

## Preventive health measures in inflammatory bowel disease

Ayokunle T Abegunde, Bashir H Muhammad, Tauseef Ali

Ayokunle T Abegunde, Tauseef Ali, Section of Digestive Diseases and Nutrition, Department of Medicine, Oklahoma University Health Sciences Center, Oklahoma City, OK 73104, United States

Bashir H Muhammad, Department of Medicine, Oklahoma University Health Sciences Center, Oklahoma City, OK 73104, United States

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**Correspondence to:** Tauseef Ali, MD, FACP, FACC, Section of Digestive Diseases and Nutrition, Department of Medicine, Oklahoma University Health Sciences Center, 920 Stanton L Young Boulevard, Oklahoma City, OK 73104, United States. [tauseef-ali@ouhsc.edu](mailto:tauseef-ali@ouhsc.edu)  
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### Abstract

We aim to review the literature and provide guidance on preventive health measures in inflammatory bowel disease (IBD). Structured searches were performed in PubMed, MEDLINE, EMBASE, Web of Science and Cochrane Library from January 1976 to June 2016 using the following keywords: (inflammatory bowel disease OR Crohn's disease OR ulcerative colitis) AND (health maintenance OR preventive health OR health promotion). Abstracts of the articles selected from each of these multiple searches were reviewed, and those meeting the inclusion criteria (that is, providing data regarding preventive health or health maintenance in IBD patients) were recorded. Reference lists from the selected articles were manually reviewed to identify further relevant studies. Patients with IBD are at increased risk of developing adverse events related to the disease course, therapeutic interventions, or non-adherence to medication. Recent studies have suggested that IBD patients do not receive preventive services with the same thoroughness as patients with other chronic diseases. Preventive health measures can avert morbidity and improve the quality of life of patients with IBD. Gastroenterologists and primary care physicians (PCPs) should have an up to date working knowledge of preventive health measures for IBD patients. A holistic approach and better communication between gastroenterologists and PCPs with explicit clarification of roles will prevent duplication of services and streamline care.

**Key words:** Health maintenance; Prevention; Ulcerative colitis; Crohn's disease

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**Core tip:** Preventive health measures can avert morbidity and improve the quality of life of patients with inflammatory bowel disease (IBD). Gastroenterologists and primary care physicians (PCPs) should have an

up to date working knowledge of preventive health measures for IBD patients. A holistic approach and better communication between gastroenterologists and PCPs with explicit clarification of roles will prevent duplication of services and streamline care.

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## INTRODUCTION

Inflammatory bowel disease (IBD) is one of the five most prevalent chronic gastrointestinal conditions in the United States, with an overall yearly health care cost of more than 1.7 billion<sup>[1]</sup>. IBD has no cure and patients commonly require a lifetime of care; thus effective preventive measures to reduce morbidity, hospitalization, and surgery are critical to improving disease free remission and quality of life. Studies have shown that IBD patients do not receive preventive services with the same thoroughness as other medical patients<sup>[2]</sup>. Several reasons for this disparity have been suggested; first, there is a greater focus on disease (symptom) control rather than preventive measures. Second, gastroenterologists are often the main care provider for patients with IBD and visits to the primary care physician (PCP) are often infrequent<sup>[2,3]</sup>. Third, there is a lack of consensus regarding which provider (gastroenterologist or PCP) should offer preventive services and the limits of responsibility for providing preventive services<sup>[2,3]</sup>. Other barriers to providing preventive services such as time constraints, patient refusal, and reimbursement issues have also been identified<sup>[2,4]</sup>. These barriers to preventive care for IBD patients may ultimately affect the quality of care and patient outcomes. Therefore, gastroenterologists need to take a proactive role in the preventive health care needs of IBD patients by clarifying with each patient the limits of responsibility for preventive health and alerting PCPs to the unique health maintenance needs of IBD patients. Identifying which preventive measures are better delivered at the primary, secondary and tertiary care level is crucial to the delivery of quality care. This article reviews health interventions to prevent morbidity and mortality in IBD patients with emphasis on the location where such interventions are best delivered.

## SEARCH STRATEGY

Bibliographical searches were performed in PubMed; MEDLINE; EMBASE; Web of Science and Cochrane Library from 1976 up to April 2016 using the following keywords: (inflammatory bowel disease OR Crohn's

disease OR ulcerative colitis) AND (health maintenance OR preventive health OR health promotion). Reference lists from the articles selected by electronic searching were manually reviewed to identify further relevant studies. Abstracts of the articles selected in each of these multiple searches were reviewed, and those meeting the inclusion criteria (that is, providing data regarding preventive health or health maintenance in IBD patients) were recorded.

## SMOKING CESSATION

Smoking has a negative effect on patients with Crohn's disease (CD) in addition to the known risks of cardiac, respiratory, and oncologic disease. A survey of 675 IBD patients found that active smoking is a risk factor for CD and passive smoking is detrimental to the prognosis of CD. Among patients with UC, active smoking shows beneficial effects<sup>[5]</sup>. Current smoking increases the risk of developing CD and worsens its course, increasing the need for steroids, immunosuppressive therapy (IST), and reoperations<sup>[5]</sup>. On the contrary, smoking protects against UC, improves its course after disease onset, and decreases the need for colectomy<sup>[5]</sup>. Therefore, achieving smoking cessation is an important goal of therapy in patients with CD. In patients with UC, the benefits of smoking on disease control must be balanced against the risk of non-IBD smoking related adverse effects. Smoking cessation is best achieved by a multidisciplinary approach through dedicated smoking cessation clinics with access to counselling, nicotine replacement therapy (NRT), and medication<sup>[6,7]</sup>. Brief interventions during clinical encounters (asking patients about current smoking habit; advising them to stop smoking; assisting with NRT and arranging follow-up) may also be effective<sup>[6,7]</sup>. Bupropion approximately doubles quit rates compared with placebo in the general population<sup>[8]</sup>. In patients with CD, bupropion has been shown to be effective as an anti-smoking agent with mood stabilizing properties. The combination of NRT and bupropion was shown to improve the chance of achieving smoking cessation in CD patients by up to 20% compared with an unassisted quit attempt<sup>[9]</sup>. NRT had no effect in modifying disease in UC patients who stopped smoking, suggesting that the beneficial effect of smoking in UC is not modulated *via* nicotine pathways. Varenicline is associated with higher rates of smoking cessation than bupropion and other forms of NRT<sup>[8]</sup>. There are no RCTs using varenicline for smoking cessation in UC or CD; however, a cohort study (TABACROHN) has reported very good outcomes in CD patients treated with varenicline<sup>[10]</sup>. Smoking cessation should be strongly advocated by gastroenterologists and PCPs in all CD patients that are current smokers because patients who quit smoking have a reduced number of relapses compared to continuing smokers [incidence rate ratio 0.84 (95%CI: 0.45-1.52) vs 1.53 (95%CI: 1.10-2.17)], which in turn reduces the use of biologics

**Table 1 Pathogenesis of micronutrient deficiency in inflammatory bowel disease**

Decreased food intake
Anorexia (TNF-mediated)
Mechanical (fistulas, post-operative)
Avoidance of high-residue food (can worsen abdominal pain/diarrhea)
Avoidance of lactose-containing foods (high rates of concomitant lactose intolerance)
Increased intestinal loss
Diarrhea (increased loss of Zn <sup>2+</sup> , K <sup>+</sup> , Mg <sup>2+</sup> )
Occult/overt blood loss (iron deficiency)
Exudative enteropathy (protein loss, and decrease in albumin-binding proteins)
Steatorrhea (fat and fat-soluble vitamins)
Malabsorption
Loss of intestinal surface area from active inflammation, resection, bypass or fistula
Terminal ileal disease associated with deficiencies in B <sub>12</sub> and fat-soluble vitamins
Hypermetabolic state
Alterations of resting energy expenditure
Drug interactions
Sulfasalazine and methotrexate inhibits folate absorption
Glucocorticoids impair Ca <sup>2+</sup> , Zn <sup>2+</sup> , and phosphorus absorption, vitamin C losses and vitamin D resistance
Cholestyramine impairs absorption of fat-soluble vitamins, vitamin B <sub>12</sub> and iron
Long-term total parenteral nutrition
Can occur with any micronutrient not added to TPN
Reported deficiencies include thiamine, vitamin, and trace elements Zn <sup>2+</sup> , Cu <sup>2+</sup> , selenium, chromium

Adapted from Hwang *et al.*<sup>[21]</sup>. TNF: Tumor necrosis factor.

and need for surgery<sup>[10]</sup>.

## PHYSICAL ACTIVITY AND EXERCISE

IBD patients may have physical and psychological complaints that may impair their quality of life. Preliminary studies demonstrate that moderate exercise may diminish some symptoms of IBD<sup>[11,12]</sup>. Additionally, the increasing prevalence of obesity in IBD patients may be associated with higher disease activity<sup>[13,14]</sup>. Physical activity improves quality of life without detrimental effect on disease activity; it may also increase muscle mass and prevent osteoporosis<sup>[14]</sup>. A retrospective cohort study of 240984 adolescent male military recruits revealed that physical fitness may reduce systemic inflammation levels relevant to the risk of symptomatic CD and UC<sup>[12]</sup>. Low fitness was associated with an increased risk of IBD [unadjusted HR = 1.62 (95%CI: 1.31-2.00) for CD and 1.36 (95%CI: 1.17-1.59)] for UC<sup>[12]</sup>. The inverse association of physical fitness with IBD risk suggests a protective role for exercise<sup>[12]</sup>. However, the association between fitness and IBD may be due to prodromal disease activity reducing exercise capacity and therefore fitness<sup>[12]</sup>. It has been hypothesized that the beneficial effect of regular exercise in IBD patients may be in part due to the anti-inflammatory effects of

myokines released during skeletal muscle contractions which inhibit the release of proinflammatory mediators from visceral fat<sup>[13]</sup>. There is some evidence that PA may improve quality of life and reduce disease activity in patients with IBD<sup>[15]</sup>. Thus PA may be useful as an adjunctive therapy in IBD by potentially improving psychological health, nutritional status, immunological response, bone mineral density and reversing the decrease of muscle mass and strength<sup>[16,17]</sup>. Further studies are required to confirm these observations and establish exercise regimes for different IBD patient groups and an acceptable limit for physical activity in IBD patients.

## NUTRITION

A diet rich in polyunsaturated fats and low in fiber may be associated with an increased risk of IBD<sup>[18]</sup>. Enteral nutrition may improve CD flares and decrease the need for steroids in children and adolescents; however, no defined diets have been shown to consistently improve the disease course in adults with CD or UC<sup>[19]</sup>. High intake of dietary fiber, particularly fruits and cruciferous vegetables is associated with decreased risk of CD, but not UC (HR = 0.59; 95%CI: 0.39-0.90)<sup>[20]</sup>. Further studies are needed to define the role of specific diets in preventing disease progression in IBD.

### Screening for malnutrition and micronutrient deficiencies

Patients with IBD are at increased risk of malnutrition *via* several mechanisms (Table 1)<sup>[21]</sup>. IBD patients with clinical symptoms should be evaluated for their micronutrient status and identified deficiencies should be corrected. In IBD patients without clinical symptoms it is advisable to screen for common micronutrient deficiencies such as folate, iron and 25-hydroxyvitamin D<sup>[21,22]</sup>. Patients with CD and extensive bowel resection are particularly at risk for vitamin B<sub>12</sub> deficiency, therefore, checking serum levels of vitamin B<sub>12</sub> is recommended<sup>[21,22]</sup>. There are no current guidelines for assessment of micronutrient deficiencies in IBD patients and recommendations are based on expert opinion<sup>[22]</sup>.

## SCREENING FOR ANEMIA

Anemia is one of the most common extra-intestinal manifestations of IBD<sup>[23]</sup>. According to one study one-third of patients with IBD have hemoglobin levels below 12 g/dL<sup>[24]</sup>. The anemic state is strongly correlated with quality of life, and is an important problem in the therapeutic management of patients with chronic disease<sup>[25]</sup>. Anemia in IBD patients involves multiple pathogenic mechanisms. Although ongoing blood loss from chronically inflamed intestinal mucosa and micronutrient deficiency (iron and B<sub>12</sub>)

are the main mechanisms underlying the development of anemia in patients with IBD, chronic inflammation, hemolysis, and medication-induced myelosuppression may also play important roles in both the development and management of anemia<sup>[26,27]</sup>. Anemia of chronic disease and iron deficiency anemia are the two most common causes of anemia in patients with IBD<sup>[28,29]</sup>. The World Health Organization defines anemia as hemoglobin levels < 13 g/dL (hematocrit < 39%) in males, < 12 g/dL (hematocrit < 36%) in non-pregnant females, and < 11 g/dL (hematocrit < 33%) in pregnant females<sup>[30]</sup>. Severe IDA is defined as hemoglobin levels < 10 g/dL. If a patient meets WHO criteria for anemia, a basic anemia workup should be initiated to determine the cause of anemia. The basic workup includes a complete blood count, serum ferritin, transferrin, transferrin saturation, and C-reactive protein. If the cause of anemia is unclear despite the results of the above workup, more extensive testing is recommended. Further tests include vitamin B<sub>12</sub>, folic acid, haptoglobin, lactate dehydrogenase, creatinine, and reticulocyte counts<sup>[31]</sup>. Based on expert opinion and common clinical practice, screening for anemia in IBD patients is recommended at least every 3 mo for outpatients with active disease, and once every 6 to 12 mo for patients in remission or with mild disease; screening is not applicable to hospitalized patients<sup>[31]</sup>. Treatment of anemia based upon the etiology should be started as soon as possible. In patients with IDA and hemoglobin > 10 g/dL, mildly active, or quiescent IBD, oral iron supplementation is adequate treatment<sup>[32]</sup>. According to an international consensus statement, the preferred route of iron supplementation in IBD is intravenous, particularly, if the patient's Hgb level is < 10 g/dL in the setting of active disease<sup>[31,33]</sup>. In a patient population with the predisposition for anemia, such as IBD patients, early diagnosis and management of iron deficiency can promptly reduce hospital visits, improve quality of life, reduce loss of work, and, ultimately, lower health care costs<sup>[31,33]</sup>.

## BONE HEALTH

### ***Prevention of osteoporosis and osteopenia***

There is a high prevalence of osteoporosis (17%-41%) and osteopenia (22%-77%) in patients with IBD<sup>[34,35]</sup>. Observational studies have shown a modest increased risk of osteoporotic fractures in patients with IBD compared to the general population<sup>[34,35]</sup>. Dual-energy X-ray absorptiometry scanning is the gold-standard test for the diagnosis of osteoporosis and osteopenia<sup>[36]</sup>. Osteoporosis is diagnosed when an individual's bone mineral density (BMD) at the hip or spine is more than 2.5 standard deviations below the mean for young healthy sex- and race-matched young adults (T-score less than -2.5). Osteopenia is diagnosed when the BMD is between -1 and -2.5 standard deviations (T-score of -1 to -2.5)<sup>[36]</sup>. IBD patients are at increased

risk of fragility fractures in the absence low BMD for reasons that are not completely understood<sup>[37]</sup>. The etiology of osteoporosis and osteopenia in IBD is multifactorial; risk factors include; corticosteroid use, age, malnutrition, vitamin D deficiency, calcium malabsorption, immobilization, degree of underlying GI inflammation and lower levels of sex hormones<sup>[38]</sup>. Corticosteroid use is the strongest risk factor associated with osteoporosis. IBD patients on steroids for greater than three months have a significant increased risk of osteoporosis and fracture<sup>[38]</sup>. Data on the prevention and treatment of osteoporosis in IBD are derived from observational studies and low quality RCTs in postmenopausal women with non-IBD inflammatory conditions<sup>[39,40]</sup>. The American Gastroenterological Association guidelines recommend DEXA screening in IBD patients with one or more risk factors: history of vertebral fractures, postmenopausal females, males > 50 years of age, chronic corticosteroid therapy, or hypogonadism<sup>[39]</sup>. If the initial DEXA is normal, the AGA recommends repeat testing in 2-3 years. If the patient has osteoporosis, or has a history of a low trauma fracture, evaluation for secondary causes should be completed. Suggested studies include a complete blood count, serum concentrations of alkaline phosphatase, calcium, creatinine, 25-OH vitamin D, serum protein electrophoresis, and testosterone level in males. Utilization of these guidelines potentially increases the number of screened patients and should lead to earlier diagnosis and treatment. In a single center cohort study of 100 consecutive IBD patients that met the AGA criteria for initial DEXA screening, osteoporosis was found in 12%, osteopenia in 44% and normal BMD in 44% of patients. Pharmacologic therapy was initiated in 89% of these patients, with 69% receiving calcium and vitamin D, and 20% receiving bisphosphonates<sup>[41]</sup>. Although this was a small study with limited generalizability, it showed that following guidelines led to interventions that might ultimately reduce fracture risk<sup>[41]</sup>. Interventions such as weight bearing, isotonic exercise, smoking cessation, avoiding alcohol excess, and maintaining adequate dietary calcium (> 1 g/d) have been shown to be beneficial in the prevention of osteoporosis in other inflammatory conditions and are recommended by the AGA<sup>[39]</sup>. Minimizing the use of glucocorticoids is the most crucial intervention to prevent osteoporosis in patients with IBD. In patients with established osteoporosis, the use of bisphosphonates, calcitonin and its derivatives, raloxifene, and teriparatide have been shown to reduce or prevent further bone loss in post-menopausal women and men with hypogonadal osteoporosis<sup>[42-44]</sup>. A recent meta-analysis showed that bisphosphonates are effective and well tolerated for the treatment of low BMD in male and female patients with IBD and reduces the risk of vertebral fractures<sup>[43]</sup>. However there was insufficient data to support the efficacy of calcium and vitamin D, fluoride, calcitonin, or low-impact exercise in IBD patients<sup>[43]</sup>. Hormone replacement therapy is no

**Table 2 Prevention of osteoporosis in inflammatory bowel disease**

Non-pharmacologic interventions
Regular weight-bearing exercise
Avoiding or quitting tobacco
Limited use of alcohol
Emphasis on better nutrition, particularly on vitamin D and calcium
Employment of fall prevention strategies
Pharmacologic interventions
Calcium and vitamin D supplementation
Bisphosphonates
Calcitonin
Cautious use of hormone replacement therapy for both women and men
Recombinant parathyroid hormone (teriparatide)
Minimizing corticosteroid use with the early use of immunomodulating agents

Adapted from Ali *et al*<sup>[54]</sup>.

longer recommended in post-menopausal women with IBD, given the increased risk of thrombosis (Table 2).

### Calcium and vitamin D supplementation

Calcium (1200 mg/d) and vitamin D (400-800 IU/d) have been shown to be effective in fracture prevention in post-menopausal women<sup>[45,46]</sup>. However, the evidence for calcium and vitamin D supplementation in the treatment of low BMD and prevention of fracture in IBD patients is limited<sup>[47-49]</sup>. Calcium plus vitamin D supplementation resulted in a non-statistically significant improvement in lumbar and hip BMD<sup>[47-49]</sup>. Further studies are needed and routine administration of calcium and vitamin D is not warranted in the absence of deficiency<sup>[43]</sup>.

## EYE HEALTH

Approximately 10%-43% of patients with IBD develop eye problems<sup>[50,51]</sup>. Ophthalmologic problems may be related to extraintestinal manifestations of IBD such as uveitis, episcleritis, or keratopathy or may be related to IBD therapy such as glucocorticoid-induced cataracts or glaucoma<sup>[52,53]</sup>. Vitamin A deficiency may result in keratoconjunctivitis sicca after bowel resection in CD. Therefore it is recommended that patients with IBD undergo annual ophthalmologic evaluation, especially those on immunosuppressive therapy<sup>[54]</sup>.

## SCREENING FOR IMPORTANT LATENT INFECTIONS

The majority of medications used to treat IBD are associated with immunosuppression which predisposes IBD patients to infection<sup>[55]</sup>. Immunosuppression is defined as treatment with glucocorticoids (*e.g.*, prednisone 20 mg/d equivalent for 14 d or more), treatment with effective doses of 6-mercaptopurine (6-MP), Azathioprine (AZA), Methotrexate and anti-

tumor necrosis factor (Anti-TNF) therapy, either currently or within 3 mo of stopping therapy with any of the aforementioned medications, and significant protein-calorie malnutrition<sup>[55]</sup>. Patients at high risk for TB infection such as those with prior exposure or patients with history of Bacillus Calmette-Guerin vaccine should be screened for latent or active TB prior to initiation of IST or biologic therapy<sup>[55-57]</sup>. T-cell-based assays such as QuantiFERON (Cellestis) or T-Spot (Oxford Immunotec) are the preferred tests<sup>[55-57]</sup>. Patients found to be positive for latent or active TB prior to initiation of IST should be referred to an infectious diseases (ID) specialist and treated before starting therapy. Similarly, patients who are found to be positive on IST should be referred to ID and treated after stopping IST<sup>[55,56]</sup>. IBD patients should be screened for hepatitis B virus (HBV) prior to initiation of IST<sup>[55-57]</sup>. Reactivation of HBV infection has been reported in IBD patients with chronic HBV (HBsAg positive) and prior exposure (HBcAb positive) on IST<sup>[55-57]</sup>. IBD patients without prior exposure to HBV should be vaccinated and those with chronic infection should be treated prior to initiation of IST<sup>[56,57]</sup>. There is no increased risk of reactivation of hepatitis C virus (HCV) with IST<sup>[58]</sup>. Therefore screening for HCV should be performed on a case-by-case basis according to CDC guidelines<sup>[59]</sup>.

## VACCINATION

Immunocompromised IBD patients are at a higher risk of infection by vaccine preventable diseases, therefore a diligent effort should be made to vaccinate all IBD patients. Ideally, these patients should be vaccinated before IST is initiated<sup>[55,57]</sup>. Despite concerns for impaired immune response in immunocompromised IBD patients, most of these patients develop adequate response after vaccination<sup>[55]</sup>. Live vaccines are contraindicated in immunocompromised IBD patients due to risks of vaccine associated infection; therefore the timing of live vaccines is particularly important when dealing with IBD patients on IST or those with plans to start IST<sup>[55,57]</sup>. Special population groups such as pregnant patients, household contacts of immunocompromised patients, and travelers, pose special challenges<sup>[55]</sup>. For example, a live vaccine administered to a household member of an immunocompromised IBD patient may expose the IBD patient to infection from the vaccinated family member. In general, it is recommended that household contacts of immunocompromised IBD patients be vaccinated according to recommended guidelines (Table 3). IBD patients embarking on foreign travel may warrant evaluation by an infectious disease specialist or travel medicine specialist<sup>[55]</sup>. Table 4 provides general considerations for timing of live immunization in IBD patients and Table 5 provides general recommendations for vaccination in special populations (pregnant women and the IBD traveler)<sup>[55]</sup>.

**Table 3 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 (MMR)	If no documented immunity: 2 doses, 4 wk apart	Yes	Contraindicated
Zoster (Shingles)	1 dose starting at 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) Male: 3 doses through age 21 (0, 2 and 6 mo)	No	Follow recommended regimen
Pneumococcal (pneumonia vaccine) for subset of patients	If no prior vaccination: (0, 2 then 5 yr) 1 dose at 65 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.

**Table 4 Live attenuated vaccines with recommended times of administration**

Vaccine	Before initiation of immunosuppressive therapy	Already on immunosuppressive therapy
MMR	Contraindicated if starting therapy in 6 wk	Contraindicated
Zoster	Contraindicated if starting therapy in 4-12 wk	Contraindicated But could consider if: On short-term corticosteroids (< 14 d) On methotrexate (< 0.4 mg/kg per week) On azathioprine (< 3.0 mg/kg per day) On 6-mercaptopurine (< 1.5 mg/kg per day)
Varicella	Contraindicated if starting therapy in 4-12 wk	Contraindicated

Adapted from Chaudrey *et al*<sup>[55]</sup>.

### SCREENING FOR SLEEP DISORDERS

Sleep disturbances have been strongly associated with IBD and other chronic inflammatory diseases such as Rheumatoid arthritis and lupus<sup>[60,61]</sup>. Sleep disturbances in these diseases are due to cytokines produced by chronic inflammation. Increased levels of IL-1 and TNF- $\alpha$  are associated with an increase in non-rapid eye movement sleep<sup>[61,62]</sup>. Nocturnal diarrhea disturbs sleep in IBD patients and the effects of slow wave sleep can lead to a decrease in colon contractility with direct effects on GI physiology such as diminished mucosal integrity<sup>[63,64]</sup>. Studies have shown that IBD patients have poorer sleep quality, prolonged sleep latency, and increased use of sleeping pills compared with healthy controls<sup>[64,65]</sup>. Furthermore, patients with clinically active IBD have significantly worse sleep than patients with inactive disease<sup>[66-68]</sup>. IBD patients in clinical remission but with abnormal sleep are at increased risk of relapse at six months when compared to patients in clinical remission with good sleep<sup>[67]</sup>. A cohort study of 3173 subjects showed that poor sleep increases the risk of relapse in patients with inactive CD but not UC<sup>[68]</sup>. Sleep disorders can be a significant

quality of life issue and all patients with IBD should be screened and treated accordingly. In the future screening and treatment of sleep disorders might have therapeutic implications for management of IBD.

### PSYCHOLOGICAL HEALTH

Psychological factors play an important role in IBD and have a wide range of impact on the social life of patients<sup>[69]</sup>. The psychological well-being of patients is often affected by the disease's chronic relapsing nature, IST, and medication side effects<sup>[69,70]</sup>. The presence of a psychological disorder in IBD is associated with poor health-related quality of life and self-perceived functional disability irrespective of symptom severity<sup>[71,72]</sup>. As a result patients with psychosocial distress are less compliant and pursue greater healthcare utilization<sup>[73,74]</sup>. Rates of depression in IBD range from 12.9%-27.2%<sup>[73-77]</sup>. A population-based study found that the lifetime prevalence for major depressive disorder was more than twice as high in the IBD sample compared with controls (27.2% vs 12.3%, OR = 2.20, 95%CI: 1.64-2.95)<sup>[77]</sup>. Although it is widely accepted that chronic diseases such as IBD

**Table 5 Vaccination in special populations of inflammatory bowel disease patients**

Category B	Pregnancy Category C	Category X
Influenza (LAIV)	PPSV 23	Varicella, if non-immune 1 dose upon completion or termination of pregnancy and before discharge from health care facility. 2 <sup>nd</sup> dose 4-8 wk later.
Influenza (IIV) Boostrix (Tdap) 1 dose of Tdap vaccine during each pregnancy regardless of immunization status	Zoster Adacel (Tdap) 1 dose of Tdap vaccine during each pregnancy regardless of immunization status	
HPV 4, HPV 2 PCV 13	Meningococcus Hepatitis A and B vaccine MMR, if non-immune 1 dose upon completion or termination of pregnancy and before discharge from health care facility. 2 <sup>nd</sup> dose 4-8 wk later.	
<b>Vaccine</b>	<b>The IBD traveler</b>	<b>Travel related indication</b>
Yellow fever	Type Live	Parts of South America and sub-Saharan Africa
Typhoid	Live and Inactivated	Asia, Africa, Central and South America, The Caribbean, Oceania
Polio	Live	
Influenza	Inactivated	
BCG vaccine	Live	Travel to highly endemic area > 1 yr
Hepatitis A	Inactivated	Central or South America, Mexico, Asia( except Japan), Africa, Eastern Europe
Meningococcal vaccine	Inactivated	sub-Saharan Africa, Saudi Arabia (during Hajj and Umrah pilgrimage)
Japanese encephalitis virus	Inactivated	Rural Japan

Adapted from Chaudrey *et al*<sup>[55]</sup>.

**Table 6 Patient health questionnaire-2**

PHQ-2
Over the past month, have you felt down, depressed, or hopeless?
Over the past month, have you felt little interest or pleasure in doing things?

Adapted from Arroll *et al*<sup>[78]</sup>.

may trigger negative psychological emotions such as hopelessness and even depression, it is not clear if it is solely a psychological response to disease related morbidity, or whether it also represents a biological response of actual disease<sup>[78,79]</sup>. Recently, a large cohort study showed that depression and anxiety were independent predictors of relapse in IBD<sup>[76]</sup>. Therefore, special attention should be paid to screening IBD patients for depression on a regular basis by using simple screening questions such as the patient health questionnaire-2 (PHQ-2) (box 1)<sup>[78,80]</sup> (Table 6). A positive answer to either of the screening questions mandates confirmatory testing with a standardized depression questionnaire such as the PHQ-9<sup>[78,80]</sup>. A multidisciplinary approach involving the PCP, psychotherapist and psychiatrist is associated with the best outcomes in IBD and non-IBD patients<sup>[75,80]</sup>. Patients with mild depression should be offered psychotherapy while patients with moderate to severe depression

should be offered psychotherapy and anti-depressant medication<sup>[80,81]</sup>. In addition to controlling symptoms of anxiety and depression, anti-depressants such as selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors have been reported to decrease pain, gut irritability, and urgency of defecation<sup>[75]</sup>.

## PREVENTION OF VENOUS THROMBOEMBOLISM

IBD patients have an increased risk of venous thromboembolism (VTE) due to the combined effects of inflammation, micronutrient deficiencies, hospitalizations, surgery and inherited prothrombotic factors<sup>[82-84]</sup>. The relative risk (RR) of VTE in patients with IBD is inversely correlated with age; however, the actual incidence of VTE increases with age (45.6 per 10000 persons-year of follow-up)<sup>[83]</sup>. IBD patients are 3.5 times more likely to develop VTE compared with age and gender matched controls in the general population<sup>[83]</sup>. The risk of recurrence 5- years after discontinuation of anticoagulation therapy for an unprovoked VTE is higher among patients with IBD than controls (HR = 2.5, 95%CI: 1.4-4.2, P = 0.001)<sup>[84]</sup>. VTE appears to carry a worse prognostic outcome for patients with IBD compared with the general population<sup>[84,85]</sup>. In an analysis of a nationwide in-patient sample of

IBD patients in Canada, the rate of VTE was higher and the length of hospitalization was longer in IBD patients compared with controls (11.7 d vs 6.1 d,  $P < 0.0001$ )<sup>[85]</sup>. Hospitalization was associated with higher costs (\$47515 vs \$21499,  $P < 0.0001$ ) and higher mortality (adjusted OR = 2.5, 95%CI: 1.83-3.43) in IBD patients compared with controls<sup>[85]</sup>. IBD patients undergoing surgery have an increased risk for post-operative VTE (OR = 1.26, 95%CI: 1.021-1.56,  $P = 0.03$ ) compared with patients undergoing surgery for colorectal cancer<sup>[86]</sup>. Therefore, it has been suggested that VTE prophylaxis in postoperative IBD patients be extended out-of-hospital for 4 wk after discharge<sup>[87,88]</sup>. Given the increased risk of VTE in IBD patients, adequate prophylaxis should be prescribed for all IBD patients who are hospitalized with flares, or undergoing surgery<sup>[87]</sup>. There are currently no clinical trials specifically addressing VTE prophylaxis and treatment in patients with IBD. However, consensus statements with specific recommendations were developed based on the 9<sup>th</sup> American College of Chest Physicians' guidelines on antithrombotic therapy and prevention of thrombosis with integration of evidence from IBD studies<sup>[88]</sup>. Anticoagulant thromboprophylaxis is recommended for IBD patients who are hospitalized with IBD flares without active bleeding and when bleeding is non severe<sup>[88]</sup>. Anticoagulant thromboprophylaxis is suggested during moderate severe IBD flares in outpatients with a history of VTE provoked by an IBD flare or an unprovoked VTE, but not otherwise<sup>[88]</sup>. The recommended duration of anticoagulation after a first VTE is based on the presence of provoking factor<sup>[87,88]</sup>. Please refer to the consensus document for details<sup>[88]</sup>.

## CARDIOVASCULAR HEALTH

### Hypertension

The increasing prevalence of obesity and metabolic syndrome in IBD patients increases the risk of primary essential hypertension<sup>[89]</sup>. IBD patients are also at increased risk for secondary hypertension due to some of the medications used in treating the disease, such as corticosteroids and cyclosporine. Majority of drug induced secondary hypertension resolves after withdrawal of the offending medication. Lifestyle interventions with proven efficacy in non-IBD populations such as weight reduction, physical activity, reduction of dietary sodium, moderation of alcohol consumption are also effective in IBD-patients<sup>[90-97]</sup>. If lifestyle interventions are not effective in lowering blood pressure, anti-hypertensive medication should be started in combination with lifestyle interventions per JNC 8 recommendations<sup>[98]</sup>.

### Cerebrovascular accident

IBD is associated with increased risk of atrial fibrillation, stroke, myocardial infarction, hospitalization for heart

failure, and cardiovascular-related death during an IBD flare and during persistent disease activity, but not during remission<sup>[99,100]</sup>. A meta-analysis of case-control and cohort studies showed that IBD is associated with a modest increase in the risk of CVA and ischemic heart disease, particularly in women<sup>[101]</sup>. The reasons for the apparent increased risk in female patients with IBD compared with men is unclear, nevertheless, all patients with IBD should be counseled routinely on aggressive risk factor modification<sup>[101]</sup>.

### Coronary artery disease

Patients with IBD have a modestly increased risk of coronary artery disease<sup>[101,102]</sup>. Cardiovascular risk is higher in women with IBD and young adults (< 40-50 years) than in older adults (> 50-60 years)<sup>[101]</sup>. Patients with IBD have evidence of premature vascular disease with structural, functional and biochemical changes indicative of subclinical atherosclerosis; IBD also promotes spontaneous platelet activation and aggregation, predisposing patients to arterial thrombosis<sup>[102]</sup>. In a retrospective cohort study of 131 patients with IBD and CAD who underwent coronary angiography, it was observed that patients with IBD were less likely to have severe left anterior descending artery disease (56% vs 73%,  $P < 0.01$ ) and multivessel disease (71% vs 79%,  $P = 0.05$ ) than non-IBD controls with CAD (524 individuals)<sup>[103]</sup>.

IBD patients were also diagnosed with CAD at a younger age, had a lower body mass index, and were less likely to be active smokers<sup>[103]</sup>. However, the results of that study should be interpreted with caution because the IBD-cohort consisted of patients with less severe CAD and low Framingham risk scores which may have biased the results towards more severe CAD in the non-IBD cohort. Though IBD disease activity (chronic inflammation) is directly related to the risk of cardiovascular events; the prevalence of traditional risk factors for CVD is not higher in IBD patients compared to the general population<sup>[103,104]</sup>. IBD is associated with an increased risk of cardiovascular morbidity without increased cardiovascular mortality because chronic inflammation in the absence of traditional risk factors is not associated with an increased risk of premature CVD events<sup>[105,106]</sup>. Screening for traditional risk factors for CVD such as HTN, diabetes, hyperlipidemia, family history, and smoking should be performed by PCPs or gastroenterologists. Non-traditional risk factors for CVD specific to IBD such as increased disease activity (elevated cytokines, CRP, ESR) should be identified by gastroenterologists<sup>[102]</sup>. Identification of these risk factors should be followed by lifestyle interventions<sup>[102]</sup>. Specific treatment should be provided by the PCP in conjunction with the cardiologist and gastroenterologist in a multidisciplinary strategy that involves aggressive use of disease-modifying biologic therapy to maintain remission in addition to the use of established evidenced based therapies such as aspirin,

statins, antihypertensives, and B-blockers<sup>[107]</sup>. Non-invasive risk stratification should be performed when indicated to determine the need for escalation of therapy. Direct evidence from interventional studies on primary and secondary prevention of CVD events in IBD patients are lacking, therefore, the majority of recommendations are based on data from non-IBD populations<sup>[107]</sup>.

## PREVENTING MEDICATION RELATED MORBIDITY

### **Corticosteroids**

Steroids are very effective for inducing remission in IBD, but ineffective for maintaining remission. Long term use is associated with steroid related adverse effects; therefore early use of steroid sparing therapy is recommended to prevent steroid related adverse effects.

### **Non-steroidal anti-inflammatory drugs**

High-dose non-steroidal anti-inflammatory drugs have been associated with an increase in disease activity in patients with CD or UC, while low-doses of NSAIDs were not associated with a higher disease activity index score among CD patients<sup>[108]</sup>. Bonner *et al.*<sup>[109]</sup> reported no association between NSAID use and increased disease activity in IBD, suggesting that NSAID use in IBD deserves further study before recommending that patients refrain from their use under all circumstances. Nonselective NSAIDs were associated with a 17%-28% relapse rate within 9 d of ingestion in patients with quiescent IBD<sup>[110]</sup>. In another study, the adjusted odds ratio between NSAID use and relapse was 6.31 (95%CI: 1.16-34.38,  $P = 0.03$ )<sup>[111]</sup>. Similarly, selective Cox-2 inhibitors have been associated with relapse in patients with CD and UC suggesting that all classes of NSAIDs are associated with relapse in IBD patients<sup>[112,113]</sup>. However, other studies have reported no increase in flares and a beneficial safety profile with Cox-2 inhibitors during short-term treatment of IBD-associated arthritis and arthralgia<sup>[114,115]</sup>. IBD patients should be advised to avoid NSAIDs; however some patients may require NSAIDs for management of arthritis. Therefore, a patient-centered approach involving discussions on the risks and benefits of NSAID use is warranted before considering NSAID use in IBD-patients.

### **Oral contraceptives**

IBD often presents during the reproductive years; thus women with the disorder need effective contraceptives to prevent unintended pregnancies<sup>[116]</sup>.

### **Efficacy of oral contraceptive pill in IBD**

Most absorption of oral contraceptive pill (OCP) steroids occurs in the small bowel<sup>[117]</sup>. Factors that may impair absorption of OC sex steroids, such as

inflammation and ulceration of the intestinal mucosa, or more rapid transit of gastrointestinal contents in patients who have undergone bowel surgery, might reduce the efficacy of OCPs<sup>[118]</sup>. Two pharmacokinetic studies compared the absorption of combined OCPs between women with UC and healthy volunteers<sup>[119,120]</sup>. These studies found no significant differences in the absorption of OCPs among women with mild UC and those with an ileostomy following proctocolectomy with small ileal resections when compared with healthy women<sup>[119,120]</sup>. It was also noted that women with the largest bowel resections and continent ileostomies had the absolute lowest plasma levels of 1-norgestrel, however the plasma levels never dropped below the threshold needed to inhibit ovulation<sup>[120]</sup>. Thus PCPs may need to decide on a higher dose of OCPs for patients with extensive bowel resections for CD.

### **Effect of OCP on incidence and relapse in IBD**

Multiple studies have examined the relationship between use of OCPs at or after a diagnosis of IBD and incidence of relapse, none of which found a significant effect of OCP use on a variety of measures of relapse<sup>[121-127]</sup>. One study found a significantly increased risk of relapse (HR = 3.0; 95%CI: 1.5-5.9) among CD patients who were current or previous OC users when the reference group was never users (including men)<sup>[123]</sup>. The increased risk was predominantly accounted for by the high rate of relapse among previous OC users (70%), which was higher than the relapse rate among current OC users (43%)<sup>[123]</sup>. However, a comparison of current users alone with never users failed to find an increased risk of relapse among current users<sup>[123]</sup>.

Another prospective cohort study found that women who continued to take OCPs were at a threefold increased risk of developing a relapse of CD; the risk was higher among women who were prescribed OCPs and smoked, suggesting that smoking was a confounding variable<sup>[125]</sup>.

### **OCP and risk of thromboembolism in IBD**

No studies were found that directly examined the risk of thrombosis among women with IBD who were using hormonal contraceptives. However, a prospective cohort study examining the risk of CD relapse among 331 women (134 oral contraceptive users and 197 nonusers) over a 12-mo period reported no cases of arterial or venous thrombosis<sup>[122]</sup>. Kane *et al.*<sup>[126]</sup> found hormone replacement therapy (HRT) to be protective against disease activity in post-menopausal women with IBD (HR = 0.18, 95%CI: 0.04-0.72). A dose-response effect was noted with longer duration of HRT; however the results should be interpreted with caution because it was a small single center retrospective study with limited generalizability<sup>[126]</sup>. The evidence regarding other adverse health outcomes associated with contraceptive use among women with IBD is

limited to a single case report that discussed the possible relationship between use of combined OCPs and the development of ischemic colitis in a woman who had recently undergone surgery for obstructing CD<sup>[127]</sup>. The balance of current evidence suggests that OCPs are associated with a reduced rate of relapse and can be used in women of childbearing age with IBD unless further large-scale studies prove otherwise. The same precautions when prescribing OCPs to women of child bearing age without IBD should be applied to women with IBD of child bearing age<sup>[128]</sup>.

### Antibiotics

Antibiotic use can induce selection pressure and alter the gut microbiome<sup>[129]</sup>. Different studies have shown that antibiotic use at different ages ranging from infancy to adulthood can increase the risk for IBD<sup>[130,131]</sup>. In contrast, antibiotics have been shown to be protective in many large scale studies in patients with established IBD. In a meta-analysis of RCTs, antibiotics were superior to placebo at inducing remission in patients with active CD (RR of CD not in remission = 0.85; 95%CI: 0.73-0.99,  $P = 0.03$ )<sup>[132]</sup>. Antibiotics were also superior to placebo for reducing fistula drainage in CD patients with perianal fistulae (RR = 0.8; 95%CI: 0.66-0.98)<sup>[132]</sup>. In patients with active UC; antibiotics were superior to placebo for inducing remission (RR of UC not in remission = 0.64; 95%CI: 0.43-0.96)<sup>[132]</sup>. Antibiotics were superior to placebo for inducing remission in patients with active CD and preventing relapse in patients with quiescent CD (RR of relapse = 0.62; 95%CI: 0.46-0.84)<sup>[132]</sup>. The evidence on the effect of antibiotics on disease activity and relapse is limited because a diverse number of antibiotics with different spectra of activity were grouped together in the meta-analysis. Specifically, Nitroimidazoles (metronidazole and ornidazole) have been shown to be effective in preventing post-operative recurrence of CD<sup>[133,134]</sup>. Although antibiotics are effective in treating mild flares of IBD and preventing post-operative recurrence in CD, caution is advised against indiscriminate use because of the risk of altering the composition of the gut microbiota which may increase the risk of a disease flare and *Clostridium difficile* infection.

### Probiotics

The effect of probiotics on IBD is unclear, multiple studies using single agent probiotics have failed to show clinical benefit for disease control and prevention of recurrence<sup>[135]</sup>. However, some studies have shown that VSL#3, a mixture of *Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *B. breve*, *B. infantis*, *Bifidobacterium longum* *L.delbrueckii* subsp. *bulgaricus*, and *Streptococcus salivarius* subsp. *thermophiles*, was able to induce remission in patients with mild-to-moderately active UC<sup>[136]</sup>. In CD patients with a history of ileocolonic resection and reanastomosis there was no statistically

significant difference between VSL#3 and placebo in preventing post-surgical recurrence of CD<sup>[137]</sup>. Based upon existing data the only proven benefit of probiotics was shown in the postoperative period in UC patients with ileal pouch-anal anastomosis (IPAA)<sup>[138]</sup>. VSL#3 has been shown to maintain remission and prevent episodes of pouchitis in UC patients with IPAA<sup>[138]</sup>.

### 5-aminosalicylic acids

5-aminosalicylic acids use has been associated with an increased risk of renal disease and folate deficiency<sup>[21,139]</sup>. Folate supplementation 1 mg/d and annual renal function monitoring is recommended for patients taking 5-Aminosalicylate medication<sup>[21,139]</sup>.

### Thiopurines

Measurement of thiopurine methyltransferase (TPMT) activity is recommended prior to starting treatment with thiopurine drugs such as AZA and 6-MP. Approximately 10% and 0.3% of the general population will have low activity and absent activity respectively<sup>[140,141]</sup>. Patients with low activity or absent activity are at an increased risk of drug-induced bone marrow toxicity and myelosuppression due to accumulation of the unmetabolized drug<sup>[140,141]</sup>. Therefore, TPMT, CBC and liver function should be checked prior to initiating therapy and CBC and liver function should be monitored while on therapy<sup>[140]</sup>.

### Methotrexate

Treatment with methotrexate suppresses the immune system and depletes folate. CBC, liver, and renal function should be checked prior to initiating therapy and monitored while on therapy. Patients should also receive daily folate supplementation 1 mg/d<sup>[140]</sup>.

### Anti-TNF-alpha agents

Anti-TNF agents are associated with immunosuppression, increased risk of infections, and reactivation of latent infections - see section on infection. CBC, liver, and renal function should be checked prior to initiating therapy and periodically monitored while on therapy<sup>[140]</sup>.

### Anti-integrin antagonists

Natalizumab a humanized monoclonal antibody against alpha-4 ( $\alpha 4$ ) integrin has been associated with reactivation of the John Cunningham (JC) virus and cases of progressive multifocal leukoencephalopathy (PML)<sup>[142]</sup>. The drug is only available through a restricted program (TOUCH Prescribing Program). It is recommended that anti-JCV antibody be checked prior to treating patients with Natalizumab. CBC and liver function should be monitored while on therapy, and patients should be monitored for any new sign or symptom suggestive of PML. Vedolizumab is a humanized monoclonal antibody against alpha-4 beta-7 ( $\alpha 4\beta 7$ ) integrin which specifically targets mucosal addressin cell adhesion molecule (MAdCAM)

resulting in gut-selective anti-inflammatory activity<sup>[143]</sup>. CBC, liver, and renal function should be checked prior to initiating therapy and monitored while on therapy.

## CANCER SCREENING

### **Skin cancer**

Several observational studies have reported an increased risk of melanoma skin cancer and non-melanoma skin cancer (NMSC) in patients with IBD<sup>[144-147]</sup>. The risk of NMSC was shown to be higher in IBD patients on antimetabolites (AZA and 6-MP), anti-TNF agents, or combination therapy (anti-TNF + AZA or 6MP)<sup>[147]</sup>. Patients should be advised to minimize exposure to UV radiation by wearing cover up clothing, UV-blocking sunglasses and a broad-brimmed hat when feasible, use broad spectrum (UVA/UVB) sunscreen with SPF of 15 or higher every day, and avoid tanning beds. For extended outdoor activity, patients should be advised to use of a water-resistant, broad spectrum (UVA/UVB) sunscreen with SPF of 30 or higher<sup>[148]</sup>. Monthly skin self-examination and annual physician skin exam should be considered in patients on immunosuppressive therapy.

### **Cervical cancer**

The incidence of abnormal Pap smears is higher in women with IBD compared to the general population, and the risk of abnormal Pap smears increases with treatment with IST<sup>[149,150]</sup>. However, other studies suggest that concurrent IST and smoking may explain the association between IBD and cervical dysplasia rather than just the diagnosis of IBD<sup>[151,152]</sup>. Kane<sup>[149]</sup> reported a 42.5% incidence of abnormal Pap smears among women with IBD compared with 7% among controls matched for age, sex and parity. Interestingly, all abnormal tests were associated with either HPV serotype 16 or 18, which underscores the importance of screening female IBD patients for cervical cancer and HPV infection before, soon after initiating, or during IST<sup>[149]</sup>. Females with IBD between the ages of 11 and 26 years on IST should be considered for the HPV vaccine<sup>[55]</sup>. All women on IST should undergo annual Pap testing as recommended by the American College of Obstetrics and Gynecology's guidelines<sup>[153]</sup>.

### **Breast cancer**

Breast cancer is the most common malignancy in United States women and the second leading cause of cancer related mortality among women in the United States<sup>[154]</sup>. Modest evidence suggests that first-degree relatives, particularly, mothers' of CD patients may have a 2-fold higher rate of breast cancer compared with controls<sup>[155]</sup>. Additional evidence suggests that CD patients with breast cancer are not treated as aggressively as controls and they have lower survival when treated, than patients without CD<sup>[156]</sup>. The majority of IBD patients are classified as average risk

for breast cancer screening purposes and should be screened according to American Cancer Society (ACS) guidelines which recommend that average-risk women should receive counseling to raise awareness of breast cancer symptoms and a clinical breast examination (CBE) every 3 years starting at the age of 20 years, followed by annual mammography and CBE beginning at the age of 40 years<sup>[154]</sup>. Female IBD-patients with high risk breast cancer genetic syndromes (*i.e.*, BRCA mutation), IBD patients with a first degree relative with a high-risk genetic syndrome or IBD patients with greater than 20% lifetime risk of breast cancer based on risk-estimation models should be considered high risk and screened according to ACS guidelines for high risk patients<sup>[154]</sup>.

### **Colorectal dysplasia and cancer**

Patients with long-standing IBD are at an increased risk for developing colorectal dysplasia and cancer<sup>[157,158]</sup>. According to the AGA guidelines, all patients, regardless of extent of disease, should undergo a screening colonoscopy<sup>[158]</sup>. There is consensus that if a patient with UC or CD is found to have confirmed low-grade dysplasia in flat mucosa, proctocolectomy or repeat surveillance within 6-mo should be offered<sup>[157,158]</sup>. Preventive surgery (proctocolectomy) is recommended in patients with high grade dysplasia. If a patient with extensive UC or CD involving the colon has had disease for 8 to 10 years, surveillance colonoscopy should be performed every 1 to 3 years<sup>[157,158]</sup>. There is ongoing debate over the optimal number biopsies that should be obtained and the endoscopic method for CRC surveillance in IBD<sup>[159,160]</sup>. However, a recent international consensus statement suggests that chromoendoscopy may be superior to white-light endoscopy for detection of dysplasia<sup>[161]</sup>. This international consensus statement also favors endoscopic management over colectomy for the management of polypoid, non-polypoid and invisible dysplasia in IBD patients; however the recommendations are based on very low quality evidence<sup>[161]</sup>. Please refer to the complete guidelines on the appropriate surveillance for colorectal cancer in IBD<sup>[157,158]</sup>.

### **Prostate cancer**

Screening for prostate cancer is controversial because a significant proportion of cases detected by screening will not cause symptoms during the lifetime of affected patients<sup>[162]</sup>. Consequently, many patients may not benefit from screening and may, be harmed by early cancer detection and treatment<sup>[154,162]</sup>. Therefore, a discussion about the potential benefits and risks associated with testing should occur between the physician and patient before testing. The ACS guidelines emphasize the importance of shared decision-making between the physician and patient and recommends PSA testing for men aged 50 years who are at average risk of prostate cancer and are expected to live at least 10 more years<sup>[154]</sup>. Patients at

**Table 7** The 8-item Morisky Medication Adherence Scale

Morisky adherence scale question	Scoring
Do you sometimes forget to take your pills?	1 for NO; 0 for YES
People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 wk, were there any days when you did not take your medication?	1 for NO; 0 for YES
Have you ever cut-back or stopped taking your medication without telling your doctor, because you felt worse when you took it.	1 for NO; 0 for YES
When you travel or leave home do you sometimes forget to take your IBD medication?	1 for NO; 0 for YES
Did you take your IBD medicine yesterday?	1 for NO; 0 for YES
When you feel that your IBD symptoms are under control do you sometimes stop taking your medication?	1 for NO; 0 for YES
Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your IBD treatment plan?	1 for NO; 0 for YES
How often do you remember to take all your IBD medications?	
Rarely/Never	1.00
Once in a while	0.75
Sometimes	0.50
Usually	0.25
Always	0.00

Adapted from Trindade *et al*<sup>[167]</sup>. Scoring: < 6 points = low adherers; 6-7 points = medium adherers; 8 points = high adherers. IBD: Inflammatory bowel disease.

high risk of developing prostate cancer such as African Americans and men who have a first-degree relative (father, brother, or son) or more than one first-degree relative diagnosed with prostate cancer at an early age (< 65 years), the ACS recommends screening at 45 years and 40 years respectively<sup>[154]</sup>. In contrast, the United States Preventive Services Task Force does not recommend PSA-screening because the benefits of PSA-based screening for prostate cancer do not outweigh the harms<sup>[162]</sup>.

## SCREENING FOR MEDICATION NON-ADHERENCE

Non-adherence to IBD therapy leads to poorer disease outcomes<sup>[163-165]</sup>. A recent case control study showed that about one-third of IBD patients were low adherers<sup>[163]</sup>, predictors of low adherence were age (< 40 years), higher educational level, being single, and mesalamine use<sup>[163]</sup>. Interestingly, being self-employed was found to be a protective factor<sup>[163]</sup>. Another study showed that non-adherence to anti-TNF agents was strongly associated with loss of response to anti-TNF agents<sup>[165]</sup>. Longer intervals between outpatient clinic visits ( $\geq 3$  mo) and limited knowledge of the prescribed medication were found to be significant predictors of non-adherence in that study<sup>[165]</sup>. Taken together, limited knowledge about IBD medication and inappropriate self-perceptions of illness play a significant role in fostering non-adherence in IBD-patients, highlighting an unmet need for patient education and interventions aimed at improving adherence. Several strategies exist for monitoring medication adherence such as pill counts, medication refill rates, checking for drug metabolites and direct inquiry about medication adherence. Standardized questionnaires such as the 8-item Morisky Medication Adherence Scale (MMAS-8) may be used

to identify patients at risk of non-adherence with IBD therapy (Table 7)<sup>[166]</sup>. The MMAS-8 has been criticized because it is a self-reported questionnaire which was validated on patients with chronic diseases that may not be entirely representative of IBD patients<sup>[166]</sup>. Consequently, IBD specific screening tools to identify patients at risk of medication non-adherence such as the modified IBD-MMAS-8 and 10-item mesalamine non-adherence questionnaire were developed<sup>[167,168]</sup>. There is modest evidence that the MMAS-8 reasonably identifies IBD patients at risk of non-adherence<sup>[167,169]</sup>. Medication non-adherence can be categorized into two conceptual frameworks; accidental non-adherence and intentional non-adherence<sup>[170]</sup>. On the basis of these categories, personalized algorithms may be developed to improve patient education, empowerment and follow-up. For example, strategies such as; patient-education, regimen simplification, use of reminder systems and organizational strategies (e.g., pill boxes) are likely to be best suited for addressing accidental nonadherence. In contrast, strategies such as teaching problem-solving skills, addressing motivational issues, and problematic patterns of family functioning are more likely to be effective in individuals displaying intentional non-adherence<sup>[170]</sup>.

## CONCLUSION

Preventive health care can avert morbidity, mortality, and reduce overall health care costs<sup>[171]</sup>. Patients with IBD require special healthcare needs at different stages of life from childhood through adolescence and adulthood. Historically, the role of the gastroenterologist was to achieve and maintain remission and monitor for adverse events. However, the potential risk of comorbidities negatively impacting IBD outcomes has mandated a working knowledge of health maintenance and a holistic approach to healthcare for IBD patients.

**Table 8 Preventive health measures in inflammatory bowel disease**

Morbidity	Preventive measures	Setting	Provider
Venous thromboembolism			
Dehydration	Encourage adequate hydration	Out-patient	PCP <sup>1</sup> , Hospitalist <sup>1</sup>
	Intravenous fluids when indicated	In-patient	Gastroenterologist <sup>2</sup>
Prolonged immobilization	Encourage physical activity	Out-patient	PCP <sup>1</sup>
	Early ambulation during hospitalization	In-patient	Hospitalist <sup>1</sup>
Indwelling catheters	Limit use of venous catheters when possible	In-patient	Hospitalist <sup>1</sup> , Gastroenterologist <sup>2</sup>
Hyperhomocysteinemia	Detection and correction of vitamin deficiencies B <sub>6</sub> , B <sub>12</sub> , folate	Out-patient	PCP <sup>1</sup>
			Gastroenterologist <sup>2</sup>
Oral contraceptives	Advise on alternative methods of contraception	Out-patient	PCP <sup>1</sup>
Active intestinal disease (inflammatory burden)	Anti-inflammatory treatment, monitoring of medication and response to therapy.	Out-patient	Gastroenterologist <sup>1</sup>
			PCP <sup>2</sup>
Cardiovascular disease			
Hypertension (Primary and secondary prevention)	Low sodium diet, smoking cessation, increased physical activity.	Out-patient	PCP <sup>1</sup>
	Anti-hypertensive medication		
Coronary artery disease (Primary and secondary prevention)	Low sodium diet, smoking cessation, increased physical activity, screening for hyperlipidemia. Statins, anti-platelet drugs,	Out-patient	PCP <sup>1</sup>
			Cardiologist <sup>1</sup> , Gastroenterologist <sup>2</sup>
Stroke (Primary and secondary prevention)	Anti-platelet therapy, statins, Anti-hypertensive medications	Out-patient	PCP <sup>1</sup> , Neurologist <sup>2</sup>
			Gastroenterologist <sup>2</sup>
Smoking			
	Smoking cessation advise, nicotine replacement therapy, smoking cessation counselling and support programs	Out-patient	PCP <sup>1</sup>
			Gastroenterologist <sup>2</sup>
Cancer			
Skin	Advise on UV exposure	Outpatient	PCP <sup>1</sup>
	Protective clothing, high SPF sunscreen		Gastroenterologist <sup>2</sup>
	Yearly physician skin exam		
Colon	Surveillance colonoscopy per IBD guidelines	Out-patient	Gastroenterologist <sup>1</sup>
			PCP <sup>2</sup>
Cervical	PAP smear	Out-patient	Gynecologist <sup>1</sup> , PCP <sup>2</sup>
Breast	Counselling on breast cancer awareness	Out-patient	PCP <sup>1</sup>
	CBE every 3 yr		
	Mammography after 40 yr		
Prostate	Counseling and Shared-decision making on PSA testing	Out-patient	PCP <sup>1</sup>
Nutritional deficiencies	Screen for and correct nutritional deficiencies	Out-patient	PCP <sup>1</sup>
			Gastroenterologist <sup>2</sup>
Osteoporosis	DEXA in patients with increased risk of osteoporosis (hx of steroid use 10 mg daily x > 3 mo) treatment with bisphosphonates if osteoporosis confirmed.	Out-patient	PCP <sup>1</sup>
			Gastroenterologist <sup>2</sup>
Infections			
Vaccine preventable infections	Vaccination	Out-patient	PCP <sup>1</sup>
			Gastroenterologist <sup>2</sup>
Reactivation of Hepatitis B virus	Screening for HBV before initiating Anti-TNF therapy	Out-patient	Gastroenterologist <sup>1</sup>
Reactivation of latent Tuberculosis	Screening for latent TB before initiating Anti-TNF therapy	Out-patient	Gastroenterologist <sup>1</sup>
Anemia	Detection and treatment of anemia	Out-patient	PCP <sup>1</sup>
			Gastroenterologist <sup>2</sup>
Depression	Depression screening PHQ 2 if positive do PHQ 9 for diagnosis	Out-patient	PCP <sup>1</sup>
	Mild depression -counselling		Gastroenterologist <sup>2</sup>
	Moderate to severe- counselling +medication		
Sleep disturbance	Screening for sleep disturbance, Counseling on sleep hygiene	Out-patient	PCP <sup>1</sup>
			Gastroenterologist <sup>2</sup>
	Medical therapy		
Medication related adverse effects	Assessing medication adverse effects and interactions	Out-patient	Gastroenterologist <sup>1</sup>
			PCP <sup>2</sup>
Medication Non-adherence	Screening for medication non-adherence	Out-patient	Gastroenterologist <sup>1</sup>
	MMAS-8 item questionnaire		PCP <sup>2</sup>
	Review frequency of medication refills		
	Drug levels for anti-TNF and thiopurines		

<sup>1</sup>Primary role in preventive care; <sup>2</sup>Secondary role in preventive care. PCP: Primary care physician; MMAS-8: 8-Morisky Medication Adherence Scale.

A recent study showed that incorporating a standard curriculum on IBD health maintenance provided fellows in training with increased awareness and guidance on managing the unique preventive care needs of patients with IBD<sup>[172]</sup>. Different tools exist to assist practicing gastroenterologists in addressing preventive health issues during clinical encounters with IBD patients, such as, the Crohn's and Colitis Foundation of America (CCFA) check list for health maintenance or clinical assessment checklist developed by specialized IBD centers<sup>[173-175]</sup>. The CCFA and AGA have publicized quality measures based on the best available evidence for processes and outcomes related to high quality care of IBD patients<sup>[56,176]</sup>. Some recommendations in this review overlap with some of the CCFA and AGA quality measures for preventive health<sup>[56,176]</sup>. Direct evidence from interventional studies in IBD patients are lacking for some preventive measures outlined in this review; therefore some recommendations are based on expert opinion and data from non-IBD populations. Additionally, this review considered the setting where each preventive intervention is best delivered (Table 8). Many of the interventions are appropriate for primary care settings and PCPs are uniquely qualified to provide interventions such as vaccination, smoking cessation, blood pressure control, referral for colon and cervical cancer screening<sup>[177,178]</sup>. An educational intervention study providing instruction on diagnoses and management of IBD to PCPs in central Italy was associated a reduced rate of hospitalizations for IBD<sup>[179]</sup>. Furthermore, a recent survey among gastroenterologists and PCPs in the United States reported that PCPs are very knowledgeable and comfortable providing primary care for IBD patients<sup>[180]</sup>. Thus, the label "IBD" should not discourage PCPs from providing preventive health services to IBD patients. Evidence suggests that building therapeutic physician-patient relationships and shared decision-making is crucial to the outcome of chronic illnesses and IBD<sup>[181,182]</sup>. Therefore, individual preference is likely to play a role in where and with whom patients choose to receive preventive health. Nevertheless, a holistic approach to care and better communication between gastroenterologists and PCPs with explicit clarification of roles will prevent duplication of services and streamline care.

## REFERENCES

- 1 CDC. 2007. Available from: URL: <http://www.cdc.gov/nccdphp/dach/ibd.htm>
- 2 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; **14**: 253-258 [PMID: 17932966 DOI: 10.1002/ibd.20266]
- 3 Selby L, Hoellein A, Wilson JF. Are primary care providers uncomfortable providing routine preventive care for inflammatory bowel disease patients? *Dig Dis Sci* 2011; **56**: 819-824 [PMID: 20668942 DOI: 10.1007/s10620-010-1329-8]
- 4 Sinclair JA, Wasan SK, Farraye FA. Health maintenance in the inflammatory bowel disease patient. *Gastroenterol Clin North Am* 2012; **41**: 325-337 [PMID: 22500521 DOI: 10.1016/j.gtc.2012.01.006]
- 5 van der Heide F, Dijkstra A, Weersma RK, Albersnagel FA, van der Logt EM, Faber KN, Sluiter WJ, Kleibeuker JH, Dijkstra G. Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 1199-1207 [PMID: 19170191 DOI: 10.1002/ibd.20884]
- 6 Fiore MC. US public health service clinical practice guideline: treating tobacco use and dependence. *Respir Care* 2000; **45**: 1200-1262 [PMID: 11054899]
- 7 Johnson GJ, Cosnes J, Mansfield JC. Review article: smoking cessation as primary therapy to modify the course of Crohn's disease. *Aliment Pharmacol Ther* 2005; **21**: 921-931 [PMID: 15813828 DOI: 10.1111/j.1365-2036.2005.02424.x]
- 8 Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013; (5): CD009329 [PMID: 23728690 DOI: 10.1002/14651858.CD009329.pub2]
- 9 Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999; **340**: 685-691 [PMID: 10053177 DOI: 10.1056/nejm199903043400903]
- 10 Nunes T, Etchevers MJ, García-Sánchez V, Ginard D, Martí E, Barreiro-de Acosta M, Gomollón F, Arroyo M, Bastida G, Gonzalez B, Monfort D, Garcia-Planella E, Figueroa C, Panés J, Sans M. Impact of Smoking Cessation on the Clinical Course of Crohn's Disease Under Current Therapeutic Algorithms: A Multicenter Prospective Study. *Am J Gastroenterol* 2016; **111**: 411-419 [PMID: 26856753 DOI: 10.1038/ajg.2015.401]
- 11 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985; **100**: 126-131 [PMID: 3920711]
- 12 Melinder C, Hiyoshi A, Hussein O, Halfvarson J, Ekblom A, Montgomery S. Physical Fitness in Adolescence and Subsequent Inflammatory Bowel Disease Risk. *Clin Transl Gastroenterol* 2015; **6**: e121 [PMID: 26540026 DOI: 10.1038/ctg.2015.49]
- 13 Boutros M, Maron D. Inflammatory bowel disease in the obese patient. *Clin Colon Rectal Surg* 2011; **24**: 244-252 [PMID: 23204939 DOI: 10.1055/s-0031-1295687]
- 14 Cosnes J. Smoking, physical activity, nutrition and lifestyle: environmental factors and their impact on IBD. *Dig Dis* 2010; **28**: 411-417 [PMID: 20926865 DOI: 10.1159/000320395]
- 15 Bilski J, Brzozowski B, Mazur-Biala A, Sliwowski Z, Brzozowski T. The role of physical exercise in inflammatory bowel disease. *Biomed Res Int* 2014; **2014**: 429031 [PMID: 24877092 DOI: 10.1155/2014/429031]
- 16 Klare P, Nigg J, Nold J, Haller B, Krug AB, Mair S, Thoeringer CK, Christle JW, Schmid RM, Halle M, Huber W. The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: a prospective randomized controlled trial. *Digestion* 2015; **91**: 239-247 [PMID: 25823689 DOI: 10.1159/000371795]
- 17 Packer N, Hoffman-Goetz L, Ward G. Does physical activity affect quality of life, disease symptoms and immune measures in patients with inflammatory bowel disease? A systematic review. *J Sports Med Phys Fitness* 2010; **50**: 1-18 [PMID: 20308966]
- 18 Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol* 2011; **106**: 563-573 [PMID: 21468064 DOI: 10.1038/ajg.2011.44]
- 19 Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. *World J Gastroenterol* 2009; **15**: 2570-2578 [PMID: 19496185]
- 20 Ananthkrishnan AN, Khalili H, Konijeti GG, Higuuchi LM, de Silva P, Korzenik JR, Fuchs CS, Willett WC, Richter JM, Chan AT. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology* 2013; **145**:

- 970-977 [PMID: 23912083 DOI: 10.1053/j.gastro.2013.07.050]
- 21 **Hwang C**, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. *Inflamm Bowel Dis* 2012; **18**: 1961-1981 [PMID: 22488830 DOI: 10.1002/ibd.22906]
  - 22 **Vagianos K**, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. *JPEN J Parenter Enteral Nutr* 2007; **31**: 311-319 [PMID: 17595441]
  - 23 **Hindryckx P**, Amininejad L, Van De Vijver E, Bossuyt P. Belgian recommendations for the management of anemia in patients with inflammatory bowel disease. *Acta Gastroenterol Belg* 2014; **77**: 333-344 [PMID: 25509205]
  - 24 **Oldenburg B**, Koningsberger JC, Van Berge Henegouwen GP, Van Asbeck BS, Marx JJ. Iron and inflammatory bowel disease. *Aliment Pharmacol Ther* 2001; **15**: 429-438 [PMID: 11284771]
  - 25 **Crawford J**. Anemia and lung cancer. *Lung Cancer* 2002; **38** Suppl 3: S75-S78 [PMID: 12468152]
  - 26 **Dallalio G**, Law E, Means RT. Hepcidin inhibits in vitro erythroid colony formation at reduced erythropoietin concentrations. *Blood* 2006; **107**: 2702-2704 [PMID: 16332970 DOI: 10.1182/blood-2005-07-2854]
  - 27 **Dieleman LA**, Heizer WD. Nutritional issues in inflammatory bowel disease. *Gastroenterol Clin North Am* 1998; **27**: 435-451 [PMID: 9650026]
  - 28 **Gomollón F**, Gisbert JP. Anemia and inflammatory bowel diseases. *World J Gastroenterol* 2009; **15**: 4659-4665 [PMID: 19787829]
  - 29 **Semrin G**, Fishman DS, Bousvaros A, Zholudev A, Saunders AC, Correia CE, Nemeth E, Grand RJ, Weinstein DA. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. *Inflamm Bowel Dis* 2006; **12**: 1101-1106 [PMID: 17119383 DOI: 10.1097/01.mib.0000235097.86360.04]
  - 30 **WHO/UNICEF/UNU**. Iron Deficiency Anemia: Assessment, Prevention and Control. 1998
  - 31 **Gasche C**, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, Gomollon F, Hjortswang H, Koutroubakis I, Kulnigg S, Oldenburg B, Rampton D, Schroeder O, Stein J, Travis S, Van Assche G. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007; **13**: 1545-1553 [PMID: 17985376 DOI: 10.1002/ibd.20285]
  - 32 **Lomer MC**, Cook WB, Jan-Mohamed HJ, Hutchinson C, Liu DY, Hider RC, Powell JJ. Iron requirements based upon iron absorption tests are poorly predicted by haematological indices in patients with inactive inflammatory bowel disease. *Br J Nutr* 2012; **107**: 1806-1811 [PMID: 22152498 DOI: 10.1017/s0007114511004971]
  - 33 **Gisbert JP**, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 1299-1307 [PMID: 18477354 DOI: 10.1111/j.1572-0241.2008.01846.x]
  - 34 **Ali T**, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. *Am J Med* 2009; **122**: 599-604 [PMID: 19559158 DOI: 10.1016/j.amjmed.2009.01.022]
  - 35 **Bernstein CN**, Blanchard JF, Leslie W, Wajda A, Yu BN. The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. *Ann Intern Med* 2000; **133**: 795-799 [PMID: 11085842]
  - 36 **Genant HK**, Cooper C, Poor G, Reid I, Ehrlich G, Kanis J, Nordin BE, Barrett-Connor E, Black D, Bonjour JP, Dawson-Hughes B, Delmas PD, Dequeker J, Ragi Eis S, Gennari C, Johnell O, Johnston CC, Lau EM, Liberman UA, Lindsay R, Martin TJ, Masri B, Mautalen CA, Meunier PJ, Khaltaev N. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. *Osteoporos Int* 1999; **10**: 259-264 [PMID: 10692972]
  - 37 **Stockbrügger RW**, Schoon EJ, Bollani S, Mills PR, Israeli E, Landgraf L, Felsenberg D, Ljunghall S, Nygard G, Persson T, Graffner H, Bianchi Porro G, Ferguson A. Discordance between the degree of osteopenia and the prevalence of spontaneous vertebral fractures in Crohn's disease. *Aliment Pharmacol Ther* 2002; **16**: 1519-1527 [PMID: 12182752]
  - 38 **Papaioannou A**, Ferko NC, Adachi JD. All patients with inflammatory bowel disease should have bone density assessment: pro. *Inflamm Bowel Dis* 2001; **7**: 158-162; discussion 168-169 [PMID: 11383589]
  - 39 **Caprilli R**, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, Hommes DW, Lochs H, Angelucci E, Cocco A, Vucelic B, Hildebrand H, Kolacek S, Riis L, Lukas M, de Franchis R, Hamilton M, Jantschek G, Michetti P, O'Morain C, Anwar MM, Freitas JL, Mouzas IA, Baert F, Mitchell R, Hawkey CJ. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006; **55** Suppl 1: i36-i58 [PMID: 16481630 DOI: 10.1136/gut.2005.081950c]
  - 40 **Bernstein CN**, Katz S. Guidelines for osteoporosis and inflammatory bowel disease. A guide to diagnosis and management for the gastroenterologist (monograph). The American College of Gastroenterology, 2003
  - 41 **Kornbluth A**, Hayes M, Feldman S, Hunt M, Fried-Boxt E, Lichtiger S, Legnani P, George J, Young J. Do guidelines matter? Implementation of the ACG and AGA osteoporosis screening guidelines in inflammatory bowel disease (IBD) patients who meet the guidelines' criteria. *Am J Gastroenterol* 2006; **101**: 1546-1550 [PMID: 16863559 DOI: 10.1111/j.1572-0241.2006.00571.x]
  - 42 **Cranney A**, Welch V, Adachi JD, Homik J, Shea B, Suarez-Almazor ME, Tugwell P, Wells G. Calcitonin for the treatment and prevention of corticosteroid-induced osteoporosis. *Cochrane Database Syst Rev* 2000; (2): CD001983 [PMID: 10796457 DOI: 10.1002/14651858.cd001983]
  - 43 **Melek J**, Sakuraba A. Efficacy and safety of medical therapy for low bone mineral density in patients with inflammatory bowel disease: a meta-analysis and systematic review. *Clin Gastroenterol Hepatol* 2014; **12**: 32-44.e5 [PMID: 23981521 DOI: 10.1016/j.jcgh.2013.08.024]
  - 44 **Neer RM**, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsmann AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344**: 1434-1441 [PMID: 11346808 DOI: 10.1056/nejm200105103441904]
  - 45 **Raisz LG**. Clinical practice. Screening for osteoporosis. *N Engl J Med* 2005; **353**: 164-171 [PMID: 16014886 DOI: 10.1056/NEJMc042092]
  - 46 **Reid IR**, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med* 1995; **98**: 331-335 [PMID: 7709944 DOI: 10.1016/s0002-9343(99)80310-6]
  - 47 **Bartram SA**, Peaston RT, Rawlings DJ, Francis RM, Thompson NP. A randomized controlled trial of calcium with vitamin D, alone or in combination with intravenous pamidronate, for the treatment of low bone mineral density associated with Crohn's disease. *Aliment Pharmacol Ther* 2003; **18**: 1121-1127 [PMID: 14653832]
  - 48 **Benchimol EI**, Ward LM, Gallagher JC, Rauch F, Barrowman N, Warren J, Beedle S, Mack DR. Effect of calcium and vitamin D supplementation on bone mineral density in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **45**: 538-545 [PMID: 18030230 DOI: 10.1097/MPG.0b013e3180dca0cc]
  - 49 **Bernstein CN**, Seeger LL, Anton PA, Artinian L, Geoffrey S, Goodman W, Belin TR, Shanahan F. A randomized, placebo-controlled trial of calcium supplementation for decreased bone density in corticosteroid-using patients with inflammatory bowel disease: a pilot study. *Aliment Pharmacol Ther* 1996; **10**: 777-786 [PMID: 8899087]
  - 50 **Felekis T**, Katsanos K, Kitsanou M, Trakos N, Theopistos V, Christodoulou D, Asproudis I, Tsianos EV. Spectrum and frequency of ophthalmologic manifestations in patients with inflammatory bowel disease: a prospective single-center study. *Inflamm Bowel Dis* 2009; **15**: 29-34 [PMID: 18626979 DOI: 10.1002/ibd.20584]
  - 51 **Mintz R**, Feller ER, Bahr RL, Shah SA. Ocular manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 135-139 [PMID: 15168814]
  - 52 **Calvo P**, Pablo L. Managing IBD outside the gut: ocular mani-

- festations. *Dig Dis* 2013; **31**: 229-232 [PMID: 24030231 DOI: 10.1159/000353375]
- 53 **Manolakis CS**, Farraye FA, Di Palma JA. Crohn's disease: the subsequent visit. *Gastroenterol Hepatol* (N Y) 2013; **9**: 16-20 [PMID: 24707229]
- 54 **Sands BE**, Cuffari C, Katz J, Kugathasan S, Onken J, Vitek C, Orenstein W. Guidelines for immunizations in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 677-692 [PMID: 15472534]
- 55 **Chaudrey K**, Salvaggio M, Ahmed A, Mahmood S, Ali T. Updates in vaccination: recommendations for adult inflammatory bowel disease patients. *World J Gastroenterol* 2015; **21**: 3184-3196 [PMID: 25805924 DOI: 10.3748/wjg.v21.i11.3184]
- 56 **Melmed GY**, Siegel CA, Spiegel BM, Allen JJ, Cima R, Colombel JF, Dassopoulos T, Denson LA, Dudley-Brown S, Garb A, Hanauer SB, Kappelman MD, Lewis JD, Lynch I, Moynihan A, Rubin DT, Sartor RB, Schwartz RM, Wolf DC, Ullman TA. Quality indicators for inflammatory bowel disease: development of process and outcome measures. *Inflamm Bowel Dis* 2013; **19**: 662-668 [PMID: 23388547 DOI: 10.1097/mib.0b013e31828278a2]
- 57 **Reddy KR**, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 215-219; e16-e17 [PMID: 25447850 DOI: 10.1053/j.gastro.2014.10.039]
- 58 **Gisbert JP**, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 619-633 [PMID: 21416659]
- 59 **Centers for Disease Control and Prevention (CDC)**. Testing for HCV infection: an update of guidance for clinicians and laboratorians. *MMWR Morb Mortal Wkly Rep* 2013; **62**: 362-365 [PMID: 23657112]
- 60 **Opp MR**. Cytokines and sleep. *Sleep Med Rev* 2005; **9**: 355-364 [PMID: 16102986 DOI: 10.1016/j.smrv.2005.01.002]
- 61 **Shearer WT**, Reuben JM, Mullington JM, Price NJ, Lee BN, Smith EO, Szuba MP, Van Dongen HP, Dinges DF. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 2001; **107**: 165-170 [PMID: 11150007 DOI: 10.1067/mai.2001.112270]
- 62 **Irwin MR**, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med* 2006; **166**: 1756-1762 [PMID: 16983055 DOI: 10.1001/archinte.166.16.1756]
- 63 **Ali T**, Orr WC. Sleep disturbances and inflammatory bowel disease. *Inflamm Bowel Dis* 2014; **20**: 1986-1995 [PMID: 25025716 DOI: 10.1097/mib.000000000000108]
- 64 **Ranjbaran Z**, Keefer L, Farhadi A, Stepanki E, Sedghi S, Keshavarzian A. Impact of sleep disturbances in inflammatory bowel disease. *J Gastroenterol Hepatol* 2007; **22**: 1748-1753 [PMID: 17914945 DOI: 10.1111/j.1440-1746.2006.04820.x]
- 65 **Graff LA**, Vincent N, Walker JR, Clara I, Carr R, Ediger J, Miller N, Rogala L, Rawsthorne P, Lix L, Bernstein CN. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 1882-1889 [PMID: 21830266 DOI: 10.1002/ibd.21580]
- 66 **Ali T**, Choe J, Awab A, Wagener TL, Orr WC. Sleep, immunity and inflammation in gastrointestinal disorders. *World J Gastroenterol* 2013; **19**: 9231-9239 [PMID: 24409051 DOI: 10.3748/wjg.v19.i48.9231]
- 67 **Ali T**, Madhoun MF, Orr WC, Rubin DT. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. *Inflamm Bowel Dis* 2013; **19**: 2440-2443 [PMID: 23945186 DOI: 10.1097/MIB.0b013e3182a0ea54]
- 68 **Ananthakrishnan AN**, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol* 2013; **11**: 965-971 [PMID: 23376797 DOI: 10.1016/j.cgh.2013.01.021]
- 69 **Bernklev T**, Jahnsen J, Lygren I, Henriksen M, Vatn M, Moum B. Health-related quality of life in patients with inflammatory bowel disease measured with the short form-36: psychometric assessments and a comparison with general population norms. *Inflamm Bowel Dis* 2005; **11**: 909-918 [PMID: 16189421]
- 70 **Janke KH**, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 272-286 [PMID: 15735434]
- 71 **Irvine EJ**, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JW. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* 1994; **106**: 287-296 [PMID: 8299896]
- 72 **Turnbull GK**, Vallis TM. Quality of life in inflammatory bowel disease: the interaction of disease activity with psychosocial function. *Am J Gastroenterol* 1995; **90**: 1450-1454 [PMID: 7661168]
- 73 **de Boer AG**, Sprangers MA, Bartelsman JF, de Haes HC. Predictors of health care utilization in patients with inflammatory bowel disease: a longitudinal study. *Eur J Gastroenterol Hepatol* 1998; **10**: 783-789 [PMID: 9831274]
- 74 **Nigro G**, Angelini G, Grosso SB, Caula G, Sategna-Guidetti C. Psychiatric predictors of noncompliance in inflammatory bowel disease: psychiatry and compliance. *J Clin Gastroenterol* 2001; **32**: 66-68 [PMID: 11154175]
- 75 **Filipovic BR**, Filipovic BF. Psychiatric comorbidity in the treatment of patients with inflammatory bowel disease. *World J Gastroenterol* 2014; **20**: 3552-3563 [PMID: 24707138 DOI: 10.3748/wjg.v20.i13.3552]
- 76 **Mikocka-Walus A**, Pittet V, Rossel JB, von Känel R. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2016; **14**: 829-835.e1 [PMID: 26820402 DOI: 10.1016/j.cgh.2015.12.045]
- 77 **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; **103**: 1989-1997 [PMID: 18796096 DOI: 10.1111/j.1572-0241.2008.01980.x]
- 78 **Arroll B**, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. *BMJ* 2003; **327**: 1144-1146 [PMID: 14615341 DOI: 10.1136/bmj.327.7424.1144]
- 79 **Bernstein CN**. Psychological Stress and Depression: Risk Factors for IBD? *Dig Dis* 2016; **34**: 58-63 [PMID: 26983009 DOI: 10.1159/000442929]
- 80 **USPSTF**. Screening for depression in adults, 2009, cited 2016-3-30. Available from: URL: <http://www.uspreventiveservicestaskforce.org/uspstf09/adultdepression/addeprrs.htm>
- 81 **American Psychiatric Association Workgroup on Major Depressive Disorder**. Practice guideline for the treatment of patients with major depressive disorder. Washington, DC: American Psychiatric Association, 2000, cited 2016-3-30. Available from: URL: [http://www.psych.org/psych\\_pract/treat/pg/Depression2e.book.cfm](http://www.psych.org/psych_pract/treat/pg/Depression2e.book.cfm)
- 82 **Magro F**, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. *World J Gastroenterol* 2014; **20**: 4857-4872 [PMID: 24803797 DOI: 10.3748/wjg.v20.i17.4857]
- 83 **Novacek G**, Weltermann A, Sobala A, Tilg H, Petritsch W, Reinsch W, Mayer A, Haas T, Kaser A, Feichtenschlager T, Fuchssteiner H, Knoflach P, Vogelsang H, Miehsler W, Platzer R, Tillinger W, Jaritz B, Schmid A, Blaha B, Dejaco C, Eichinger S. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology* 2010; **139**: 779-787, 787.e1 [PMID: 20546736 DOI: 10.1053/j.gastro.2010.05.026]
- 84 **Bernstein CN**, Blanchard JF, Houston DS, Wajda A. The

- incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemost* 2001; **85**: 430-434 [PMID: 11307809]
- 85 **Nguyen GC**, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008; **103**: 2272-2280 [PMID: 18684186 DOI: 10.1111/j.1572-0241.2008.02052.x]
- 86 **Gross ME**, Vogler SA, Mone MC, Sheng X, Sklow B. The importance of extended postoperative venous thromboembolism prophylaxis in IBD: a National Surgical Quality Improvement Program analysis. *Dis Colon Rectum* 2014; **57**: 482-489 [PMID: 24608305 DOI: 10.1097/dcr.000000000000090]
- 87 **Nguyen GC**, Bernstein CN. Duration of anticoagulation for the management of venous thromboembolism in inflammatory bowel disease: a decision analysis. *Am J Gastroenterol* 2013; **108**: 1486-1495 [PMID: 23857476 DOI: 10.1038/ajg.2013.220]
- 88 **Nguyen GC**, Bernstein CN, Bitton A, Chan AK, Griffiths AM, Leontiadis GI, Geerts W, Bressler B, Butzner JD, Carrier M, Chande N, Marshall JK, Williams C, Kearon C. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology* 2014; **146**: 835-848.e6 [PMID: 24462530 DOI: 10.1053/j.gastro.2014.01.042]
- 89 **Seminario JL**, Koutroubakis IE, Ramos-Rivers C, Hashash JG, Dudekula A, Regueiro M, Baidoo L, Barrie A, Swoger J, Schwartz M, Weyant K, Dunn MA, Binion DG. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2015; **21**: 2857-2863 [PMID: 26241001 DOI: 10.1097/mib.0000000000000560]
- 90 **He J**, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. *Hypertension* 2000; **35**: 544-549 [PMID: 10679495]
- 91 **Sacks FM**, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, Simons-Morton DG, Karanja N, Lin PH. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; **344**: 3-10 [PMID: 11136953 DOI: 10.1056/NEJM200101043440101]
- 92 **Vollmer WM**, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, Conlin PR, Svetkey LP, Erlinger TP, Moore TJ, Karanja N. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001; **135**: 1019-1028 [PMID: 11747380]
- 93 **Chobanian AV**, Hill M. National Heart, Lung, and Blood Institute Workshop on Sodium and Blood Pressure : a critical review of current scientific evidence. *Hypertension* 2000; **35**: 858-863 [PMID: 10775551]
- 94 **Kelley GA**, Kelley KS. Progressive resistance exercise and resting blood pressure : A meta-analysis of randomized controlled trials. *Hypertension* 2000; **35**: 838-843 [PMID: 10720604]
- 95 **Whelton SP**, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2002; **136**: 493-503 [PMID: 11926784]
- 96 **Xin X**, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 2001; **38**: 1112-1117 [PMID: 11711507]
- 97 **Cushman WC**, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, Black HR, Hamilton BP, Holland J, Nwachuku C, Papademetriou V, Probstfield J, Wright JT, Alderman MH, Weiss RJ, Piller L, Bettencourt J, Walsh SM; ALLHAT Collaborative Research Group. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)* 2002; **4**: 393-404 [PMID: 12461301]
- 98 **James PA**, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520 [PMID: 24352797 DOI: 10.1001/jama.2013.284427]
- 99 **Kristensen SL**, Lindhardsen J, Ahlehoff O, Erichsen R, Lamberts M, Khalid U, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace* 2014; **16**: 477-484 [PMID: 24108228 DOI: 10.1093/europace/eut312]
- 100 **Kristensen SL**, Ahlehoff O, Lindhardsen J, Erichsen R, Jensen GV, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death--a Danish nationwide cohort study. *PLoS One* 2013; **8**: e56944 [PMID: 23457642 DOI: 10.1371/journal.pone.0056944]
- 101 **Singh S**, Singh H, Loftus EV, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 382-393.e1: quiz e22 [PMID: 23978350 DOI: 10.1016/j.cgh.2013.08.023]
- 102 **Singh S**, Kullo IJ, Pardi DS, Loftus EV. Epidemiology, risk factors and management of cardiovascular diseases in IBD. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 26-35 [PMID: 25446727 DOI: 10.1038/nrgastro.2014.202]
- 103 **Aggarwal A**, Atreja A, Kapadia S, Lopez R, Achkar JP. Conventional risk factors and cardiovascular outcomes of patients with inflammatory bowel disease with confirmed coronary artery disease. *Inflamm Bowel Dis* 2014; **20**: 1593-1601 [PMID: 25105946 DOI: 10.1097/mib.0000000000000109]
- 104 **Ruisi P**, Makaryus JN, Ruisi M, Makaryus AN. Inflammatory bowel disease as a risk factor for premature coronary artery disease. *J Clin Med Res* 2015; **7**: 257-261 [PMID: 25699123 DOI: 10.14740/jocmr2102w]
- 105 **Dorn SD**, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. *Am J Gastroenterol* 2007; **102**: 662-667 [PMID: 17156143 DOI: 10.1111/j.1572-0241.2006.01018.x]
- 106 **Fumery M**, Xiaocang C, Dauchet L, Gower-Rousseau C, Peyrin-Biroulet L, Colombel JF. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis* 2014; **8**: 469-479 [PMID: 24183231 DOI: 10.1016/j.crohns.2013.09.021]
- 107 **Karmali KN**, Lloyd-Jones DM, Berendsen MA, Goff DC, Sanghavi DM, Brown NC, Korenovska L, Huffman MD. Drugs for Primary Prevention of Atherosclerotic Cardiovascular Disease: An Overview of Systematic Reviews. *JAMA Cardiol* 2016; **1**: 341-349 [PMID: 27438118 DOI: 10.1001/jamacardio.2016.0218]
- 108 **Bonner GF**, Fakhri A, Vennamaneni SR. A long-term cohort study of nonsteroidal anti-inflammatory drug use and disease activity in outpatients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 751-757 [PMID: 15626893]
- 109 **Bonner GF**, Walczak M, Kitchen L, Bayona M. Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 1946-1948 [PMID: 10950040 DOI: 10.1111/j.1572-0241.2000.02263.x]
- 110 **Takeuchi K**, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B, Bjornsson E, Bjarnason I. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006; **4**: 196-202 [PMID: 16469680]
- 111 **Meyer AM**, Ramzan NN, Heigh RI, Leighton JA. Relapse of inflammatory bowel disease associated with use of nonsteroidal anti-inflammatory drugs. *Dig Dis Sci* 2006; **51**: 168-172 [PMID: 16416231 DOI: 10.1007/s10620-006-3103-5]
- 112 **Biancone L**, Tosti C, Geremia A, Fina D, Petruzzello C, Emerenziani S, Pallone F. Rofecoxib and early relapse of inflammatory bowel disease: an open-label trial. *Aliment Pharmacol Ther* 2004; **19**: 755-764 [PMID: 15043516 DOI:

- 10.1111/j.1365-2036.2004.01907.x]
- 113 **Matuk R**, Crawford J, Abreu MT, Targan SR, Vasiliauskas EA, Papadakis KA. The spectrum of gastrointestinal toxicity and effect on disease activity of selective cyclooxygenase-2 inhibitors in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 352-356 [PMID: 15475742]
  - 114 **Mahadevan U**, Loftus EV, Tremaine WJ, Sandborn WJ. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. *Am J Gastroenterol* 2002; **97**: 910-914 [PMID: 12008668 DOI: 10.1111/j.1572-0241.2002.05608.x]
  - 115 **Reinisch W**, Miehsler W, Dejaco C, Harrer M, Waldhoer T, Lichtenberger C, Vogelsang H. An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia. *Aliment Pharmacol Ther* 2003; **17**: 1371-1380 [PMID: 12786631]
  - 116 **Faculty of Family Planning & Reproductive Health Care, Clinical Effectiveness Unit**. Contraceptive choices for women with inflammatory bowel disease. *J Fam Plann Reprod Health Care* 2003; **29**: 127-135 [PMID: 12885304]
  - 117 **Victor A**, Odland V, Kral JG. Oral contraceptive absorption and sex hormone binding globulins in obese women: effects of jejunoileal bypass. *Gastroenterol Clin North Am* 1987; **16**: 483-491 [PMID: 2449395]
  - 118 **Hanker JP**. Gastrointestinal disease and oral contraception. *Am J Obstet Gynecol* 1990; **163**: 2204-2207 [PMID: 2256527]
  - 119 **Grimmer SF**, Back DJ, Orme ML, Cowie A, Gilmore I, Tjia J. The bioavailability of ethinylloestradiol and levonorgestrel in patients with an ileostomy. *Contraception* 1986; **33**: 51-59 [PMID: 3082591]
  - 120 **Nilsson LO**, Victor A, Kral JG, Johansson ED, Kock NG. Absorption of an oral contraceptive gestagen in ulcerative colitis before and after proctocolectomy and construction of a continent ileostomy. *Contraception* 1985; **31**: 195-204 [PMID: 3921310]
  - 121 **Cosnes J**, Carbonnel F, Carrat F, Beauverie L, Gendre JP. Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study. *Gut* 1999; **45**: 218-222 [PMID: 10403733]
  - 122 **Sutherland LR**, Ramcharan S, Bryant H, Fick G. Effect of oral contraceptive use on reoperation following surgery for Crohn's disease. *Dig Dis Sci* 1992; **37**: 1377-1382 [PMID: 1505289]
  - 123 **Timmer A**, Sutherland LR, Martin F. Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology* 1998; **114**: 1143-1150 [PMID: 9618650]
  - 124 **Wright JP**. Factors influencing first relapse in patients with Crohn's disease. *J Clin Gastroenterol* 1992; **15**: 12-16 [PMID: 1500656]
  - 125 **Bitton A**, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, Ransil B, Wild G, Cohen A, Edwardes MD, Stevens AC. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. *Gastroenterology* 2001; **120**: 13-20 [PMID: 11208709]
  - 126 **Kane SV**, Reddy D. Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 1193-1196 [PMID: 18177456 DOI: 10.1111/j.1572-0241.2007.01700.x]
  - 127 **Rutgeerts L**, Ghillebert G, Drognee W, Tanghe W, Vuylsteke P, Decoster M. Ischemic colitis in a patient with Crohn's disease taking an oral contraceptive and an ergotamine alkaloid. *Acta Clin Belg* 1993; **48**: 48-51 [PMID: 8388603]
  - 128 **Klein DA**, Arnold JJ, Reese ES. Provision of Contraception: Key Recommendations from the CDC. *Am Fam Physician* 2015; **91**: 625-633 [PMID: 25955737]
  - 129 **Shaw SY**, Blanchard JF, Bernstein CN. Association between the use of antibiotics and new diagnoses of Crohn's disease and ulcerative colitis. *Am J Gastroenterol* 2011; **106**: 2133-2142 [PMID: 21912437 DOI: 10.1038/ajg.2011.304]
  - 130 **Card T**, Logan RF, Rodrigues LC, Wheeler JG. Antibiotic use and the development of Crohn's disease. *Gut* 2004; **53**: 246-250 [PMID: 14724158]
  - 131 **Hildebrand H**, Malmborg P, Asklng J, Ekblom A, Montgomery SM. Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. *Scand J Gastroenterol* 2008; **43**: 961-966 [PMID: 19086166]
  - 132 **Khan KJ**, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 661-673 [PMID: 21407187 DOI: 10.1038/ajg.2011.72]
  - 133 **Rutgeerts P**, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, Kerremans R. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995; **108**: 1617-1621 [PMID: 7768364]
  - 134 **Rutgeerts P**, Van Assche G, Vermeire S, D'Haens G, Baert F, Noman M, Aerden I, De Hertogh G, Geboes K, Hiele M, D'Hoore A, Penninckx F. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2005; **128**: 856-861 [PMID: 15825069]
  - 135 **Sokol H**. Probiotics and antibiotics in IBD. *Dig Dis* 2014; **32** Suppl 1: 10-17 [PMID: 25531348 DOI: 10.1159/000367820]
  - 136 **Sood A**, Midha V, Makharia GK, Ahuja V, Singal D, Goswami P, Tandon RK. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; **7**: 1202-1209, 1209.e1 [PMID: 19631292 DOI: 10.1016/j.cgh.2009.07.016]
  - 137 **Fedorak RN**, Feagan BG, Hotte N, Leddin D, Dieleman LA, Petrunia DM, Enns R, Bitton A, Chiba N, Paré P, Rostom A, Marshall J, Depew W, Bernstein CN, Panaccione R, Aumais G, Steinhart AH, Cockeram A, Bailey RJ, Gionchetti P, Wong C, Madsen K. The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. *Clin Gastroenterol Hepatol* 2015; **13**: 928-35.e2 [PMID: 25460016 DOI: 10.1016/j.cgh.2014.10.031]
  - 138 **Singh S**, Stroud AM, Holubar SD, Sandborn WJ, Pardi DS. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst Rev* 2015; **(11)**: CD001176 [PMID: 26593456 DOI: 10.1002/14651858.CD001176.pub3]
  - 139 **Van Staa TP**, Travis S, Leufkens HG, Logan RF. 5-aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology* 2004; **126**: 1733-1739 [PMID: 15188168]
  - 140 **Lichtenstein GR**, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006; **130**: 940-987 [PMID: 16530532 DOI: 10.1053/j.gastro.2006.01.048]
  - 141 **Evans WE**. Pharmacogenetics of thiopurine S-methyltransferase and thiopurine therapy. *Ther Drug Monit* 2004; **26**: 186-191 [PMID: 15228163]
  - 142 **Van Assche G**, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; **353**: 362-368 [PMID: 15947080 DOI: 10.1056/NEJMoa051586]
  - 143 **Fedyk ER**, Wyant T, Yang LL, Csizmadia V, Burke K, Yang H, Kadambi VJ. Exclusive antagonism of the  $\alpha 4 \beta 7$  integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis* 2012; **18**: 2107-2119 [PMID: 22419649 DOI: 10.1002/ibd.22940]
  - 144 **Abbas AM**, Almukhtar RM, Loftus EV, Lichtenstein GR, Khan N. Risk of melanoma and non-melanoma skin cancer in ulcerative colitis patients treated with thiopurines: a nationwide retrospective cohort. *Am J Gastroenterol* 2014; **109**: 1781-1793 [PMID: 25244964 DOI: 10.1038/ajg.2014.298]
  - 145 **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 Gastroenterol Hepatol* 2010; **8**: 268-274 [PMID: 20005977 DOI: 10.1016/j.cgh.2009.11.024]
  - 146 **Long MD**, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer

- among patients with inflammatory bowel disease. *Gastroenterology* 2012; **143**: 390-399.e1 [PMID: 22584081 DOI: 10.1053/j.gastro.2012.05.004]
- 147 **Singh JA**, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011; (2): CD008794 [PMID: 21328309 DOI: 10.1002/14651858.CD008794.pub2]
- 148 **Linos E**, Katz KA, Colditz GA. Skin Cancer-The Importance of Prevention. *JAMA Intern Med* 2016; Epub ahead of print [PMID: 27459394 DOI: 10.1001/jamainternmed.2016.5008]
- 149 **Kane S**. Abnormal Pap smears in inflammatory bowel disease. *Inflamm Bowel Dis* 2008; **14**: 1158-1160 [PMID: 18266234 DOI: 10.1002/ibd.20391]
- 150 **Kane S**, Khatibi B, Reddy D. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 631-636 [PMID: 17941962 DOI: 10.1111/j.1572-0241.2007.01582.x]
- 151 **Lees CW**, Critchley J, Chee N, Beez T, Gailer RE, Williams AR, Shand AG, Arnott ID, Satsangi J. Lack of association between cervical dysplasia and IBD: a large case-control study. *Inflamm Bowel Dis* 2009; **15**: 1621-1629 [PMID: 19618462 DOI: 10.1002/ibd.20959]
- 152 **Singh H**, Demers AA, Nugent Z, Mahmud SM, Kliewer EV, Bernstein CN. Risk of cervical abnormalities in women with inflammatory bowel disease: a population-based nested case-control study. *Gastroenterology* 2009; **136**: 451-458 [PMID: 18996382 DOI: 10.1053/j.gastro.2008.10.021]
- 153 **ACOG Committee on Practice Bulletins--Gynecology**. ACOG Practice Bulletin no. 109: Cervical cytology screening. *Obstet Gynecol* 2009; **114**: 1409-1420 [PMID: 20134296 DOI: 10.1097/AOG.0b013e3181c6f8a4]
- 154 **Smith RA**, Manassaram-Baptiste D, Brooks D, Cokkinides V, Doroshenk M, Saslow D, Wender RC, Brawley OW. Cancer screening in the United States, 2014: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin* 2014; **64**: 30-51 [PMID: 24408568 DOI: 10.3322/caac.21212]
- 155 **Riegler G**, Caserta L, Castiglione F, Esposito I, Valpiani D, Annesse V, Zoli G, Gionchetti P, Viscido A, Sturniolo GC, Rispo A, De Filippo FR, de Leone A, Carratu R. Increased risk of breast cancer in first-degree relatives of Crohn's disease patients. An IG-IBD study. *Dig Liver Dis* 2006; **38**: 18-23 [PMID: 16169781 DOI: 10.1016/j.dld.2005.07.006]
- 156 **Sogaard KK**, Cronin-Fenton DP, Pedersen L, Sørensen HT, Lash TL. Survival in Danish patients with breast cancer and inflammatory bowel disease: a nationwide cohort study. *Inflamm Bowel Dis* 2008; **14**: 519-525 [PMID: 18069672 DOI: 10.1002/ibd.20341]
- 157 **Annesse V**, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kiebllich R, Ordás I, Repici A, Rosa B, Sebastian S, Kucharzik T, Eliakim R. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013; **7**: 982-1018 [PMID: 24184171 DOI: 10.1016/j.crohns.2013.09.016]
- 158 **Farraye FA**, Odze RD, Eaden J, Itzkowitz SH, McCabe RP, Dassopoulos T, Lewis JD, Ullman TA, James T, McLeod R, Burgart LJ, Allen J, Brill JV. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010; **138**: 738-745 [PMID: 20141808 DOI: 10.1053/j.gastro.2009.12.037]
- 159 **Mooiweer E**, Oldenburg B. The Debate Continues Over the Best Method of Endoscopic Surveillance for Colorectal Cancer in Patients With Colitis. *Clin Gastroenterol Hepatol* 2015; **13**: 1782-1784 [PMID: 26122766 DOI: 10.1016/j.cgh.2015.06.030]
- 160 **Abegunde AT**. Chromoendoscopy, White-Light, or Narrow-Band Imaging Colonoscopy in Colorectal Cancer Surveillance in Inflammatory Bowel Disease: True Illumination or Game of Shadows. *Clin Gastroenterol Hepatol* 2016; **14**: 1062 [PMID: 26453956 DOI: 10.1016/j.cgh.2015.09.035]
- 161 **Laine L**, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointest Endosc* 2015; **81**: 489-501.e26 [PMID: 25708752 DOI: 10.1016/j.gie.2014.12.009]
- 162 **USPSTF**. Final Recommendation Statement: Prostate Cancer: Screening, 2014, cited 2016-03-30. Available from: URL: <http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening>
- 163 **Coenen S**, Weys E, Ballet V, Noman M, Van Assche G, Vermeire S, Van Emelen J, Ferrante M. Identifying predictors of low adherence in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2016; **28**: 503-507 [PMID: 26760588 DOI: 10.1097/MEG.0000000000000570]
- 164 **Tae CH**, Jung SA, Moon HS, Seo JA, Song HK, Moon CM, Kim SE, Shim KN, Jung HK. Importance of Patients' Knowledge of Their Prescribed Medication in Improving Treatment Adherence in Inflammatory Bowel Disease. *J Clin Gastroenterol* 2016; **50**: 157-162 [PMID: 26501880 DOI: 10.1097/MCG.0000000000000431]
- 165 **van der Have M**, Oldenburg B, Kaptein AA, Jansen JM, Scheffer RC, van Tuyl BA, van der Meulen-de Jong AE, Pierik M, Siersema PD, van Oijen MG, Fidler HH. Non-adherence to Anti-TNF Therapy is Associated with Illness Perceptions and Clinical Outcomes in Outpatients with Inflammatory Bowel Disease: Results from a Prospective Multicentre Study. *J Crohns Colitis* 2016; **10**: 549-555 [PMID: 26738757 DOI: 10.1093/ecco-jcc/jjw002]
- 166 **Kane S**, Becker B, Harmsen WS, Kurian A, Morisky DE, Zinsmeister AR. Use of a screening tool to determine nonadherent behavior in inflammatory bowel disease. *Am J Gastroenterol* 2012; **107**: 154-160 [PMID: 22306937 DOI: 10.1038/ajg.2011.317]
- 167 **Trindade AJ**, Ehrlich A, Kornbluth A, Ullman TA. Are your patients taking their medicine? Validation of a new adherence scale in patients with inflammatory bowel disease and comparison with physician perception of adherence. *Inflamm Bowel Dis* 2011; **17**: 599-604 [PMID: 20848512 DOI: 10.1002/ibd.21310]
- 168 **Moss AC**, Lillis Y, Edwards George JB, Choudhry NK, Berg AH, Cheifetz AS, Horowitz G, Leffler DA. Attitudes to mesalamine questionnaire: a novel tool to predict mesalamine nonadherence in patients with IBD. *Am J Gastroenterol* 2014; **109**: 1850-1855 [PMID: 24913040 DOI: 10.1038/ajg.2014.158]
- 169 **Trindade AJ**, Tinsley A, Kornbluth A, Ullman TA. The MMAS-8, a screening tool for determining nonadherent behavior, should not be dismissed in IBD. *Am J Gastroenterol* 2012; **107**: 951-952; author reply 952 [PMID: 22664851 DOI: 10.1038/ajg.2012.73]
- 170 **Greeney RN**, Kunz JH, Walter J, Hommel KA. Practical strategies for enhancing adherence to treatment regimen in inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 1534-1545 [PMID: 23635715 DOI: 10.1097/MIB.0b013e3182813482]
- 171 **Eggert RW**, Parkinson MD. Preventive medicine and health system reform. Improving physician education, training, and practice. *JAMA* 1994; **272**: 688-693 [PMID: 8064984]
- 172 **Lee AJ**, Kraemer DF, Smotherman C, Eid E. Providing Our Fellows in Training with Education on Inflammatory Bowel Disease Health Maintenance to Improve the Quality of Care in Our Health Care System. *Inflamm Bowel Dis* 2016; **22**: 187-193 [PMID: 26332311 DOI: 10.1097/mib.0000000000000573]
- 173 **Moscandrew M**, Mahadevan U, Kane S. General health maintenance in IBD. *Inflamm Bowel Dis* 2009; **15**: 1399-1409 [PMID: 19591135 DOI: 10.1002/ibd.20944]
- 174 **Maisa A**, Jennifer L, Ashok S, Lawrence S, Thomas W, De Cross A. The performance of an electronic interactive flow sheet to improve preventive health care in inflammatory bowel disease patients. 2014 Advances in Inflammatory Bowel Diseases Crohn's and Colitis Foundation's National Clinical and Research Conference; 2014 Dec 4-6; Orlando, FL, United States. *Inflamm Bowel Dis*

2014; **20**: S57-S59

- 175 **Knudsen C**, Manolakis CS, Di Palma JA. A checklist improves vaccination, health maintenance and drug monitoring adherence in inflammatory bowel diseases. *DDW 2015: Digestive Disease Week 2015*; 2015 May 15-19; Washington, DC, United States. *Gastroenterology* 2015; **148** Suppl 1: S855
- 176 **American Gastroenterological Association**. Adult inflammatory bowel disease physician performance measure set. Revised October 26, 2011-10-26, cited 2016-2-22. Available from: URL: [http://www.gastro.org/practice/quality-initiatives/IBD\\_Measures.pdf](http://www.gastro.org/practice/quality-initiatives/IBD_Measures.pdf)
- 177 **Boulware LE**, Marinopoulos S, Phillips KA, Hwang CW, Maynor K, Merenstein D, Wilson RF, Barnes GJ, Bass EB, Powe NR, Daumit GL. Systematic review: the value of the periodic health evaluation. *Ann Intern Med* 2007; **146**: 289-300 [PMID: 17310053]
- 178 **Scott JG**, Cohen D, Diccico-Bloom B, Miller WL, Stange KC, Crabtree BF. Understanding healing relationships in primary care. *Ann Fam Med* 2008; **6**: 315-322 [PMID: 18626031 DOI: 10.1370/afm.860]
- 179 **Sossai P**, Filippetti F, Muselmani AA, Catalini G. Inflammatory bowel diseases and the general practitioner's role in a region of Central Italy. *Clin Exp Gastroenterol* 2010; **3**: 27-31 [PMID: 21694843]
- 180 **Anyane-Yebo A**, Khiani V, Khamo N, Abdou S. The primary care physician (PCP) and the gastroenterologist: What is your view on the management of patients with inflammatory bowel disease (IBD)? 80th Annual Scientific Meeting of the American College of Gastroenterology; 2015 Oct 16-21; Honolulu, HI, United States. *Am J Gastroenterol* 2015; **110**: S842
- 181 **Peek ME**, Drum M, Cooper LA. The Association of Patient Chronic Disease Burden and Self-Management Requirements With Shared Decision Making in Primary Care Visits. *Health Serv Res Manag Epidemiol* 2014; **1**: pii 2333392814538775 [PMID: 26640812 DOI: 10.1177/2333392814538775]
- 182 **Siegel CA**. Shared decision making in inflammatory bowel disease: helping patients understand the tradeoffs between treatment options. *Gut* 2012; **61**: 459-465 [PMID: 22187072 DOI: 10.1136/gutjnl-2011-300988]

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