Human Papillomavirus in Inflammatory Bowel Disease: Disease, Prevention and Future Challenges

Immunomodulators and biologics are commonly used medications in Inflammatory Bowel Disease (IBD). IBD patients on immunosuppressive therapies have shown some increased risk of cervical dysplasia and, therefore, likely cervical cancer, caused by the Human Papillomavirus (HPV). HPV vaccination has been recommended for all women 9-26 years of age, including immunosuppressed patients, for the prevention of cervical cancer. In addition, the vaccine is now also recommended for males aged 9 to 21, for the prevention of genital warts. HPV also has a role in other anogenital cancers, head and neck cancers and non-cancerous conditions. The HPV vaccine could also prevent these other conditions – making HPV vaccination even more important. Unfortunately, HPV vaccination uptake rates have fallen in the general population and several studies have shown even lower rates of vaccination among immunocompromised patients, such as those IBD patients on immunomodulators and biologics. Many potential barriers have been cited for this discrepancy.

BACKGROUND

Immunomodulators and biologics are commonly used therapies for patients with IBD, including Crohn’s disease and ulcerative colitis. These therapies improve quality of life and reduce the risk of relapse. Unfortunately, this immune suppression can make IBD patients more susceptible to acquiring infections. Many infections are preventable through vaccination and guidelines have been developed for vaccination of IBD patients (Table 1). These guidelines recommend against the use of live vaccines in patients on immunosuppressive medications, but encourage the use of non-live vaccines, such as the HPV vaccine.

The HPV vaccine is one of the recommended vaccines for patients with IBD. HPV affects approximately 20 million Americans. Most HPV infections are transient and asymptomatic, but certain
types of the HPV virus can persist and lead to anogenital cancers, head and neck cancers and non-cancerous diseases, such as genital warts and recurrent respiratory papillomatosis.

Cervical cancer is the most well-recognized outcome from persistent HPV infection. Approximately 12,000 women are diagnosed in the United States with cervical cancer each year and about one-third that number die from the disease. However, other cancers can also be caused by HPV and their incidence is increasing. For example, the incidence of HPV-related oropharyngeal cancers increased from 16% in 1984 to 72% in 2004. Based on these trends, it estimated that the annual number of HPV-positive oropharyngeal cancers will exceed the annual number of cervical cancers in the United States by the year 2020.9

**HPV in IBD**

One of the reasons that the HPV vaccine is recommended in IBD patients is the growing concern that female IBD patients are at an increased risk of developing cervical dysplasia, which could lead to cervical cancer. Many studies have analyzed the risk of cervical dysplasia in IBD patients with mixed results. Several controlled trials have shown statistically significant increases in cervical dysplasia among patients with IBD compared to controls.10-11 A large case-control study by Marehbian et al. showed that patients with Crohn’s disease had higher rates of cervical dysplasia compared to controls. In addition, it also showed that among patients with Crohn’s, those on any immunosuppressive medication were at an increased risk of cervical dysplasia compared to those not on immunosuppressive therapies.

### Table 1. Inactivated Vaccine Recommendations for Immunosuppressed Adults

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Timing</th>
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<tr>
<td>HPV</td>
<td>0, 2 and 6 months in females aged 9-26 and males 9-21 (immunocompromised or high-risk males 21-26), not previously vaccinated</td>
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<tr>
<td>Hepatitis A</td>
<td>0, 0-12 months (or 6-18 months), booster &gt; 10 years</td>
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<tr>
<td>Hepatitis B</td>
<td>1,1-2,4-6 months - check titers to ensure response, if none repeat vaccination with double dose</td>
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<tr>
<td>Influenza</td>
<td>Annual trivalent inactivated vaccine (avoid live vaccine, FluMist)</td>
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<tr>
<td>Meningococcal</td>
<td>Vaccinate if at risk and if not previously vaccinated</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Vaccinate if not previously vaccinated, one-time revaccination after 5 years of immunosuppressive therapy</td>
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<tr>
<td>Td/Tdap</td>
<td>Vaccinate with Td if not had in the last 10 years and previously vaccinated with Tdap; Give Tdap if only ever received Td and it has been &gt;2 years since last Td</td>
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Furthermore, those Crohn’s patients on more than one immunosuppressive medication were at an even higher risk of cervical dysplasia. However, there are other studies that do not confirm these findings, but many of these studies did show differences in subgroup analyses. Therefore, there may be an increased risk of cervical dysplasia among women with IBD, but further research is necessary to clarify any potentially confounding variables, such as total exposure to immunosuppressive medications.

While some trials suggest increased rates of cervical dysplasia among women with IBD, studies have not confirmed an association between cervical cancer and IBD. There are only a few small trials that have looked at this association between cervical cancer and IBD, necessitating further research to identify the possibility of any true association.

Other HPV-Related Diseases
HPV has been implicated in other cancers, including other anogenital (vulvar, vaginal, penile, and anal) malignancies and oropharyngeal cancers. In addition, there is a possible association with esophageal and lung cancers.

The number of non-cervical HPV-related malignancies in the US is equal to the number or cervical malignancies. The incidence of these non-cervical HPV-related malignancies has been increasing, while the incidence of cervical cancer has been declining. The decline in cervical cancer is likely related to screening with Papanicolaou (Pap) smears. However, these other HPV-related cancers have no well-accepted and routinely used screening tests.

Head and neck cancers are the most common of the non-cervical HPV-related malignancies. HPV-related oropharyngeal cancers have better outcomes than those not associated with the virus, with 28-80% lower mortality. In addition, these patients are typically younger with a better performance status. The rise of oropharyngeal cancers in young patients may at least in part be related to changes in sexual behavior. HPV infection in the oropharynx, as in the cervix, has been associated with high-risk sexual behavior. Many studies have suggested that orogential sex is one of these high-risk behaviors.

HPV has also been associated with non-malignant conditions, such as genital warts and recurrent respiratory papillomatosis (RRP). Genital warts increase the transmission of the virus to others and potentially places more people at risk for HPV-related malignancies. RRP is generally a benign recurrent condition that affects both children and adults, with a bi-modal distribution – affecting those less than 5 years of age from vertical transmission and those between 20-30 years from acquired HPV infection. RRP is an HPV infection of the upper aerodigestive tract with a variable course – from aggressive with pulmonary involvement (continued on page 22)
to isolated laryngeal disease. The former presentation tends to be more aggressive and very rarely there is a conversion to malignancy. While RRP is a rare disease, it does have a substantial burden on both the affected patients and society, as the disease involves frequent recurrences and multiple surgical treatments.\textsuperscript{18}

There are no studies looking at these other HPV-related diseases specifically in the IBD population. However, there has been some association between the presence of HIV and increased risk for many of these non-cervical HPV-related conditions.\textsuperscript{19} Given that many IBD patients treated with immunomodulators and biologics are immunosuppressed it is reasonable to consider that they may also be at increased risk for developing HPV-related diseases.

**HPV Vaccine**

There are two HPV vaccines licensed by the Food and Drug Administration (FDA). The bivalent vaccine, Cervarix, prevents the two most virulent types of HPV – 16 and 18. These two strains of HPV cause approximately 70\% of cervical cancers. The quadrivalent HPV vaccine, Gardasil, prevents four different types of HPV – 16, 18, 6 and 11. HPV 6 and 11 are responsible for 90\% of genital warts. HPV 16 is also the most common cause of HPV-related cancers of the head and neck and anus.

Both the bivalent and quadrivalent vaccines are administered in a 3-dose series. The second dose is given 1-2 months after the first dose and the third dose is given 6 months after the first dose, and at least 24 weeks after the first dose.

Either the bivalent or quadrivalent vaccines are recommended for females at ages 11 or 12 years. The vaccine can be started as early as 9 years of age and is recommended for those aged 13-26 who have not been previously vaccinated.

In addition, only the quadrivalent, and not the bivalent, vaccine is now also recommended for males aged 11 or 12 years. As with females, the vaccination can be administered starting at age 9. For those who have not been previously vaccinated, catch-up vaccination can be administered to males aged 13-21 years. In addition, vaccination is routinely recommended for men who have sex with men and immunocompromised men between the ages of 22-26.

The quadrivalent HPV vaccine has shown 98\%-100\% efficacy in HPV-naïve females for the prevention of cervical intraepithelial lesions of grade 2 or worse.\textsuperscript{9} However, when looking at sexually active females the efficacy rates decreased substantially to 34-44\%. Therefore, it is preferred that vaccination occurs prior to the initiation of sexual activity. However, even if patients have already been infected with HPV, they still have protection from the vaccine types that they have not previously acquired.

**Future Challenges**

Despite all the previously mentioned benefits of HPV vaccination, vaccine uptake rates continue to remain low in the general population. Furthermore, vaccination rates among those with IBD are often lower than the general population. The reasons for decreased uptake rates of the HPV vaccine among the general population is likely related to parental attitudes and concerns for safety. Decreased immunization rates among IBD patients is further explained by concerns about vaccinating patients while on immunosuppressive medications and specialists’ reliance on primary care providers to vaccinate.

The National Immunization Survey has consistently shown low uptake rates of the HPV vaccine since its approval for use. While the uptake rates have been low, this survey had shown a slight trend upward.\textsuperscript{20-22} However, recent data from an article published in *Pediatrics* shows growing concerns among parents regarding the vaccine’s safety and utility. These concerns translated into an increasing number of parents that are not planning to vaccinate their children against the HPV vaccination. (Graph 1 \textsuperscript{23}) The article postulates that since parents are less likely to vaccinate their children, despite clinician recommendations, additional education, possibly through social marketing campaigns, is warranted.\textsuperscript{23}

While the HPV vaccination uptake rate among the general population is low and decreasing, vaccine uptake among IBD patients is even lower. One small study among IBD patients showed that only 17.1\% had even received counseling about the HPV vaccine.\textsuperscript{24} In addition to parental concerns about the vaccine, IBD patients may have suboptimal utilization of the HPV vaccine because of primary care physician’s (PCP’s) discomfort in utilizing vaccines in immunosuppressed patients and ambiguity regarding who should be providing the vaccine. In one survey of PCPs, only
30% felt comfortable providing immunizations to immunosuppressed patients. In a survey conducted of American College of Gastroenterology members, 64% believed that PCPs should determine which vaccines to give and when to give them. Furthermore, 83% of these same physicians felt that the PCP should also administer these vaccines. This discrepancy between PCPs comfort with vaccinations in immunosuppressed patients and gastroenterologists’ beliefs that PCPs should be providing these preventive services leaves many patients who are at greatest need for vaccination without such services.

CONCLUSION
IBD patients are commonly treated with immunosuppressive therapies to maintain remission and increase quality of life. This immunosuppression may increase the risk of HPV-related malignancies and diseases among this patient population. HPV vaccination is recommended for all females 9-26 years of age and all males 9-21. In addition, immunosuppressed males should receive the vaccine up to age 26. However, rates of the HPV vaccine uptake are low in the general population and possibly even lower among IBD patients. Parental attitudes, PCP’s discomfort with immunizations in immunosuppressed patients and ambiguity as to which provider should administer vaccines are all possible reasons for these low uptake rates of the HPV vaccine.

References