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ORIGINAL ARTICLE

Many Inflammatory Bowel Disease Patients Are Not Immune to Measles or Pertussis

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Abstract
Background Current guidelines emphasize vaccination for influenza and pneumococcus for IBD patients and the avoidance of live virus vaccines for those who are on immunosuppressive (ISS) therapy. Given the recent resurgence of measles and pertussis infections, we assessed the immune status of our IBD population in order to advise about these risks.
Methods We prospectively collected measles and pertussis titers in our IBD patients from February 1–May 1, 2015. Immune status based on standard threshold values was determined: measles antibodies $\leq$0.8 antibody index (AI) = negative immunity, 0.9–1.1 AI = equivocal immunity and titers $\geq$1.2 AI = positive immunity. For pertussis immunity, anti-pertussis antibodies $\leq$5 IU/mL were considered negative immunity. Univariate analysis was performed to examine predictive factors including age, disease duration, and current medical therapies.
Results A total of 122 patients' titers were assessed (77 Crohn's disease, 1 indeterminate colitis, and 45 ulcerative colitis). Sixteen (13.1 %) patients lacked detectable immunity to measles, and four (3 %) had equivocal immunity. Twelve (75 %) of the measles non-immune patients were on ISS therapy versus 65 (64 %) of 102 immune patients (OR 1.7, 95 % CI 0.5–5.9, $p = 0.34$). Out of 96 patients, 58 (60 %) were not immune to pertussis. Disease duration $\geq$10 years and age $\geq$50 were associated with significant lower measles titers.
Conclusions A significant number of our IBD patients lack immunity to measles, and a majority of our IBD patients do not have detectable immunity to pertussis. Importantly, the majority of the measles non-immune patients are on ISS therapy and therefore unable to receive a booster.

Keywords Measles · Pertussis · Inflammatory bowel disease · MMR · Tdap · Vaccination

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that includes Crohn's disease (CD) and ulcerative colitis (UC). An estimated 1.6 million Americans currently suffer from inflammatory bowel disease (IBD) [1]. Standard management of IBD often includes the use of immunosuppressant therapies, and such patients have been associated with an increased risk of infections, including some vaccine-preventable infections [2, 3].

Recently reported has been the resurgence of measles and pertussis infections in the USA, two infections that were essentially almost eradicated with the widespread vaccination schedules implemented in this country years ago. Measles is a highly contagious infection caused by the *measles* virus, which by 2000 was eliminated in the USA (elimination is defined by the absence of endemic transmission in a geographic area for at least 12 months)[4]. However, since 2004 there has been a resurgence, which is attributed to unvaccinated individuals and in part to the so-called anti-vaxxers, a group of people who intentionally have not vaccinated their children [5, 6].

Pertussis, more commonly known as whooping cough, is a highly communicable disease caused by *Bordetella*

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pertussis. Cases of pertussis have gradually been increasing since 1980s and peaked in 2014 with more than 32,000 cases reported nationwide [7]. The increasing prevalence of pertussis is thought to be due to the well-described waning immunity to pertussis among young adults, further supported by studies demonstrating transmission to be secondary to adult carriers transmitting the organism to infants [8, 9].

Given these public health concerns, we were interested in assessing the potential risk for these infections in our large IBD population, many of whom are immune-compromised. Of particular interest was the immune status of patients on immunosuppressive therapies including anti-tumor necrosis factor (anti-TNF), as these patients are unable to receive the live MMR vaccine, which is contraindicated in immunocompromised individuals [10].

We hypothesized that a significant number of our IBD patients would have low or undetectable titers to the *measles* virus and to *Bordetella pertussis* and that there would be a greater number of patients who are non-immune receiving immune suppressive therapy.

Materials and Methods

This was an institutional review board-approved retrospective study of all IBD patients who were seen at the University of Chicago from February 1, 2015 up until May 1, 2015, the time we implemented the standard of practice in our IBD center to obtain immunization titers for measles virus and *Bordetella pertussis.*

In our IBD center, we utilize an electronic medical record that includes the Physician Quality Reporting System (PQRS) measures, as well as other maintenance items, including annual vaccination against influenza and 5-yearly pneumococcal vaccination (at least one time). Although not built into our templates, we also routinely discuss varicella zoster, human papilloma virus, meningococcal, and hepatitis vaccinations. Most recently, due to the public health concerns mentioned above, we incorporated routine assessment of measles and pertussis immunity and vaccination status in a single practitioner's clinical practice. This was done with the intention of reporting our results and advising patients of their risks and need for vaccination or avoidance plans, as appropriate.

For this study, we included consecutive patients who were 18 years of age and older with clinical, endoscopic, and histologic confirmation of UC or CD who had measles and or pertussis titers levels obtained. We obtained disease-related and patient-related variables including age, gender, IBD diagnosis, disease duration, measles and *Bordetella pertussis* titer levels, and immunomodulation or immunosuppressive (ISS) therapies at the time of titers being drawn, including anti-TNF, anti integrin, azathioprine (AZA)/6-mercaptopurine (6-MP), and methotrexate (MTX). We also obtained history of childhood vaccination and subsequent boosters to measles and pertussis. The vaccination history was compared to patients' immune status.

Immune Status

We defined immune status based on standard threshold values as follows: Measles antibodies $\leq$0.8 antibody index (AI) was considered not immune, 0.9–1.1 AI was considered equivocal immunity and titers $\geq$1.2 AI was positive immunity. For pertussis immunity, anti-pertussis toxin (PT) antibodies level of $\leq$5 IU/mL was considered not immune. Given that there is no standard threshold for anti-filamentous hemagglutinin (anti-FHA) titers, this could not be interpreted and therefore was not included in our final analysis. The appropriateness for booster immunity was determined based on these results and ISS therapy.

Using simple statistics, we determined the immune status of all our patients. We then performed univariate analyses to examine predictive factors including age, disease duration, and current medical therapies. We used Chi-square test and Fisher's exact test with a two-sided p value of 0.05 to test for statistical significance. The odds ratio (OR) of non-immunity on ISS therapies versus being immune on these therapies was calculated.

Results

A total of 122 patients' titers were assessed (77 CD, 1 indeterminate colitis, and 45 UC) with a median age of 39 (range 19–76). Fifty-seven of 122 patients (47 %) were on MTX, AZA, or MP, 53 (43 %) were on anti-TNF, and 18 (15 %) were receiving anti-integrin therapy.

Measles Immunity

Of the 122 patients assessed, 16 (13.1 %) lacked detectable immunity to measles with titer levels $\leq$0.8 IA, four (3 %) had equivocal immunity (titers 0.9–1.1 AI), and 102 (83.6 %) were immune (titers $\geq$ 1.2 AI). Twelve (75.0 %) of the measles non-immune patients were on ISS therapy compared with 65 (63.7 %) of 102 immune patients; OR 1.7, 95 % CI 0.5–5.9, $p = 0.34$. Two of the 16 non-immune patients were on an anti-integrin, and seven (43.8 %) were females of childbearing age.

Disease duration of 10 years or greater ($n = 65$) was associated with mean titer levels of 7 AI compared to 12 AI in those with disease duration of less than 10 years ($n = 55$), $p = 0.04$. Similarly, the mean titer levels in

patients 50 year of age or older ($n = 37$) was 6 AI versus a mean titer level of 10.5 in patients younger then 50 years (=85), $p = <0.0001$. The mean titer levels of patients on ISS therapies was 4.4 versus 5.3, $p =$ NS, among those who were on non-ISS therapies (Table 1).

Pertussis Immunity

Ninety-six patients had anti-PT titers measured and 58 (60.4 %) were not immune, with titer levels measuring ≤5 IU/mL. Thirty-seven (63.8 %) of 58 non-immune patients were on ISS therapy, compared with 24 (63.2 %) of 38 pertussis immune patients who were on ISS therapy, OR 1.03, 95 % CI 6.2–12, $p = 0.95$.

Patients with disease duration of greater than or equal to 10 years had a mean pertussis titer level of 5 IU/mL, compared with patients with disease duration of less than 10 years, whose mean pertussis titer was 4 IU/mL ($p = 0.04$). Similarly, patients 50 years of age and older had mean titer levels of 7.1 IU/mL compared with patients younger than 50 years of age, whose mean titers were 3.7 IU/ml ($p = 0.03$). The median titer levels for patients receiving ISS was 8.6 IU/mL compared to 10 IU/mL in patients receiving non-ISS therapies ($p =$ NS) (Table 1).

Vaccination History

Eighty-eight patients (72 %) agreed to provide their vaccination history. Sixty-two (70 %) and 60 (68 %) patients reported childhood vaccinations to measles and pertussis, respectively. Twenty (23 %) in both groups did not know their childhood vaccination history. Fifty-three (85 %) of those who recalled receiving the childhood vaccination for measles were also found to be immune, and 18 (30 %) of those who recalled receiving pertussis vaccinations were immune. All six patients who reported not receiving childhood measles vaccination had positive titers (without reporting a history of being infected with measles or receiving a booster), and five of eight patients (62 %) who reported not receiving the pertussis vaccination or booster were immune. Eleven of 12 (92 %) patients who reportedly received a booster to measles were also found to be immune; however, only four of eight (50 %) who received a booster to pertussis were immune.

Table 1 Assessment of selective risk factors and measles and pertussis immune status of IBD patients

Group	Mean pertussis titer (IU/mL)	Mean measles titer (AI)
Age (years)		
≥50	7.1 ($n = 30$)	6 ($n = 37$)
<50	3.7 ($n = 66$)	10.5 ($n = 85$)
	($p = 0.03$)	($p \leq 0.0001$)
Disease duration (years)		
≥10	5 ($n = 56$)*	7 ($n = 65$)*
<10	4 ($n = 39$)*	12 ($n = 55$)*
	($p = 0.04$)	($p = 0.04$)
Current therapy		
ISS	8.6 ($n = 61$)	4.4 ($n = 79$)
No ISS	10 ($n = 35$)	5.2 ($n = 43$)
	($p = 0.3$)	($p = 0.08$)

ISS = Immunosuppressant therapy (methotrexate, 6-mercaptopurine, azathioprine and/or Anti-TNF)

* Two patients did not have record of year of diagnosis (one whose both measles and pertussis titers were assessed and one with only measles titer)

Discussion

This is the first study to assess measles immunity and the largest study to assess pertussis titers in patients with IBD. We found that a significant number of our IBD patients lack immunity to measles, and a majority of our IBD patients do not have detectable immunity to pertussis. We also found that patient recall of vaccination history was not predictive of immune status.

It is well known that patients with IBD, and especially those who are receiving immunosuppressive therapies, are at increased risk of both opportunistic and non-opportunistic infections [11], which have been in part attributed to immunomodulation and immunosuppressive therapies. Toruner and colleagues demonstrated that corticosteroids, thiopurines (AZA, [6-MP]), and anti-TNF agents are individually associated with this increased risk (OR 2.9, 95 % CI 1.5–5.3), and the combination of these agents increased this risk multiple fold (OR 14.5, 95 % CI 4.9–43). Age 50 years and older compared with 24 and younger was also associated with a greater risk of opportunistic infections among IBD patients (OR 3.0, 95 % CI 1.2–7.2)[12]. In addition, the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry, a long-term follow-up study identified moderate-to-severe disease activity (HR 2.24, 95 % CI 1.57, 3.19, $p < 0.001$), narcotic analgesic treatment (HR 1.98, 95 % CI 1.44, 2.73, $p < 0.001$), prednisone therapy (HR 1.57, 95 % CI 1.17, 2.10, $p = 0.002$), and infliximab treatment (HR 1.43, 95 % CI 1.11, 1.84, p 0.006) to be independent risk factors for serious infections among CD patients [13].

Because of these risks, patients with IBD are recommended to receive vaccination against vaccine-preventable illnesses. The current IBD-related guidelines and quality measures have focused primarily on influenza, pneumococcal infection, meningococcal infection, HPV, and varicella zoster [10, 14] with particular emphasis on

vaccination prior to initiation of immune suppression due to a well-described attenuated immune response while on such therapies. Such attenuated vaccine responses have been demonstrated in the IBD population in a study by Melmed and colleagues, in which 64 IBD patients received pneumococcal vaccine. Of those receiving immune-suppressive therapies, only 45 % developed active immunity, compared with a "control" group of IBD patients who were not receiving immune suppressive therapies in which 80 % developed active immunity ($p \leq 0.01$)[15]. Similarly, Dezfoli and colleagues from the same institution reported the outcome of tetanus and pertussis vaccinations in IBD patients receiving immunosuppression and found that patients on combined immunosuppression with anti-TNF and thiopurines or methotrexate were less likely to develop active immunity than those on no therapy or in healthy controls [16]. Most recently, deBruyn and colleagues demonstrated an attenuated response to influenza vaccine in IBD patients receiving infliximab therapy [17].

Little or no attention has been paid to measles virus infection, in part because measles was thought to have been nearly eradicated previously. Because of the recent resurgence of measles infection, understanding the risk in IBD patients is of particular importance. In our study, 19 % of the patients lacked detectable immunity to measles or had equivocal immunity. Importantly, a majority of these patients were receiving ISS therapy and therefore could not receive the live virus booster vaccination. We also found that disease duration $\geq$10 years and age $\geq$50 were associated with significant lower measles titers. These patients are at particular risk of a serious infection with the measles virus and need counseling regarding such risk and precautions to avoid exposure to infected individuals. It is of further interest to note that many of our patients did not know their vaccination history, and of those who did recall their vaccination history or booster history, it did not correlate with the subsequent titer results and immune status. While knowing a patient's vaccination history may be helpful, our study suggests that there appears to be no substitute for knowing their actual immune status.

Although pertussis infection has never been eradicated, it also has had resurgence, with similar concerns for those who are immune-compromised. In this study, 60 % of the patients were not immune to pertussis. Opposite to our findings with measles immunity, patients with disease duration <10 years and age <50 were associated with non-immunity to pertussis. This was not an expected finding, given the known attenuation of immunity over time. However, this may be due to these patients having received the combined diphtheria, tetanus and pertussis (Tdap) booster vaccine, per the CDC guidelines.

We believe that our findings add important information to the national discussion about vaccinations and safety of therapies in the IBD population. At the same time, there has been a movement to better define the risk of live virus vaccines in such patients, with a recent claims data analysis demonstrating the apparent safety of the live virus varicella zoster vaccine administered to rheumatoid arthritis and IBD patients who were receiving anti-TNF therapies [18]. This added to the literature and a previous study that had demonstrated similar safety of zoster vaccination in patients receiving steroids or immunomodulation therapy with thiopurines and MTX [19]. The implication of these large studies is that administration of such viruses may be safer than previously believed. Nonetheless, our guidelines have not changed, and clinicians must still carefully weigh the relative risks and benefits of such vaccinations in these patients [20].

There are several limitations to this study. Firstly, it is an observational study performed in a tertiary IBD clinic, so the patient population included may not be generalizable to all IBD patients. In addition, we were unable to assess the relationship between immune-based therapies or even disease activity and immunity in this study. Future prospective studies will be required to clarify these issues.

Summary and Conclusions

In this study we have identified a significant infectious risk in our immune-compromised IBD population, which we believe should be incorporated into current and future plans for IBD management. A significant number of our IBD patients were found to be non-immune to measles and a majority of our IBD patients did not have detectable immunity to pertussis. Given the recent resurgence and ongoing public health risks of these particular infections, we suggest that assessment of immune status against these infections should be part of the routine health maintenance for IBD patients. Importantly, this assessment should be performed prior to initiation of immune suppressive therapies, as booster vaccinations for measles are contraindicated in those receiving immune suppression. In addition, clinicians should consider further confirmation of conversion to active immunity after providing initial vaccination or boosters in such patients. Ongoing efforts to educate the general (non-IBD) public about the safety and importance of vaccinations must continue and future strategies to confirm and communicate these findings and recommendations are needed.

Compliance with ethical standards

Conflicts of interest The authors have no relevant conflict of interest.

References

1. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126:1504–1517.
2. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of pneumonia among patients with inflammatory bowel disease. *Am J Gastroenterol*. 2013;108:240–248.
3. Tinsley A, Williams E, Liu G, Elwir S, Yoo L, Melmed G, Sands B. The incidence of influenza and influenza-related complications in inflammatory bowel disease patients across the united states. *Presented at the 2013 Annual Scientific Meeting of the American College of Gastroenterology*. San Diego, CA. 2013; Abstract 70.
4. Measles history. [Web]. 2014; http://www.cdc.gov/measles/about/history.html. Accessed January 1, 2016.
5. Zipprich J, Winter K, Hacker J, Xia D, Watt J, Harriman K. Measles Outbreak–California, December 2014–February 2015. [Web]. 2015; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6406a5.htm?s_cid=mm6406a5_w. Accessed April 4, 2015.
6. Slade TA, Klekamp BG, Rico E, Mejia-Echeverry A. Measles Outbreak in an Unvaccinated Family and a Possibly Associated International Traveler—Orange County, Florida, December 2012–January 2013. [Web]. 2014; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6336a1.htm. Accessed April 4, 2015.
7. Pertussis (Whooping Cough) Surveillance and Reporting. [Web]. 2015; http://www.cdc.gov/pertussis/surv-reporting.html. Accessed January 5, 2015.
8. Wendelboe AM, Njamkepo E, Bourillon A, et al. Transmission of bordetella pertussis to young infants. *Pediatr Infect Dis J*. 2007;26:293–299.
9. Skoff TH, Kenyon C, Cocoros N, et al. Sources of infant pertussis infection in the united states. *Pediatrics*. 2015;136:635–641.
10. Sands BE, Cuffari C, Katz J, et al. Guidelines for immunizations in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2004;10:677–692.
11. Dave M, Purohit T, Razonable R, Loftus EV Jr. Opportunistic infections due to inflammatory bowel disease therapy. *Inflamm Bowel Dis*. 2014;20:196–212.
12. Toruner M, Loftus EV Jr, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. 2008;134:929–936.
13. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the treat registry. *Am J Gastroenterol*. 2012;107:1409–1422.
14. Dezfoli S, Melmed GY. Vaccination issues in patients with inflammatory bowel disease receiving immunosuppression. *Gastroenterol Hepatol (N Y)*. 2012;8:504–512.
15. Melmed GY, Agarwal N, Frenck RW, et al. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2010;105:148–154.
16. Dezfoli S, Horton HA, Thepyasuwan N, et al. Combined immunosuppression impairs immunogenicity to tetanus and pertussis vaccination among patients with inflammatory bowel disease. *Inflamm Bowel Dis.*. 2015;21:1754–1760.
17. deBruyn J, Fonseca K, Ghosh S, et al. Immunogenicity of influenza vaccine for patients with inflammatory bowel disease on maintenance infliximab therapy: a randomized trial. *Inflamm Bowel Dis*. 2016;22:638–647.
18. Winthrop KL, Baddley JW, Chen L, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. *JAMA*. 2013;309:887–895.
19. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA*. 2012;308:43–49.
20. Heijstek MW, Kamphuis S, Armbrust W, et al. Effects of the live attenuated measles–mumps–rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. *JAMA*. 2013;309:2449–2456.