IBD patients were vaccinated against pneumococcus, 28% against influenza, and 45% against tetanus.[18] No data exist on rates of vaccination against VZV in this population. According to a recent study, only 14% of gastroenterologists inquired about vaccination history.[19]

The current case highlights the risk of the severe, potentially disabling infections that can occur when clinicians fail to vaccinate patients prior to initiating chronic immunosuppressive therapy. Although primary care providers coordinate patient care among specialists, immunosuppressive medications are often initiated by gastroenterologists or rheumatologists, and these specialists share the responsibility for assessing patients' vaccination status and providing patients with the appropriate vaccines. Protecting patients prior to initiating immunosuppressive therapy will help to ensure that the cure is not worse than the disease.

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Review

Varicella Zoster Virus Infection in Patients with Inflammatory Bowel Disease

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Varicella zoster virus (VZV) may cause either varicella (chickenpox) or herpes zoster (shingles). When VZV is contracted in childhood, the infection causes chickenpox and is characterized by a diffuse vesicular rash. Later in life, the virus may reactivate as herpes zoster, which typically causes a skin rash localized to a single dermatome. This infection may be followed by postherpetic neuralgia in 10–20% of cases. In an immunocompromised host, primary and reactivated VZV infection may cause disseminated disease—including hepatitis, pneumonia, and/or encephalitis—as described in our recent case report.[1] Corticosteroids, thiopurines, and anti–tumor necrosis factor (anti-TNF) agents are all associated with an increased risk of infection. The combination of any of these immunomodulatory agents further increases the risk of VZV reactivation.[1]

The case reported by Elwir and associates highlights the importance of identifying patients who may require immunosuppressive therapy and considering appropriate

vaccinations prior to initiating such therapy.[2] Physicians should therefore query patients with inflammatory bowel disease (IBD) regarding their vaccination history and VZV exposure at the initial visit. VZV titers should be obtained prior to starting immunosuppressive therapy if prior exposure is uncertain. As the case by Elwir and colleagues demonstrates, however, although a patient may recall having chickenpox in childhood, history alone may not be adequate to assess for seropositivity.[2] In 1 study of 104 patients who remembered being exposed to VZV, 7 patients had negative or indeterminate VZV immunoglobulin (Ig) G titers. Of the 17 patients who reported a negative history of chickenpox, all had positive VZV IgG titers.[3] If patients have no prior history of VZV or a negative serology result and immunosuppressive therapy is not imminent, they should be vaccinated against VZV. Additionally, nonimmunosuppressed patients aged 50 years or older should be given the zoster vaccine, which has been shown to decrease the incidence of herpes zoster by 51.3% and the incidence of postherpetic neuralgia by 66.5%.[4] Unfortunately, a study by Melmed and colleagues showed that 11% of IBD patients did not reliably recall a history of chickenpox or varicella vaccination, and 75% of seronegative patients were receiving immunosuppressive therapy.[5]

Once patients are already immunosuppressed, the appropriateness of live vaccines is less clear. The concern is that the administration of live vaccines to immunosuppressed individuals may be associated with an increased risk of disseminated infection. Some doctors recommend that varicella vaccination be administered at least 1–3 months prior to initiating immunosuppressive therapy, but this recommendation is not based on a strong level of evidence.[6,7] European guidelines state that the varicella vaccine may be administered up to 3 weeks prior to initiating immunomodulators.[7] Additionally, recommendations state that the vaccine should not be given for at least 3 months following immunosuppressive therapy.[7] While there are no clear guidelines regarding the timing of herpes zoster vaccination, a similar schedule can be considered. Although most physicians avoid live vaccination in immunosuppressed patients, the Advisory Committee on Immunization Practices advises that zoster vaccination may be considered in patients receiving short-term corticosteroid therapy (<14 days) or low doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6-mercaptopurine (<1.5 mg/kg/day).[6]

A recent retrospective cohort study evaluated patients with immune-mediated diseases (including IBD) who had received herpes zoster vaccination.[8] Six hundred and thirty-three of these patients were receiving biologic agents at the time of vaccination, including 551 patients who were receiving anti-TNF therapy. None of the patients developed varicella or herpes zoster within 42 days of vaccination. Importantly, vaccination decreased the overall rates of herpes zoster in all patients, including those receiving biologic agents and steroids.

In addition to the potential risk of disseminated infection from live vaccines, some evidence suggests that vaccines may be less effective in patients who are immunosuppressed. However, this conclusion is also controversial. Children with IBD who were on immunosuppressive therapy and received the varicella vaccine were found to tolerate the vaccine well and to achieve appropriate seroconversion.[9] A study of adult IBD patients receiving thiopurines found that they were able to generate a normal immune response to pneumococcal, tetanus, and *Haemophilus influenzae* type b vaccines.[10] However, another study of IBD patients found that individuals receiving corticosteroids, biologic agents, and/or immunomodulators had a lower seroprotection rate following H1N1 influenza vaccination.[11] Seroprotection decreased with combination immunosuppressive therapy compared to monotherapy. Despite these data, vaccinating immunosuppressed patients with non-live vaccines in the hope of preventing infections is still reasonable and recommended.[6]

Once an IBD patient develops VZV infection, guidelines are unclear on the management of either primary varicella or reactivation of prior infection. While reactivation of VZV may be severe and can require hospitalization and/or cessation of immunosuppression, primary varicella infection is of particular concern due to the risk of significant morbidity and mortality.[12,13] For an immunosuppressed IBD patient with either primary varicella or herpes zoster who appears to be well, treatment may consist of oral antiviral medication.[1] In more severe disease, intravenous antiviral therapy should be initiated, and an infectious disease consultation is recommended. Based on available (albeit limited) data, we would favor withdrawing immunosuppressive therapy in cases of primary varicella, although continuing immunosuppressive therapy in conjunction with antiviral therapy could be considered in cases of uncomplicated herpes zoster. If immunosuppressive therapy is withdrawn, clinicians can consider restarting this therapy once the patient's vesicles have resolved. However, reinitiation of immunosuppressive therapy should probably be done in consultation with an infectious disease specialist.

In summary, patients who are diagnosed with IBD should be queried about their history of VZV exposure at their initial visit. Patients who cannot recall a history of chickenpox in childhood should have their VZV IgG titers checked, and they should be advised to undergo vaccination if they are seronegative, provided that immunosuppressive therapy is not imminent. Providers

should also be aware that, while vaccinations may not be as effective in immunosuppressed individuals, they are nonetheless recommended. Treatment of VZV infection and management of the underlying immunosuppressive therapy varies depending on the severity of the disease and whether the infection is a primary infection or reactivation (shingles). Consultation with an infectious disease specialist is recommended.

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