.

### *Pneumococcal Infection and IBD*

Major risk factors for pneumococcal disease include immunocompromising conditions, chronic medical conditions, functional or anatomic asplenia, CSF

**Table 1 Definition of the immune compromised inflammatory bowel disease patient<sup>[1]</sup>**

|  |
|--|
| Treatment with glucocorticoids: > prednisone 20 mg/d equivalent for 2 wk or more                                     |
| Ongoing treatment with effective doses of 6-mercaptopurine, AZT, Methotrexate and anti tumor necrosis factor therapy |
| Within 3 mo of stopping the above listed immunosuppressive therapies   |
| Significant protein-calorie malnutrition   |

**Table 2 Risk factors for pneumococcal disease**

|  |
|--|
| All adults 65 and older                                  |
| Symptomatic or asymptomatic human immunodeficiency virus |
| Chronic lung disease (COPD, emphysema, and asthma)       |
| Chronic cardiovascular diseases                          |
| Diabetes mellitus  |
| Chronic renal failure                                    |
| Nephrotic syndrome                                       |
| Chronic liver disease (including cirrhosis)              |
| Alcoholism   |
| Cochlear implants  |
| Cerebrospinal fluid leaks                                |
| Immunocompromising conditions                            |
| Functional or anatomic asplenia                          |
| Residents of nursing homes or long-term care facilities  |
| Smokers  |

COPD: Chronic obstructive pulmonary diseases.

leaks and cochlear implants. They are listed in detail in Table 2. Salient factors applicable to IBD patients are age 65 years and older, smoking and use of immunosuppressive agents<sup>[5-7]</sup>.

### ***Pneumococcal vaccination recommendations***

For an adult who has already received 4 doses during childhood, the first revaccination is to be given 5 years after the last dose administered, followed by a lifetime revaccination dose at age 65 years or above<sup>[5]</sup>. For an adult who has not been vaccinated as a child, two doses are given 8 wk apart. This is followed by first revaccination to be given 5 years since the last dose administered, followed by a lifetime revaccination at age 65 years or above. There are two types of pneumococcal vaccines available: Pneumococcal polysaccharide (PPSV23) vaccination (Brand name Pneumovax) and Pneumococcal conjugate 13-valent (PCV13) vaccination (Brand name Prevnar). PPSV23 is the commonly used and recommended vaccine for all adults. However for a subset of adults including immunocompromised IBD patients, at least one dose of PCV13 is recommended to be included in their vaccination regimen. Whenever PCV13 is indicated, it is preferred to be administered before PPSV23 is administered. CDC and ACIP recommend that PCV13 be given in addition to, not instead of, PPSV23 to all immunocompromised adults of all ages. For an adult who has an indication for PCV13 but has not previously received PPSV23, should receive a single dose of PCV13 followed by PPSV23 at least 8

wk later if indicated. If one or more doses of PPSV23 have previously been administered then a dose of PCV13 should be administered at least one year after the last PPSV23 dose was received. Interestingly, PCV13 is not FDA approved for ages less than 50<sup>[5]</sup>. When immunosuppressive therapy is being considered, the interval between pneumococcal vaccination and initiation of immunosuppressive therapy should be at least 2 wk. PCV13 and PPSV23 is now recommended for all adults 65 years or older. If not previously vaccinated, PCV13 should be given first followed by PPSV23 6-12 mo later. If PPSV23 has been given previously, PCV13 should be given  $\geq$  12 mo after<sup>[8]</sup>.

### **Pneumococcal vaccination and IBD**

Studies by Melmed *et al*<sup>[9]</sup> and Dotan *et al*<sup>[10]</sup> provided evidence that neither IBD nor monotherapy with immunomodulators impair vaccine response, however the combined use of anti-tumor necrosis factors (TNF) agents with immunomodulators may diminish response to pneumococcal vaccine 23. Fiorino *et al*<sup>[11]</sup> have demonstrated significantly dampened response to pneumococcal vaccination in IBD patients receiving an anti-TNF agent alone or in combination with azathioprine. Melmed *et al*<sup>[9]</sup> assessed serological responses to PPSV23 in 21 IBD patients on combined immunomodulator and biologic therapy vs 25 non-immunosuppressed patients. Patients on combined therapy had a significantly lower response rate compared to non-immunosuppressed patients (45% vs 85%,  $P = 0.01$ ). Serologic response rates were similar between non-immunosuppressed patients and 19 healthy controls (80% vs 85%). In a prospective cohort study, Dotan *et al*<sup>[10]</sup> found that 75% of 28 IBD patients vaccinated with Pneumovax had at least a 2-fold increase between pre- and post-vaccination titers to at least 4 out of 14 serotypic determinants. All patients initiated thiopurine therapy at or near the time of vaccination. Fiorino *et al*<sup>[11]</sup> evaluated the response rates to pneumococcal vaccination in four different treatment groups: mesalamine, azathioprine, infliximab, and infliximab plus azathioprine. Patients administered infliximab or the combination immunosuppressive therapy had significantly lower response rates (57.6% and 62.5%, respectively) compared with the group on mesalamine (88.6%;  $P < 0.05$  for both comparisons). Azathioprine alone did not influence the response rate to vaccination (78.9%;  $P = 0.43$  vs mesalamine group).

## **INFLUENZA VACCINE**

### **Influenza infection**

Influenza is a highly infectious viral illness that can be fatal as primary infection and may also be complicated by superimposed bacterial infections.

### **Influenza infection and IBD**

Currently there is no knowledge of increased predisposition to influenza infection in non-immunocompromised IBD

patients compared to general population. However, morbidity and mortality are both increased in individuals who are immunocompromised. A multicenter, prospective study was conducted in Tokyo to investigate the age distribution associated with H1N1 influenza in immunocompromised IBD patients. A significantly higher incidence of H1N1 influenza infections in patients aged less than 20 years was noted, however this was comparable to the trend seen in the general population<sup>[12]</sup>.

### **Influenza vaccination recommendations**

Annual vaccination against influenza is recommended for all adult IBD patients. Intranasal live attenuated influenza vaccine (LAIV) and inactive influenza vaccine (IIV)/trivalent inactivated vaccine (TIV) that can be administered intramuscularly or intranasally. All non-pregnant and non-immunocompromised IBD patients can receive either form of vaccine<sup>[8]</sup>. Pregnant, immunocompromised IBD patients and household contacts of immunocompromised patients should not receive live vaccine. Adults aged 65 years and older can receive the standard dose IIV or the high-dose IIV (Fluzone High-Dose). Due to known antigenic drift, a new vaccine is produced annually. As of 2010 the annual influenza vaccine also contains the H1N1 component.

### **Influenza vaccination and IBD**

Based on the currently available data, influenza vaccine is safe and well tolerated in IBD patients. Annual vaccination appears to impart adequate immunogenic response against strain A, irrespective of immunosuppression status. However, seroprotection against strain B strain is impaired and is further blunted due to immunosuppression. In a prospective open label study, Lu *et al*<sup>[13]</sup> found more children with IBD were seroprotected against strains influenza A/H1N1 and influenza A/H3N2 than influenza B strain ( $P < 0.02$ ), regardless of immunosuppression status. Further sub-analysis showed patients on anti-TNF were less protected against B strain compared to non-immunosuppressed IBD patients (14% vs 39%,  $P = 0.025$ ). In their prospective cohort study, deBruyn *et al*<sup>[14]</sup>, children with IBD achieved appropriate immunogenicity to influenza A, immunogenicity to influenza B appears to be diminished, especially with immunosuppressive therapy. For influenza B, 53% children with IBD mounted an immunogenic response compared to 81% in controls ( $P = 0.0009$ ) and 79% immunosuppressed IBD children achieved serologic protection compared to 100% non-immunosuppressed children with IBD ( $P = 0.02$ ). Cullen *et al*<sup>[15]</sup> conducted an observational prospective open-label study and found decreased postvaccine response in patients on combination immunosuppression as compared to non-immunosuppressed patients (36% vs 64%,  $P = 0.02$ ), particularly to 2009 H1N1 influenza strain. Also patients receiving combined immunosuppression had a significantly less increase in geometric mean titers than those on monotherapy immunosuppression (3.5

vs 11.5,  $P = 0.03$ ). A multicenter observational cohort by Rahier *et al.*<sup>[16]</sup>, found H1N1 vaccine to be well tolerated by IBD patients, regardless of therapy and the risk of IBD related-flare was concluded to be low.

## TETANUS, DIPHTHERIA, ACCELLULAR PERTUSSIS VACCINE

### **Tetanus and diphtheria**

Neurotoxin released by *Clostridium tetani* causes neuromuscular excitability leading to prolonged muscle contractions. Those exposed to trauma with contaminated wounds are at risk for this condition<sup>[17]</sup>. Diphtheria is an acute, toxin-mediated respiratory tract illness caused by the corynebacterium diphtheriae.

### **Tetanus, diphtheria and IBD**

All IBD patients are at risk for tetanus after exposure through a contaminated wound<sup>[1,2,18,19]</sup>. There has been a marked decline in the incidence of Diphtheria due to vaccinations<sup>[20]</sup>. A case report of severe infection with a non-toxigenic strain of *C. diphtheria* in immunocompromised patients was reported by Wojewoda *et al.*<sup>[21]</sup>.

### **Tetanus and diphtheria vaccination recommendations**

Tetanus and diphtheria (Td) is recommended as part of the childhood DTaP 5 series injection<sup>[22]</sup>, followed by Td once every 10 years<sup>[22-26]</sup>. All adults with unknown or incomplete history of vaccination should complete a 3-dose primary vaccination series and all pregnant women need to be vaccinated during each pregnancy (preferred during 27-36 wk gestation), regardless of number of years since prior Td or tetanus, diphtheria, acellular, pertussis (TDAP) vaccination<sup>[27]</sup>.

### **Tetanus, diphtheria vaccine and IBD**

Data to date examining efficacy of tetanus vaccination in IBD patients is inconsistent, however tetanus vaccine be administered to all IBD patients irrespective of their immunization status. Nielsen *et al.*<sup>[3]</sup>, revealed that post vaccination increase in antitetanus antibody levels in 10 patients with clinically inactive Crohn's disease (CD) was comparable to 12 healthy controls. Dotan *et al.*<sup>[10]</sup>, found that in 37 patients with IBD who initiated thiopurine therapy at or around the time of Td administration, 73% had seroconversion. Brogan *et al.*<sup>[28]</sup>, suggested an impaired response to the booster vaccination in patients with IBD. Dezfoli *et al.*<sup>[29]</sup>, categorized 59 patients based on their level of immunosuppression (*i.e.*, no therapy, immunomodulator monotherapy, biologic monotherapy, or combined immunomodulator and biologic therapy). Booster response rates with serum antibody levels and geometric mean titers (GMTs) were measured at baseline and approximately 4 wk after vaccination. Protective tetanus titers were achieved in all patients either on an anti-TNF or an immunosuppressant alone

compared to 78% of those on combined therapy ( $P = 0.01$ ).

### **Pertussis**

"Whooping Cough", a highly contagious upper respiratory infection caused by *Bordetella pertussis* can be associated with sequelae including pneumonia, encephalopathy and seizures<sup>[19,30]</sup>. A pertussis epidemic was reported in state of Washington by the Secretary of Health in 2012. About 2520 (37.5 cases per 100000 residents) were reported, a 300% increase compared with the same period in 2011 and the highest number of cases reported in any year since 1942<sup>[31]</sup>.

### **Pertussis and IBD**

A steady increase in risk of pertussis infection in the years after completion of the 5-dose DTaP series has been reported<sup>[32]</sup>. The risk likely continues through adulthood and is attributable, in part, to waning immunity from DTaP vaccines. This increased risk is applicable to IBD patients.

### **Pertussis vaccination recommendations**

For all adults, replacing 1 scheduled Td booster with Tdap is recommended. In an adult with unknown vaccination status, administer the first 2 doses at least 4 wk apart and then third dose 6-12 mo after the second with at least one injection being Tdap<sup>[25]</sup>. For an incompletely vaccinated adult *i.e.*, less than 3 doses, administer remaining doses.

### **Pertussis vaccination and IBD**

IBD patients should receive the Tdap vaccine according to current guidelines, preferably before initiation of immunomodulator therapy. Dezfoli *et al.*<sup>[29]</sup>, prospectively examined 59 consecutive adults with IBD who received a booster vaccination for tetanus, diphtheria and acellular pertussis. Patients were categorized based on their level of immunosuppression (*i.e.*, no therapy, immunomodulator monotherapy, biologic monotherapy, or combined immunomodulator and biologic therapy). Outcomes for these patient groups were compared with a control group of IBS patients receiving mesalamine. Serum antibody titers against pertussis toxoid (PT) and pertussis filamentous hemagglutinin (FHA) were measured at baseline and 4 wk after vaccination. Response rates to pertussis toxoid were 68% in the mesalamine group, 67% in the biologic monotherapy group and 44% in both the immunosuppressive monotherapy and combination therapy groups. Similarly, 84%, 87%, 69% and 67% of the four groups, respectively, achieved response to pertussis filamentous hemagglutinin. No difference in response rates between patients off medications or on biologic monotherapy was noted, as mentioned above. However, response to PT was lower in patients on immunomodulator monotherapy, and postvaccination

**Table 3 Risk factors for meningococcal disease**

|   |
|---|
| College freshman living in dormitories  |
| Microbiologists routinely exposed to <i>Neisseria meningitidis</i>  |
| Military recruits   |
| Persons who travel to or reside in countries where <i>Neisseria meningitidis</i> is hyper-endemic or epidemic particularly if contact with the local population will be prolonged |
| Persons with persistent complement component deficiency   |
| Persons with anatomic or functional asplenia  |
| Persons with human immunodeficiency virus infection   |

titers were lowest to FHA in those on combined immunomodulator and biologic therapy<sup>[29]</sup>.

## HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) is the most common sexually transmitted infection in the world<sup>[33]</sup>. An estimated 20 million persons are currently infected, and an estimated 6.2 million new HPV infections occur annually<sup>[34]</sup>. HPV is known to cause genital warts, cervical, vulvar, vaginal, penile, anal and oropharyngeal cancers. High-risk types of HPV (e.g., types 16 and 18) are associated with 70% of all cervical and anogenital cancers.

### HPV and IBD

Diagnosis of IBD in women is related to an increased risk of abnormal Pap smear<sup>[35-37]</sup>. Immunosuppressive therapy and smoking have been shown to exhibit an association between IBD and cervical dysplasia rather than just the diagnosis of IBD<sup>[38,39]</sup>.

### HPV vaccination recommendations

Physician vigilance is especially warranted for IBD patients transitioning from pediatric age group. Misconception that HPV is not an adult vaccine and also assumption that patients might have been vaccinated already, may lead to HPV under vaccination. Two vaccines are licensed for use in females, bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4), and one HPV vaccine for use in males (HPV4). Vaccination can be used for all IBD patients including immunocompromised patients. A complete series for either HPV4 or HPV2 consists of 3 doses. The second dose should be administered 1-2 mo after the first dose; the third dose should be administered 6 mo after the first dose (at least 24 wk after the first dose). For females, either HPV4 or HPV2 is recommended in a 3-dose series for routine vaccination at age 11 or 12 years, and for those aged 13 through 26 years, if not previously vaccinated. HPV vaccination should not be administered during pregnancy, but a pregnancy test is not required before giving vaccination. If woman is found to be pregnant after vaccination, no intervention is needed and rest of the series should be delayed till after delivery<sup>[8]</sup>. For males, HPV4 is recommended in a 3-dose series for routine vaccination at age 11 or 12

years, and for those aged 13 through 21 years, if not previously vaccinated. Males aged 22 through 26 years may be vaccinated<sup>[40-44]</sup>.

### HPV vaccination and IBD

HPV4 vaccine is safe and immunogenic in most women with IBD including those on immunosuppressive therapy. Jacobson *et al.*<sup>[45]</sup>, administered 3-dose HPV vaccine to 37 IBD females aged 9 to 26 years on immunosuppressive therapy. Geometric mean titers (GMTs) were determined before dose 1 and 1 mo after dose 3. Seropositivity after dose 3 was 100% and GMTs were qualitatively comparable to healthy females. No serious adverse events were attributable to the vaccine.

## MENINGOCOCCAL VACCINE

*Neisseria meningitidis* causes meningitis and sepsis. Risk factors for the development of meningococcal disease include antecedent viral infection, household crowding, chronic underlying illness, and both active and passive smoking<sup>[46]</sup>. They are listed in Table 3.

### Meningococcal disease and IBD

IBD patients with the above risk factors are at increased risk for developing meningococcal disease.

### Meningococcal vaccine recommendations

The two forms of the meningococcal vaccine include polysaccharide vaccine MPSV4 as well as a conjugate vaccine MCV4. The MCV4 vaccine is the vaccine of choice where indicated because it elicits improved primary immune response, as well as strong anamnestic response<sup>[47]</sup>. Administer 2 doses of MCV4 at least 2 mo apart to adults with functional asplenia or persistent complement component deficiencies. First-year college students up through age 21 years who are living in residence halls should be vaccinated if they have not received a dose on or after their 16<sup>th</sup> birthday. For immunocompromised IBD patients, revaccination with MCV4 every 5 years is recommended<sup>[46]</sup>. Human immunodeficiency virus (HIV) infection is not an indication for MCV4, if vaccinated two doses at least 2 mo apart should be given<sup>[8]</sup>. MPSV4 is preferred for people aged 56 and older who have not received MCV4 previously and who only need a single dose, e.g., travelers.

### Meningococcal vaccine and IBD

No studies have evaluated the immunogenic profile of the meningococcal vaccine in the IBD population.

## HEPATITIS B VACCINE

### Hepatitis B

Hepatitis B is one of the most common infections in the world with approximately two billion people

**Table 4 Risk factors for hepatitis**

| Risk factors for hepatitis A                                | Risk factors for hepatitis B   |
|---|--|
| 18 yr and older who care for an international adopted child | Polygamous relationship ( <i>e.g.</i> , persons with more than one sex partner during the previous 6 mo)   |
| IV and non IV illicit drug users                            | Persons seeking evaluation or treatment for a sexually transmitted disease   |
| Homosexual males  | Current or recent injection-drug users   |
| Chronic liver disease patient                               | Homosexual male  |
| Patients awaiting transplant                                | Health-care personnel and public-safety workers who are potentially exposed to blood or other infectious body fluids   |
| Occupational exposure to Hep A                              | All diabetics younger than age 60 yr   |
| Persons who receive clotting factor concentrates            | Diabetics 60 yr or older at the discretion of the treating clinician   |
| Travel to endemic areas                                     | ESRD, HD   |
|   | Human immunodeficiency virus chronic liver disease   |
|   | Household contacts and sex partners of hepatitis B surface antigen positive persons; clients and staff members of institutions for persons with developmental disabilities |
|   | International travelers to countries with high or intermediate prevalence of chronic HBV infection   |

ESRD: End-stage renal disease.

showing an evidence of prior or current infection and approximately 1.5 million dying annually from sequelae such as cirrhosis and hepatocellular carcinoma<sup>[48]</sup>.

### Hepatitis B and IBD

Prior studies comparing the prevalence of HBV in healthy controls and IBD patients showed higher prevalence of HBV in IBD patients. This was attributed to the increased number of blood transfusions, endoscopic and surgical interventions for diagnostic and therapeutic purposes during the course of the disease. However relatively newer studies have demonstrated equal prevalence of HBV in IBD patients as compared to the general population<sup>[49-51]</sup>. Reactivation of chronic HBV also remains a concern in IBD patients on immunosuppressants especially those on dual immunosuppression<sup>[52]</sup>. Fulminant or fatal infections have been reported in patients with IBD receiving immunosuppressive treatment<sup>[51]</sup>.

### Hepatitis B vaccination recommendations

HBV vaccination is recommended in all IBD adults not vaccinated against HBV in childhood or who fall in the CDC identified susceptible group shown in Table 4. CDC 2014 standard recommendation is 0, 1, 4 mo regimen<sup>[8]</sup>. If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, then 3 doses at 0, 1, and 6 mo are indicated. Alternatively, a 4-dose Twinrix schedule, administered on days 0, 7, and 21-30 followed by a booster dose at month 12 may be used. In immunocompromised IBD adults, 3 doses at 0, 1, 6

mo schedule with Recombivax HB 40 µg or 4 doses at 0, 1, 2, 6 mo schedule with 2 doses of 20 µg/mL Engerix is advised. Routine serology testing for immunity is not required after vaccination in healthy individuals. Post vaccination titer testing is recommended for person whose subsequent clinical management depends on knowledge of their immune status, including immunocompromised IBD patients<sup>[53]</sup>. Serologic testing of immunocompromised persons with quantitative anti-HBs is recommended 1-2 mo after administration of the final dose of the primary vaccine series to determine the need for revaccination. A concentration of anti-HBs  $\geq 10$  mIU/mL establishes immunity. Revaccination of immunocompromised patients is achieved by administering Recombivax HB 40 µg/mL on a 3-dose schedule at 0, 1, and 6 mo or 2 doses of Engerix-B 20 µg/mL administered simultaneously on a 4-dose schedule at 0, 1, 2, and 6 mo. Persons who do not have a protective concentration of anti-HBs after revaccination should be tested for HBsAg. If the HBsAg test result is positive, the person should receive appropriate management. Persons who test negative for HBsAg should be considered susceptible to HBV infection and should be counseled about precautions to prevent HBV infection and the need to obtain HBIG post exposure prophylaxis for any known or likely parenteral exposure to HBsAg-positive blood<sup>[53]</sup>. Immunocompromised persons might need annual testing to assess anti-HBs concentrations. For immunocompromised persons the need for booster doses has not been determined. When anti-HBs levels decline to  $< 10$  mIU/mL, annual booster doses should be considered for persons with an ongoing risk for exposure<sup>[53]</sup>. Whenever possible, vaccination is recommended before starting treatment with immunosuppressive agents, preferably at the time of diagnosis.

### HBV vaccine and IBD

Unlike healthy adults where the 3-dose vaccine series produces a protective antibody response in  $> 90\%$  subjects<sup>[53]</sup>, immunogenicity in IBD patients, particularly those on immunosuppressive therapy, has been reported to be low in several studies. Melmed *et al.*<sup>[18]</sup>, Vida *et al.*<sup>[54]</sup>, and Altunöz *et al.*<sup>[55]</sup>, respectively detected anti-HBs antibody in only 33%, 36% and 76% of immunized IBD patients. Gisbert *et al.*<sup>[48]</sup> assessed the effectiveness of HBV vaccine with a double dose at 0, 1 and 2 mo in 241 patients with IBD. Response was achieved in only 59% of patients. Nyström *et al.*<sup>[56]</sup> successfully re-vaccinated HBV vaccine non-responders using a double dose of the combined HAV and HBV vaccine. Forty-four patients who failed to mount an appropriate post vaccination response to a standard hepatitis B vaccination schedule were revaccinated with double-dose combined hepatitis A and B vaccine. An adequate rise in anti-HBs antibody titers was seen in 95% of previous non-responders.

## HEPATITIS A VACCINE

### **Hepatitis A**

Hepatitis A is a common worldwide infection commonly transmitted *via* feco-oral route.

### **HAV and IBD**

Risk factors for hepatitis A virus infection among individuals with IBD are the same as for those without IBD<sup>[3]</sup> (Table 4).

### **HAV vaccine recommendations**

All IBD adults not vaccinated against Hepatitis A in childhood who seek protection against this preventable disease or are categorized to be in the CDC identified susceptible group, should be offered the vaccine. Single-antigen vaccine formulations should be administered in a 2-dose schedule at either 0 and 6-12 mo (Havrix), or 0 and 6-18 mo (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 mo; alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21-30, followed by a booster dose at month 12<sup>[22]</sup>.

### **HAV vaccination and IBD**

Hepatitis A vaccine is an inactivated vaccine that is safe and well tolerated in IBD patients. Data about the immunogenicity of the vaccine primarily comes from pediatric IBD patients. Radzikowski *et al.*<sup>[57]</sup> conducted an open, prospective, and controlled study on anti-HAV-negative IBD patients aged 2-18 years with IBD. HAV vaccine was administered at 0 mo and at 6-12 mo. Seroconversion and GMTs were measured after each vaccine dose. A total of 134 subjects (66 patients and 68 controls) completed the whole study course consisting of two doses of vaccine and six serum samples. There was no significant difference in the rate of seroconversion between 66 IBD patients and 68 controls when measured after the second dose of vaccine (97% vs 100%,  $P = 0.2407$ ). 6-Mercaptopurine (6-MP) or azathioprine (AZA) treatment with and without steroids did not affect seroconversion rates. There were no serious adverse events related to HAV vaccination during the study<sup>[57]</sup>.

Twelve anti HAV-negative patients with IBD were vaccinated using 0 and 6-12 mo schedule. An overall seroconversion rate of 92% was reported. All of the patients were receiving infliximab at the time of vaccination. Two of the patients were receiving concurrent methotrexate, both of whom responded to the HAV vaccine. The authors concluded that pediatric IBD patients on a wide variety of medications for control of their disease are likely able to respond adequately to the HAV vaccine<sup>[58]</sup>. This seems to be questioned in a recent open prospective study that evaluated the efficacy of HAV vaccination in 419 anti-HAV-negative adult patients with IBD. It was concluded

that although HAV vaccination is generally effective in patients with IBD, the seroconversion rates are noted to be lower in patients receiving anti-TNF agents<sup>[59]</sup>.

## VARICELLA: CHICKEN POX VACCINE

### **Varicella: Chicken pox**

Primary infection with Varicella Zoster virus (VZV) is highly contagious condition. Immunocompromised patients are especially at risk for severe infection, severe disease occurs in approximately 30% of such persons with primary infection<sup>[60]</sup>.

### **VZV and IBD**

Most IBD adults are generally considered to have acquired immunity to VZV either from childhood infection or vaccination. Interestingly, a 5 year retrospective review of charts of the newly diagnosed 163 IBD patients at University of Buffalo found that a total of 66% of all of the patients had a history of disease or vaccination. Measurable titers against varicella were found in only 77% of all of the patients<sup>[61]</sup>. There have been several reports of severe, disseminated and occasionally fatal primary varicella infection in immunosuppressed IBD patients. Corticosteroids and combination immunosuppression appeared to be a particular risk for contracting this infection<sup>[62]</sup>.

### **VZV vaccine recommendations**

CDC recommends that all adults without evidence of immunity to varicella should receive 2 doses of single-antigen varicella vaccine or a second dose if they have received only 1 dose. Adult IBD patients should be evaluated for immunity to VZV as soon as the diagnosis is made. Table 5 explains how to establish evidence of immunity to varicella in adults. Unimmunized, immunocompetent IBD adults should receive immunization with a two-dose series of live varicella vaccine as above at least 3 wk before the start of immunosuppressive therapy. For immunocompromised patients, live-virus varicella vaccine is contraindicated until immunosuppressive therapy has been discontinued for at least 3 mo<sup>[1,22,63]</sup>.

### **VZV vaccination in IBD**

Data about the immunogenicity and safety of this live vaccine especially in immunocompromised IBD patients remains scarce. In 2008, Levin<sup>[64]</sup> analyzed clinical trials of varicella vaccine administration to immunocompromised children that were reported since 1975. It was suggested that varicella vaccine is safe and effective in immunocompromised patients. This has been most successful when vaccination occurs during periods of limited immune suppression, such as before treatment with immunosuppressive therapy, when therapy is stopped temporarily, or when maintenance immune suppression is low. However,

**Table 5 Evidence of immunity to varicella in adults includes any of the following**

|  |
|--|
| Documentation of 2 doses of varicella vaccine at least 4 wk apart  |
| United States-born before 1980 except health-care personnel and pregnant women                                 |
| History of varicella based on diagnosis or verification of varicella disease by a health-care provider         |
| History of herpes zoster based on diagnosis or verification of herpes zoster disease by a health-care provider |
| Laboratory evidence of immunity or laboratory confirmation of disease  |

in patients with IBD receiving immunosuppressants, temporary withdrawal from immunosuppression might pose considerable risks of disease recurrence or flare. Therefore in immunocompromised IBD patients at increased risk of exposure to varicella *e.g.*, primary school teachers, health-care workers and patients with no prior immunity, the risks of acquiring the infection need to be weighed against the potential risks and benefits of vaccinations<sup>[18,51]</sup>.

## ZOSTER: SHINGLES VACCINE

### *Herpes zoster*

After primary infection, VZV persists as a latent infection in sensory nerve ganglia. The virus can reactivate after a period of latency, causing herpes zoster (HZ) especially in the elderly and those who are immunocompromised. The most common complication of shingles is postherpetic neuralgia. Other less common complications include meningoencephalitis, cerebellitis, herpes zoster ophthalmicus, and Ramsay-Hunt syndrome. In immunocompromised individuals, reactivation can be complicated by disseminated infection and can be potentially fatal<sup>[65]</sup>.

### *HZ and IBD*

Patients with IBD, especially those on immunosuppression, are at increased risk for herpes zoster. Gupta *et al.*<sup>[66]</sup>, in their retrospective cohort and nested case-control study demonstrated that patients with IBD, especially those on immunosuppressive medications, are at higher risk for herpes zoster compared with the general population. In another large retrospective cohort and nested case-control study including more than 100000 patients, Long *et al.*<sup>[67]</sup>, found an increased risk of HZ among IBD patients as compared to non-IBD patients. Use of thiopurines, anti-TNF agents, combination therapy and corticosteroids increases HZ risk.

### *HZ vaccine recommendation*

A single dose of zoster vaccine for all IBD adults 60 years and older, regardless of previous shingles. HZ vaccine is contraindicated in immunosuppressed patients. However, the current ACIP recommendations report that patients receiving short-term (*i.e.*, < 14 d) or low-to-moderate dose (*i.e.*, < 20 mg/d)

corticosteroid therapy are not considered to be sufficiently immunosuppressed to justify avoiding the live zoster vaccine. This is also applicable to patients on low-dose methotrexate (*i.e.*,  $\leq 0.4$  mg/kg per week), azathioprine ( $\leq 3.0$  mg/kg per day), or 6-mercaptopurine ( $\leq 1.5$  mg/kg per day)<sup>[65]</sup>. This opinion does not extend to other live vaccines and patients on anti-TNF therapy<sup>[68]</sup>.

### *HZ vaccine and IBD*

Zhang *et al.*<sup>[69]</sup>, examined the association between HZ vaccine and HZ incidence within and beyond 42 d after vaccination in patients with selected immune-mediated diseases and in relation to biologics and other therapies used to treat these conditions. Retrospective cohort study of 463541 Medicare beneficiaries 60 years and older with 66751 patients with inflammatory bowel disease were included in the study. Receipt of HZ vaccine was not associated with a short-term increase in HZ incidence among Medicare beneficiaries with selected immune-mediated diseases, including those exposed to biologics. The vaccine was associated with a lower HZ incidence over a median of 2 years of follow-up.

## MEASLES, MUMPS, RUBELLA VACCINE

### *Measles, mumps, rubella*

The developed world has seen a remarkable drop in the incidence of measles, mumps, rubella (MMR) after the introduction of universal vaccination protocols<sup>[70]</sup>.

### *MMR and IBD*

Even though immunocompetent IBD patients do not appear to be at higher risk than general patients, measles can be severe and prolonged among immunocompromised persons<sup>[71]</sup>. Naganuma *et al.*<sup>[72]</sup>, in their study of IBD patients found a significant number of patients seronegative for rubella, measles and mumps (30%, 34%, and 37% respectively). Almost 30% of the patients with a past history of rubella or measles did not have seropositive antibody levels and a total of 54% of the patients being treated with immunosuppressant displayed seronegative levels of antibodies specific for at least one of the viruses.

### *MMR vaccine recommendations*

Individuals born before 1957 are considered immune to measles and mumps. Immunity is established by documenting lab titers, clinically diagnosed disease is not acceptable as an evidence of MMR immunity. CDC 2014 guidelines recommend that all adults born in 1957 or later should have documentation of 1 or more doses of MMR vaccine (unless vaccine is contraindicated) if they have not already been vaccinated in childhood. MMR vaccine is contraindicated in immunocompromised IBD patients and considering the risk for prolonged viremia, vaccine should not be



**Table 6 Live attenuated vaccines with recommended times of administration<sup>[2]</sup>**

| Vaccine   | Before initiation of immunosuppressive therapy      | Already on immunosuppressive therapy   |
|-----------|---|--|
| MMR       | Contraindicated if plans to start therapy in 6 wk   | Contraindicated  |
| Zoster    | Contraindicated if plans to start therapy in 1-3 mo | Contraindicated-could consider if:<br>On short-term corticosteroids (< 14 d)<br>On Methotrexate (< 0.4 mg/kg per week)<br>On Azathioprine (< 3.0 mg/kg per day)<br>On 6-mercaptopurine (< 1.5 mg/kg per day) |
| Varicella | Contraindicated if plans to start therapy in 1-3 mo | Contraindicated  |

MMR: Measles, mumps, rubella.

**Table 7 Inflammatory bowel disease traveler**

| Vaccine                     | Type                 | Travel related indication   |
|-----------------------------|----------------------|---|
| Yellow fever                | Live                 | Parts of South America and Sub-Saharan Africa                                     |
| Typhoid                     | Live and inactivated | Asia, Africa, Latin America, The Caribbean, and Oceania                           |
| polio                       |                      |   |
| influenza                   |                      |   |
| BCG vaccine                 | Live                 | Highly endemic area > 1 yr  |
| Hepatitis A                 | inactivated          | Central or South America, Mexico, Asia (except Japan), Africa, and Eastern Europe |
| Meningococcal vaccine       | Inactivated          | Africa  |
| Japanese encephalitis virus | Inactivated          | Rural Japan   |

BCG: Bacillus Calmette-Gue'rin.

given to patients expected to start immunosuppressive agents in < 6 wk<sup>[73]</sup>. The MMR vaccine is considered safe for household contacts of immunosuppressed persons with IBD<sup>[74]</sup>.

**MMR vaccine and IBD**

Early on there was concern about a possible link between measles virus containing vaccines and inflammatory bowel disease (IBD). This was raised by Thompson *et al*<sup>[75]</sup> in 1995 when their study in United Kingdom suggested that measles virus containing vaccine recipients had an up to 3-fold increased risk for subsequently developing Crohn's disease and ulcerative colitis. However several larger studies have now demonstrated that there is no increased risk of IBD with MMR vaccination<sup>[76,77]</sup> ACIP concurs with the conclusion<sup>[71]</sup>.

**TIMING OF LIVE VACCINE IN PATIENTS ON IMMUNOSUPPRESSIVE THERAPY OR CONSIDERING INITIATION**

Timing of live vaccines is particularly important when dealing with IBD patients on immunosuppressants or those with plans to start immunosuppression. Table 6 provides general considerations for timing of live immunization in IBD patients<sup>[2]</sup>.

**SPECIAL SITUATIONS SUCH AS PREGNANCY, HOUSEHOLD CONTACTS AND THE TRAVELER WITH IBD**

Within IBD patients, special population groups such as pregnant patients, household contacts of immunocompromised patients and travelers pose special challenges. In general, it is recommended that the household contacts of immunocompromised IBD patients be vaccinated according to recommended guidelines. However if a live vaccine is administered, an immunocompromised patient may be predisposed to exposure from the vaccinated family member. If the vaccinated household contact is noticed to have a rash that developed after a live vaccine as varicella, standard contact precautions should be observed. An IBD traveler may warrant evaluation by an infectious disease specialist or travel medicine specialist. Table 7 details recommended vaccines for IBD traveler.

Pregnancy safety categories are applicable to all vaccinations and are a helpful guide to a physician when administering vaccines to this subgroup. Table 8 summarizes pregnancy safety categories of different vaccines. An immunocompromised mother caring for a newborn should be aware of live vaccines that are administered to newborns and can inadvertently expose her to live pathogens as Rotavirus vaccines. Administration of one dose of Tdap vaccine to pregnant women during each pregnancy (preferred during 27-36 wk gestation), regardless of number of years since prior Td or Tdap vaccination is recommended. HPV vaccines are not recommended for use in pregnant women. Pregnant women should be assessed for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the health-care facility. The second dose should be administered 4-8 wk after the first dose<sup>[23]</sup>. For women of childbearing age, regardless of birth year, rubella immunity should be determined. Pregnant women who do not have evidence of immunity should receive MMR vaccine

**Table 8 Vaccination in pregnancy**

| Category B  | Category C  | Category X  |
|---|---|---|
| Influenza (LAIV)  | PPSV23<br>Adacel( Tdap)   | Varicella; non-immune<br>1 <sup>st</sup> dose. Upon completion or termination of pregnancy and before discharge from the health care facility |
| Influenza (IIV)   | 1 dose of Tdap vaccine during each pregnancy regardless of immunization status  | 2 <sup>nd</sup> dose. 4-8 wk later  |
| Boostrix (Tdap)<br>1 dose of Tdap vaccine during each pregnancy regardless of immunization status | Zoster<br>Meningococcus<br>Hep A and B  |   |
| HPV 4, HPV 2  | MMR. Non-immune<br>1 <sup>st</sup> dose. Upon completion or termination of pregnancy and before discharge from the health care facility |   |
| PCV 13  | 2 <sup>nd</sup> dose. 4-8 wk later  |   |

Newborns of immunosuppressed mothers must not receive any live vaccination up to first 6 mo. Tdap: Tetanus, diphtheria, acellular, pertussis; HPV: Human papillomavirus vaccine.

**Table 9 Vaccinations in inflammatory bowel disease summary (quick reference)**

| Vaccine   | How often  | Live vaccine | Patients on immunosuppressive therapy |
|---|--|--------------|---------------------------------------|
| Influenza (Flu Vaccine)                                   | 1 dose every year  | Nasal spray  | Use flu shot only                     |
| Varicella (Chicken Pox)                                   | If no documented immunity: 2 doses 4-8 wk apart  | Yes          | Contraindicated                       |
| Measles, mumps, rubella                                   | If no documented immunity: 2 doses, 4 wk apart   | Yes          | Contraindicated                       |
| Zoster (Shingles)   | 1 dose starting at age 60 yr or older  | Yes          | Contraindicated                       |
| Tetanus, Diphtheria, Acellular Pertussis (Td/Tdap)        | If no prior vaccination: 3 doses (0, 1, 6-12). Then 1 dose of Tdap followed by a booster of Td every 10 yr   | No           | Follow recommended regimen            |
| Human papilloma virus                                     | Female: 3 doses through age 26 (0, 2 and 6 mo)   | No           | Follow recommended regimen            |
| Pneumococcal (pneumonia vaccine) for subset of patients   | Male: 3 doses through age 21 (0, 2 and 6 mo)<br>If no prior vaccination: (0, 2 then 5 yr) 1 dose at 65<br>If had prior vaccination: 1 dose 5 yr after the last dose and 1 dose at age 65 | No           | Follow recommended regimen            |
| Meningococcal (meningitis vaccine) for subset of patients | 2 doses, 2 mo apart  | No           | Follow recommended regimen            |
| Hepatitis A   | 2 doses, 6 mo apart  | No           | Follow recommended regimen            |
| Hepatitis B   | 3 doses (0, 1 and 6 mo)  | No           | Follow recommended regimen            |

Centers for Disease Control and Prevention recommended vaccines for adults 2014, modified for inflammatory bowel disease patients.

upon completion or termination of pregnancy and before discharge from the health-care facility.

## CONCLUSION

Vaccinations offer immunity against preventable diseases. A diligent effort should be made to vaccinate all IBD patients. Immunocompromised IBD patients are at a higher risk of infection with vaccine preventable diseases. Optimally, these patients should be vaccinated before immunosuppressive therapy is initiated. Live vaccines are contraindicated in immunocompromised patient due to risks of vaccine-associated infection. Despite the concerns for impaired immune response in immunocompromised IBD patients, most of these patients develop adequate response after vaccination. Table 9 provides a quick reference guide for vaccinating IBD patients.

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