UT Southwestern Medical Center

Health Maintenance and IBD
- Collaborative approach between PCP and Specialist

Tasneem Ahmed, DO

Internal Medicine Grand Rounds

UT Southwestern Medical Center

August 22, 2014

This is to acknowledge that Dr Tasneem Ahmed has disclosed that she does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Ahmed will not be discussing off-label uses in her presentation.

Biographical Information

Tasneem Ahmed is an Assistant Professor in the Division of Digestive and Liver Disease. She graduated from University of Texas at Austin and University of North Texas Health Sciences Center after which she completed her medicine and fellowship training at Cleveland Clinic. Dr Ahmed is an IBD specialist focusing on the care of patients with Crohn's disease and Ulcerative colitis. Her specific interests within this area include women's issues in IBD, disease outcomes in different ethnicities, and quality improvement in IBD.

Purpose and Overview

This presentation will review the basics of Inflammatory bowel disease and the importance of preventive health services in this population. The main purposes are to highlight the importance of making a timely diagnosis, importance of vaccinations in IBD, and risks of osteoporosis and extraintestinal malignancies associated with IBD and immunosuppression.

Educational Objectives:

1. To understand the basics of Inflammatory Bowel disease and the importance of timely referral to subspecialist.

2. To understand the importance of appropriate vaccinations in IBD patients who are on immunosuppressive therapy in order to decrease the risk of vaccine preventable illnesses.

3. To understand the risk for osteoporosis and extraintestinal malignancies associated with IBD and immunosuppression.

4. To understand the benefits of smoking cessation in Crohn's disease.

What is Inflammatory Bowel Disease (IBD)?

Crohn's disease (CD) and Ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract, collectively termed IBD. Both diseases manifest in a variety of different ways but are characterized as having a relapsing and remitting course as evidenced by episodes of acute flares in symptoms and periods of remission. The onset of IBD typically occurs in the second and third decades of life with a second peak in the sixth and seventh decade. The prevalence of both CD and UC is highest in North America, northern Europe, and the United Kingdom with averages ranging 100 to 200 cases per 100,000 (1). Lower rates have been reported in African Americans and the lowest rates have been in the Hispanic and Asian populations. It is interesting to note that countries with historically low rates of IBD have been witnessing a rise in incidence in the past one to two decades, particularly for Crohn's disease (2). This pattern of increase in CD in developing countries has suggested that environmental factors play a larger role than previously thought in disease pathogenesis. (See Figures 1 and 2)

In America, it is estimated that 1.5 million people are affected accounting for 2.3 million physician visits and 180,000 hospital admissions annually (1). Moreover, the economic cost of IBD is estimated at $6.3 billion annually (1).

Figure 1

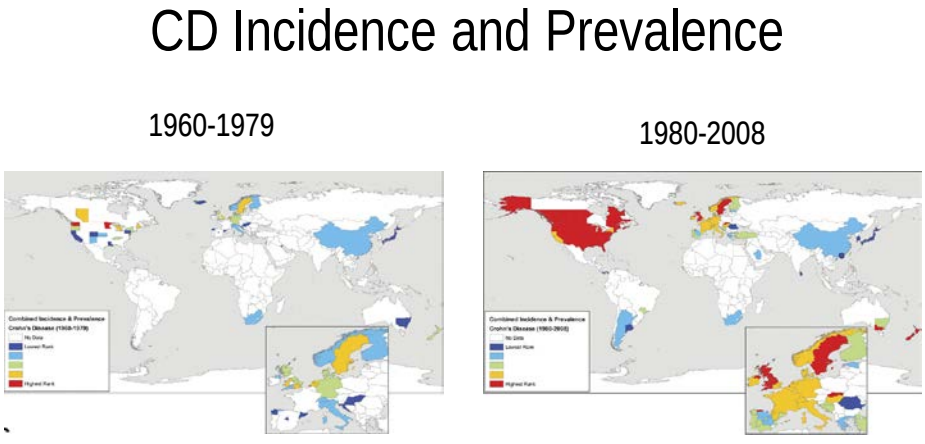
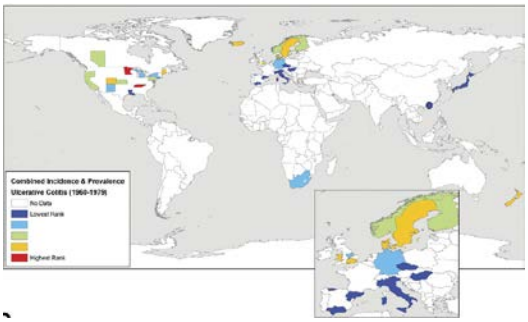


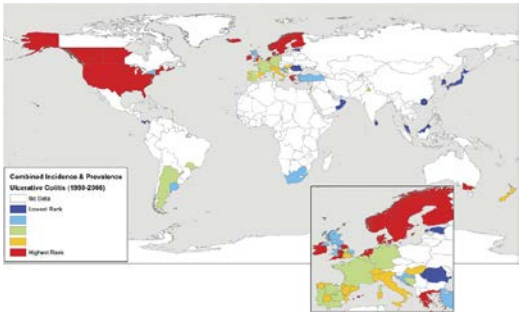
Figure 2

UC Incidence and Prevalence

1960-1979



1980-2008



The pathophysiology is not completely understood but thought to be a disordered immune response to bacterial flora in genetically predisposed individuals. The most widely accepted theory is that intestinal microbiota activates immune cells leading to dysregulated cytokine production leading to intestinal inflammation. An additional proposed mechanism is that these increased cytokines may modulate composition of commensal flora or alter gene expression in specific bacterial subgroups causing increased growth rates and virulence leading to inflammation (1).

The key features of both UC and CD are listed below. It is important to keep in mind that up to 15% of patients will have an initial diagnosis of indeterminate colitis.

Table 1. Key Features of UC and CD

Ulcerative colitis	Crohn's disease
Bloody diarrhea, urgency, tenesmus	Chronic and occasional nocturnal diarrhea, abdominal pain, weight loss, fevers
Mucosal inflammation	Transmural inflammation
Extends from rectum proximally in a continuous fashion	Affects any site of GI tract (Terminal ileum most common) Patchy and segmental

When to refer a patient to the IBD clinic?

The diagnosis of IBD can be challenging at times. The diagnosis is made based on a composite of clinical, endoscopic, pathologic, and radiological features. There is no single laboratory test diagnostic of IBD. Patients may have mild anemia- likely iron deficiency, leukocytosis and thrombocytosis reflecting systemic inflammation, low serum albumin indicating protein loss and malnutrition, decreased electrolytes and vitamin levels, and elevated inflammatory markers- ESR and CRP. More recently, stool studies such as fecal calprotectin and serological markers have also been implicated in aiding with the diagnosis as well as prognostication of disease course. Fecal calprotectin has been shown to correlate with mucosal disease activity and can help to predict response to treatment or relapse (3). It has shown to be more useful when compared to fecal lactoferrin. Fecal calprotectin can be used as a non-invasive marker to screen for inflammation in those patients suspect to have IBD when presenting to their primary care physician. The IBD serological markers have been widely studied and have been shown to be more useful as supportive data for the diagnosis but not recommended as a screening tool for diagnosis. These markers are currently being studied for their possible utility in risk stratification of severe disease and prognostication. To make the diagnosis, endoscopy and histologic findings of chronic inflammation is still needed and of the utmost importance. Of note, there is a significant overlap in the symptoms between IBD and Irritable bowel syndrome (IBS) as shown below in Table 2.

Table 2. How to differentiate between IBD and IBS

Symptom	IBD	IBS
Abdominal pain	x	x
Diarrhea	x	x
Bloating	x	x
Constipation	x	x
Mucus in stools	x	x
Rectal bleeding/urgency	x	
Weight loss	x	
Nocturnal symptoms	x	
Anemia	x	
Elevated inflammatory markers	x	
Extraintestinal manifestations	x	

Oftentimes, these symptoms of IBS are reported before the diagnosis of IBD which can delay a timely diagnosis. Schoepfer and colleagues analyzed a cohort of 905 CD patients and found the median diagnostic delay was 9 months (4). More importantly, the authors found the length of diagnostic delay correlated with the occurrence of bowel stenosis (OR 1.76, p=0.011) and intestinal surgery (OR 2.03, p=0.003) for delay of ≥ 25 months (4).

Timely diagnosis is essential in IBD for the following reasons:

1) Decrease duration of symptoms
2) Increase response to medical therapy
3) Minimize complications from disease
4) Decrease rates of hospitalizations
5) Minimize risk of surgery

Therefore, it is important for the primary care physician to recognize some of the “red flag” symptoms associated with IBD such as rectal bleeding, nocturnal symptoms, abdominal pain, and weight loss in conjunction with appropriate laboratory abnormalities in order to make timely referrals to a specialist.

Vaccinations and IBD

IBD patients are often treated with a host of immunosuppressive medications including steroids, immunomodulators (thiopurines and methotrexate), and anti-TNF agents. The use of these medications is associated with an increased risk of infectious complications related to the immunosuppressant (5). Some of these infections are vaccine preventable. With all this in mind, it is important to remember the need for vaccination is increased in IBD patients given their chronic illness and immunosuppression (5). Unfortunately, multiple studies have reported the rate of immunization to be quite low among IBD patients. For example, one tertiary care center study of 169 IBD patients found only 28% received annual influenza vaccine and only 9% received pneumococcal vaccine (5). Of note, in that group, 86% of patients had past or current immunosuppressive medication use. This study underscores the opportunity for improvement in this area of IBD management. Reasons for these low immunization rates have purported to be related to lack of awareness and concern for side effects by patients, suggesting we as providers are not appropriately educating patients. Likewise, physicians' knowledge of immunization schedules is poor. A recent survey found that one-third of gastroenterologists would mistakenly prescribe live vaccines to their immunosuppressed patients, one half incorrectly withheld inactivated vaccines to immunosuppressed patients, and one-third would avoid live vaccines in their immunocompetent patients (6). On a separate note, it appears both gastroenterologists and primary care providers are hesitant to take ownership for vaccinating these patients. In a survey of 108 gastroenterologists, 83% felt it was the PCP's responsibility while in a different survey of family care physicians, 29% felt comfortable making immunization recommendations (7, 8). With all this in mind, we recommend both specialists and PCPs should obtain a good vaccine history and accept a shared responsibility. Specialists should provide clear recommendations for the appropriate vaccines to be administered and both physician groups should educate patients on importance of vaccination.

In general, IBD patients should follow the same vaccination schedule as the general population. However, there are a few special considerations to keep in mind. First, patients who are immunosuppressed which include those on prednisone >20 mg/day for 2 or more weeks, Methotrexate >0.4 mg/kg/day, Azathioprine >3.0 mg/kg/day, 6-MP >1.5 mg/kg/day, and anti-TNF therapy should avoid live vaccines (10-11). Additionally, patients with significant protein-calorie malnutrition are also considered immunosuppressed.

Table 3. Live Vaccines

- BCG
- Intranasal influenza
- Measles, mumps, rubella (MMR)
- Typhoid (oral)
- Smallpox
- Varicella
- Yellow fever
- Zoster

Physicians should assess immune status on a case by case basis to determine risks versus benefits. Vaccinations should be deferred for at least one month after discontinuation of therapy (10-11). All patients should receive an annual influenza vaccine (intranasal is contraindicated if on immunosuppression), pneumococcal vaccine, Td/Tdap, Hepatitis B vaccine (very important in those starting anti-TNF therapy), and Hepatitis A vaccine (10-11). Special considerations are the following:

- Meningococcal vaccination which is important for our young patients who are entering college (10)
- HPV vaccine which should be considered for older patients who are negative for HPV on pap smear and older males given increased risk of HPV with immunosuppression and anal cancer with perianal Crohn's disease (10)

In conclusion, it is important to remember the best time to vaccinate is when patients are newly diagnosed with IBD and not yet started on any form of immunosuppression (10-12). Vaccination history should be checked and updated periodically especially when patients are on immunosuppressive therapy. Patients with IBD generally follow the same vaccination guidelines as general public with the exception of live vaccines. Lastly, because vaccination rates remain low in IBD patients, it is very important for vaccinations to be co-managed between the specialist and primary care physician in order decrease risk for vaccine preventable illnesses.

Osteoporosis and IBD

Osteoporosis has proven to be a common problem in IBD. It is defined as a bone mineral density (BMD) from dual x-ray absorptiometry (DXA) of the proximal femur or lumbar spine 2.5 or more standard deviations below what would be expected for a healthy young adult (T score<-2.5) (10). It is estimated to affect 14-42% of patients with IBD (13). Although this is an asymptomatic disease itself, it significantly increases fracture risk resulting in severe morbidity and excess mortality. Each standard deviation decline in BMD has been roughly associated with a doubling in the risk of fracture (13-14). Thus, the prevention and treatment of this disease process is very important.

Factors most commonly associated with osteoporosis in IBD include older age, female sex, low BMI, malabsorption and decreased dietary intake of calcium and vitamin D, poor nutritional status, smoking, sedentary lifestyle, and use of certain medications which can affect bone metabolism (10,13,14). Additionally, this increased risk of osteoporosis is thought to be related to the underlying inflammatory process (13). While cyclosporine and methotrexate have been associated with low BMD, steroid use is perhaps the most common factor associated with bone loss in IBD patients (13, 14). It is important to recognize the greatest bone loss occurs in first six months of the initial steroid course (14). Moreover, it is also important to be aware of the cumulative steroid use over a patient's disease course. Prolonged steroid use was defined as >20 mg for more than 3 months (10-14). For these patients, the best intervention has been shown to be minimization of steroid use.

As bone loss does not cause any specific signs or symptoms before the development of a fracture, it is important to appropriately screen these patients according to established guidelines for the general population. The practice guidelines for the diagnosis and management of osteoporosis in IBD by the American Gastroenterology Association (AGA) and American College of Gastroenterology (ACG) published in 2003 recommend DXA testing in a select group of IBD patients. This group included postmenopausal women or men over the age of 50, patients with prolonged steroid use, patients with a personal history of a low trauma fracture, and patients with hypogonadism (15). If the initial DXA is normal, the AGA recommends repeat testing in 2-3 years. Important interventions to discuss include smoking cessation, regular weight bearing exercise, minimize alcohol and caffeine intake, and minimize medications which can affect perception/balance (TCAs, BZDs, antihistamines, etc) (13-15). Adequate calcium and vitamin D intake should be encouraged and all patients with IBD should be assessed for low Vitamin D and treated accordingly. It is

highly important to recognize this disease process with appropriate screening in order to treat and decrease risk of future fractures.

Extraintestinal malignancies and IBD

In recent years, the medical management of CD and UC has evolved dramatically from mesalamine and steroid use to immunomodulators and anti-TNF agents. The immunomodulators (thiopurines and methotrexate) and anti-TNF agents (infliximab, adalimumab, and certolizumab pegol) have been shown to improve IBD-related symptoms, induce/maintain steroid free remission, heal inflamed mucosa, and decrease rates of hospitalizations and surgeries (1). Current guidelines recommend use of these medications in the treatment of moderate-to-severe CD and UC as well as their continued use in those who attain remission. Moreover, there is an increasing trend to use these agents earlier in disease course. While these agents confer substantial benefits, there is ever growing concern that there may be an associated increased risk of cancer. Of note, thiopurines, methotrexate, and the anti-TNF agents do carry a black box warning regarding their neoplastic potential. Patients and clinicians are often unfamiliar with the specific types of malignancy as well as the extent of their risk. Here, we will focus on skin cancers and cervical cancer.

Skin cancer

The great majority of evidence linking risk of skin cancer with immunosuppression stems from the transplant literature. Nonmelanoma skin cancers (NMSC) account for over 90% of all skin cancers post-transplantation (10). The two main subtypes: squamous cell cancer and basal cell cancer have also been found to be higher in transplant patients when compared to the general population with squamous cell cancer being the most common skin cancer in this group. This cancer occurs 65 to 250 times higher than the general population, whereas basal cell cancer is only 10 times higher in transplant patients (10).

Long and colleagues studied a cohort of 53,377 IBD patients in order to evaluate the risk of NMSC in patients with and without IBD as well as those IBD patients who use or do not use immunosuppressive medications. The authors found that persistent exposure to thiopurines (≥365 days) had more than a four-fold risk of NMSC compared to IBD patients not exposed to thiopurines (16). Recent exposure to thiopurines (≤90 days) significantly increased the

risk of NMSC (OR 3.56). Additionally, recent or persistent exposure to Adalimumab or Infliximab had more than a two-fold risk of NSMC compared to those receiving no meds (16). This risk was increased in those patients on combination therapy to more than seven-fold. A study by a different group did not find that methotrexate exposure increased risk of NMSC in IBD compared to methotrexate naïve non-IBD patients (17).

Melanoma is the fifth most common cancer in men with more than 76,000 cases diagnosed annually in America (18). While the incidence is increasing, there is no decrease in mortality rate with approximately 9,000 Americans dying of melanoma each year (18). Data has been conflicting in the overall risk of melanoma related to IBD specific immunosuppression. Earlier this year, Singh and colleagues performed a systematic review with a meta-analysis of 12 studies examining this issue. At total of 172,837 patients with IBD were pooled in which 179 cases of melanoma from 1940 to 2009 were identified. It was found that IBD was overall associated with a 37% increased risk of melanoma (18). This risk was seen in both patients with CD and UC. The risk was seen in cohort studies before the use of immunomodulators and during the use of immunomodulators. Thus, the authors found no increased risk of melanoma with thiopurine use. More importantly, it was found that the risk of melanoma was higher in studies performed before the introduction of biologic therapies in 1998 but not in those after 1998 when Infliximab was introduced. Therefore, we can conclude that the increased risk of melanoma is independent of immunomodulator and anti-TNF use. The pathogenesis of melanoma in IBD is poorly understood. One can postulate that perhaps the increased risk is related to the underlying immune dysfunction resulting in altered tumor surveillance. Alternatively, the melanoma rate may be overestimated in the IBD population due to detection bias in light of increased health care access and use by these patients.

In conclusion, both the specialist and the primary care physician should counsel patients on potential risks and remain vigilant to the development of concerning skin lesions. All patients, regardless of thiopurine or anti-TNF use, should adopt sun-protective measures including sunscreen with SPF ≥30, sun-protective clothes, and minimize exposure to UV radiation.

Cervical cancer

Cervical cancer was once one of the most common causes of cancer death in US women. The mortality rate dramatically decreased by over 70% between 1955-1992 due to mass screening with the Papanicolau (Pap) smear (10) Women with IBD have been found to have

a higher prevalence of abnormal pap smears than age-matched controls. Kane and colleagues found the incidence in women with IBD to be as high as 42.5% versus 7% among age-matched controls. The authors also found these women to have higher-grade lesions than controls (OR=3.1, $p<0.001$) (19). There is conflicting data on whether this is associated with immunomodulator or anti-TNF therapy. What is known is that the most important factor is persistent HPV infection. HPV has been found to be the key risk factor in development of cervical cancer. Most HPV infections spontaneously regress over months to years in the general population (10, 19, 20). It is hypothesized that immunosuppression therapy in IBD and/or underlying immunological changes in IBD may lead to increased risk of cervical cancer due to impaired ability to clear HPV. As recommended by the American College of Obstetrics and Gynecology, all women with IBD on immunosuppressive therapy should undergo annual Pap testing and these women should also be considered for the HPV vaccine (10, 20). The HPV vaccine is indicated for the prevention of disease caused by HPV types 16 and 18, which has been associated with 70% of cervical cancers as well as types 6 and 11 which are associated with genital warts (11). Both the specialist and primary care provider should encourage and strongly advise women with IBD to follow the screening program for cervical cancer and clinicians should be aware of the slightly increased risk of HPV related cancer in this group.

Tobacco and IBD

Smoking is perhaps the most well established environmental risk factor, increasing risk for CD by approximately two fold. In patients with CD, smokers have been found to have more severe ileal disease, more frequent flares, and higher rates of surgery (10, 11, 23). Moreover, an increased need for steroids and immunomodulators has been found in smokers with CD (10, 11, 23). Lastly, smoking has been linked with early post-operative recurrence of CD following surgery (10, 11, 23). Smoking cessation has been associated with a decrease risk of relapses thus decreasing need for steroids, hospitalization, and surgery. The negative effects of smoking have been found to be dose dependent, thus any decrease in number of cigarettes smoked daily would be beneficial in disease activity. With this in mind, it is important to understand the importance of smoking cessation counseling and the significant impact it has on the patient's clinical course. The prevalence of smoking remains high in CD suggesting the "prescription" for smoking cessation as therapy is vastly underutilized. Smoking cessation is a key treatment in the algorithm of CD management

and must be co-managed by the specialist and the primary care provider in order to optimize the IBD patient's care.

Among patients with UC, smoking has a rather opposite influence on disease activity with more favorable effects. Multiple studies have demonstrated that smoking not only protects against development of UC, but does indeed improve the clinical disease course. It has been found that current smokers have less relapses, reduced need for steroid and immunomodulators, and require less hospitalization (24). Moreover, being an ex-smoker increases the risk of developing UC two-fold and those who quit smoking after diagnosis of UC often experience a flare, have increased need for steroids and immunomodulators as well as increased need for hospitalizations (24). Despite the benefits of smoking on UC, these benefits clearly do not outweigh the risks of this type of therapy for UC. Smoking is associated with a wide spectrum of diseases causing significant morbidity and mortality. For the overall health of the patient, smoking cessation should be actively advised and encouraged. While it is important to underscore the overall negative impact smoking has on health and the positive effects of smoking cessation, an open and frank discussion must be done in order to make the patient aware of the possible rebound exacerbation of disease activity after smoking cessation is achieved. These patients who have quit smoking should be monitored closely the first few months to a year by both the specialist as well as the primary care physician in order to promptly identify and treat UC exacerbation. This in turn will help ease the patient's anxiety associated with quitting smoking.

All IBD patients should be encouraged to stop smoking. In Crohn's disease, the detrimental effect of smoking is clear and should be the cornerstone of therapy in IBD patients who smoke. While smoking is protective in UC, the overall benefit of this does not outweigh the risks and smoking cessation counseling should be undertaken.

Depression and IBD

Depression is a common problem in patients with chronic medical conditions leading to a great deal of disability and functional impairment. Likewise, depression and anxiety are thought to exacerbate disease activity. In IBD, it is estimated that depression affects between 15% and 35% of patients (25). A study looking at a population-based cohort of 351 IBD patients found the lifetime rate of major depressive disorder to be more than twice as high in the IBD cohort and occurring in more than a quarter of those with IBD (25). In

addition, an earlier age of onset of IBD symptoms and diagnosis was found in this study (25). These findings have important implications for IBD management. Several factors specific to IBD play into the psychological well-being of the IBD patient including the chronic relapsing/remitting nature of the disease, use of immunosuppressive agents (such as steroids), and medication side effects (25-27). It has also been shown that those with significant depressive symptoms had more frequent relapses, more disease activity, and earlier need for more aggressive therapy (11, 25). Additionally, the presence of depression has been shown to be associated with decreased compliance and greater health care utilization of resources (11). Lastly, these patients have a poorer health-related quality of life and a self-perceived functional disability regardless of their symptom severity.

The American College of Preventive Medicine (ACPM) refers to several studies which show that effective screening can be performed with the following 2 short questions:

1. Over the past month, have you felt down, depressed, or hopeless?
2. Over the past month, have you felt little interest or pleasure in doing things? (11)

It is important for the primary care physician to recognize the increased risk of depression in IBD patients and its effect on disease course. Moreover, to screen and treat appropriately and/or refer to a mental health professional can be very vital to the care and management of an IBD patient

Conclusions:

- Timely recognition of signs and symptoms suggestive for IBD is important to avoid diagnostic delay
- Prompt referral to IBD center important to attain response and remission of disease activity
- Need for vaccination is increased in IBD patients as they are at increased risk for infections
- Vaccination history should be checked and updated
- Risk of osteoporosis in IBD is significant
- Be cognizant of steroid exposure in IBD patients
- Consider DXA scan early in disease process
- Consider skin cancer screening in IBD patients on immunosuppression
- Emphasize importance of annual pap smear in female IBD patients
- Smoking cessation counseling integral to Crohn's therapy
- Screen for depression

References

1. Talley NJ, Abreu MT, Achkar JP, Bernstein CN, Dubinsky MC, Hanauer SB, Kane SV, Sandborn WJ, Ullman TA, Moayyedi P; American College of Gastroenterology IBD Task Force. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol. 2011 Apr; 106 Suppl 1:S2-25.
2. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan; 142(1):46-54.
3. Smith LA, Gaya DR. Utility of faecal calprotectin analysis in adult inflammatory bowel disease. World J Gastroenterol. 2012 Dec 14; 18(46):6782-9.
4. Schoepfer AM, Dehlavi MA, Fournier N, Safroneeva E, Straumann A, Pittet V, Peyrin-Biroulet L, Michetti P, Rogler G, Vavricka SR. Diagnositc delay in crohn's disease is associated with a complicated disease course and increased operation rate. Am J Gastroenterol. 2013; 108: 1744-1753.
5. Melmed GY, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, Frenck RW, Targan SR, Vasiliauskas EA. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. Am J Gastroenterol. 2006 Aug; 101(8):1834-40.
6. Wasan SK, Coukos JA, Farraye FA. Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists knowledge. Inflamm Bowel Dis. 2011 Dec; 17(12):2536-40.
7. Wasan SK, Calderwood AH, Long MD, Kappelman MD, Sandler RS, Farraye FA. Immunization rates and vaccine beliefs among patients with inflammatory bowel disease: an opportunity for improvement. Inflamm Bowel Dis. 2014 Feb; 20(2):246-50.
8. Selby L, Hoellein A, Wilson JF. Are primary care providers uncomfortable providing routine preventive care for inflammatory bowel disease patients? Dig Dis Sci. 2011 Mar; 56(3):819-24.
9. Melmed GY. Vaccination strategies for patients with inflammatory bowel disease on immunomodulators and biologics. Inflamm Bowel Dis. 2009 Sep; 15(9):1410-6.
10. Moscandrew M, Mahadevan U, Kane S. General health maintenance in IBD. Inflamm Bowel Dis. 2009 Sep; 15(9):1399-409.
11. Sinclair JA, Wasan SK, Farraye FA. Health maintenance in the inflammatory bowel disease patient. Gastroenterol Clin North Am. 2012 Jun; 41(2):325-37.

12. Agarwal N, Ollington K, Kaneshiro M, Frenck R, Melmed GY. Are immunosuppressive medications associated with decreased responses to routine immunizations? A systematic review. Vaccine. 2012 Feb 14;30(8):1413-24.
13. Targownik LE, Bernstein CN, Leslie WD. Risk factors and management of osteoporosis in inflammatory bowel disease. Curr Opin Gastroenterol. 2014 Mar; 30(2):168-74
14. Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. Am J Med. 2009 Jul;122(7):599-604
15. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology. 2003 Mar; 124(3):795-841.
16. Long MD, Herfarth HH, Pipkin CA, Porter CQ, Sandler RS, Kappelman MD. Increased risk for non-melanoma skin cancer in patients with Inflammatory Bowel Disease. Clin Gastro Hep. 2010;8:268-274.
17. Mason M, Siegel CA. Do inflammatory bowel disease therapies cause cancer? Inflamm Bowel Dis. 2013 May; 19(6):1306-21.
18. Singh S, Nagpal SJ, Murad MH, Yadav S, Kane SV, Pardi DS, Talwalkar JA, Loftus EV Jr. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014 Feb; 12(2):210-8.
19. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. Am J Gastroenterol. 2008 Mar; 103(3):631-6.
20. Rungoe C, Simonsen J, Riis L, Frisch M, Langholz E, Jess T. Inflammatory Bowel Disease and Cervical Neoplasia: A population-based nationwide cohort study. Clin Gastroenterol Hepatol. 2014 Jul 30. pii: S1542-3565(14)01081-7.
21. Targownik LE, Bernstein CN. Infectious and malignant complications of TNF inhibitor therapy in IBD. Am J Gastroenterol. 2013 Dec;108(12):1835-42, quiz 1843.
22. Kappelman MD, Farkas DK, Long MD, Erichsen R, Sandler RS, Sørensen HT, Baron JA. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. Clin Gastroenterol Hepatol. 2014 Feb; 12(2):265-73.e1.
23. Andrews JM, Mountifield RE, Van Langenberg DR, Bampton PA, Holtmann GJ. Un-promoted issues in inflammatory bowel disease: opportunities to optimize care. Intern Med J. 2010 Mar; 40(3):173-82.
24. Lunney PC, Leong RW. Review article: Ulcerative colitis, smoking and nicotine therapy. Aliment Pharmacol Ther. 2012 Dec; 36(11-12):997-1008.

25. Walker JR, Ediger JP, Graff LA, Greenfeld JM, Clara I, Lix L, Rawsthorne P, Miller N, Rogala L, McPhail CM, Bernstein CN. The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. Am J Gastroenterol. 2008 Aug; 103(8):1989-97.
26. Panara AJ, Yarur AJ, Rieders B, Proksell S, Deshpande AR, Abreu MT, Sussman DA. The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. Aliment Pharmacol Ther. 2014 Apr; 39(8):802-10.
27. Häuser W, Moser G, Klose P, Mikocka-Walus A. Psychosocial issues in evidence-based guidelines on inflammatory bowel diseases: a review. World J Gastroenterol. 2014 Apr 7; 20(13):3663-71.
28. Thomas A, Lodhia N. Advanced therapy for inflammatory bowel disease: a guide for the primary care physician. J Am Board Fam Med. 2014 May-Jun; 27(3):411-20.
29. De Luca JF, Severino R, Lee YS, Johnson D. Dermatologist and gastroenterologist awareness of the potential of immunosuppressants used to treat inflammatory bowel disease to cause non-melanoma skin cancer. Int J Dermatol. 2013 Aug; 52(8):955-9.
30. Tan M, Holloway RH, Lange K, Andrews JM. General practitioners' knowledge of and attitudes to inflammatory bowel disease. Intern Med J. 2012 Jul; 42(7):801-7.
31. Selby L, Kane S, Wilson J, Balla P, Riff B, Bingcang C, Hoellein A, Pande S, de Villiers WJ. Receipt of preventive health services by IBD patients is significantly lower than by primary care patients. Inflamm Bowel Dis. 2008 Feb; 14(2):253-8.
32. Whitehead WE, Palsson OS, Levy RR, Feld AD, Turner M, Von Korff M. Comorbidity in irritable bowel syndrome. Am J Gastroenterol. 2007 Dec;102(12):2767-76.