Inflammatory Bowel Disease

12

Elana Maser and Anish Patel

Case Presentation

Michelle is an 18-year-old woman with Crohn's disease who presents for initial evaluation to an adult internal medicine office accompanied by her parents. She was diagnosed at age 12 years. She had severe disease, requiring two small bowel resections by ages 14 and 15 years due to recurrent Crohn's strictures. She has been maintained on biologic therapy since her last surgery and is planning on leaving for college out of state in 6 months. Her parents wanted her to establish care prior to her departure as was recommended by their pediatrician.

Michelle is a well-groomed, well-mannered patient. She is slightly timid and quiet. Her parents speak the majority of the time. She only speaks when spoken to directly, with frequent interjections by her parents. She reports good compliance with her medication, but her mother notes "missed timing" of doses on frequent occasions. She appears healthy, is an appropriate weight, and has almost reached the height of her parents. There are no abnormalities on physical exam other than well-healed abdominal surgical scars.

Michelle's parents have voiced three concerns: They are uneasy about leaving their lifelong and beloved pediatrician, they have concerns about their daughter's compliance with medications, and they are worried about their daughter having reduced access to the appropriate care while in college.

Case Discussion

Transition is a very difficult and often fearful time for families, especially for patients with severe Crohn's disease [1]. Pediatric gastroenterologists often develop strong bonds with their patients and families. However, limited time is spent on the preparation for transition to adult providers [2, 3]. Difficulties arise in the transition to adult care as adult providers are often faced with patients who have limited knowledge of their complicated medical, surgical, and drug history.

This case is a common scenario in the adult medicine realm. Michelle has severe Crohn's disease requiring multiple surgeries at an early age and requires biologic drugs to maintain remission. Her parents are apprehensive about letting her go alone to an out-of-state college where access to specialists or generalists who

E. Maser
Division of Gastroenterology, Mt. Sinai Hospital, 17 East 102nd Street, 5th Floor, New York, NY 10029, USA
e-mail: elana.maser@mountsinai.org

A. Patel (✉)
Department of Gastroenterology/Hepatology, Carl R. Darnall Army Medical Center, 36000 Darnall Loop, Ft. Hood, TX 76544, USA
e-mail: anishpa81@gmail.com

M. Pilapil et al. (eds.), *Care of Adults with Chronic Childhood Conditions*,
DOI 10.1007/978-3-319-43827-6_12

understand Crohn's disease may be scarce and access to biologic drugs may be difficult as well.

For Michelle, developing a good rapport with and trust in her adult doctor is critical to a successful transition and ongoing care. Discussions need to focus on adherence to medication and risks to her health and quality of life if regimens are not maintained. As new generations of adolescents are more involved with technology, discussions about maintaining communication, whether via email and/or patient portals, could help reduce the stress experienced by patients and their parents. To alleviate fears about Michelle's relocation out of state, identifying a local physician for emergency purposes would be helpful. She should contact her insurance provider to find a local infusion center that is able to administer biologics unless she is able to make arrangements to come home for infusions. Switching biologics (often from infusion to self injection) should be avoided if Michelle is in remission. Switching biologics puts patients at risk of a flare, which would be undesirable during this stressful period [4].

Overview

Epidemiology

Crohn's disease (CD) and ulcerative colitis (UC) affect more than 5 million people worldwide, with more than 1.7 million in the United States and about 3 million in Europe [5]. Higher rates occur in industrialized countries [6, 7]. The lifetime risk of developing inflammatory bowel disease (IBD), including both CD and UC, is approximately 1 %.

Over one-quarter of all patients will first be diagnosed in childhood or adolescence. While the incidence in adults seems to be stabilizing, the incidence rates in pediatrics are currently rising [8]. The annual incidence has doubled over an 11-year span from 1.1/100,000 to 2.4/100,000 in the pediatric population [9]. Following childhood, the diagnosis of IBD can occur at any age but there are two peaks of higher incidence around ages 20 and 50 years [7, 10].

There are no significant gender differences found in the prevalence of UC, but there is a slightly higher incidence of CD among women as compared to men [11, 12].

IBD is thought to be a disease that affects mostly Ashkenazi Jews, however, Sephardic Jews are affected as well, albeit with a lower incidence [13]. IBD is not a disease reserved only for those of Jewish descent though. While these populations have the highest incidence, IBD can occur in any race [13].

Pathophysiology

The term IBD includes Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by chronic, relapsing inflammation within the gastrointestinal tract. One has to have a genetic predisposition and be exposed to an environmental trigger in order to develop the disease. There have been more than 100 genes identified in the pathogenesis of IBD, and numerous environmental factors including smoking, the use of oral contraceptives, and exposure to antibiotics have been suggested, though none have been clearly implicated [14, 15].

Current literature suggests that the inflammation is a result of inappropriate and ongoing activation of the innate immune system of the gut mucosa, driven by the commensal luminal flora in a genetically susceptible host [16, 17]. Once the inflammation has been initiated, it has difficulty resolving without the help of medication. It is not yet clear which commensal flora are responsible; however, a more limited variation in gut bacteria is typically seen in an IBD host [18]. Current understanding is that both CD and UC have a similar pathogenesis, but clinically they have varying characteristics. The characteristic features are summarized in Table 12.1.

Table 12.1 Comparison of Crohn's disease and ulcerative colitis

Feature	Crohn's disease	Ulcerative colitis
Site of origin	Terminal ileum (can occur anywhere in gastrointestinal tract)	Colon
Pattern of progression	"Skip" lesions/irregular	Contiguous
Histopathology	Transmural disease Deep ulcers, granulomas, "cobblestoning"	Submucosa/mucosa
Complications	Fistulas/abscesses/obstruction	Bleeding/toxic megacolon
Radiographic findings	String sign	Lead pipe colon
Clinical features	Crampy abdominal pain	Bloody diarrhea

Clinical Definition, Presentation, and Natural History of IBD

Ulcerative Colitis

UC is a chronic inflammatory disease affecting the mucosal layer of the colon and rectum. The disease is relapsing and remitting. When the disease is active, also called "flaring," patients typically suffer from urgent and frequent bouts of bloody diarrhea. Flares are intermittent, unpredictable, and vary in severity. Most commonly, UC is painless unless the disease is severe. Endoscopically, inflammation is continuous from the anal verge extending proximally. One-third of patients have mild disease requiring minimal medication, one-third of patients require chronic maintenance medication, and 20–30 % will need colectomy [19]. Patients with UC develop colorectal cancer at twice the population risk. Therefore, guidelines suggest screening patients with annual colonoscopies, as is further discussed later in this chapter [20]. Patients with proctitis do not have an increased risk of colon cancer and therefore should not be screened more frequently than the general population. This disease can affect quality of life but not duration of life. A normal life span should be expected [5].

Crohn's Disease

CD is also a chronic inflammatory condition with periods of wellness interspersed with flares. In contrast to UC, CD affects all layers of the bowel and can occur in any part of the gastrointestinal tract from mouth to anus. The most common presentation is terminal ileitis. A child may present with weight loss or poor growth and have no other symptoms. Pain is more commonly seen in patients with CD as compared to those with UC. Symptoms can range from mild abdominal cramping to severe diarrhea or symptoms of intestinal obstruction. Perianal disease is common and can manifest as abnormal anal skin tags, deep anal fissures, and fistulae. Endoscopically, inflammation can occur in patches with normal mucosa interspersed with inflamed mucosa. There is no single test to diagnose CD, however, rarely granulomas are seen on histopathology. When these are seen, CD can be differentiated from UC.

The disease course can range from mild intermittent flares to the more severe cases that are difficult to control. Up to 70 % of patients with CD will require at least 1 surgery [21]. Risk of colon cancer is also increased in patients with CD, and like patients with UC, patients with colonic Crohn's should have annual colonoscopies, again as will be further discussed later in this chapter [22]. Patients with CD are also at higher risk for nutritional deficiencies and should be monitored for deficiencies in folate and vitamins B12 and D. In severe cases, total parenteral nutrition (TPN) may be required. Like UC, quality of life may be affected, however, the vast majority of patients with CD have a normal life span.

Risk Factors

The etiology for the development of mucosal inflammation is multifactorial. Current theories focus on genetic factors, immunoregulatory defects, microbial exposure, and environmental triggers [23].

Microbial Exposure

The epithelial layer of intestinal mucosa plays an essential role in maintaining functional equilibrium within the lumen from the spectrum of microbial species and their byproducts. Barrier defects within the mucosa increase microbial and antigen presentation, leading to perturbations in the immune response causing IBD. Growing evidence suggests a significant dysbiosis or imbalance among protective and harmful species of microbiota within the intestinal lumen [24]. IBD patients have demonstrated a lack of diversity among species, but no specific species has been implicated as a causative agent in IBD [25]. Identifying the key factors and/or species that shape microbiota-host interactions in the structure and function of the immune response will be a key to the further understanding of the pathogenesis of IBD.

Immunoregulatory Defects

The loss of barrier function can lead to microbial and antigen penetration into the intestinal mucosa, causing immune activation. Both the innate and acquired immune systems are activated with antigen presentation, but differences have been demonstrated within the IBD subtypes. CD results in Th1 and/or Th17 responses with subsequent production of proinflammatory cytokines (i.e., IL-12, IL-18, IFN-γ[gamma]) [26]. The cascade of proinflammatory mediators with CD leads to activation of proteases and metalloproteinases causing tissue destruction and sustained chronic inflammation. The mediator response with UC was previously theorized as a Th2 response, but this is still under investigation [26].

Genetics

Epidemiological and clinical data from Europe and North America have provided strong evidence that CD and UC are related polygenic disorders, and genetic factors play a role in susceptibility to IBD [27, 28]. Up to 14 % of patients with IBD will report a family history of either CD or UC [29]. The relative risk of developing IBD for a first-degree relative is up to 8 % for CD and 5 % for UC, but the risk is increased to 30 % for offspring of parents both affected with IBD [30, 31]. Familial studies have demonstrated a significant genetic link with IBD; however, it appears that IBD is not inherited in simple Mendelian fashion. Rather, it has a complex genetic basis with multiple contributing genes [32].

Genetic linkage studies have demonstrated numerous IBD loci overlapping between UC and CD, with one of the earliest and clearest linkages on chromosome 16 for nucleotide-binding oligomerization domain 2 (NOD2), also known as caspase activation and recruitment domain 15 (CARD15) [33, 34]. NOD2/CARD15 defects have been associated with up to 25 % of CD cases [35]. Homozygosity is associated with a >20-fold increased risk of the development of CD, with heterozygosity conferring a two- to fourfold increased risk [35, 36]. Despite having significant advances in identifying genetic risk factors, genetics may account for <25 % of the pathogenesis of IBD, further suggesting the strong role played by environmental factors [29].

Environmental

Hygiene Similar to other autoimmune diseases such as rheumatoid arthritis, IBD confers an inverse-relationship with sanitation. In other words, poor sanitation appears to protect against

IBD [23]. A 1989 study citing the rising incidence of autoimmune diseases, such as IBD, in developing countries was the first to propose the "hygiene hypothesis." [37] Factors including number of siblings, larger family size, living on a farm, and pet exposures in childhood have been implicated with a reported decreased risk of developing IBD, but such studies were limited in size and subject to significant bias [38, 39]. Less robust associations have been made on the mode of childbirth (potential increased risk with cesarean delivery) and role of breastfeeding (decreased risk) in the development of IBD [40, 41].

Smoking One of the strongest environmental risk factors is smoking tobacco. Patients with CD who smoke have a more aggressive disease course. They typically require more immunosuppression, earlier surgery, and have a higher risk of disease recurrence after ileocecal resection [42]. A 2006 meta-analysis demonstrated an almost twofold increased risk of developing CD associated with smoking; conversely, a strong inverse association with active smoking and UC was seen [43]. Current smoking appears to reduce the risk of developing UC. In a cohort of female nurses, there was an increased risk of developing UC within 5 years of smoking cessation. This risk remained elevated for up to 20 years [44]. Passive smoking had similar effects [45]. While it appears that smoking can reduce inflammation in patients with UC, it is not a recommended habit due to the other well-described health concerns.

Medications Antibiotics have been implicated as a potential risk factor for IBD due to the alteration of the gut flora. A 2014 study reported an almost twofold increased risk for developing CD from prior antibiotic exposure, though the same risk did not apply to UC [46]. The association of IBD with antibiotics has also been shown to be stronger with exposure in the first year of life compared with later use [47]. However, conflicting evidence from Asia has demonstrated a protective association of antibiotic exposure with the development of IBD [48]. Nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk of IBD, but the absolute risk is small [49, 50]. The association was strongest with higher doses and longer duration of therapy. The conferred risk was similar for both CD and UC [51, 52]. Avoidance of NSAIDs is recommended; however, occasional use likely presents an acceptable risk.

Prior case reports have suggested an association between IBD and isotretinoin, used in the treatment of acne vulgaris [53, 54]. However, in a meta-analysis, pooled results from the United States claims database did not support this association [55]. Therefore, clinicians should not avoid prescribing retinoic acid when other drugs fail. Acne carries a high psychosocial burden and the association between retinoic acid and IBD has not been confirmed.

Current oral contraceptive use poses a very minor increased risk for developing CD, and the risk is even lower for past users [56, 57]. The same risk was not seen with UC. Lower-estrogen formulations of contraception may be safer. Because the overall risk is so low, avoidance of oral contraceptive use cannot be recommended.

Stress Most patients with IBD note that their disease often flares during stressful events. Large observational studies support an association between major life stressors, anxiety, depression, and the risk of IBD development [58–61]. Due to the unpredictable nature of IBD, anxiety is a major concern, especially for adolescents. Working with a psychologist is often helpful. Newer cognitive behavioral techniques and mindfulness training are currently being investigated in patients with IBD.

Obesity An association between IBD and obesity still remains unclear [62, 63]. In CD patients, the accumulation of intra-abdominal fat may play a role in mucosal inflammation and progression of disease [64]. Obese patients have been shown to have higher rates of hospitalizations and are

more likely to require IBD-related surgery [65, 66]. A 2013 prospective study demonstrated that intense physical activity had a >40 % risk reduction in the development of CD, but there was no significant association with UC [67].

Sleep Sleep quality and duration can have an impact on IBD. Sleep deprivation has been associated with an increased risk of UC, and poor sleep quality was implicated with higher risk of relapse [68, 69].

Clinical Considerations in Individuals with IBD

The role of the primary care provider (PCP) in the co-management of IBD with the subspecialist is essential in optimizing the clinical care of the IBD patient.

Sexual and Reproductive Health

Ideally, dialogue about the impact that IBD has on intimacy, reproduction, and pregnancy should have already been initiated by the patient's pediatric or adolescent provider. However, this is not always the case. Conversations with an adult provider about intimacy and sexuality may therefore be welcome [70]. In fact, this may be a useful way for the young adult to separate from his or her parents and develop an independent relationship with the adult provider.

One-third of CD patients say IBD has a major impact on their sexual life. Impaired body image has been reported in 35 % of women and 13 % of men [71]. There may be disfiguration of the rectovaginal area, abdominal scars, or the presence of an ostomy. About 58 % of patients report decreased libido caused by diarrhea, fever, and/or abdominal pain [72]. Patients need a safe place to discuss these issues. They may want to know how and when to disclose their chronic condition to their partners. Unfortunately, 1 study reported that 40 % of IBD patients feel that the disease prevents an intimate relationship altogether [73]. While it may not be practical for the adult physician to provide extensive counseling, the acknowledgement that these are important quality-of-life issues can help patients feel comfortable with their new adult doctor.

Fecundity, the probability of becoming pregnant per month by unprotected intercourse, is normal in female IBD patients. The exceptions are active disease and pelvic surgery—most commonly the creation of an ileal pouch after total colectomy [74]. There is, however, a decrease in fertility by as much as 14–36 % due to voluntary childlessness among both male and female patients with IBD. They may be afraid of passing on the disease to their offspring, be concerned about medication teratogenicity, or be worried about the difficulty of raising a child when they themselves have active and unpredictable disease [75, 76]. By establishing a positive relationship with young adult patients, adult physicians can educate patients and help them overcome these barriers.

Pregnancy outcomes have been well studied in IBD patients. A majority of the literature demonstrates a slightly higher risk of IBD-related pregnancy complications that include preterm birth and low birth weight, but there is not a significant increased risk of congenital abnormalities [77–79]. Patients should understand that these risks are caused by active inflammation and not by their medications. The majority of medications, including the thiopurines and biologics, are safe for use during pregnancy with the exception of methotrexate, which is a category X agent. Patients should be encouraged to continue to take their medications throughout their pregnancy in order to allow for the best outcome. Pregnancy has not shown a higher likelihood to induce flares, but active disease at conception has been associated with higher rates of disease worsening throughout pregnancy [80, 81].

The role of the PCP is to acknowledge the need to discuss the impact of IBD on intimacy, sexuality, and fertility with both male and female patients. It is important to maintain good communication with the patient's gastroenterologist so that the same messages are conveyed and reinforced. Conflicting messages can be harmful to patients and may cause unnecessary anxiety.

The strong bond between the PCP and patient allows for open discussion of these delicate yet important topics.

Preventive Care

Preventive care has traditionally been in the domain of the PCP. With the increased use of immunomodulators and biologics, the task of providing proper preventive measures can be daunting. Important preventive health considerations for individuals with IBD include cancer screening and prevention, osteoporosis screening and prevention, and immunizations.

Cancer Screening and Prevention

In patients with IBD, the risk of colon cancer is much higher than in the general population. General population screening without risk factors begins at age 50 years. For patients with IBD, it is recommended that patients with 8–10 years of Crohn's colitis (Crohn's that involves the large bowel) or UC have an annual or biannual surveillance colonoscopy with multiple biopsies [20]. For patients with concomitant primary sclerosing cholangitis, colonoscopic surveillance should begin immediately. Patients with isolated ulcerative proctitis (colitis involving the rectum only) do not have an increased risk of colon cancer beyond that of the general population. Therefore, increased screening is not required.

Women with IBD, especially those requiring use of immunomodulators and biologics, have a higher prevalence of abnormal Pap smears [82, 83]. The American College of Obstetrics and Gynecology (ACOG) recommends screening of women starting at 21 years of age with Pap smears and then every 3 years thereafter [84]. However, due to the increased risk among women on immunosuppressive therapy, expert recommendations are for yearly screening with Pap smears in patients on immunomodulator and/or biologic therapy once sexual activity has begun [85].

IBD patients, especially those on immunomodulators and/or biologics, have an increased risk of skin cancers compared to the general population. Thiopurine use is associated with an increased risk of nonmelanoma skin cancers, particularly basal cell carcinoma and squamous cell carcinoma, with an incidence rate of 1.1 cases per 1000 person-years [86]. With respect to melanoma, patients exposed to tumor necrosis factor-alpha (TNF-α[alpha]) antagonists have a twofold higher risk than in unexposed patients, with an incidence rate of about 0.5 cases per 1000 person-years [87]. Experts recommend yearly visual skin exam by a dermatologist for patients on immunomodulators and/or TNF-α(alpha) antagonists in combination with appropriate sun exposure precautions.

Osteoporosis Screening and Prevention

IBD itself, along with an increased use of corticosteroids, puts this population at risk for osteoporosis. Nutritional assessments, such as vitamin D testing, are recommended to be performed at least annually, with appropriate repletion for those individuals with a deficiency. Bone density assessment is in line with the U.S. Preventative Services Task Force recommendations, but with additional considerations:

1. Steroid use >3 months
2. Inactive disease but past chronic steroid use of at least 1 year within the past 2 years
3. Inactive disease but maternal history of osteoporosis
4. Inactive disease but malnourished or very thin
5. Inactive disease but amenorrhiec.

Consideration should be made to screen patients earlier than normal if such risk factors exist [85, 88].

Immunizations

As the rates of use for immunosuppressive drugs in IBD increases, optimal preventable measures, such as vaccinations, can help limit the risk of infectious complications. Patients often turn to their PCP who had been responsible for administering vaccines throughout their life. Therefore, the role of the PCP in managing vaccine administration is pivotal.

Adult patients are often unaware of the recommended adult immunization schedule, and this may be especially concerning for those who

Table 12.2 Live and inactivated adult vaccines in the United States

Live	Inactivated
Live attenuated influenza vaccine (LAIV)	Inactivated Influenza Vaccine (IIV)
Varicella (chicken pox)	Tetanus/diphtheria/pertussis (Tdap)
Zoster (shingles)	Pneumococcal 13 valent (PCV-13)
Measles, mumps, and rubella (MMR)	Pneumococcal polysaccharide (PPSV23)
Yellow fever	Meningococcal
	Hepatitis A and B
	Human papilloma virus

are immunosuppressed and may require additional vaccinations. Patients with IBD have a higher risk of pneumonia [89]. Therefore, if the pneumococcal 13-valent and 23-valent vaccines were not administered during childhood, they should be offered to adult patients. Unfortunately, current vaccination rates in IBD populations are suboptimal with <90 % of patients receiving yearly influenza vaccinations and <50 % receiving pneumococcal vaccinations [90, 91]. To help improve these rates, patients should be advised to bring updated vaccination records to their adult provider.

There are special considerations for vaccinating patients who are on immunosuppressive therapy. Administering a live vaccine to an immunosuppressed patient can be life threatening [92]. All live vaccines that are available in the United States are listed in Table 12.2. Ideally, live vaccines should be administered more than 4 weeks before immunosuppression is initiated. However, there are some exceptions. For IBD patients on low levels of immunosuppression—defined as methotrexate <0.4 mg/kg per week, azathioprine <3 mg/kg per day, and 6-mercaptopurine <1.5 mg/kg per day—live vaccines, such as the varicella vaccination, can be considered. For highly immunosuppressed patients—defined as individuals with primary immunodeficiency disorder, cancer chemotherapy, within 2 months of solid organ transplant, human immunodeficiency virus (HIV) infection with a CD4 T-cell count <200/mm^3, systemic corticosteroid >20 mg/day for more than 14 days, anti-TNF agent use or rituximab use—live vaccines should be avoided altogether [93]. Unlike live vaccines, inactivated vaccines can be administered at any point while on immunosuppression. To allow adequate time for development of protective antibodies, inactivated vaccines should be administered at least 2 weeks prior to initiation of immunosuppression. Therefore, it is good practice to vaccinate patients with IBD when they are well, even if they are not on immunosuppressive therapy. This will allow for the immediate initiation of treatment should a flare occur. A complete vaccine dosing schedule can be found through the Centers for Disease Control and Prevention [94].

There have been many newly licensed vaccines, and the recommendations for vaccine administration for immunosuppressed patients are rapidly evolving. Having both the PCP and the gastroenterologist offer these important vaccines in comanagement of patients could increase the vaccination rates.

Diet

It would be clearly beneficial if following a specific diet could cure or improve symptoms in patients with IBD. However, because strictly controlling diet is difficult, prospective studies are limited. It is known, though, that food plays an important role. Strict enteral nutrition has shown benefits in the induction and maintenance of remission in IBD, particularly in children [95].

Patients frequently scour the Internet for special diets, hoping to manage their disease without the use of medication. Popular diets include the specific carbohydrate diet; the low fermentable

oligosaccharides, disaccharides, and monosaccharides (FODMAP) diet; a paleolithic (paleo) diet; or a vegan diet [96]. For some, these diets work tremendously well. For the majority, they do not. Currently there is no diet that can be prescribed for everyone. The most important point to emphasize is that a balanced healthy diet be followed. Many of these well-meaning diets cause weight loss, which can be dangerous. Some are so difficult to follow that it leads to unnecessary stress.

Avoiding dairy is also a popular fad diet, but this puts patients at an even higher risk for osteoporosis and there is no current evidence to support this practice. A vegan diet increases the risk for vitamin D and vitamin B12 deficiency.

There is scientific evidence that particular dietary factors may influence the risk of developing IBD. Dietary fiber intake has been associated with a lower risk of developing CD, but not UC [97]. The consumption of greater amounts of red meat and fats, particularly polyunsaturated fatty acids (PUFAs) and omega-6 (n-6) fatty acids, increases the risk of developing IBD as opposed to a diet high in fiber, fruits, and vegetables [98]. Ingested iron, particularly iron sulfate, has been directly linked with intestinal inflammation; however, the effects of iron from red meat is unknown [99]. Dietary calcium and vitamin D are important for IBD patients, not only for bone health but also because vitamin D is involved in anti-inflammatory pathways [100].

Some specific dietary recommendations can include reducing red meat and saturated fats, and increasing dietary fiber, such as oatmeal. For patients with known stenosis or those in the first 6 weeks after a partial bowel resection, a low residue diet is recommended to avoid the risk of possible obstruction. Following a low residue diet means avoiding peanuts, popcorn, raw vegetables, skins of vegetables, and high fiber foods.

At this time, there is no diet that can cure or reduce existing inflammation. The role of the PCP is to recommend eating a healthy balanced diet, replenish possible nutrient deficiencies, and encourage avoidance of extreme, possibly stressful diets. If the patient is at risk of poor nutrient intake, a multivitamin can be supplemented.

Drug Monitoring/Side Effect Management

Over the last decade, a large number of therapeutic options has become available for the treatment of IBD. These drugs include mesalamines, thiopurines, and, more recently, biological agents with multiple different mechanisms of action. The majority of such medications will be under the management of a gastroenterologist, but the PCP can still play a key role when drug side effects arise or in routine lab monitoring.

One of the first-line class choices for treatment of IBD is the mesalamine-based (5-ASA) drugs. Mesalamine has an advantage in UC, but there is limited data to support its use in CD [101, 102]. There are minimal side effects associated with the newer generation 5-ASA drugs. However, headaches, hair loss, and, rarely, pancreatitis have been reported. Because there is a small but real risk of developing interstitial nephritis, routine assessment of renal function every 6–12 months and a yearly urinalysis are recommended [103].

Corticosteroids are often needed to provide immediate relief for patients with UC. They are used in UC when mesalamines do not control the inflammation and in CD when the symptoms are severe or a biologic is not available. Steroid use is typically recommended for shorter durations due to the significant side effect profile. Along with the known side effects of corticosteroids, patients with CD can develop fistulae or opportunistic infections. Because patients with IBD are often on steroids along with other immunosuppressive agents, prophylaxis against *Pneumocystis* pneumonia, which can be initiated by the PCP, is important. Management of side effects requires the use of steroid-sparing drugs.

Immunomodulators are steroid-sparing drugs that work by inhibiting the proliferation and activation of lymphocytes. Common drugs in this class include azathioprine (AZA), 6-mercaptopurine

(6-MP), and methotrexate (MTX). AZA and 6MP are also called thiopurines and follow weight-based dosing. Gastroenterologists can optimize the dose by using biomarkers such as thiopurine methyltransferase (TPMT) activity and drug metabolites such as 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). Side effects include agranulocytosis and hepatotoxicity [104]. Other complications include autoimmune hepatitis, fatigue, and pancreatitis. Severe effects such as myelosuppression and pancreatitis can be managed with discontinuation of therapy and supportive care. To minimize complications, routine lab monitoring with complete blood count (CBC) with differential and hepatic function should be performed every 3 months. A reduction in the white blood cell (WBC) count is desired, but if it falls to $<4.0 \times 10^3$ cells/μ(mu)L, the drug should be held and restarted at a lower dose once the WBC count returns to normal. Methotrexate is an alternative to the thiopurines and is used more commonly in CD. Major complications include hepatotoxicity, myelosuppression, and pneumonitis, which occur in <10 % of patients [105]. This agent should always be taken in conjunction with folic acid to avoid anemia. Chest X-ray and baseline liver function tests, followed by an assessment of CBC with differential and hepatic function every 3 months, are recommended. Consideration for liver biopsy is suggested for patients with liver enzymes that remain persistently elevated for more than 12 months [106].

The use of biologic drugs, such as anti-TNFα (alpha), has had a significant impact on the treatment of IBD. The medications included in this class are infliximab, adalimumab, and certolizumab. Numerous clinical trials have demonstrated efficacy for use in moderate to severe CD and UC [107–109]. These drugs are very well tolerated and have minimal side effects. Side effects include infusion or injection site reactions, opportunistic infections, autoimmune hepatitis, and psoriasis. Rarely, there are neurological side effects including unmasking of underlying multiple sclerosis. The most feared side effect is hepatosplenic T-cell lymphoma. This occurs rarely, seen in approximately 4–5/10,000 patients. The demographic most often affected are men under the age of 35 years [110]. A thorough exam for lymphadenopathy and splenomegaly is required at every visit. Prior to drug initiation, latent tuberculosis infection and hepatitis B virus infection should be ruled out to prevent dissemination. The PCP can assist with routine lab testing, which should be drawn every 3–6 months.

Extraintestinal Manifestations

An extraintestinal manifestation (EIM) is a disease that occurs outside of the bowel and is associated with IBD. At least 25 % of patients with IBD are affected [111]. While there are numerous EIMs, the most common include arthropathy, cutaneous lesions, and ocular inflammation (see Table 12.3). Unfortunately, the underlying pathogenesis of EIM development

Table 12.3 Common extraintestinal manifestations (EIM) and relationship to IBD activity

EIM	Paralleling disease activity	Independent of disease activity	Either parallel or independent of activity
Axial arthropathy		**X**	
Peripheral arthropathy	**X (Type I)**	**X (Type II)**	
Erythema nodosum	**X**		
Pyoderma gangrenosum			**X**
Oral apthous ulcers	**X**		
Episcleritis	**X**		
Uveitis			**X**
Primary sclerosing cholangitis			**X**

in IBD is not well understood. EIMs can either parallel or be independent of disease activity. They can be the first presenting feature of IBD, and the finding of 1 of these conditions should trigger a referral to a gastroenterologist. Pediatric patients have been shown to have a higher prevalence of EIMs in comparison to adult patients [112]. Furthermore, because patients with IBD are often unaware of EIM, they may first seek care for them from their PCP. It is critical that the PCP coordinate appropriate evaluation with the gastroenterologist when this occurs.

Arthropathy

Joint pain or inflammation is the most common EIM in IBD, occurring in up to 40 % of IBD patients [113]. Peripheral arthralgia can occur in up to 10 % of UC patients and 20 % of CD patients. It is characterized as seronegative, and classified into 2 distinct categories. Type I (pauciarticular) involves <5 large joints and is dependent on disease activity. Type II (polyarticular) involves >5 large joints, and its severity is independent of disease activity. Knees tend to be the most commonly affected joints, but differentiation of Type I versus Type II is seldom clinically relevant. Treating the underlying bowel inflammation can help in the control of joint symptoms, but further evaluation by rheumatology is recommended in refractory cases. The use of NSAIDs is discouraged due to the potential for worsening of underlying IBD [114].

Skin/Mucosal Lesions

Cutaneous disorders associated with IBD can occur in up to 15 % of patients [115]. Erythema nodosum (EN) is characterized as raised, tender, red/violet subcutaneous nodules measuring up to 5 cm in diameter. They are typically located on the anterior surface of the lower extremities (Fig. 12.1) [116]. EN usually resolves when the bowel inflammation is treated. Pyoderma gangrenosum (PG), on the other hand, has an unpredictable course and does not parallel disease activity. It is characterized initially with an erythematous pustule/nodule, followed by rapid local spread and development into a burrowing ulcer with irregular violaceous edges (Fig. 12.2) [117]. The same drugs used to treat IBD are used to treat PG. However, refractory cases have shown benefit with intralesional steroids and/or cyclosporine [118]. PG typically involves expert consultation with a dermatologist.

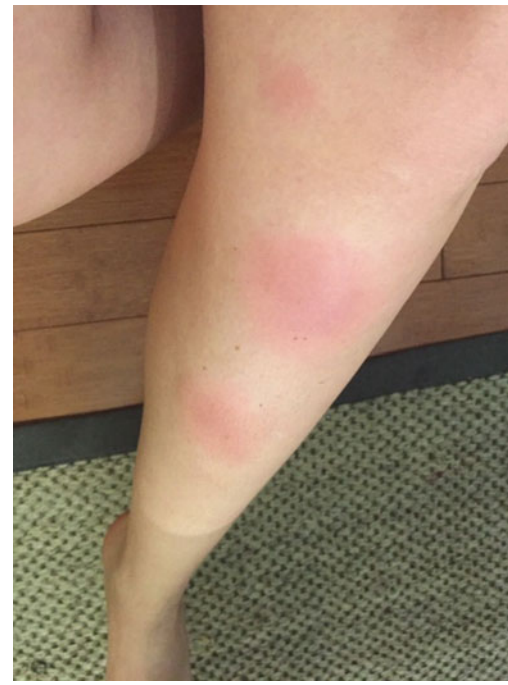

Fig. 12.1 Erythema nodosum of the anterior left leg in a patient with ulcerative colitis. (Courtesy of Dr. Elana Maser)

Apthous ulcers in the oral cavity typically occur in conjunction with IBD activity and are localized to the buccal mucosa, with occasional appearances on the tongue. Treatment typically involves therapy of underlying IBD in combination with antiseptic mouthwashes and topical steroid dental paste.

Ophthalmologic Manifestations

Up to 5 % of IBD patients will present with ocular manifestations [119]. Episcleritis is characterized as a painless hyperemia of the conjunctiva and often parallels IBD activity. Treatment of the underlying bowel inflammation, along with topical steroids, is used to relieve symptoms. Alternatively, the temporal correlation of uveitis with IBD is unpredictable. Uveitis

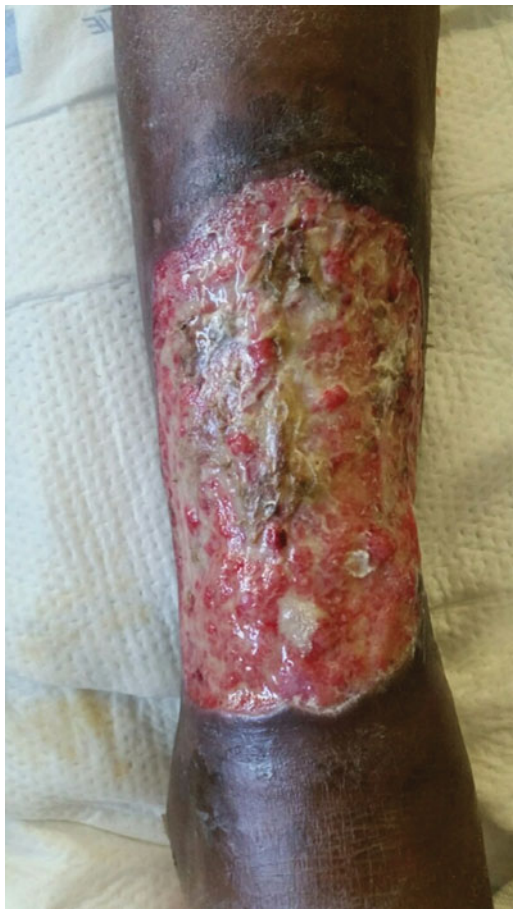

Fig. 12.2 Pyoderma gangrenosum of the anterior left leg in a patient with ulcerative colitis. Note the "violaceous" hue along the borders. (Courtesy of Dr. David Faleck and Dr. Serre-yu Wong)

may present as ocular pain, blurred vision, or photophobia. Uveitis can progress to blindness, thus all patients with IBD who present with any ocular symptoms should be immediately referred to an ophthalmologist in addition to annual ophthalmological evaluation.

Special Issues in the Transition to Adult Care

With the rising incidence of pediatric IBD, a larger number of young patients are transitioning to adult care. Adult providers need to be ready to manage young adults who may lack the readiness to cope with their illness independently. With evidence from chronic disease models, poorer outcomes have been demonstrated in young adults transitioning to adult healthcare, partly due to the expectation of increased autonomy [120, 121].

One of the major issues with transition of care based on a survey of adult gastroenterologists was the lack of specific adolescent training [122]. Gastroenterology fellowship programs provide minimal, if any, training in the care of adolescents. The care of young adults in other chronic conditions, such as rheumatologic and cardiac diseases, presents similar concerns [123, 124]. Adult providers will need to be aware of their patients developing independence, differences in the adolescent's style of communication, body image concerns, navigating intimate relationships, and missed school or work [125]. Finally, coordinating insurance coverage as the adolescent transitions off their parents' insurance plan is particularly important because treating IBD often requires expensive biologic drugs, and such advanced preparation may help in avoiding gaps in care.

Some adolescents arrive at the adult gastroenterologist ready to take control of their own health care, while others continue to communicate through their parents. Every adolescent grows at his or her own pace. The first step is for the provider to assess the patient's current level of independence and build from there. Part of fostering independence includes helping adolescents understand what it means to manage IBD. Having IBD often involves frequent lab testing, imaging, and annual screening colonoscopies, procedures that may not have needed to be initiated by their pediatric gastroenterologist.

Fostering independence also includes encouraging adolescents to communicate directly with their physician rather than through their parents. Having this direct connection will help establish trust. Because adolescents often prefer to communicate through email and text, the use of patient portals that allow for electronic communication may be helpful. In gastroenterology, there are many emerging applications (a.k.a. "apps") for disease education and monitoring.

Once communication and trust have been established, there can be an opening to discuss the impact of IBD on body image and sexuality. The diagnosis of IBD is often made in adolescence when body image is forming. Up to two-thirds of adult IBD patients report impaired body image, and one-third blame IBD for negatively affecting their sexual desire and satisfaction [71, 73]. The presence of disfiguring abdominal scars or the presence of an ostomy may lead patients to withdraw from active sexual relationships and have difficulty initiating new ones, especially during the sensitive adolescent period. Patients may want advice on how and when to disclose that they have a chronic illness to their partners. Unfortunately, adequate counseling, especially for women, on sexual health IBD remains low [126]. Not all primary care physicians or gastroenterologists are able to counsel patients. However, they can explain that these important issues are being considered when making medical decisions. For example, if colectomy is required, it is helpful to discuss with patients that an ostomy can be well hidden under clothing and that there are bathing suits that are designed to hide ostomies. PCPs can help advocate for their patients if these sensitive topics are more easily discussed with them than with a gastroenterologist. Whether or not the adolescent seems well adjusted, referral to a psychologist should be offered to all patients to support them while they navigate this sensitive time.

Missed school or work can be difficult for young adults as they attempt to establish themselves in their careers. The indirect costs of missed work and unemployment are estimated at $3.6 billion per year [127]. Physicians can help minimize the disruption to the lives of their patients by being sensitive to the possible need to delay a surgery or start a new medication when conflicts with work, school, weddings, or travel may exist. College students can be advised that they may be eligible for exam extensions or taking a leave from school if necessary. Many pharmaceutical companies offer scholarships to help support patients with IBD. There are also camps for children with Crohn's (Camp Oasis), where an adolescent can provide counsel to younger children navigating their disease and allow them to meet others with similar issues.

As children grow up, they eventually age off of their parent's health insurance. A 2014 survey demonstrated that only up to 24 % of young adults received counseling with respect to obtaining insurance coverage [128]. Interruption in the administration of biological agents can prevent their usefulness in the future. Therefore, notifying patients to be proactive regarding their coverage can be life changing. If possible, access to a social worker would be helpful.

Conclusion

Acknowledging issues that are important to adolescents with IBD when they arrive in an adult practice will establish trust and ultimately lead to better patient outcomes and satisfaction ("Appendix"). It is important to maintain careful coordination of care between the PCP and subspecialist to assure the delivery of comprehensive care to patients with IBD.

Appendix

Inflammatory bowel disease (IBD) fact sheet	
Definition	**Inflammatory Bowel Disease (IBD)** is characterized by chronic, relapsing inflammation within the gastrointestinal tract. IBD consists of Crohn's disease (CD) and ulcerative colitis (UC). • UC: affects the mucosal layer of the colon and rectum • CD: affects all layers of the bowel and can occur in any part of the gastrointestinal tract from mouth to anus.
Prevalence	• Affects more than 5 million people worldwide, with more than 1.7 million in the United States • Lifetime risk of development is 1 % • ¼ of patients are diagnosed in childhood or adolescence
Pathophysiology	Inflammation is a result of inappropriate and ongoing activation of the innate immune system of the gut mucosa, driven by the commensal luminal flora in a genetically susceptible host • Unclear as to specific flora responsible for activation • Limited variation in gut bacteria is typically seen in an IBD host
Symptoms	Symptoms can overlap between CD and UC but each has distinctive attributes that can help differentiate: • Abdominal pain, diarrhea • Perianal fistulas (CD) • Weight loss • Anemia, vitamin deficiencies • Bloody stools (higher risk in UC)
Challenges in transition	The transition from pediatric to adult care can be complicated due to the complexity of disease management. • Complications related to the underlying disease and advanced therapies in IBD can be difficult to assess. • Limited scope on routine health maintenance, to include vaccinations and cancer screening (for example, annual colon cancer screening with colonoscopy) • Compliance of medication therapy • Access to therapy and care if college-bound • Discussions in intimacy and pregnancy • Gaining trust in new provider • Dietary management
Helpful resources	• Crohn's and Colitis Foundation of America (resources for patients and family members, may include local chapters in communities throughout the US): http://www.ccfa.org • American College of Gastroenterology Guidelines on Crohn's disease and Ulcerative Colitis management (developed by expert panel): http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/

References

1. Escher J. Transition from pediatrics to adult health care in inflammatory bowel disease. Dig Dis. 2009;27:382–6.
2. Dabadie A, Troadec F, Heresbach D, Siproudhis L, Pagenault M, Bretagne JF. Transition of patients with inflammatory bowel disease from pediatric to adult care. Gastroenterol Clin Biol. 2008;32(5 Pt 1):451–9.
3. El-Matary W. Transition of children with inflammatory bowel disease: big task, little evidence. World J Gastroenterol. 2009;15(30):3744.
4. Van Assche G, Vermeire S, Ballet V, Gabriels F, Noman M, D'Haens G, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised switch trial. Gut. 2012;61(2):229–34.
5. Burisch J, Jess T, Martinato M, Lakatos PL. The burden of inflammatory bowel disease in Europe. J Crohns Colitis. 2013;7(4):322–37.

6. Bernstein C, Wajda A, Svenson L, MacKenzie A, Koehoorn M, Jackson M. The epidemiology of inflammatory bowel disease in canada: a population-based study. Am J Gastroenterol. 2006;101:1559–68.
7. Burisch J, Pedersen N, Cukovic-Cavka S, Brinar M, Kaimakliotis I, Duricova D, et al. East-west gradient in the incidence of inflammatory bowel disease in Europe: the ecco-epicom inception cohort. Gut. 2014;63(4):588–97.
8. Sawczenko A, Sandhu BK, Logan RFA, Jenkins H, Taylor CJ, Mian S, et al. Prospective survey of childhood inflammatory bowel disease in the british isles. Lancet. 2001;357(9262):1093–4.
9. Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD. Rising incidence of inflammatory bowel disease among children: a 12-year study. J Pediatr Gastroenterol Nutr. 2010;50(1):27–31.
10. Loftus CG, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ 3rd, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in olmsted county, minnesota, 1940-2000. Inflamm Bowel Dis. 2007;13(3):254–61.
11. Romberg-Camps MJL, Hesselink-van de Kruijs MAM, Schouten LJ, Dagnelie PC, Limonard CB, Kester AD. Inflammatory bowel disease in South Limburg (the Netherlands) 1991–2002: incidence, diagnostic delay, and seasonal variations in onset of symptoms. J Crohns Colitis. 2009;3:115–24.
12. Trallori G, Palli D, Saieva C, Bardazzi G, Bonanomi A, D'Albasio G. A population-based study of inflammatory bowel disease in florence over 15 years (1978-92). Scand J Gastroenterol. 1996;31:892–9.
13. Robison WW, Bentlif PS, Kelsey JR. Observations on 261 consecutive patients with inflammatory bowel disease seen in the southwest united states. Dig Dis Sci. 1980;25:198–204.
14. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet. 2011;43(3):246–52.
15. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet. 2010;42(12):1118–25.
16. Bellaguarda E, Chang EB. IBD and the gut microbiota–from bench to personalized medicine. Curr Gastroenterol Rep. 2015;17(4):15.
17. Hart AL, Ng SC, Mann E, Al-Hassi HO, Bernardo D, Knight SC. Homing of immune cells: role in homeostasis and intestinal inflammation. Inflamm Bowel Dis. 2010;16(11):1969–77.
18. Hold GL, Smith M, Grange C, Watt ER, El-Omar EM, Mukhopadhya I. Role of the gut microbiota in inflammatory bowel disease pathogenesis: what have we learnt in the past 10 years? World J Gastroenterol. 2014;20(5):1192–210.
19. Monstad I, Hovde O, Solberg IC, Moum BA. Clinical course and prognosis in ulcerative colitis: results from population-based and observational studies. Ann Gastroenterol. 2014;27(2):95–104.
20. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of G. Ulcerative colitis practice guidelines in adults: American college of gastroenterology, practice parameters committee. Am J Gastroenterol. 2010;105(3):501–23 (quiz 524).
21. Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the vienna classification: changing pattern over the course of the disease. Gut. 2001;49(6):777–82.
22. Maser EA, Sachar DB, Kruse D, Harpaz N, Ullman T, Bauer JJ. High rates of metachronous colon cancer or dysplasia after segmental resection or subtotal colectomy in Crohn's colitis. Inflamm Bowel Dis. 2013;19(9):1827–32.
23. Hanauer S. Epidemiology, pathogenesis, and treatment of ibd. Inflamm Bowel Dis. 2006;12(1):S3–9.
24. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA. 2007;104(34):13780–5.
25. Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut. 2006;55(2):205–11.
26. Papadakis KA, Targan SR. Role of cytokines in the pathogenesis of inflammatory bowel disease. Annu Rev Med. 2000;51:289–98.
27. Satsangi J, Jewell D, Bell J. The genetics of inflammatory bowel disease. Gut. 1997;40(5):572.
28. Satsangi J, Morecroft J, Shah N, Nimmo E. Genetics of inflammatory bowel disease: scientific and clinical implications. Best Pract Res Clin Gastroenterol. 2003;17(1):3–18.
29. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474(7351):307–17.
30. Halme L, Paavola-Sakki P, Turunen U, Lappalainen M, Farkkila M, Kontula K. Family and twin studies in inflammatory bowel disease. World J Gastroenterol. 2006;12(23):3668–72.
31. Yang H, McElree C, Roth M, Shanahan F, Targan S, Rotter J. Familial empirical risks for inflammatory bowel disease: differences between jews and non-jews. Gut. 1993;34(4):517–24.
32. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol. 2003;3(7):521–33.
33. Hugot J, Laurent-Puig P, Gower-Rousseau C, Olson J, Lee J, Beaugerie L, et al. Mapping a

susceptibility locus for Crohn's disease on chromosome 16. Nature. 1996;379(6568):821–3.
34. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491 (7422):119–24.
35. Hugot J, Chamaillard M, Zouali H, Lesage S, Cezard J, Belaiche J, et al. Association of nod2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001;411(6837):599–603.
36. Ogura Y, Bonen D, Inohara N, Nicolae D, Chen F, Ramos R, et al. A frameshift mutation in nod2 associated with susceptibility to Crohn's disease. Nature. 2001;411(6837):603–6.
37. Strachan D. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259–60.
38. Radon K, Windstetter D, Poluda AL, Mueller B, von Mutius E, Koletzko S, et al. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. Pediatrics. 2007;120(2):354–61.
39. Van Kruiningen H, Joosens M, Vermeire S, Joosens S, Debeugny S, Gower-Rousseau C, et al. Environmental factors in familial Crohn's disease in belgium. Inflamm Bowel Dis. 2005;11(4):360–5.
40. Bager P, Simonsen J, Nielsen NM, Frisch M. Cesarean section and offspring's risk of inflammatory bowel disease: a national cohort study. Inflamm Bowel Dis. 2012;18(5):857–62.
41. Barclay A, Russell R, Wilson M, Gilmour W, Satsangi J, Wilson D. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pedatr. 2009;155(3):421–6.
42. Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre J. Effects of cigarette smoking on the long-term course of Crohn's disease. Gastroenterology. 1996;110(2):424–31.
43. Mahid S, Minor K, Soto R, Hornung C, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006;81 (11):1462–71.
44. Higuchi LM, Khalili H, Chan AT, Richter JM, Bousvaros A, Fuchs CS. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. Am J Gastroenterol. 2012;107(9):1399–406.
45. Mahid SS, Minor KS, Stromberg AJ, Galandiuk S. Active and passive smoking in childhood is related to the development of inflammatory bowel disease. Inflamm Bowel Dis. 2007;13(4):431–8.
46. Ungaro R, Bernstein CN, Gearry R, Hviid A, Kolho KL, Kronman MP, et al. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. Am J Gastroenterol. 2014;109(11):1728–38.
47. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE. Antibiotic exposure and ibd development among children: a population-based cohort study. Pediatrics. 2012;130(4):e794–803.
48. Gevers D, Kugathasan S, Denson LA, Vazquez-Baeza Y, Van Treuren W, Ren B, et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014;15 (3):382–92.
49. Felder J, Korelitz B, Rajapakse R, Schwarz S, Horatagis A, Gleim G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. Am J Gastroenterol. 2000;95(8):1949.
50. Kaufmann H, Taubin H. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. Ann Intern Med. 1987;107 (4):513.
51. Ananthakrishnan A, Higuchi L, Huang E, Khalili H, Richter J, Fuchs C, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis a cohort study. Ann Intern Med. 2012;156(5):350–9.
52. Tanner A, Raghunath A. Colonic inflammation and nonsteroidal anti-inflammatory drug administration: an assessment of the frequency of the problem. Digestion. 1988;41(2):116.
53. Bankar R, Dafe C, Kohnke A, Babu P. Ulcerative colitis probably associated with isotretinoin. Indian J Gastroenterol. 2006;25(3):171–2.
54. Bernstein CN, Nugent Z, Longobardi T, Blanchard JF. Isotretinoin is not associated with inflammatory bowel disease: a population-based case-control study. Am J Gastroenterol. 2009;104 (11):2774–8.
55. Etminan M, Bird ST, Delaney JA, Bressler B, Brophy JM. Isotretinoin and risk for inflammatory bowel disease: a nested case-control study and meta-analysis of published and unpublished data. JAMA Dermatol. 2013;149(2):216–20.
56. Khalili H, Higuchi LM, Ananthakrishnan AN, Manson JE, Feskanich D, Richter JM, et al. Hormone therapy increases risk of ulcerative colitis but not Crohn's disease. Gastroenterology. 2012;143 (5):1199–206.
57. Khalili H, Higuchi LM, Ananthakrishnan AN, Richter JM, Feskanich D, Fuchs CS, et al. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. Gut. 2013;62(8):1153–9.
58. Ananthakrishnan AN, Khalili H, Pan A, Higuchi LM, de Silva P, Richter JM, et al. Association between depressive symptoms and incidence of Crohn's disease and ulcerative colitis: results from the nurses' health study. Clin Gastroenterol Hepatol. 2013;11(1):57–62.
59. Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut. 2008;57(10):1386–92.
60. Goodhand JR, Wahed M, Mawdsley JE, Farmer AD, Aziz Q, Rampton DS. Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. Inflamm Bowel Dis. 2012;18(12):2301–9.

61. Triantafillidis JK, Merikas E, Gikas A. Psychological factors and stress in inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2013;7(3):225–38.
62. Chan SS, Luben R, Olsen A, Tjonneland A, Kaaks R, Teucher B, et al. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European prospective cohort study (the ibd in epic study). Am J Gastroenterol. 2013;108(4):575–82.
63. Mendall MA, Gunasekera AV, John BJ, Kumar D. Is obesity a risk factor for Crohn's disease? Dig Dis Sci. 2011;56(3):837–44.
64. Desreumaux P, Ernst O, Geboes K, Gambiez L, Berrebi D, Muller-Alouf H, et al. Inflammatory alterations in mesenteic adipose tissue in Crohn's disease. Gastroenterology. 1999;117(1):73–81.
65. Blain A, Cattan S, Beaugerie L, Carbonnel F, Gendre JP, Cosnes J. Crohn's disease clinical course and severity in obese patients. Clin Nutr. 2002;21(1):51–7.
66. Long MD, Crandall WV, Leibowitz IH, Duffy L, del Rosario F, Kim SC, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17(10):2162–8.
67. Khalili H, Ananthakrishnan AN, Konijeti GG, Liao X, Higuchi LM, Fuchs CS, et al. Physical activity and risk of inflammatory bowel disease: prospective study from the nurses' health study cohorts. BMJ. 2013;347:f6633.
68. 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(11):2440–3.
69. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Fuchs CS, et al. Sleep duration affects risk for ulcerative colitis: a prospective cohort study. Clin Gastroenterol Hepatol. 2014;12(11):1879–86.
70. Drossman D, Leserman J, Li Z, Mitchell C, Zagami E, Patrick D. The rating form of ibd patient concerns: a new measure of health status. Psychosom Med. 1991;53(6):701–12.
71. Marin L, Manosa M, Garcia-Planella E, Gordillo J, Zabana Y, Cabre E, et al. Sexual function and patients' perceptions in inflammatory bowel disease: a case-control survey. J Gastroenterol. 2013;48(6):713–20.
72. Timmer A, Bauer A, Dignass A, Rogler G. Sexual function in persons with inflammatory bowel disease: a survey with matched controls. Clin Gastroenterol Hepatol. 2007;5(1):87–94.
73. Muller KR, Prosser R, Bampton P, Mountifield R, Andrews JM. Female gender and surgery impair relationships, body image, and sexuality in inflammatory bowel disease: patient perceptions. Inflamm Bowel Dis. 2010;16(4):657–63.
74. Johnson P, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, et al. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum. 2004;47(7):1119–26.
75. Mountifield R, Bampton P, Prosser R, Muller K, Andrews JM. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. Inflamm Bowel Dis. 2009;15(5):720–5.
76. Tavernier N, Fumery M, Peyrin-Biroulet L, Colombel JF, Gower-Rousseau C. Systematic review: fertility in non-surgically treated inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(8):847–53.
77. Fonager K, Sorensen H, Olsen J, Dahlerup J, Rasmussen S. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. Am J Gastroenterol. 1998;93(12):2426–30.
78. Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from northern california. Gastroenterology. 2007;133(4):1106–12.
79. Norgard B, Fonager K, Sorensen H, Olsen J. Birth outcomes of women with ulcerative colitis: a nationwide danish cohort study. Am J Gastroenterol. 2000;95(11):3165–70.
80. Katz J. Pregnancy and inflammatory bowel disease. Curr Opin Gastroenterol. 2004;20(4):328–32.
81. Ujihara M, Ando T, Ishiguro K. Appropriate pharmaceutical management is crucial for pregnant women complicated by ulcerative colitis. San Diego, CA: Digestive Disease Week San Diego; 2012. p. 19–22.
82. Bhatia J, Bratcher J, Korelitz B, Vakher K, Mannor S, Shevchuk M, et al. Abnormalities of uterine cervix in women with inflammatory bowel disease. World J Gastroenterol. 2006;12(38):6167–71.
83. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal pap smears in women with inflammatory bowel disease. Am J Gastroenterol. 2008;103(3):631–6.
84. ACOG. ACOG practice bulletin no. 131: screening for cervical cancer. Obstet Gynecol. 2012;120:1222–38.
85. Moscandrew M, Mahadevan U, Kane S. General health maintenance in ibd. Inflamm Bowel Dis. 2009;15(9):1399–409.
86. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141(5):1621–8 (e1621–1625).
87. Nyboe Andersen N, Pasternak B, Basit S, Andersson M, Svanstrom H, Caspersen S, et al. Association between tumor necrosis factor-alpha antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA. 2014;311(23):2406–13.
88. USPTF. Screening for osteoporosis: U.S. Preventative services task force recommendation statement. Ann Intern Med. 2011;154(5):356–64.

89. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of pneumonia among patients with inflammatory bowel disease. Am J Gastroenterol. 2013;108(2):240–8.
90. Melmed GY, Ippoliti AF, Papadakis KA, Tran TT, Birt JL, Lee SK, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. Am J Gastroenterol. 2006;101(8):1834–40.
91. Wasan SK, Calderwood AH, Long MD, Kappelman MD, Sandler RS, Farraye FA. Immunization rates and vaccine beliefs among patients with inflammatory bowel disease: an opportunity for improvement. Inflamm Bowel Dis. 2014;20(2):246–50.
92. Dezfoli S, Melmed GY. Vaccination issues in patients with inflammatory bowel disease receiving immunosuppression. Gastroenterol Hepatol (NY). 2012;8(8):504–12.
93. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 idsa clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309–18.
94. Desjardins C, Duling BR. Heparinase treatment suggests a role for the endothelial cell glycocalyx in regulation of capillary hematocrit. Am J Physiol. 1990;258(3 Pt 2):H647–54.
95. Sandhu BK, Fell JM, Beattie RM, Mitton SG, Wilson DC, Jenkins H, et al. Guidelines for the management of inflammatory bowel disease in children in the united kingdom. J Pediatr Gastroenterol Nutr. 2010;50(Suppl 1):S1–13.
96. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol. 2006;4(6):744–53.
97. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Korzenik JR, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. Gastroenterology. 2013;145(5):970–7.
98. 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(4):563–73.
99. Weiss G. Iron in the inflammed gut: another pro-inflammatory hit? Gut. 2011;60(3):287–8.
100. Cantorna M, Zhu Y, Froicu M, Wittke A. Vitamin d status, 1,25-dihyroxyvitamin d3, and the immune system. Am J Clin Nutr. 2004;80(6):17175–205.
101. Ford AC, Kane SV, Khan KJ, Achkar JP, Talley NJ, Marshall JK, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):617–29.
102. Gordon GL, Zakko S, Murthy U, Sedghi S, Pruitt R, Barrett AC, et al. Once-daily mesalamine formulation for maintenance of remission in ulcerative colitis: a randomized, placebo-controlled clinical trial. J Clin Gastroenterol. 2016;50(4):318–25.
103. World M, Stevens P, Ashton M, Rainford D. Mesalazine-associated interstitial nephritis. Nephrol Dial Transplant. 1996;11:614–21.
104. Connell W, Kamm M, Ritchie J, Lennard-Jones J. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut. 1993;34:1081–5.
105. Moshkowitz M, Oren R, Tishler M, Konikoff F, Graff E, Brill S, et al. The absorption of low-dose methotrexate in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 1997;11:569–73.
106. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 american college of rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(5):625–39.
107. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the accent i randomised trial. Lancet. 2002;359(9317):1541–9.
108. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–72.
109. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004;350(9):876–85.
110. Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, et al. A systematic review of factors that contribute to hepatosplenic t-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):36–41 e31.
111. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2001;96(4):1116–22.
112. Stawarski A, Iwańczak B, Krzesiek E, Iwańczak F. Intestinal complications and extraintestinal manifestations in children with inflammatory bowel disease. Pol Merkur Lekarski. 2006;20(115):22–5.
113. Smale S, Natt RS, Orchard TR, Russell AS, Bjamason I. Inflammatory bowel disease and spondylarthropathy. Arthritis Rheum. 2001;44(12):2728–36.
114. Felder JB, Korelitz B, Rajapakse R, Schwarz S, Horatagis AP, Gleim G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. Am J Gastroenterol. 2000;95(8):1949–54.
115. Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106(1):110–9.

116. Requena L, Yus ES. Erythema nodosum. Dermatol Clin. 2008;26(4):425–38 (v).
117. DeFilippis EM, Feldman SR, Huang WW. The genetics of pyoderma gangrenosum and implications for treatment: a systematic review. Br J Dermatol. 2015;172(6):1487–97.
118. Callen JP. Pyoderma gangrenosum. Lancet. 1998;351:581–5.
119. Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Clin North Am. 2002;31(1):307–27.
120. Annunziato RA, Emre S, Shneider B, Barton C, Dugan CA, Shemesh E. Adherence and medical outcomes in pediatric liver transplant recipients who transition to adult services. Pediatr Transplant. 2007;11(6):608–14.
121. Hersh AO, Pang S, Curran ML, Milojevic DS, von Scheven E. The challenges of transferring chronic illness patients to adult care: reflections from pediatric and adult rheumatology at a us academic center. Pediatr Rheumatol Online J. 2009;7:13.
122. Sebastian S, Jenkins H, McCartney S, Ahmad T, Arnott I, Croft N, et al. The requirements and barriers to successful transition of adolescents with inflammatory bowel disease: differing perceptions from a survey of adult and paediatric gastroenterologists. J Crohns Colitis. 2012;6(8):830–44.
123. Reid GJ, Irvine MJ, McCrindle BW, Sananes R, Ritvo PG, Siu SC, et al. Prevalence and correlates of successful transfer from pediatric to adult health care among a cohort of young adults with complex congenital heart defects. Pediatrics. 2004;113(3):e197–205.
124. McDonagh JE, Southwood TR, Shaw KL, British Paediatric Rheumatology G. Unmet education and training needs of rheumatology health professionals in adolescent health and transitional care. Rheumatology (Oxford). 2004;43(6):737–43.
125. Trivedi I, Keefer L. The emerging adult with inflammatory bowel disease: challenges and recommendations for the adult gastroenterologist. Gastroenterol Res Pract. 2015;2015:260807.
126. Gawron LM, Hammond C, Keefer L. Documentation of reproductive health counseling and contraception in women with inflammatory bowel diseases. Patient Educ Couns. 2014;94(1):134–7.
127. Longobardi T. Work losses related to inflammatory bowel disease in the united states results from the national health interview survey. Am J Gastroenterol. 2003;98(5):1064–72.
128. Sawicki GS, Whitworth R, Gunn L, Butterfield R, Lukens-Bull K, Wood D. Receipt of health care transition counseling in the national survey of adult transition and health. Pediatrics. 2011;128(3):e521–9.