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Russell D. Cohen *Editor*

Inflammatory Bowel Disease

Diagnosis and Therapeutics

Third Edition

Humana Press

CLINICAL GASTROENTEROLOGY

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To my wife Cheryl and my daughters Samantha and Madeline: your individual drives for greatness provide the fuel to my fire.

Preface

The number three has played an important role in our culture. The Bible speaks of three wise men, children sing of three blind mice, and the three musketeers have come to the rescue of many a damsel in distress. In the magical land of Oz, Dorothy met three characters while she traversed the yellow brick road, fearful of three wild creatures (lions, tigers, etc.), and she clicked her heels three magic times to get back to her beloved Kansas. Yes, Kansas.

Three goals in hockey are a "hat trick"; three strikes in baseball make an out, and a triple play has been the dream of baseball infielders for generations. Three teaspoons make a tablespoon, the three-second rule is memorized by student drivers, and, apparently, the third time's the charm.

With that illuminous backdrop, I am happy to provide to my readers the third edition of *Inflammatory Bowel Disease: Diagnosis and Therapeutics.* This third time truly is the charm, as this new edition will introduce to the readers many exciting new concepts in our ever-changing understanding of these challenging diseases, as well as new breakthroughs in their treatment.

In the first chapter, "The New Face of IBD," Ashwin Ananthakrishnan takes us to parts of the world where IBD was not traditionally seen and documents the staggered emergence of ulcerative colitis followed one to two decades later by Crohn's disease. He also gives us insight into the potential pathogenesis of IBD with studies of populations that have migrated from low- to high-risk countries, which also may impact the application of various treatment regimens for these diseases. These principles are then picked up in the next chapter by Stephanie Coward and Gilaad Kaplan, "IBD in the New World, Old World, Your World," in which they examine the potential impact of smoking, medications, diet, industrialization, and other hypotheses in an attempt to crack the mystery driving these diseases. And then Mark Silverberg and Sarah O'Donnell tackle the ever-expanding topic, "Do Genes Matter," as they look not only at what we currently know about IBD genetics but what we may be using genetics for in the not-too-distant future.

This third edition of *Inflammatory Bowel Disease: Diagnosis and Therapeutics* contains many more chapters to allow the readers to customize their learning experience. Clinicians are offered the latest in diagnostic studies, a full range of therapeutics, "alternative therapies," and a sneak peek into the biosimilar revolution that is upon us. Those in the surgical fields will find chapters such as "Playing Houdini," "New Tricks for the IBD Surgeon," and "Do Not Fear to Ostomy" to be essential reading.

Unlike most chronic diseases, IBD impacts many patients within the first few decades of life. The unique issues to these age groups are thoroughly updated in the chapters "Size Matters: The Pediatric IBD Patient" and "By the Way, I'm Pregnant," providing invaluable information for patients and families alike. Insight into nutrition and diet helps guide patients (and their caregivers) in answering what is arguably the most common question that I hear, "Yes, but what can I eat?"

Specialists of many arts may find the chapters looking at diagnostics, modern colonoscopic surveillance techniques, advances in radiographic imaging, and deciphering histological findings in disease and dysplasia of particular interest. And for those of us practicing (or paying for) medicine in the twenty-first century, the very timely chapters regarding the role of APNs and PAs in an IBD practice, the application of quality outcomes into practice, and the modern economics of IBD amid the biologic revolution are truly "must-read" topics.

So please enjoy this newest and most expanded coverage of the topics that matter in inflammatory bowel diseases. I guarantee that the collection of authors in this edition will provide an exceptional background for a wide variety of readers. I hope you enjoy!

Chicago, Illinois, USA Russell D. Cohen
November 2016

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Chapter 1
The New Face of IBD

Ashwin N. Ananthakrishnan

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are traditionally considered as diseases affecting mostly the Caucasian population residing in the Western Hemisphere.

- Recent data suggest an emergence of the disease in populations previously considered low risk including those in the Middle East, South, and East Asia.
- Emergence in these populations is initially seen as a rise in UC followed one or two decades later by an increase in prevalence of CD.
- Migration studies offer important insights into disease pathogenesis. There appears to be an increase in risk of IBD in the second-generation immigrants moving from low-risk to high-incidence countries.
- The next few decades are going to witness a growing burden of IBD in low-risk regions as well as minority racial and ethnic populations in the West.

Inflammatory bowel diseases (IBD: Crohn's disease [CD] and ulcerative colitis [UC]) are chronic immunologically mediated diseases that arise as a result of a dysregulated immune response to a normal or altered gut microbiome in a genetically susceptible individual [1–3]. Affecting an estimated 1.5 million individuals in the United States, 2.2 million in Europe, and several thousands more worldwide [4], they account for a significant morbidity and impact on quality of life by virtue of

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their onset in childhood or early adulthood and a protracted course characterized by remissions and relapse. From the initial recognition of the familial nature of these diseases, to the first single nucleotide polymorphism associated with CD at the Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) locus [5, 6], advances in genetics have led to the identification of 163 distinct genetic alleles that modify the risk of CD or UC, with most contributing to a modest increase in risk [7]. However, the emergence of IBD in new populations as well as temporal increases in disease incidence over the short span of a few decades has brought into focus the role of the changing external or internal (microbiome) environment in influencing the epidemiology of these complex diseases. Further adding to the complexity is that neither genetic nor the environmental risk factors appear to be consistent across all populations. For example, while the NOD2 allele is the strongest risk factor for CD in the Caucasian population [5, 6], its role in Asian CD subpopulations appears to be less clear [8] and alternate genetic risk factors may play a more important role [9, 10]. A similar trend is seen for environmental risk factors where gender and ethnic origin render specific associations as significant or insignificant.

This chapter examines the changes in epidemiology of IBD in populations traditionally considered at high risk, namely those of Caucasian origin residing in Western Europe, Scandinavia, or North America. However, minority racial and ethnic groups within the same populations are also being recognized as having significant morbidity associated with a rising incidence of IBD. Additionally, elsewhere in regions of the world where a diagnosis of IBD was considered a rarity, the emergence of both UC and CD, and, in particular, patterns of evolution of these diseases has contributed important new data points for our understanding of the pathogenesis of these complex conditions (Table 1.1).

Table 1.1 Factors contributing to the "changing face" of IBD

1. Evolving environmental factors
(a) Decreasing frequency of smoking
(b) "Westernization" of diet
1. Increased saturated fats, processed foods, and sugar
2. Decreasing intake of fruits, vegetables, and other fibers
(c) Growing industrialization and air pollution
(d) Prevalence of antibiotic utilization
(e) Changing prevalent environmental hygiene factors (clean water, overcrowding, and early life infections)
(f) Stress and depression
2. Migration
(a) From rural to urban areas
(b) From low-risk to high-risk areas
3. Changing diagnostic modalities
(a) More widespread use of radiologic and endoscopic investigations
4. Aging of the population and increasing life expectancy

Epidemiology of IBD in the West

Much of the data on the incidence and prevalence of IBD have come from population-based cohorts from Olmsted County in the United States, Scandinavia, and Western Europe. A population-based estimate of the incidence of IBD in the United States was first reported from the Olmsted County cohort by Sedlack et al., who examined trends in disease incidence over a 41-year period between 1935 and 1975 [11]. The age-adjusted incidence of CD rose from 1.9 cases per 100,000 in the period 1935–1954 to 4.0 per 100,000 in 1955–1964, and as high as 6.6 per 100,000 by 1975 [11]. The increase in incidence of disease among 20–29 year olds was the strongest contributor to this secular rise. A subsequent update by Loftus et al. demonstrated a continued, albeit less steep, increase in risk of disease to 6.9 cases per 100,000 person-years in 1984–1993 [12], and further leveling-off to 7.9 per 100,000 in 2000 [13]. Corresponding data in UC similarly demonstrated a significant increase in risk of disease from 1940 (incidence 0.6 cases per 100,000 person-years) to 1993 (incidence 8.3 cases per 100,000 person-years) [14], stabilizing over the next decade to 8.8 cases per 100,000 person-years by 2000 [13].

An elegant systematic review by Molodecky et al. synthesized incidence and prevalence data from population-based cohorts from diverse geographic locations over a period ranging from 1930 to 2004 [4]. Encompassing a total of 262 included studies, the annual incidence of UC was noted to be the highest in Europe (24.3 per 100,000 in Iceland) and North America (19.2 per 100,000 in Nova Scotia Province in Canada). Similarly, the incidence of CD was reported to reach 12.7/100,000 in Europe (Italy) and 20.2/100,000 in North America (Quebec province, Canada). Consistent with the secular trend identified in North America, three-quarters of the studies in CD (75%) and nearly two-thirds of UC studies (60%) demonstrated a statistically significant increase in disease incidence over the period of study [4]. While this may in part reflect greater awareness of disease and a heightened frequency of diagnostic testing, the consistency of this secular trend and its persistence in countries where the threshold for invasive investigations and availability of such testing have likely not changed as steeply, there does appear to be a true increase in risk of development of IBD. While the exact reasons for this increase are unknown, one can speculate that changing behavior, lifestyle, and external environment with growing urbanization may contribute to an immune response or alteration in the gut microbiome that predisposes toward development of IBD.

Even within this population at "high risk" for development of IBD, there appear to be variations on a smaller geographic scale. For example, a north-south gradient in disease risk has been described where individuals residing at latitudes distant from the equator [15], both in the Northern and Southern Hemispheres (e.g., Australia and New Zealand) [16], are at a higher risk for development of IBD than those residing closer to the equator. Even within specific countries such as the United States or France, those residing in Northern latitudes have a higher risk [15, 17–19], perhaps reflecting the role of ultraviolet light exposure and vitamin D status in modifying the risk of disease [20].

The peak age of onset for IBD is in the second and third decades of life [3, 21]. More inconsistently, a second, smaller peak has been described in the sixth and seventh decades of life and more commonly for UC though this has not been reported consistently in all populations [3, 21]. The reason for this second peak is unclear and, in particular, whether it represents cumulative adult lifetime environmental exposure. There have been no significant changes in the disease location, behavior (in CD) or extent (in UC) over time, or for the age of diagnosis. However, reflecting the aging of the population globally but particularly in western countries, there is growing recognition of both established and new onset IBD in older IBD patients [22–24]. The natural history of disease in this elderly IBD population also remains unclear as some but not all studies have suggested a milder course with less frequent use of aggressive medical or surgical therapy [22–24]. However, to what extent this reflects reluctance to adopt such approaches on the part of both the patient and the provider and how much it is a reflection of the disease biology remain to be clearly established. While initial studies cast doubt on secular reductions in the need for surgery or hospitalizations that affect over half of the patients with CD and a smaller subset of UC [25], more recent cohorts examining patients newly diagnosed after availability of effective biologic therapies have demonstrated a reduction in the rate of surgery in both CD and UC [26].

IBD in the West: Minority Racial and Ethnic Groups (Hispanics and African Americans)

While traditionally considered a disease of the Caucasian population, several recent studies have highlighted the recognition of IBD as an important source of morbidity in minority racial and ethnic groups including African Americans and Hispanics. An elegant systematic review by Hou et al. summarized 28 publications, comprising 1272 Hispanic and 547 African Americans [27]. The included studies were from geographically diverse settings worldwide and identified interesting phenotypic similarities and differences between the various populations. In both Hispanics and Asians, a diagnosis of UC was noted more frequently than CD while the inverse was true in unselected African-American populations where CD was the most frequent form of IBD. The age at diagnosis in African-American patients was also younger compared to the other ethnic groups, but the disease location, extent, and fistulizing complications were similar in all patients with a similar prevalence of perianal disease. A family history of IBD was less common in minority populations suggesting perhaps a weaker genetic contribution to disease in this population compared to Whites [27, 28]. However, the literature on phenotype and natural history in this minority population is both sparse and inconsistent with data from the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)-IBD consortium suggesting more frequent colorectal diseases, perianal involvement, and extraintestinal manifestations (particularly uveitis and sacroiliitis) among African-American

patients when compared to Hispanics or Whites [28]. Such differences based on ethnicity have also been observed in pediatric IBD though, similar to the adult literature, the findings are often conflicting with many studies lacking robust statistical power to identify true differences [29].

IBD in the East

There is a growing wealth of literature examining the incidence, phenotype, and natural history of IBD in regions of the world where both CD and UC were traditionally considered uncommon [30, 31]. Much of this is possible because of population-based cohorts that have systematically evaluated new diagnosis of IBD with careful longitudinal follow-up. Such rigor is particularly essential given the spectrum of competing clinical scenarios in these populations including enteric infections and gastrointestinal tuberculosis that sometimes make establishment of a firm diagnosis of IBD challenging.

The most recent estimates of incidence of IBD in Asia have come from the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) [32]. This cohort estimated incidence and phenotype of IBD in eight countries across Asia and Australia over a 1 year period between 2011 and 2012. A total of 419 new cases of IBD (232 UC and 187 CD) were identified. The overall crude incidence was 1.4 per 100,000 in Asia compared to 23.7 per 100,000 in Australia (similar differences were seen for both UC and CD) [32]. However, even within Asia, there was significant variation in disease risk ranging from 3.4 per 100,000 in China to 0.6 per 100,000 in Thailand. As has been noted in many other cohorts from regions witnessing an emergence of IBD, UC comprised only one-third of the new diagnoses of IBD in Australia but over two-thirds of new cases in the other countries in Asia. The reason for the initial emergence of UC followed one or two decades later by an increase in incidence of CD, eventually reaching the incidence of UC, is unclear but is perhaps due to differences in environmental influences or in the lag time for development of inflammation or symptoms leading to diagnoses. The age of diagnoses was similar across both Asia and Australia though the former had more severe disease defined as penetrating behavior in CD. As noted in minority racial and ethnic groups in the United States and elsewhere, family history of IBD was infrequent (3%) among patients in Asia compared to Australia where nearly one in five reported such a history (17%, $p < 0.001$) [32].

In addition to such cross-sectional estimates of disease burden across Asia, a few studies have examined temporal trends in disease incidence and prevalence similar to what has been examined in Western Europe and North America. Some of the best studies on such secular trends in IBD incidence in Asia have been from Japan where nationwide epidemiological studies of IBD have been systematically conducted since 1973 [30]. Though IBD remains uncommon, there has been a significant increase in the incidence of UC from 0.02 to 1.9 per 100,000 between 1961 and 1991, while a similar increase in CD was also noted from 0.6 to 1.2 per 100,000

between 1986 and 1998 [33–35]. This increase was not restricted to Japan and was also noted in Korea where a similar nearly tenfold increase in incidence was noted for both UC and CD from 1986 to 2008 [36, 37].

The reasons for this increase in incidence are unclear. Genetic risk factors are unlikely to play a role in this short-term increase in risk of disease. Several studies have highlighted that the genetic risk alleles described in the Western population (such as NOD2) appear to have more modest or no effects in Asian cohorts [8] where distinct polymorphisms (such as tumor necrosis factor receptor super family) may play a more important role [10]. In contrast, rising incidence may be due to growing prevalence of an industrialized external environment and changes in lifestyle, behavior, and westernization of diet altering the internal gut flora and microenvironment. While some environmental factors play similar roles in both the East and the West such as smoking [38, 39], other risk factors such as those related to environmental hygiene may play different roles. For example, while antibiotics have been reported as exposures that increase risk of IBD in several western cohorts [40, 41], it was associated with lower risk of both CD and UC in both the Asia-Pacific IBD registry [38] and the Middle-Eastern migrants to Australia [39]. Most markers of hygiene (rural dwelling, farm and animal contact) were associated with lower risk of IBD in Asian and Middle-Eastern populations but not Caucasians [39].

The Middle East offers an interesting window into the role of ethnicity of origin on the pathogenesis of IBD by comparing incidence and prevalence rates among the Jewish population residing in Israel to Arabs residing either in Israel or in surrounding countries where there has been an emergence of both CD and UC [42]. Several studies from Israel reported a much lower incidence of IBD in Arab residents compared to native-born Jews. In an elegant study by Odes et al., the prevalence of UC among Bedouin Arabs of South Israel was $9.8/10^5$ and $3.2/10^5$ for CD. In contrast, the corresponding rates in the Jewish population were significantly greater at $89/10^5$ for UC and $30/10^5$ for CD [43, 44]. The clinical characteristics of CD and UC in the emerging IBD population in the Middle East are similar to that noted in the Caucasian population. As noted elsewhere in Asia, there continues to be a striking increase in incidence over time in both pediatric and adult IBD patients suggesting that the burden due to IBD in these emerging populations is only likely to increase further [45].

Migration and Risk of IBD

Examination of changes in the risk of IBD with migration has proven to be a useful tool to determine the relative contribution of genetics and environment in the pathogenesis of CD and UC. Immigrants, while retaining the genetic architecture of their region of origin, over time adopt some or all of the customs, lifestyle, and behavior of their new country of residence. Thus, persistence of risk at the original level of the country of origin suggests a strong genetic component to the disease while gradual convergence with the disease risk in the country of residence suggests an important environmental component.

Some of the elegant work on the risk of IBD in this population has been from population-based studies among South-Asian immigrants to the UK. Probert et al. first examined the risk of UC in Indian migrants to Leicestershire during the period 1972–1989 and compared the rates to that in the local UK population [46]. Interestingly, despite South Asians traditionally being considered as a "low-risk" population for the development of IBD, the incidence of UC among Hindu and Sikh immigrants was similar to the native European control population [46]. The annual incidence in the South Asian population ranged from 10.8/10,000 compared to 5.3/10,000 in Europeans. In contrast, the standardized incidence of CD was lower in South Asians when compared to Europeans with estimates of 2.4/100,000 and 4.7/10,000, respectively [47]. In a subsequent follow-up study, Tsironi et al. demonstrated that the incidence of both UC and CD in Bangladeshi immigrants to East London had doubled from the rate in 1981–1989 by the year 2001. In contrast, other more common alternate diagnoses like abdominal tuberculosis had fallen by the same proportion [48].

Thus, migration from a low-incidence area to one of higher incidence is associated with an increase in risk of IBD, reaching that of the country of residence. However, this risk is not uniform and is based on the country of origin (and thus, genotype) as evidenced by two elegant studies from Sweden and Canada. Li et al. identified all cases of CD and UC developing in the first- and second-generation immigrants in Sweden using a national research database [49]. Compared to native-born Swedes, there was a lower risk of both CD and UC in all the first-generation immigrants. There was significant heterogeneity across countries with the greater decrease in risk seen for immigrants from Africa, Asia, and Latin America while modest or no reduction in risk noted in immigrants from Western or Central Europe or North America [49]. In contrast, the combined group of all the second-generation immigrants showed a similar standardized incidence ratio (SIR) of both CD (SIR 0.98, 95% CI 0.94–1.02) and UC (SIR 0.98, 95% CI 0.94–1.02) suggesting that any attenuation of risk in the first generation is lost by the second generation. However, this effect was not uniform with immigrants from some countries such as Iran or Iraq actually having an elevated risk compared to native-born Swedes while others from Latin America continued to have a lower risk of UC. A similar region-specific association was identified by Benchimol et al. who linked a population-based cohort of IBD from the Ontario province identified using validated administrative data to data from Immigration Canada [50]. The incidence of IBD in immigrants was 7.3 per 100,000 and significantly lower than the rate in nonimmigrants (23.9 per 100,000), while the effect on the first-generation population was uniform across immigrants from nearly all regions (with the strongest effects seen in those from East Asia and the Pacific and more modest effects in those from Western Europe and the Middle East). However, among Ontario-born children of immigrants, while the overall risk of CD was low, this reduction in risk was of the greatest magnitude among children born to immigrant mothers from East Asia and the Pacific. However, children born to mothers from South Asia, Africa, Western Europe, or the Middle East did not demonstrate this reduction in risk [50]. A later age of migration was associated with a lower risk of development of disease. Using a national population

database of over one million patients undergoing ileocolonic biopsies (arguably a skewed and a select population), Malhotra et al. demonstrated a higher prevalence of UC among Indians compared to other ethnic groups including Asians, Hispanics, Jewish population, and other controls, while a similar effect was not identified with CD [51].

Thus far, migration studies have mostly focused on emigration from countries of low incidence (usually Asia or the Middle East) to high-incidence countries (Western Europe, Scandinavia, and North America). While it has been well recognized by several initial landmark studies that migration from a "low-risk" country to a "high-risk" country is associated with an increase in risk of IBD, there is limited data examining the effect of migrating from a high-incidence country to a low-incidence region and if alteration of lifestyle and environmental factors to mimic that in regions of the world associated with low risk of IBD will ameliorate risk of disease in individuals at "normal" or "increased risk." Additionally, studies examining the specific environmental factors that mediate this alteration in risk are important as there appears to be a difference in role of factors such as environmental hygiene in Caucasian compared to non-Caucasian cohorts [39].

Studies have also compared the phenotype and natural history of IBD as it develops in this immigrant population. In the study by Probert et al., despite a similar incidence of UC, the natural history of the disease in South-Asian immigrants was characterized by a milder course and lower incidence of complications or need for surgery [46, 52]. Data from the United States mostly stem from studies comparing the phenotype and natural history of disease in Hispanic immigrants to US-born Hispanic and Caucasian controls. In one of the larger studies on this that included 325 patients, foreign-born Hispanics were diagnosed with IBD at an older age (45 years), than US-born Hispanics (25 years) and non-Hispanic Whites (27 years), and were more likely to have UC and less likely to have prescriptions for immunomodulators, biologics, or require surgery when compared to non-Hispanic Whites [53]. Thus, it appears that the first-generation immigrants from low- to high-risk areas are more likely to have UC, also consistent with the data from the UK and Canada where the incidence of UC in this population is up to twofold that of CD with a trend toward milder phenotype of disease measured by endpoints of surgery or medication prescription. To what extent the milder phenotype is driven by disease biology compared to differences in health-seeking behavior or acceptability of aggressive medical or surgical therapy remains to be clearly established.

Future Directions and Conclusions

Inflammatory bowel diseases are rising in incidence worldwide with emergence in populations previously considered as low risk. This likely reflects the influence of a changing external environment and offers a window onto the pathogenesis of CD and UC. As well, change in disease risk with migration offers a unique opportunity into examining the role of dynamic changes in behavior, lifestyle, and diet on the

risk of development of IBD. Thus, these emerging populations offer insights into disease pathogenesis that may be translated into therapy in all patients. There is an important need for study of changes in the natural history of disease in established and emerging populations, and, in particular, understanding the differences in treatment preferences as well as true evolution of disease.

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Chapter 2
IBD in the New World, Old World, and Your World

Stephanie Coward and Gilaad G. Kaplan

Abbreviations

CAD	Canadian dollar
CD	Crohn's disease
IBD	Inflammatory bowel disease
NSAID	Nonsteroidal antiinflammatory drugs
UC	Ulcerative colitis
USD	United States dollar

Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD) or ulcerative colitis (UC), was recorded in medical documents in the nineteenth century before coming to the forefront as an entrenched chronic disease in the 1900s [1–3]. Over the past century, the incidence and prevalence of IBD have significantly increased in the Western world, with the highest rates recorded in highly industrialized nations [4]. Toward the end of the twentieth century, the incidence of IBD began to rise in newly industrialized countries in Asia, South America, and the Middle East. Exploring these epidemiologic trends may provide clues to IBD's etiology.

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The pathogenesis of IBD remains elusive; however, our understanding suggests that IBD's cause and progression are driven by multifactorial interactions of genetic loci [5, 6], environmental factors [7], and the gut microbiome [8, 9]. Metaanalyses of genetic studies suggest that over 200 different genetic risk loci are associated with the development of IBD, with some specific to Crohn's disease or ulcerative colitis but many are shared [10, 11]. Most of these genes are responsible for the interplay between the gut's immune system and the microbiome. Nonetheless, genetic factors alone are not sufficient to explain the global increase in the incidence of IBD. Environmental determinants are key to understanding the global patterns of IBD incidence. Several environmental factors have been found to be associated with IBD such as smoking, hygiene, antibiotics, stress, and diet [7].

Historically, the incidence and prevalence of IBD have been the highest in the highly industrialized countries of the Western world, but now newly industrialized nations are reporting steadily increasing incidence and prevalence [12]. Historical trends that were initially apparent within the Western world have now been mimicked by newly industrialized countries [2, 13]. Comparing the highly industrialized countries to the newly industrialized countries may provide clues to the etiology of IBD. The differences currently seen within epidemiologic comparisons between the highly and newly industrialized countries may be explained through genetics and environmental factors [7].

IBD is most commonly diagnosed in young individuals between the ages of 18 and 35 years [14], although IBD can be diagnosed at any age [15]. IBD is a chronic and incurable disease that alternates between active and inactive periods. Due to low mortality, IBD exhibits compounding prevalence or an exponential increase in prevalence over time where new incident patients are added every year and few patients die [12]. The combination of high cost of disease treatment and compounding prevalence requires mitigation strategies or IBD will become unmanageable in countries throughout the world.

The high incidence and prevalence seen within the West have led to high annual costs to the healthcare system. In 2004, the estimated cost of IBD in the United States was nearly $6 billion United States Dollars (USD) in direct costs, while Canada's estimated cost in 2012 was $1.2 billion Canadian dollars (CAD) [16, 17]. Although the prevalence of IBD is low in newly industrialized countries, the combination of rising incidence and large base-populations will dramatically escalate the cost of managing IBD across the world. Accordingly, addressing the impending global burden of IBD must include mitigation in newly industrialized nations.

This chapter will introduce the historical epidemiology of IBD and then describe the current landscape of IBD. Further, in order to provide an overview of the impending burden, this chapter will align the past landscapes of IBD seen within highly industrialized countries with what is now happening in newly industrialized nations. The purpose of this chapter is to provide rationale for the need to mitigate the impending burden of IBD throughout the world.

IBD in Highly Industrialized Countries of the Western World

Historical and Current Perspective

While IBD is entrenched within Western society, it is a relatively new disease [1–3]. Dr. Samuel Wilks published the first case report in 1859 in England [18]. He described an autopsy of a woman who was thought by individuals in the medical community to have died of dysentery; however, Dr. Wilks reported on an inflammatory process seen within the terminal end of the ileum, extending throughout the large intestine [18]. He specifically noted that her autopsy was unique and bore no resemblance to previous bowel diseases that he was accustomed to [18]. Nearly 20 years later, in 1875, Dr. Wilks introduced the diagnosis of "ulcerative colitis" to the medical community [18, 19]. Following this raised awareness, more cases of ulcerative colitis were recognized in England, leading to the 1909 publication including over 300 patients with ulcerative colitis admitted to five hospitals throughout London.

In 1932, the term "regional ileitis," a preliminary term for Crohn's disease, was reported which led to the differentiation of IBD into two distinct diseases. Crohn et al. described a disease in patients that had similar clinical features to ulcerative colitis, yet involving the terminal ileum [20]. By the middle of the twentieth century, ulcerative colitis and Crohn's disease were established diseases of the West with consistent reporting of rising incidence.

Incidence and Prevalence

Numerous epidemiological studies were published on the incidence and prevalence of Crohn's disease and ulcerative colitis throughout the twentieth century [4]. The earliest studies, which led to rising reported incidence, may have been influenced by a diagnostic bias caused by increased awareness of IBD and advances in endoscopic modalities to diagnose IBD [12]. Some of the first studies on incidence and prevalence of IBD came from Europe and North America, with countries in more northern latitudes reporting the highest incidence.

Current Landscape

In 2002, 1.3 million people with IBD were estimated to live in North America. IBD has become an immense burden on the individual and on the healthcare system. While IBD can be diagnosed at any age, most individuals are diagnosed in the prime of their lives during adolescence and early adulthood [21]. Initially, IBD was thought of as a disease of Caucasian individuals; more recent studies have shown

that the disease can be diagnosed in virtually all ethnicities [4]. Immigration studies suggest that first-degree offspring of immigrants from regions with low prevalence of IBD to countries of high prevalence have similar risk of IBD as individuals who were born in and remained in Western countries [22].

Multidecade longitudinal epidemiologic studies in Cardiff (UK) and Olmsted County (United States) demonstrate consistently increasing incidence rates throughout the twentieth century and into the twenty-first century [4]. A recent global meta-analysis of incidence and prevalence of IBD found that, as of 2010, the highest incidence of UC was seen in Europe (24.3 per 100,000 person-years) and the highest incidence of CD was seen in North America (20.2 per 100,000 person-years). Many of the studies that reported longitudinal data suggest that the incidence of CD and UC was significantly increasing [4]. More recent epidemiologic studies from Canada highlight that the incidence of pediatric-onset IBD, particularly very early onset IBD (below the age of 6 years), is rising [23]. In contrast, adult-onset IBD is starting to stabilize and, in some regions, even declining [24, 25].

The highest prevalence for UC and CD is in Western countries of Europe, North America, and Australia [4]. In Canada alone it is estimated that over 233,000 individuals have IBD, equating to 0.67% of the population [16]. Over one million individuals are estimated to be living with IBD in the United States, with over $6 billion USD spent on direct healthcare costs [17, 26]. In Europe, approximately 2.5–3 million residents are estimated to live with IBD, with direct healthcare costs exceeding €4.5 billion annually.

Due to the high prevalence of IBD, healthcare systems have been faced with substantial burdens. Individuals with IBD utilize healthcare resources more frequently than their non-IBD counterparts. This includes hospitalizations, emergency department visits, doctor office visits, and endoscopic procedures [27]. Initially, the hospitalization rates for CD and UC were significantly increasing by 4.3% and 3.0%, respectively [28]. However, a metaanalysis of the cumulative risk of surgery has demonstrated that the risk of surgery for CD and UC has significantly decreased over the past generation [29]. The risks of surgery have been decreasing primarily due to the advent, and increased prescription, of antitumor necrosis factor (anti-TNF) therapies. Unfortunately, these agents come with a substantial tradeoff from high drug costs [30].

Environmental Risk Factors in the Western World

Several environmental risk factors have been shown to affect the diagnosis and prognosis of IBD [7, 9]. Environmental determinates that have been consistently demonstrated in Western countries include smoking, appendectomy, early-life exposures, diet, vitamin D, and medications such as nonsteroidal antiinflammatory drugs (NSAIDs) and antibiotics (Fig. 2.1).

Smoking is one of the most studied and consistently associated environmental factors. Smoking has a deleterious effect on the development and prognosis of CD,

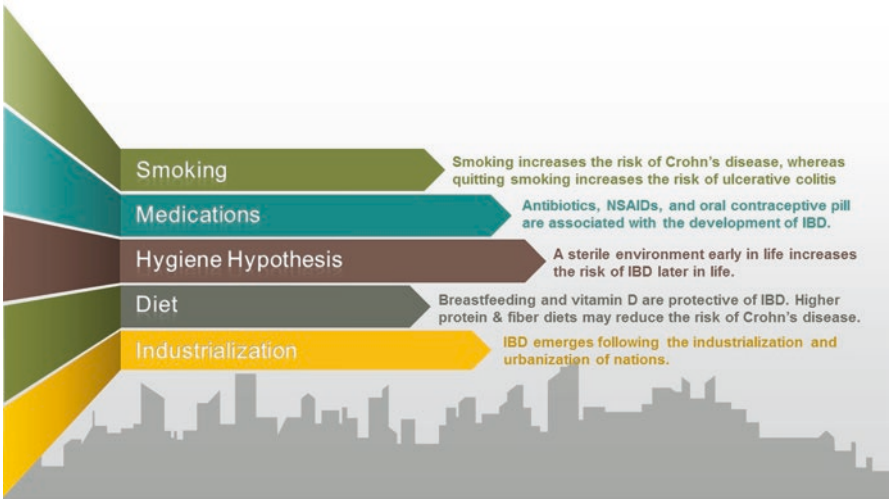

Fig. 2.1 Environmental factors associated with development of IBD in industrialized countries (Image provided by Presenter Media)

with current smokers at two times increased risk of disease development. Compared to never smokers, current smokers experience more flares after diagnosis and are more likely to require early surgery, and then experience postoperative relapse, while current smokers who quit after diagnosis experience rates of flares similar to never smokers [31–35]. Contrary to this is smoking's effect on UC whereby both never smokers and former smokers are more likely than current smokers to be diagnosed with UC. Further, former smokers are more likely to need an early colectomy as compared to never smokers [31]. The mechanism of smoking's effect on IBD is unclear, but recent studies suggest that smoking may modulate the intestinal microbiome [36].

Appendicitis, particularly in those under the age of 10, is protective in the diagnosis of UC [37]. Initially it appeared that appendectomy led to an increased risk of CD [38]. A population-based study and subsequent metaanalysis took a more in-depth look at this association, discovering that the association between appendectomy and the diagnosis of CD was dependent on time, where the highest risk of CD occurred within 6 months of the appendectomy, which was likely indicative of misclassification bias regarding the diagnosis of appendicitis [39, 40].

Medications have been correlated with IBD. Antibiotics during childhood are linked to an increased risk of pediatric-onset IBD; in particular, CD [41]. A dose-response relationship was noted with individuals who had more than one course of antibiotics also having increased odds of developing IBD [41]. Use of nonsteroidal antiinflammatory drugs led to increased risk of disease development and worsened disease activity [42, 43]. As well, a metaanalysis on the effect of oral contraceptives on IBD found an increased risk for both CD and UC [44].

Various aspects of diet have been associated with IBD. However, many dietary studies need to be interpreted cautiously because earlier studies were case-control studies subject to recall bias as well as diagnostic bias whereby change in dietary behavior was influenced by the symptoms of IBD. More recent prospective cohort studies have overcome limitations of these earlier studies by using validated food frequency questionnaires collected prior to the diagnosis of IBD. These cohort studies suggest that consumption of animal protein leads to increased risk of development of IBD and increased dietary fiber intake reduces the risk of CD [45, 46]. However, the cohorts were conducted in adults and which meant the majority of IBD patients were diagnosed in middle age. While these studies provide insight into the effect of diet on adult-onset IBD, few have evaluated diets in early life. This is a major gap in the literature as most scientists speculate that exposures early in life are likely to have the strongest effect on the development of IBD.

Breastfeeding is the most widely studied early-life exposure among patients with IBD. Metaanalysis studies have consistently demonstrated that breastfeeding has a protective effect on the development of IBD [47, 48]. The hygiene hypothesis postulates that IBD emerged in urban areas due to increased sanitation that reduced childhood exposure to enteric pathogens. Metaanalysis studies have demonstrated that CD occurs more commonly in urban areas than in rural areas [49, 50]. Additional evidence supporting the hygiene hypothesis includes a decreased risk of CD associated with living on a farm, drinking unpasteurized milk, early exposure to cats, lower birth order, and larger housing density due to larger families [51–53].

Several other environmental risk factors have been explored in IBD. Young individuals living in regions exposed to high concentrations of traffic-related pollutants (i.e., nitrogen dioxide) were at increased risk of developing CD [54]. A north-south gradient, whereby higher incidence of IBD was seen in northern countries as compared to southern countries, has been long reported. In part, the difference in incidence across geographic latitudes has been postulated to be secondary to differential sun exposure with lower levels of Vitamin D in the North.

Each of these environmental risk factors is prevalent within Western countries. As a country becomes industrialized, there is higher utilization of medications, a movement toward Western diets, and greater urbanization of the population.

IBD in Newly Industrialized Countries Outside the Western World

Historical and Current Perspective

As IBD grew in epidemic proportions in Western countries during the twentieth century, the prevalence of IBD in newly industrialized countries outside the West was extremely low. However, during the latter part of the twentieth century, numerous countries in Asia, South America, and the Middle East transitioned from

developing countries to newly industrialized countries. Through this economic and societal transition, UC appeared followed closely by CD. Although well-designed population-based studies are absent for many industrializing and newly industrialized countries, the epidemiologic studies that have been published reveal an escalation in the incidence of IBD. The evolution of IBD in newly industrialized countries appears to mimic the early days of Western countries [4]. Together, these studies paint a dim picture of the future where IBD is evolving from a rare disease of the Western world into a global phenomenon.

Incidence and Prevalence

Epidemiologic studies from newly industrialized countries are limited because surveillance healthcare tracking systems, which are the hallmark of many Western countries, are lacking. Moreover, differential access to healthcare, technology, and diagnostic modalities differs between countries as well as within countries by socioeconomic status. The disparity of healthcare is magnified when comparing rural areas to urban areas of newly industrialized countries. Additionally, misdiagnosis of IBD as an infectious disease may be a common occurrence until physicians in newly industrialized countries gain awareness of IBD as an emerging problem. Collectively, these factors translate to either sparse published data or early studies reporting very low incidence and prevalence. Fortunately, over the past generation, many of these challenges have been overcome in newly industrialized countries of Asia, South America, and the Middle East, painting a clearer picture of the rising incidence of IBD outside the Western world.

The emergence of IBD in Asia is now established. One-hundred years after Dr. Wilks published a case report of IBD in 1859, the first case of UC was reported in China [55, 56]. From this single case, the incidence of UC expanded rapidly in China. A systematic analysis of over 1500 studies published in the Chinese literature documented a steady rise in incidence, with over 10,000 cases of UC diagnosed in China by the year 2000 [56]. A follow-up study suggested that the number of cases of UC rose dramatically to over 260,000 by the year 2010 [57]. Similar to Western countries, the appearance and rise in incidence of CD lagged behind UC in Asia. Accordingly, over the past 30 years, the ratio of diagnosis of UC versus CD in Asia has dropped from 8:1 to nearly 1:1 [58]. The rapid rise in the incidence of IBD in Asia has been documented in several temporal trend analyses. The temporal trends seen within Asia in the last generation have outpaced all the data arising from Western countries during the same time period. For example, in South Korea the annual percentage changes in the incidence of IBD were 21% and 18% for CD and UC, respectively, from 1986 to 1997 [59, 60].

The most profound description of the epidemiology of IBD in Asia has been documented by the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) cohort study, which includes 21 medical centers from 8 countries in Asia (and Australia as a control Western country). Within the ACCESS cohort, a population-based

inception cohort of newly diagnosed patients with IBD from 2011 to 2012 was identified, reporting that the incidence of ulcerative colitis and Crohn's disease in Asia ranged from 0.24 to 2.05 and 0.05 to 1.25 per 100,000 persons, respectively [61]. The variability in incidence between regions and countries in Asia was explained by several factors including surveillance methodology, urban versus rural residence, economic advancement, and Westernization of diet and lifestyle. While incidence and prevalence in Asia are still not as high as what is observed in Western countries, the rising incidence rates in conjunction with large population sizes act as a prelude to Asia matching and, possibly exceeding, the burden of IBD seen in Western countries.

Epidemiologic studies arising from South America are not as a rich as those published in Asia. However, several studies have shed light on the emergence of IBD. From 1987 to 1993, clinicians from Panama recorded that the incidence of UC was 1.2 per 100,000 person-years, whereas no cases of CD were classified [62]. In contrast, a study from Brazil recorded a similar incidence of CD (2.5 per 100,000 person-years) and UC (2.4 per 100,000 person-years) from 1980 to 1999 [63]. Temporal trend analyses showed that the annual percentage changes in the incidence of CD and UC were 4.0% and 0.2% per year during this time period, respectively [63]. Victoria et al. subsequently determined that the estimated prevalence of CD and UC in 2009 were 15.0 and 76.1 per 100,000, respectively [64]. The data from South America is sparse; however, the increasing incidence over time and the current high prevalence are both indicative of a historical progression similar to that seen in Western countries.

The Middle East shows similar trends at the end of the twentieth century to those seen in South America, even approximating the incidence and prevalence reported in Western countries. The incidence for CD ranged from 1.1 to 4.2 per 100,000 person-years, with marginally higher rates observed for UC, ranging from 2.3 to 6.3 per 100,000 person-years [65–68]. The highest significant annual percentage changes recorded in the Middle East were 14.3% and 7.5% for CD and UC, respectively [4]. Similar to what was seen in the Western world in the 1960s, the prevalence estimates in the 1970s in the Middle East were 12.3 per 100,000 persons for CD and 37.4 per 100,000 persons for UC [69, 70]. In the latter part of the twentieth century, these estimates were similar to Western countries: 67.9 per 100,000 persons for CD and 168.3 per 100,000 persons for UC [71, 72]. While the CD estimates in the Middle East are approximately a third of the Western world, the UC estimates are now aligned [4]. This rapid rise in incidence of IBD in the Middle East implies that, in the next generation, prevalence estimates of newly industrialized countries may match those in highly industrialized countries.

South America, the Middle East, and Asia had relatively low prevalence during the twentieth century, but are now experiencing a rapid rise in incidence. While their prevalence estimates are still a fraction of those recorded in Western countries, prevalence of IBD in newly industrialized countries is steadily climbing. Moreover, the large population sizes of many newly industrialized countries (e.g., there are over two billion people in China and India) mean that even marginal elevation in prevalence translates to large absolute numbers of patients. Consequently, the challenges

faced by countries in the Western world will soon be faced by newly industrialized countries throughout the world. Thus, the implementation of strategies to mitigate the impending global burden of IBD is essential. The primary way to address the global rise of IBD is to understand the environmental factors that drive the development of IBD, using that information to develop preventative strategies.

Environmental Risk Factors in Contrast to the Western World

Nonindustrialized countries favor rural living and agriculture. Countries that sustain themselves through these means have a lower prevalence of IBD than their industrialized counterparts [4]. As countries become industrialized they undergo a transition from their prior culture to one that mirrors what is seen in highly industrialized countries. Individuals move from rural cites to urban centers where manufacturing is favored over agriculture. There are also changes to lifestyle behaviors prevalent within Western countries such as environmental factors associated with IBD: smoking, hygiene, medications, diet, and air pollution [12]. Specifically, people are more likely to take up smoking, environments become cleaner and therefore the microbes people are exposed to have changed, there is greater access to Western medicine [73], breastfeeding decreases, intake of dietary fiber decreases, and air pollution levels increase due to increased motor vehicle usage and increased development of industries [73].

IBD in Your World: Importance of the Global Rise of IBD

Burden of IBD Today

Within newly industrialized countries, it is estimated that over four million people have IBD with this estimate rising annually [4, 16, 74, 75]. A chronic disease imparts a substantial burden on both the individual and the healthcare system. As each year passes an increased number of people are diagnosed with IBD. Given the low mortality of the disease coupled with the young age of diagnosis, the number of individuals affected by IBD rises, causing the effect known as compound prevalence. This is a relatively new epidemiologic phenomenon seen with chronic diseases, but as IBD is commonly diagnosed earlier in life, compound prevalence of IBD impacts highly industrialized countries while, at the same time, is presently in its infancy in newly industrialized countries. Gradually, incidence and prevalence in the industrializing and newly industrializing countries are increasing, yet they are still much lower than what is seen in highly industrialized countries [4, 76]. So far, the newly industrialized countries have not yet experienced the substantial burden felt in the highly industrialized countries. However, given similar temporal trends, newly industrialized

countries need to capitalize on the lessons learned in the West. The result of increasing incidence and prevalence is an inevitable increase in the already substantial costs on the healthcare system. The question that arises is, what will that burden be? In order to prepare, it is necessary to predict what will happen.

Predicting the Future in Highly Industrialized Countries

Preliminary analysis of the temporal trends and predictive models suggests that within North America the prevalence of IBD may rise from 0.5% of the population in 2015 to 0.7% in 2025. In Canada the final percentage affected in 2025 is even higher at approximately 0.9% ([77]; Canadian Digestive Disease Week; Montreal, Canada). While the annual percentage change and overall prevalence is lower within the United States, the burden is higher due to the larger at-risk population. The financial burden on the healthcare system will be over ten times the cost in the United States than in Canada. If something is not done to mitigate this burden, each country's respective healthcare system may be overwhelmed (Fig. 2.2).

Within the Western world there are various factors that will impact the future incidence, prevalence, and costs of IBD. An aging IBD population in Western countries will complicate clinical practice due to managing comorbidities. These factors are indicative of an increasing burden that will be felt by Western countries.

As the burden increases, the healthcare system may be overwhelmed. While surgical rates for IBD are decreasing, the increasing prevalence of the disease, as a function of the increasing population and incidence, along with the increased utilization of biologics, the Western world will experience a significant rise in costs. The overall burden of the disease, the costs, and total affected population, will keep rising. By 2030 the current approach for dealing with IBD maybe unsustainable.

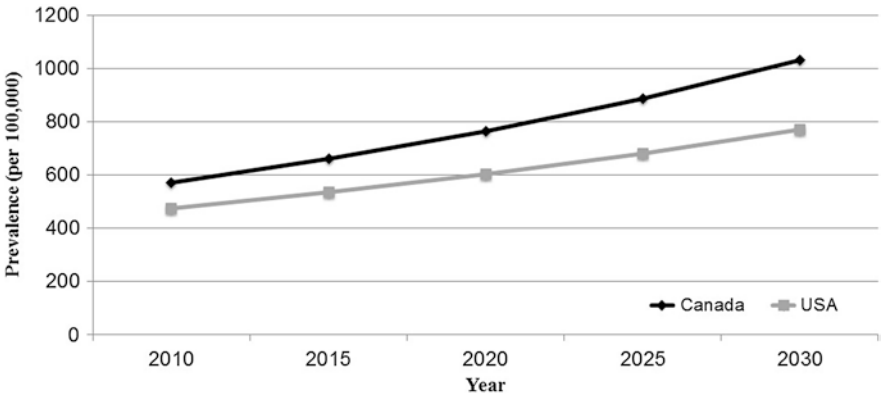

Fig. 2.2 Predictive trends showing the rise in prevalence of IBD in Canada and the United States from 2010 to 2030 (Adapted from Coward et al. [77]; Canadian Digestive Disease Week; Montreal, Canada. Images provided by Presenter Media)

Predicating the Future in Newly Industrialized Countries

With rapidly rising incidence rates seen in newly industrialized countries, these countries are at risk of matching the prevalence of Western nations overtime. Unfortunately, a Western-level prevalence may have a greater impact on some of these newly industrialized countries (e.g., China and India) than what is seen in Western countries due to high population size [78]. Given that newly industrialized countries will have higher absolute population numbers affected by IBD, the overall burden and costs could be higher. Moreover, disparity of care for IBD may exist within newly industrialized countries whereby patients with higher socioeconomic status may have greater access to management (e.g., biologics) than impoverished patients. In order for these newly industrialized countries to handle the impending burden, various methodologies need to be employed with restructuring of health-care delivery models to adapt to the rising burden of IBD.

Mitigating the Rising Burden of IBD

While there are developments regarding the etiology of IBD, we have not yet fully discovered it. The origins and mechanisms of IBD are aspects of the disease that we could use to address the impending burden. By looking closer at environmental factors that interact with genetic loci and gut microbiota, we can better understand the origins, then pathogenesis, of IBD. We can utilize this information to develop alternative strategies that involve manipulating our environment to prevent disease development and mitigate the rising global prevalence of IBD.

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Chapter 3
Do Genes Matter?

Mark Silverberg and Sarah O'Donnell

Chapter Highlights

- The relative risk to a sibling of a CD case developing CD is up to 35 times the population risk, highlighting the importance of genetics in the aetiopathogenesis of IBD.
- Genome-wide association studies have to date led to the identification of 206 IBD susceptibility loci. The pathways uncovered have provided a further understanding of aetiologic mechanisms in IBD and have led to the development of novel therapies.
- Genotype-phenotype associations have been less forthcoming; this may be due to the small effect size of individual polymorphisms, inadequately powered studies or the heterogeneity of CD cases.
- TPMT genotyping is currently the only example of genetic testing that has penetrated into clinical use. Advances in the pharmacogenetics of anti-TNF response have been made in recent years.
- A better understanding of gene-environmental interactions and their functional consequences may provide important insights.

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Do Genes Matter?

The aetiopathology of inflammatory bowel disease (IBD) remains unclear; however, it is hypothesised that exposure to environmental triggers in a genetically susceptible person leads to an aberrant immune response resulting in a chronic inflammatory process [1–3].

Population studies, and in particular twin studies, initially demonstrated a strong genetic component to the development of inflammatory bowel disease [4–7]. A Swedish group first showed a 58.3% concordance rate for Crohn's disease (CD) but only 6.3% for ulcerative colitis (UC) amongst monozygotic twins suggesting a genetic basis for CD and to a lesser extent UC [6]. A similar Danish study also found a 58.3% CD concordance rate for monozygotic twins but 0% for dizygotic twins, with concordance rates of 18.2% and 4.5%, respectively, for UC [4]. The relative risk to a sibling of an index case is estimated to be between 15 and 35 for CD [8]. The risk is greater in siblings than in other family members. The relative risk for UC in first-degree relatives is consistently lower than for CD. A recent Danish study found the risk of CD to be eightfold higher for those with a first-degree relative with CD whereas there was only a fourfold increase risk of UC for those with an effected first-degree relative [9].

Over the past 20 years there have been many advances in identifying the genetic components of IBD. In 1996, Hugot and colleagues performed the first genome-wide scan using linkage analysis [10]. They used a positional cloning strategy in two consecutive and independent panels of families, 78 families in total, with multiple-affected members and identified a putative CD-susceptibility locus on Chromosome 16. This became known as IBD1. Since then the NOD2/CARD15 gene has been identified within the IBD1 locus as a susceptibility gene in CD [11–13]. A follow-up study of Danish twins with inflammatory bowel disease showed a high NOD2/CARD15 mutation frequency amongst CD twins and their healthy siblings [14]. Multiple studies have now evaluated NOD2/CARD15 variant frequency in both sporadic and familial cases of CD and concluded that NOD2 mutations are significantly more common in both familial and sporadic cases of CD; however, these studies have also demonstrated variable penetrance [15–17]. This implies that the NOD2 variants are neither necessary nor sufficient for disease expression and that multiple other genetic and environmental factors are at play. Many subsequent studies using a similar approach identified several genomic regions also purported to contain IBD susceptibility genes.

Progress in genetic-testing technology allowed the evolution of studies to more densely map the genome through association studies containing many hundreds of thousands of markers known as single nucleotide polymorphisms (SNPs). Multiple studies with large patient numbers using genome-wide association studies (GWAS) followed to identify IBD susceptibility loci [18–23]. Despite the large numbers in each of these individual studies, it has been the resultant meta-analyses which have really aided in the identification of a larger number of IBD susceptibility loci [24, 25]. These works have culminated in the publication of a meta-analysis of GWAS

and the identification of 163 IBD susceptibility loci, 30 of which are classified as CD-specific and 23 as UC-specific [25]. Subsequent studies have increased this number to 206 known IBD susceptibility genes [26, 27]. Advancing the understanding of genetic determinants of IBD has been a recent multi-national immunochip study which suggested that there may in fact be three genetically distinct subphenotypes of IBD: ileal CD, colonic CD and ulcerative colitis [28].

There has clearly been success over the past 20 years in elucidating the genetic architecture of IBD, and gene variant identification has helped to consolidate pathways that are likely to be defective in sub-sets of IBD patients and thus may help to classify IBD patients through these categories. Examples include defects in the innate immune system, in the genes regulating autophagy and in the IL 23 signalling. Such discoveries have provided a further understanding of etiologic mechanisms in IBD and have led to the development of novel therapies. However, GWA studies have yet to account for the heritability estimates of IBD suggested in twin studies. This is known as missing heritability and it highlights some of the flaws of GWA studies in identifying causal genetic variants for diseases which are both phenotypically as well as genetically complex [29, 30]. Cohorts are heterogeneous and the SNP coverage in GWA studies can be incomplete. The variable role of environmental risk factors cannot be fully accounted for in studies. Large datasets have been combined in meta-analyses in order to adequately power studies to identify IBD susceptibility loci. Many of the alleles identified in these studies are relatively common, with MAF >5% (minor allele frequency) and with low effect sizes. Therefore, it is felt that IBD is multi-factorial requiring multiple genetic risk factors combined with environmental exposures. An increasing genetic burden of the aforementioned 163 IBD susceptibility genes has been associated with earlier onset of disease in CD [31]. One exception to this has been the identification of a number of monogenic disorders associated with very early onset IBD [32]. For example IL-10 receptor mutations result in a severe, early onset colitis, which has been successfully treated by bone marrow transplant [33, 34]. However, the differing phenotype and treatment of these monogenic disorders suggest they may be a different entity to more conventional IBD.

Prediction of Disease Severity and Patterns

Cosnes et al. reported in their pivotal paper that up to 70% of CD cases will develop a complicated phenotype during their disease course [35]. Others have reported rates of disease progression to stricturing or penetrating complications of up to 50% over the first 10–20 years [36–38]. Over half of the cases will need surgery during their disease course. Meta-analyses have demonstrated that the risk of intestinal resection after 10 years from diagnosis was 47% and the risk of a second resection was 35% within 10 years following the first operation [39, 40]. It remains a challenge for physicians diagnosing and managing patients with CD to identify patients at risk of rapidly progressive disease, those who may benefit from early use of

medical therapies that have the potential to reduce the frequency of disease-related complications. For example, studies have suggested that the early introduction of anti-TNF (tumour necrosis factor) therapies result in better response rates than when introduced later in the disease course [41–43]. These may offer the opportunity to alter the natural history of IBD and have been proven to reduce the need for hospitalisations and surgery [44–46]. Conversely a proportion of patients with CD follow a more benign disease course and therefore exposing this group to immunosuppressive therapies puts them at risk of over treatment and the risk of side effects may outweigh any potential benefits. Consequently, there is a clear need to develop markers of prognosis to most efficiently target therapy. Genetic markers are stable over time and therefore, could, represent a biomarker for disease progression, but do we have enough evidence for their use in clinical practice? The World Health Organisation has defined a biomarker as any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of an outcome or disease. When identifying biomarkers as surrogate endpoints, it is required that they show both relevance and validity [47]. Here we will examine whether we can use genes as a biomarker to predict disease severity and outcomes.

While progress has been made in the identification of CD-associated genetic variants, with numerous IBD susceptibility loci identified [25], efforts to elucidate the genetic basis for disease progression have been less fruitful. There has been some success in identifying genetic markers associated with disease location, but this phenotype tends to be relatively stable over time and therefore of less use clinically. Results of studies assessing genotype-phenotype associations have varied, with inconsistent associations of single nucleotide polymorphisms (SNPs) with stenosing or penetrating disease behaviour, as well as need for surgery [48–58]. Definitions of disease outcomes as well as cut-off for level of statistical significance of SNP associations have been heterogeneous. The investigation of genotype-phenotype associations has traditionally been through candidate SNP analyses, sometimes with small cohorts of patients. Therefore, the results of these studies have been incongruous. Candidate gene studies have reported, for example, associations between *TLR10* and inflammatory behaviour and requirement for bowel resection [59], *TNF-α-308* and fistulising behaviour as well as surgery [48] and the *IRGM* rs4958847 polymorphism with fistulising behaviour [49]. However, other studies examining targeted groups of SNPs have found no association with a need for surgery or disease behaviour [50–57, 60]. The association between *NOD2* and disease phenotype has been most consistent. *NOD2* polymorphisms have been shown to be associated with ileal location, complicated disease behaviour and need for surgery in multiple studies [58, 61–67]. However, the relationship between *NOD2* and complicated disease behaviour may be confounded by its relationship to ileal location [68].

In recent years, there have been a number of larger scale GWA studies. Dubinsky et al. examined the association between known and novel loci and the need for surgery within 5 years of diagnosis, as well as the time to surgery [69]. Surgery was defined as an intestinal resection for stricturing or penetrating CD. They reported four SNPs that were associated with time to abdominal surgery, utilising $p < 0.05$ as

a threshold for statistical significance, given that these SNPs had previously been identified as CD-susceptibility loci. One of these, an *IL12B* variant, was associated with both the need for surgery and the time to surgery. Prior to that, the Leuven group had examined the association between, the then, 50 known susceptibility loci and disease progression [70]. In multi-variate analysis, they found that homozygosity for the minor G-allele at rs1363670, also associated with the *IL12B* gene, was the only genetic risk factor for stricturing disease. While this same SNP was associated with the need for IBD-related surgery ($p = 0.03$), this result was not statistically significant once correction for baseline clinical risk factors was performed in a multi-variate analysis. None of the genetic factors in that study were associated with risk for surgery. As in many other studies, ileal location at diagnosis and the development of stricturing and penetrating disease behaviour were associated with the need for surgery and ileal disease with time to surgery [70–73].

Results of studies determining genotype-phenotype associations have varied, with inconsistent associations with stenosing or penetrating disease behaviour as well as need for surgery. Definitions of disease outcomes as well as the cut-off for level of statistical significance have been heterogeneous in previous studies. Given the large number of tests performed in a GWA studies, a strict cut-off for the threshold of significance is usually taken at 1×10^{-8} to exclude false positive results. Given this stringency, it is also true that positive associations may be missed. For example, *NOD2* polymorphisms have been shown to be associated with ileal location, complicated disease behaviour and need for surgery in multiple studies [58, 61, 63, 64, 74]. A European study utilising the immunochip as a genetic platform reported the carriage of any *NOD2* variant to be predictive of ileal location, stenosing and penetrating disease as well as a need for surgery [75]. However, NOD2 was not significantly associated with a need for surgery or stricture development in the Leuven study in multi-variate analysis; nor was it reported as significant in a large GWA study identifying genetic risk factors for a need for early surgery and time to surgery [69]. Meta-analyses have also shown *NOD2* mutations to be associated with complicated CD; however, the predictive power associated with these mutations is low [76, 77]. The relative risk of the presence of any *NOD2* variant allele for complicated disease was only 1.17 in a 2011 meta-analysis [77]. A recent international study including nearly 35,000 IBD cases from 49 centres dissected out the relationship between disease location and NOD2 and found that it was not associated with stricturing disease after accounting for ileal location [28]. This same study found little or no genetic association with disease behaviour after correcting for disease location and age at onset of disease. However, disease behaviour in that study was recorded in a cross-sectional manner as disease behaviour evolves over time and a genetic marker for rapid progression would be more clinically relevant. The authors hypothesise that given the lack of SNP associations with sub-phenotypes in their study compared to those found in similarly powered studies examining IBD susceptibility, environmental factors may be strong contributors to disease sub-phenotype.

To be clinically relevant, a genetic risk factor would need to be reliably associated with the development of a complication early in the disease process. To date,

studies have not consistently replicated any genetic risk factors for complicated disease that are associated with a high-risk ratio. Dubinsky et al. reported that a SNP associated with the *IL12B* gene was associated with a need for early surgery; the odds ratio for surgery within 5 years of diagnosis was 1.6 [(95% CI 1.3–2.0) $p = 1.5 \times 10^{-4}$] [69]. Likewise in the European IBDChip study, *JAK2* was associated with a need for bowel resection in a sub-group analysis excluding cases who had surgery within the first year after diagnosis with an odds ratio of 1.28 [(95% CI 1.02–1.62), $p = 3.75 \times 10^{-2}$] [75]. These modest odds ratios are insufficient to allow for the application of genetic markers in predicting clinical outcomes in individual patients. It is possible that any genetic contribution to a complicated disease phenotype is additive and may involve a complex interplay between multiple genes resulting from a cumulative burden of risk loci [31, 78]. A study examining the utility of a genetic risk score on predicting phenotype in CD and UC concluded that an increasing genetic burden is associated with early age of diagnosis in CD, but not UC. They felt a panel of IBD risk loci explained only a fraction of variance of disease phenotype, suggesting limited clinical utility of genetics in predicting natural history [31].

Approximately 10% of individuals with UC will have a colectomy for medically refractory disease over the first 10 years of their disease course [79–81]. Previous studies have identified age at diagnosis, extensive distribution and never or ex-smoking as risk factors [82–85]. Anti-TNF therapies may be effective in reducing colectomy rates in UC [86, 87], but it remains unclear if earlier identification of cases at risk of fulminant colitis can change the natural history. A number of studies have identified genetic loci implicated in the development of extensive and acute severe UC including the multi-drug resistance gene 1 (*MDR1*) and polymorphisms in the major histocompatability complex (MHC) [88–91]. A risk score based on 46 SNPs has been shown to help predict those at risk of colectomy for medically refractory UC but has yet to be validated in an independent cohort [85]. A recent study, aiming to identify markers predicting prognosis in UC, found no association between a number of genetic markers, using the immunochip as a platform, and a more severe disease course [82]. For now, clinical predictors such as bowel frequency, C-reactive protein (CRP), and albumin and steroid responsiveness remain the best predictors of colectomy in those presenting with acute severe UC.

Pharmacogenomics: Has the Time Finally Arrived?

Pharmacogenomics is the study of how genes affect a person's response to drugs. Pharmacogenetics is commonly employed in IBD clinics when placing patients on thiopurine therapy. Thiopurines (azathioprine/6-mercaptopurine) are commonly used in clinical practice for maintenance of remission in CD and UC. 6MP and its prodrug, azathioprine, demonstrate wide inter-individual variability in terms of response and up to 30% of patients are intolerant or experience adverse events. Neither 6MP nor azathioprine have biological activity and need to undergo

metabolism via a complex, multi-step enzymatic pathway to 6 thioguanine nucleotides (6TG) to exert their immune-suppressive activity. The thiopurine methyltransferase (TPMT) enzyme plays a central role in this metabolism, but its activity shows a wide inter-individual variability [92]. Testing for TPMT variation is frequently used to help identify patients at risk of bone marrow toxicity due to variation in enzyme activity [93]. Over 30 variants of TPMT have been identified, with 0.5% of Caucasians having low or deficient activity indicating a risk of bone marrow suppression with thiopurine therapy [93–95]. However, other genetic factors have been identified which influence drug metabolism and the risk of azathioprine-associated adverse events [96]. TPMT genotyping is currently the only example of genetic testing that has penetrated into clinical use. There are other examples with promising data but which have not as yet been implemented in the clinic. A *NUDT15* polymorphism has been associated with both early and late leucopenia after thiopurine therapy and has a greater effect than TPMT activity in some populations [97]. HLA-DQA1-HLA-DRB1 variants have been shown to confer susceptibility to pancreatitis secondary to thiopurine therapy [98]. Polymorphisms in genes affecting other enzymatic pathways of thiopurine metabolism such as aldehyde oxidase have also been shown to affect treatment outcomes [99].

Studies have looked at genetic predictors for response to other drugs such as anti-TNF therapies in IBD. Candidate gene studies examining the role of polymorphisms in tumour necrosis factor cell-surface receptor, IgG Fc receptor, as well as apoptosis-inducing ligand FasL genes have not shown consistent associations with response to infliximab (IFX) in IBD [100–107]. To date, associations with TNF receptor superfamily genetic variants have been the most robust [100, 102, 103]. However, a model incorporating clinical factors (age at first IFX, body mass index [BMI] and previous surgery) out-performed a combination of serological and IBD risk loci in predicting primary response to infliximab in CD [108].

While pharmacogenomics are becoming more mainstream in personalising therapies for many types of cancer, its role in IBD remains limited [109]. TPMT remains a good example of the use of pharmacogenetics to guide clinical care, predict response to thiopurine therapy as well as the risk of adverse events. Larger studies are required to examine if any of the pharmacogenetic variants described above may find a role in clinical management of IBD. At present genetic polymorphisms play no role in predicting a patient's response to biologic therapy in clinical practice but studies are ongoing in this area.

Genetic Testing in IBD: Can We, Should We?

While our understanding of IBD pathogenesis has been advanced in recent years through the success of identifying susceptibility genes and pathways for IBD, this success has not translated into widespread clinical utility. Despite this, there have been a number of panels that combine genetic markers with other biomarkers or have used other types of biomarkers such as transcriptomic tests (mRNA/miRNA)

that are either in commercial use or being tested for clinical use. Examples include an IBD diagnostic test and a CD prognostic panel which incorporate NOD2 polymorphisms and other IBD genetic markers with serological markers and inflammatory markers [110–112]. Many of the serologic markers within these tests have been shown to be predictive of prognosis in cross-sectional studies, with increasing numbers of positive antibodies being associated with an increased risk of stenosing and penetrating disease as well as a need for small bowel surgery [113–117]. The utility of adding genetic markers to the serum biomarkers is still somewhat unclear.

The future may lie in a better understanding of the interaction between genes and environmental factors and the resultant effects in gene expression and transcription. Environmental factors such as smoking, antibiotics and diet have all long been implicated in the aetiology of IBD through epidemiologic studies [118]. There is an expanding literature on epigenetics and the microbiome and their interactions with genes in IBD [119–121]. Alterations in gene expression can be made by changes in the structure and function of chromatin without making any alteration to the DNA sequence. The main mechanisms through which such changes are made include DNA methylation, histone modification and micro-RNA expression. These mechanisms are collectively termed epigenetics and they represent gene-environment interactions. The increasing incidence of IBD in the developing world cannot be explained by genetic shift [3] as well as the potential changing face of phenotypic expression of IBD over a relatively short timeline. This along with the impact of immigration on IBD rates demonstrates the importance of environmental factors [122]. Patterns in disease location and severity differ geographically; these differences likely reflect different genetic profiles as well as environmental exposures across the continents [123]. A recent study has shown that the majority of IBD risk loci are consistent across European and non-European cohorts, both in direction and magnitude [27]. However, there was significant heterogeneity in susceptibility odds ratios at several loci such as ATG16L1; this variance may be explained by gene-environment interactions, thus highlighting the importance of environmental exposures in IBD. Equally the importance of quantitative gene expression has come to the forefront in recent times. Expression quantitative trait loci (eQTL) affect levels of gene expression and therefore modulate phenotypic traits. A better understanding of eQTL may help to explain the lack of success to date with genotype-phenotype studies [119]. Our rapidly expanding understanding of the role of the microbiome in IBD and interaction between the genome and the microbiome may provide further answers and potentially more clinically useful biomarkers [124–129]. Specific gene expression and microbial profiles have been identified in the unaffected ilea of patients with colonic-only CD, which can differentiate this from UC [130, 131]. In this same inception, cohort researchers were able to demonstrate an association between baseline expression of *APOA1* and specific microbiota in predicting 6 month remission rates after controlling for clinical factors and exposure to anti-TNF therapy. Moving beyond simple genotyping and exploring gene expression profiles, the interaction with the microbiome is perhaps where we should be moving.

Summary

The success of GWA studies in identifying IBD susceptibility loci has increased our understanding of the pathways underlying the aetiology of IBD. This in turn has highlighted the important targets for novel therapies. To date there has been a failure to incorporate genetics into clinical practice; a better understanding of gene- environment and microbiome interactions may be the future.

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Chapter 4
State of the Art and Future Predictions: Isn't There a Test for That? Diagnosing IBD

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New, Good Stuff and Future Predictions

Inflammatory bowel disease (IBD) is an immune-mediated disorder of unclear etiology that requires a clinical suspicion to initiate further diagnostic workup. The utility of endoscopic, histologic, serological, and radiographic findings has been extensively explored in medical literature. Technical improvements in cross-sectional imaging, such as the advent of magnetic resonance enterography (MRE) and computed tomographic enterography (CTE), have allowed the replacement of older radiographic techniques such as barium-based examinations. Additional studies are required and are ongoing to assess and establish the diagnostic accuracy of diffusion-weighted imaging compared to contrast-enhanced studies. Positron emission tomography, along with magnetic resonance imaging and computed tomography, provides information on molecular and morphological events without the use of ionizing radiations and can be the future diagnostic tools. Small-intestine contrast ultrasound (US) that utilizes nonabsorbable contrast solution prior to the abdominal US may also find a place in the diagnostic paradigm of IBD in future.

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder that includes Crohn's disease (CD) and ulcerative colitis (UC). While often the presenting symptoms are highly suggestive of IBD (e.g., bloody diarrhea with UC), it can be a diagnostic challenge at times. The diagnosis is often established by utilizing a combination of clinical presentation, laboratory tests, imaging modalities, endoscopy, and

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histopathology. These diagnostic tests assist in establishing the diagnosis of IBD, possibly distinguishing CD from UC, assessing disease activity, and excluding other competing diseases in the differential diagnoses. This chapter reviews the diagnostic tests available for establishing the diagnosis of IBD.

Diagnostic Approach to IBD

Clinical suspicion of IBD is often triggered by the presenting symptoms of diarrhea with or without blood, abdominal pain, hematochezia, weight loss, perianal abscesses, fistulae, and fissures. Upper gastrointestinal (GI) involvement with CD can present with symptoms of nausea, vomiting, epigastric pain, or dyspepsia. Extraintestinal symptoms may include oral ulcers, arthralgias, skin rash or ulcers, red eye, or ocular pain. The diagnostic approach depends on a compendium of clinical, radiographic, endoscopic, and histologic findings. Most patients need all or most of these diagnostic modalities. However, the order of the evaluation methods depends on the severity, suspected location, and extent of the disease. Some additional testing may be required to rule out other diagnoses.

Stool Testing for Enteric Pathogens

Infectious etiologies of colitis can present with diarrhea, especially bloody diarrhea, that can mimic or exacerbate IBD. A history of recent travel, sick contact, or use of antibiotics is more of a risk factor for infectious colitis than for IBD. Stool studies, including culture for enteric pathogens, and tests for *Clostridium difficile* toxin or polymerase chain reaction (PCR) should be employed [1]. Infectious enterocolitis can mimic IBD and has also been implicated as a precipitating factor for IBD. A concomitant infection does not exclude the possibility of IBD and warrants treatment [2]. If colonoscopy is performed, chronicity on the histopathologic features suggests diagnosis of IBD rather than an infectious colitis.

Laboratory Testing

Laboratory studies are of supportive value in establishing the diagnosis of IBD. Laboratory tests may be used as surrogate markers for inflammation, to assess patients' nutritional status, and to evaluate for specific vitamin and mineral deficiencies.

Serum C-reactive protein (CRP) is a widely available and relatively noninvasive serum inflammatory marker in detecting IBD, but the diagnostic yield ranges between 50% and 60% for UC, between 70% and 100% for CD, and is affected by

the cutoff value used. Using more sensitive cutoff values may allow an increase in sensitivity to 100% [3, 4]. However, other causes of inflammation, such as infection, can elevate CRP levels.

Endoscopy

Colonoscopy, with or without esophagogastroduodenoscopy (EGD), is one of the first-line diagnostic modalities when IBD is suspected. A clinical suspicion is enough to trigger a referral for these procedures even if the tell-tale signs are not present. During colonoscopy, an effort should be made to intubate and examine the terminal ileum. In our opinion, random biopsies should be performed from the terminal ileum and from the colon even if endoscopically normal. The specimens should be submitted separately for histopathological assessment to document the location of microscopic abnormalities. An upper endoscopy with small-bowel and gastric biopsies can investigate any upper-GI symptoms such as nausea or epigastric pain or weight loss, and also assists in differentiating between UC and CD, especially when there is macroscopic evidence of inflammation in the gastroduodenum.

CD often shows segmental colitis due to its skipping nature and discontinuous lesions. Additional endoscopic features suggesting CD over UC include ileal inflammation, aphthous ulcers, serpiginous ulcers, cobblestoning, and rectal sparing [5–12]. Endoscopic features suggestive of UC include continuous circumferential inflammation proximal to the anal canal, granularity, loss of the normal vascular pattern, friability, spontaneous bleeding, pseudopolyps, superficial ulcerations, and often an abrupt transition between normal and diseased mucosa at the proximal extent of the colitis [11].

Colonoscopy, together with other diagnostic modalities, can differentiate CD from UC in approximately 90% of patients, and the index colonoscopy alone can accurately distinguishing CD from UC in 89% of cases [7, 13]. However, some endoscopic findings can confound the diagnosis. For example, backwash ileitis occurs in up to 25% of patients with extensive UC and is characterized by a mild mixed inflammatory infiltrate of the lamina propria without crypt distortion, atrophy, or epithelial changes [10, 11]. CD ileitis is favored when the ileal inflammation is extensive and/or patchy, when concomitant pancolitis is absent, when the degree of ileal inflammation is of greater severity than that of the cecum, or when there are discrete ulcers or stricturing of the terminal ileum [11]. The presence of a "cecal patch" or periappendiceal patch in the setting of UC with an otherwise normal right side of the colon does not necessarily establish the diagnosis of CD [14–16]. Occasionally, patients with treated UC will demonstrate rectal sparing (in the case of topical therapy) or patchy distribution of disease. The prevalence of these findings is likely overestimated by colonoscopy and endoscopic biopsy [5, 17]. Pseudopolyps are non-neoplastic inflammatory polyps that can be found in approximately 20% of UC patients [18]. Up to 54% of

patients with active small-bowel CD can have a normal ileoscopy. Therefore, reliance on ileoscopy alone to assess the small bowel in CD will sometimes lead to false negative results [19].

The presence of chronicity on biopsies is a hallmark indicator of IBD, although no single histological criterion can conclusively establish a diagnosis of IBD [9, 11, 12, 20–22]. Features suggestive of chronicity include architectural distortion, basal plasmacytosis, increased cellularity of the lamina propria, pyloric gland metaplasia, and Paneth cell metaplasia in the left side of the colon [23]. The diagnosis of CD is strongly supported by the presence of epithelioid granulomas; however, their presence is neither required nor pathognomonic for CD. The frequency of detecting granulomas on biopsies varies from 13.6% to 55.6% [24–26]. The presence of granulomas in the lamina propria, not associated with crypt injury, supports a diagnosis of CD [9].

Upper-GI involvement occurs in up to 16% of adult patients with CD and any part of mucosa proximal to the ligament of Treitz can be involved [27, 28]. Endoscopic findings include erythema, aphthous lesions, ulcerations, strictures, and fistula openings. It is important to note that chronic gastritis without aphthae can be seen in patients with UC; thus, microscopic involvement cannot be used to distinguish between UC and CD [11]. Histologic findings consistent with CD include mucosal edema, inflammatory infiltrate, erosions, ulcerations, villous distortion and attenuation, and granulomas [27].

Flexible sigmoidoscopy is rarely used as the first-line endoscopic tool to diagnose IBD, except when colonoscopy is considered high risk at the time of initial presentation, such as in fulminant colitis [29]. Push enteroscopy or device-assisted enteroscopy, such as single-balloon or double-balloon enteroscopy, is rarely used in the initial evaluation of patients with suspected CD because of the high diagnostic yields of other modalities such as wireless capsule endoscopy (WCE) and radiologic small-bowel imaging that are less invasive. The overall diagnostic yield of balloon-assisted enteroscopy ranges from 30% to 59% [30–32]. A systematic review of diagnostic double-balloon enteroscopy found a pooled detection rate of 63.4% (95% confidence interval, 42–82.3%) in patients with suspected CD [33].

Several endoscopic indices have been developed to assess the severity of the endoscopic lesions in IBD. They have been used more often in therapeutic trials rather than day-to-day clinical practice, but this is gradually changing, especially with the increasing availability of endoscopic reporting software that incorporates these indices. The Mayo endoscopic subscore is most commonly used for UC and ranges from 0 to 3, with higher scores corresponding with more severe disease [34]. Two indices developed for the assessment of the severity of endoscopic lesions in CD are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the simplified endoscopic activity score for Crohn's disease (SES-CD). These scores are used mostly in clinical drug trials in CD, in which mucosal healing has become one of the major endpoints [35, 36].

Imaging

Diagnostic imaging is primarily directed at assessing the small bowel. It has a vital role in distinguishing UC and CD, especially since most of the small bowel is endoscopically inaccessible on routine upper endoscopy or colonoscopy. Cross-sectional imaging determines the location, extent, and severity of the disease, as well as the presence of intestinal complications. Additional information about disease phenotype is also reported. Luminal inflammation presents as bowel-wall hyperenhancement, bowel-wall thickening, the "comb sign" (engorged vasa recta), and fibrostenotic strictures. Transmural findings such as fistulas and abscess can also be diagnosed on the imaging.

Traditionally utilized, upper-GI (UGI) series with small-bowel follow-through (SBFT) is only being used sparingly now. It exposes the patient to a moderate amount of radiation with provision of only limited information compared to computed tomography enterography (CTE) and magnetic resonance enterography (MRE). In a study of 17 patients with CD, the diagnostic yield was the lowest with SBFT at 24% compared with WCE at 71%, ileoscopy at 65%, and CTE at 53% [37]. In a study of 23 CD patients, the sensitivity and specificity of SBFT were 62% and 90%, compared with 78% and 83% for CTE, respectively. SBFT was less sensitive than CTE for the detection of abscesses and fistulas [38].

Magnetic resonance imaging (MRI) is increasingly being used for imaging of the small bowel and extraintestinal findings such as perianal fistula. The main advantage of MRI is the lack of radiation exposure related with CT and UGI/SBFT. MRE requires large-volume oral contrast, intravenous administration of a gadolinium-based contrast material, and patient's cooperation to hold the breath. However, limiting factors include cost, long procedure time, compromised resolution in the obese population, and patient's intolerability of a confined space. Glucagon used during the procedure may cause nausea/vomiting, and patients with respiratory issues might not be able to hold their breath. CT with oral contrast is highly advantageous for imaging luminal disease, transmural disease, and extraintestinal complications such as an abscess. Radiation concern with serial CTEs remains controversial, as there is little evidence that diagnostic medical imaging increases the risk of cancer. Low-dose CTE has been used and has shown sufficient sensitivity and specificity making it a better imaging option. Assuming a linear-no threshold cancer risk model, it is cost effective to perform serial CTE (vs. MRE) in patients over the age of 35–50 years. If the effective dose of radiation with CTE is less than 6 millisieverts (mSV), then serial CTE at all ages is more cost effective than MRE [29, 39, 40].

Several studies have compared the accuracy of CTE and MRE as diagnostic modalities for small-bowel CD. The two imaging techniques have similar sensitivities in diagnosing CD; however, CTE generates better quality images. CTE and MRE showed comparable accuracy in identifying active CD of the small bowel, with sensitivities of 89% and 83%, and specificities of 80% and 100%, respectively [41]. Prospective comparison has also shown similar results: CTE has a sensitivity and specificity of 95.2% and 88.9%, respectively, with interobserver agreement of

0.76. MRE has a sensitivity and specificity of 90.5% and 66.7%, respectively, with interobserver agreement of 0.63 [42].

Ultrasound (US) for the diagnosis of IBD is quite operator-dependent, and not routinely used in clinical practice in North America at this time, although it is more frequently being used in Europe. Its role in UC is less clear compared to CD. Small-bowel CD can sonographically be detected as bowel-wall thickening, stiffness, and alteration in the bowel-wall stratification. Color or Doppler imaging and contrast-enhanced US provide details about mural and extraintestinal vascularity, which reflect inflammatory disease activity [43]. The sensitivity and specificity are variable due to operator experience, but are reported to be between 75% to 88%, and 93% to 97%, respectively [44–46].

The utility of positron emission tomography/computed tomography (PET/CT) has been reported in several studies, while PET/MRI lacks published data for its role in the diagnosis of IBD [47–49]. PET can provide information on the dynamic inflammatory changes occurring in IBD, particularly CD, being a useful diagnostic tool.

IBD Serologies

IBD patients are known to have several autoantibodies. Tests are commercially available to detect these antibodies individually or as panels. Perinuclear antineutrophil cytoplasmic antibody (pANCA) may be elevated in patients with UC, and anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been reported to be elevated in CD patients. They have been suggested as means of diagnosing IBD and distinguishing CD from UC [50]. In a study of 582 adult patients with established diagnoses of IBD – 407 with CD, 147 with UC, and 28 with indeterminate colitis (IC) – the antibody tests alone or in combination had a sensitivity of 40–60%, and the specificity was greater than 90% for distinguishing patients with IBD from controls [51]. The specificity was slightly less for distinguishing UC from CD. Several other reports have reproduced similar results [52]. Due to lack of sensitivity and specificity, they are not recommended for routine screening for IBD and are not a part of the initial diagnostic evaluation. However, they may be helpful in the subtype of IC, even though more studies are needed. One of the largest prospective studies addressed this question by focusing on 97 adults who underwent antibody testing and then were followed clinically [53]. The combination of ASCA+/pANCA− predicted CD in 80% of patients with IC and ASCA−/pANCA+ predicted UC in 63.6%. Interestingly, 48.5% of patients did not show antibodies against ASCA or pANCA. This is further elaborated in Table 4.1.

Additional antibodies against OmpC, laminaribioside, chitobioside, mannan, and CBir1 flagellin have been discovered and their role in implicating disease course and severity has been proposed. However, accuracy and predictive value of serological tests in this setting need to be elucidated more [54, 55].

Table 4.1 IBD serological markers [50]

Antibody	Antigen	Non-IBD (%)	CD (%)	UC (%)
ASCA	*Saccharomyces cerevisiae* cell wall	5–10	29–69	5–15
DNase-sensitive pANCA	Unclear	<5–48	2–28	45–82
OmpC	*Escherichia coli* OMP	<5	24–55	5–28
I2	Pseudomonas protein	15	36–60	42
Cbir-1	Bacterial flagellin	8–15	50–57	6–16

Fecal Biomarkers

Fecal biomarkers are found to be useful for the diagnosis of IBD. Patients presenting with gastrointestinal symptoms may or may not have organic disease. Initial testing of fecal biomarkers helps risk-stratify patients who need further endoscopic evaluation.

Several fecal biomarkers have been evaluated for their clinical utility in diagnosing IBD. The two most commonly studied are fecal calprotectin and fecal lactoferrin that are significantly and consistently increased in IBD patients [56–65]. The fecal lactoferrin cutoff level most commonly used is 7.25 μg/g stool and has been shown to correlate with clinical symptoms and active endoscopic inflammation [63, 64, 66–68]. A fecal calprotectin value of 50 μg/g has commonly been reported as a cutoff value for distinguishing IBD from non-IBD patients with gastrointestinal symptoms [69]. With a fecal calprotectin cutoff of 50 μg/g, the diagnostic sensitivity and specificity for IBD are 0.78–1.00 and 0.44–1.00, respectively, with positive predictive value of 28–100% and negative predictive value of 67–100% [61–64, 70–79].

Inexpensive, noninvasive, and reproducible fecal biomarkers can be utilized in the diagnosis of CD [80]. In patients with gastrointestinal symptoms, fecal calprotectin is sensitive for the detection of colonic and small-bowel CD [58, 81]. In a prospective study, 83 patients that referred to a gastrointestinal clinic for evaluation of suspected CD underwent fecal calprotectin testing during diagnostic workup [82]. Diagnostic gold standards included ileocolonoscopy, WCE, or surgery for the presence and location of CD. Median fecal calprotectin concentrations of 890 and 830 μg/g were noted in patients with small-bowel and colonic CD, respectively. The diagnostic sensitivities of fecal calprotectin for small-bowel and colonic CD were 0.92 and 0.94, respectively [82]. Some studies have found a higher correlation between endoscopic activity of CD and fecal calprotectin in ileocolonic than in colonic or ileal disease [67, 83].

Wireless Capsule Endoscopy

WCE is a valuable adjunctive diagnostic tool that provides direct visualization of the small bowel and is being used increasingly for the diagnosis of small-bowel CD. Findings on WCE consistent with CD include erythema, villous atrophy, erosions, ulcerations, and strictures [30]. However, there is no agreement as to which findings are specific to CD. It is especially helpful in patients in whom the diagnosis is elusive [84]. Its use is contraindicated in patients with a suspected or established intestinal stricture, as capsule retention is a recognized problem in these patients and may require surgical removal [85]. In one study, up to 13% of patients with known CD who underwent a capsule study had capsule retention, even after an initial small-bowel study was performed [86]. A negative SBFT that does not reveal strictures does not necessarily rule out strictures. A patency capsule comes handy to assess the patency of the small bowel in subset of patients who are at high risk for having strictures. In patients at lower risk as asymptomatic small-bowel CD patients, evaluations with a CTE or MRE are acceptable alternatives to patency capsule.

The diagnostic yield of CE ranges from 26% to 71%, depending on the clinical setting [11, 30]. A more recent large meta-analysis reported overall detection rate by WCE of 55% [87]. Comparison of WCE with other diagnostic modalities for the diagnosis of CD has yielded contrasting results. In a blinded study of 35 patients with suspected CD, all patients underwent SBFT, and if there was no contraindication, they swallowed the capsule, followed by a routine CT scan. Diagnosis of CD was made in 77% by using a WCE versus 23% by SBFT and 20% by CT scan [88]. WCE detected all of the lesions diagnosed by SBFT and CT. WCE is superior to enteroclysis in estimating the presence and extent of small-bowel CD. In a prospective, blinded study of 31 patients with known CD, the diagnostic yield of WCE was superior to CT enteroclysis in terminal ileal disease (71% vs. 25.8%; $P < .001$) and in proximal small-bowel disease (46% vs. 13%; $P < .001$) [89]. A large, prospective, blinded study of 93 patients with newly diagnosed CD examined the performance of ileocolonoscopy, MRE, CTE, and WCE. WCE was superior over MRE and CTE for both sensitivity (100% vs. 81% vs. 76%, respectively) and specificity (91% vs. 86% vs. 85%, respectively) [90]. A meta-analysis of 12 studies found that WCE had an overall diagnostic yield of 50–70% for CD compared to 22% in small-bowel series, 48% with ileocolonoscopy, 8% with push enteroscopy, or 31% with CTE/CT enteroclysis [91]. In terms of diagnostic yield for disease location, WCE has a sensitivity of 100% for detecting terminal ileal CD, which is significantly higher than that for CTE (76%) and MRE (81%). All modalities had comparable specificities 91%, 85%, and 86%, respectively. Overall, the diagnostic yield of WCE for CD in any portion of the small bowel did not differ significantly (30% vs. 33% and 28%, respectively), although it did detect more cases of CD proximal to the ileum (18 vs. 6 and 2 cases, respectively) [90]. Few studies have directly compared WCE with MR enteroclysis for the evaluation of small-bowel CD. In patients with CD,

WCE detected significantly more inflammatory lesions in the first two segments of the small bowel compared with MR enteroclysis (12 patients vs. 1 patient, $p = 0.016$) [92]. Both modalities detected comparable numbers of inflammatory lesions in the terminal ileum.

However, other studies have shown no superiority of WCE over various radiographic modalities. One prospective, blinded trial of 41 patients with suspected or established CD demonstrated no significant difference between WCE and CTE or SBFT in detecting active disease (83% vs. 82% vs. 65%, respectively). Comparative specificity for WCE versus CTE or SBFT was significantly lower (53% vs. 89% vs. 94%; $P < .05$) [93]. A single-center study comparing diagnostic yields between double-balloon enteroscopy (DBE) and WCE demonstrated superior results with DBE; however, these results were not measured within the same cohorts [94]. Overall, most studies suggest superior sensitivity of WCE for detection of small-bowel CD compared with other radiologic studies; however, the specificity is variable.

One of the diagnostic limitations is the inability to obtain tissue specimen for confirmation of the diagnosis. Incidental findings can also create a diagnostic dilemma. For example, up to 13.8% of asymptomatic healthy individuals without nonsteroidal anti-inflammatory drugs exposure can have mucosal lesions which are not related to CD and can be detected on WCE [95]. The Lewis score and the Capsule Endoscopy Crohn's Disease Activity Index are two useful validated WCE severity scales that have been developed to limit interobserver variability; however, their utility in day-to-day clinical practice remains limited [96–99]. Patient tolerability is better for WCE compared to balloon enteroscopy by patients [94, 100]. WCE is not deemed cost-effective as a third-line test after a negative ileocolonoscopy, CTE, or SBFT [101].

Summary

- IBD patients present with multitude of symptoms such as diarrhea, which is frequently associated with blood, abdominal pain, urgency, hematochezia, or weight loss. A diagnostic workup is triggered by these clinical symptoms.
- The clinical presentation, laboratory parameters, endoscopic appearance, and radiology findings are interpreted in conjunction to establish the diagnosis.
- Endoscopic and histological features are usually not specific for UC or CD but are required to exclude other competing diagnoses, establish extent, location, and histological chronicity. Colonoscopy with intubation of the terminal ileum is used as the first-line diagnostic tool.
- Different imaging modalities are available to evaluate the small bowel in IBD.
- Several serologic markers for IBD are commercially available; however, the accuracy of these markers for the diagnosis of IBD remains limited.

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Chapter 5
Not Your Grandma's Colonoscope: Novel Endoscopic Approaches

Andrew Ross and Christopher Chapman

Introduction

The therapeutic armamentarium available to practitioners managing inflammatory bowel disease (IBD) has expanded significantly in the past two decades. This rapid and dramatic increase in novel therapeutic options has effectively exposed the limitations of prior clinical management strategies and is driving an evolution of endpoints in pursuit of altering the natural history of disease. As the focus of IBD therapy evolves into disease modification to improve outcomes via effective personalized treatment strategies, modalities to objectively assess for evidence of mucosal healing and colitis-associated dysplasia are becoming increasingly utilized. Advances in endoscope technology have mirrored this evolution in management endpoints and are increasingly being used and developed to aid in the management of patients with IBD.

The ability to achieve mucosal healing is the preliminary step to moving toward a state of deep remission, which has been defined as a resolution of not only symptoms, but also one or more objective measures of inflammation (endoscopy, biomarkers, and imaging). Improving objective measures of inflammation with resolution of symptoms is more likely to prevent the progression or initiation of dysplasia as well as structural damage that would otherwise lead to surgery and disability. An endpoint that emphasizes disease modification thereby preventing the progressive structural bowel damage and lowering the risk for colitis- associated

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complications, including cancer, hospitalization, and surgery, is currently the targeted endpoint in medical therapy for IBD. Fully embracing this evolution in IBD management has required the development of endoscopic technologies for objective diagnostic and therapeutic monitoring strategies.

This chapter will discuss recent advances in endoscopic technology that have the potential to aid in the management of IBD.

The Colonoscope

Standard ileocolonoscopy is the current gold standard for assessing mucosal healing response to therapy and completing surveillance for colitis-associated dysplasia in patients with IBD. Due in large part to advances in endoscope technology, it is now understood that most colonic dysplasia and colorectal cancers are visible in patients with ulcerative colitis (UC) [1, 2]. The ability to identify pathologic lesions within the gastrointestinal tract is dependent on the resolution and capability to magnify the endoscopic image. Recent enhancements to the standard issue colonoscope that have aided the assessment for mucosal healing include high-definition and magnification systems, contrast image enhancement modalities, over-the-scope caps/devices, and through-the-scope tools, including endoscope-based confocal laser endomicroscopy (CLE), optical coherence tomography (OCT), and new wide field-of-view colonoscopes such as the Fuse Full Spectrum Endoscopy system (Boston Scientific, Natick, MA, USA).

Resolution: Standard White-Light Versus High-Definition Versus Ultra-High-Definition

Standard-definition (SD) white-light systems generate images with 300,000–400,000 total pixels with a 4:3 (width-to-height) aspect ratio and resolutions of 640–700 (width/pixels) × 480–525 (height/vertical) pixels. Endoscopes providing SD images contain a charge-coupled device (CCD) chip that senses light and produces an image with a signal of 100,000–400,000 pixels. The advancements in CCD chip technology, including the complementary metal-oxide semiconductor (CMOS), have allowed for the development of smaller chips with a larger number of pixels and increased resolution.

In contrast to SD technology, high-definition (HD) endoscopes produce images with 850,000 to more than 1,000,000 total pixel counts. Three main features characterize HD video: lines of vertical display resolution, imaging scanning method (progressive or interlaced), and the number of frames per second (Hz). HD video typically has 720 or 1080 lines of resolution. The refresh rate of the lines, or the image scanning method, can be “progressive” or “interlaced” with progressive

scanning redrawing each line of the image and interlaced scanning alternating between every other line. Progressive scanning is generally accepted to provide higher resolution, smoother video with moving objects. The frame speed for HD video can vary between 24 and 60 frames per second. A HD endoscopy system requires a high-definition endoscope, but also HD processor, cabling, and monitor.

As of 2014, in the USA, there were three video colonoscope systems available with high-definition capabilities and proprietary image enhancement features. Olympus America (Center Valley, PA, USA) 190 series colonoscopes offer an HD format with 1280 × 1024 pixel frame, dual focus or "near focus" mode allowing increased resolving power to provide an ultra-sharp to 2 mm, and narrow band imaging (NBI) is a true light-based optical contrast-enhancement imaging modality. In contrast, the previous 160 series model colonoscopes featured a 640 × 480 pixel frame. Pentax Medical (Montvale, NJ, USA) Series i colonoscopes boast at 1920 × 1080 pixel frame (> 2,000,000 pixels). The Fujinon Inc. (Wayne, NJ, USA) EC 590 series colonoscopes have a 1280 × 1080i pixel frame.

In the future, the resolution of the endoscopic images is likely to continue to advance with emerging 4 K ultra-high-definition (UHD) technology. The Olympus Visera 4 K UHD system supports both 4 K UHD (3840 × 2160) and Full 4 K (4096 × 2160) resolutions as well as generates a wider color gamut, potentially allowing endoscopists to observe fine patterns and structures with higher precision. With transition from the operating room to the endoscopy suite, this technology has the potential to provide endoscopists with higher resolution images than conventional full 1080 HD imaging systems.

High Magnification: Optical Versus Digital

High-magnification endoscopes are defined by the capacity to enlarge a portion of the endoscopic image using optical or digital zoom and allow precise views of surface mucosa pit patterns and capillary networks [3–5]. Optical zoom utilizes the mechanical movement of a lens at the tip of the endoscope and maintains the resolution of the image without loss of quality. This is contrasted by digital magnification, in which the image is enlarged from 1.5× to 2× with pixel enlargement or loss of pixel density and ultimately, decreased resolution. Standard endoscopes have the capacity to enlarge an image ×30; however, high-magnification endoscopes can provide optical enlargement up to ×150 depending on monitor size [3, 6]. The most recent Olympus endoscopes have implemented a dual focus technology which utilizes a two-stage optical lens to allow rapid depth of field switching from a normal focus mode (5–100 mm) to near focus mode (within 2–6 mm). The Fujinon 600 and 700 series of gastroscopes and colonoscopes both offer stages of low, medium, and high optical magnification ranging from zooms of ×60, ×85, and ×135, respectively. Recently Pentax has released their MagniView gastroscopes (EG-2990Zi) and colonoscopes (EC-3890LZi/FZi/MZi) that provide HD ×136 optical zoom.

SD Versus HD and High Magnification in IBD

An increasing number of studies have examined these enhancements in the IBD population. While dysplastic lesions have been reported to be frequently visible, the lesions are acknowledged to be subtle, multifocal, and flat, thus advances to standard white-light endoscopy are needed to accurately identify precancerous or cancerous lesions and, if amenable to resection, their borders. In 2013, a retrospective cohort study of patients with long-standing colonic IBD comparing SD white-light colonoscopy to HD colonoscopy reported a higher dysplasia detection rate with HD. HD colonoscopy significantly improved detection of dysplastic lesions relative to SD endoscopy with an adjusted prevalence ratio of 2.2 (95% confidence interval [CI], 1.1–4.5). HD colonoscopy also increased the yield of targeted biopsies, with HD colonoscopy being three times more likely to pick up a dysplastic lesion than SD colonoscopy when targeted biopsies were obtained. This enhanced detection was especially notable in the right colon, which frequently has flat or sessile lesions [7]. As a result of these and other studies, the use of high definition over standard definition for surveillance colonoscopy in patients with IBD was one of the key recommendations by the SCENIC International Consensus Statement on Surveillance and Management of Dysplasia in Inflammatory Bowel Disease (SCENIC) [8].

Several studies evaluating high-magnification colonoscopy, frequently in combination with methylene blue chromoendoscopy, have reported to correlate positively with histologic disease activity and predicted relapse in quiescent UC [9–12].

Endoscope-Based Contrast Image Enhancement Modalities: NBI, I-Scan, FICE

Endoscope-based optical contrast image enhancement technologies, or real-time electronic chromoendoscopy techniques, are endoscope advances that enhance the visualization of surface mucosal structures and vasculature. Currently available contrast image enhancement technologies are physical filter based, e.g., narrow band imaging (NBI, Olympus), or software/digital based, e.g., *i*-scan (Pentax) and Fuji Intelligent Chromo Endoscopy (FICE, Fujinon) [13, 14]. NBI utilizes two physical filters to limit light centered to the specific wavelengths of 415 nm (blue) and 540 nm (green). This shorter wavelength light penetrates the tissue less deeply and corresponds to the secondary hemoglobin absorption peaks, and as a result, there is improved contrast between the vasculature (capillaries and submucosal vessels appearing darker) and the superficial mucosa. In contrast, *i*-scan is a software-based technology that utilizes three post-processing algorithms on white-light images: Surface Enhancement (SE), Contrast Enhancement (CE), and Tone Enhancement (TE). SE can help visualize the edges of anatomical structures; CE can help visualize depressed areas through colored presentation of low-density

areas; and TE can help tailor enhancement by modifying the colorization of each pixel. Similarly, FICE is a digital image post-processing system that uses standard white-light endoscopic images and arithmetically processes, estimates, and produces an image of a given, dedicated wavelength of light. Three single-wavelength images are randomly selected and assigned to the red, green, and blue channels to create virtual composite chromoendoscopy image.

NBI is the most well-studied virtual chromoendoscopy technology with two randomized controlled trials evaluating NBI in patients with UC undergoing surveillance colonoscopy for neoplasia detection [15, 16]. In 2011, Van den Broek et al. completed a randomized crossover trial in which 48 patients with UC underwent both NBI and HD colonoscopy in random order at least 3 weeks apart by separate endoscopists. They found that NBI did not improve the detection of neoplasia in patients with ulcerative colitis compared to HD colonoscopy [16]. Ignjatovic et al. subsequently followed in 2012 with a randomized, parallel-group trial of 112 patients with long-standing UC comparing colonic extubation with NBI versus HD colonoscopy. Similar to the other group, there was no difference with five patients having at least one dysplastic lesion in each group (odds ratio [OR] 1.00, 95% confidence interval (95% CI) 0.27–3.67, p = 1.00) [16]. Four prospective studies, including three randomized trial studies comparing NBI versus dye-based chromoendoscopy (CE), found a greater number of patients with dysplasia (range 0.1–22%) using dye-based CE than NBI, but with no statistical significance. This data led SCENIC to recommend that when performing surveillance with HD colonoscopy or dye-based CE, NBI is not suggested to be used in place of white-light colonoscopy or dye-based CE (conditional recommendation, moderate-quality evidence) [8].

In addition to detecting IBD-associated neoplasia, NBI has also been used to assess disease activity in UC. In 30 patients with either inactive or mildly active UC (26 vs. 4 according to clinical activity index), Kudo et al. evaluated the mucosal vascular pattern (MVP) using NBI compared to conventional colonoscopy [17]. They found that NBI correlated well with histological findings with marked acute inflammatory cell infiltration (26% vs. 0%, p = 0.0001) and goblet cell depletion (32% vs. 5%, p = 0.0006) the most frequently observed in the segments with obscure MVP as compared to clear MVP. They concluded that NBI colonoscopy may be of value in determining the grade of inflammation in quiescent UC; however, they questioned the clinical utility given the strong correlation between histology and clinical course.

In addition to NBI, *i*-scan has been compared to HD colonoscopy in assessing severity and extent in patients with mild or inactive IBD. Neumann et al. completed a prospective randomized controlled trial in 78 patients with IBD (HD, n = 39; *i*-scan, n = 39) comparing HD versus *i*-scan in determining severity of inflammation on withdrawal [18]. Their group found a statistically significant increase in agreement between *i*-scan and histology as compared to HD and histology (92.31% (36/39) vs. 48.71% (19/39), p = 0.0009). In 2015, an abstract published the preliminary findings of a prospective, randomized, single-operator, parallel study that compared FICE with standard definition white-light endoscopy (SD-WLE) for the surveillance of 91 patients with long-standing UC (FICE, n = 41 or SD-WLE,

$n = 50$) [19]. The sensitivity of FICE was higher than SD-WLE, both overall and after exclusion of random biopsies (95% vs. 63% in both cases; $p = 0.0000$), and the specificity was significantly higher using targeted biopsies of flat visible and raised suspicious lesions. The only other study of FICE in IBD was in three patients with small-bowel Crohn's disease when assessed during double-balloon enteroscopy, and it was reported to have only limited benefit [20].

Wide-Field Colonoscopy

Fuse

The Fuse® Full Spectrum Endoscopy® system (Boston Scientific, Natick, MA, USA) provides an increased panoramic 330° field of view compared to most standard forward-viewing colonoscopes that provide a relatively more narrowed 170° field of view. The advantage from the widened field of view is the ability to see in difficult places including flexures, behind haustral folds, and altered anatomic locations. The Fuse colonoscopes are available in a traditional size as well as a slim version. The slim version has an 11.5 mm insertion tube outer diameter and 11.7 mm distal tip outer diameter, but maintains a 330° field of view and a larger 3.8 mm working channel, typically reserved for traditional, 12.8 mm colonoscopes. The Fuse system portfolio also includes a FuseBox® HD Processor with Lumos™ Adaptive Matrix Imaging™ which was recently FDA cleared in 2016. The Lumos Adaptive Matrix Imaging is a white-light smart enhancement that can be continuously activated to detect structures that need to be seen in their natural colors and to visualize anatomical details. The technology can aid in viewing mucosal vascularity and texture by toggling between two settings. The first setting is designed to selectively enhance tissue and may remain on throughout the procedure, while the second setting allows for a more in-depth inspection once suspect tissue has been identified. This technology is unique in that it only enhances anatomy with variable textures, vascularity, or other anatomy allowing focus on diseased tissue.

Previous studies in tandem colonoscopy patients have demonstrated that standard forward-viewing endoscopes can have an adenoma miss rate ranging from 20% to 25% [21]. In 2014, a multicentered, international, randomized trial of patients undergoing screening colonoscopy, the adenoma miss rate was significantly lower in patients in the Fuse first-group than in those in the standard forward-viewing colonoscope first-group with a 7% miss rate versus 41% miss rate, respectively [22].

In 2015, the preliminary findings of a prospective, randomized, crossover tandem surveillance colonoscopy trial in patients with IBD comparing standard forward-viewing colonoscopes versus the Fuse colonoscope were reported. In this trial, 24 patients with colonic IBD (CD colitis $n = 16$, UC $n = 8$) with a mean disease duration of 13.5 years received same-day, back-to-back, tandem forward-viewing colonoscopy and FUSE colonoscopy. There was no significant difference in mean

cecal intubation times for FUSE and standard colonoscopes and all patients had successful ileal intubation. The mean lesion detection with FUSE versus FVC was 1.62 versus 0.45 ($p < 0.05$), while the mean dysplasia detection was 0.30 versus 0.09, respectively ($p = 0.21$). FUSE had a lesion miss rate of 31% compared to an unexpectedly high miss rate of 78% with standard FVCs and a dysplasia miss rate of 0% versus 66.7%, respectively. These data, although preliminary and need to be validated in a larger cohort, suggest FUSE may increase dysplasia detection in IBD surveillance.

Through-the-Scope Tools

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is a real-time, optical endoscopic imaging technique that uses a 488 nm laser beam through a focusing lens to provide in vivo 1000× magnified images at depths up to 250 μm.

Due to low background mucosal autofluorescence, a topical (i.e., cresyl violet, acriflavin hydrochloride) or intravenous fluorescent agent (i.e., fluorescein sodium) is required, and when used, it has been reported to be similar to histopathology [23]. Upon excitation of the fluorescent agent, photons are emitted in all directions; however, with CLE, the reflection of the light from a single plane is refocused through a pinhole aperture detection system. The remaining reflected light at other depths are scattered at different angles preventing detection, thereby providing a monochromatic image with a focus at a single tissue depth. CLE was first introduced in 2003, and there are currently two FDA-approved systems available for commercial use. The two systems include a through-the-scope probe system (Cellvizio, Mauna Kea Technologies, Cambridge, MA, USA) and an scope-integrated CLE dedicated high-definition upper endoscope and colonoscope (Pentax Medical, Tokyo, Japan).

CLE has shown significant promise in the management of IBD, including assessment of disease activity, dysplasia, and, most recently, predicting response to therapy. CLE has the potential to predict histologically active IBD in real time and to identify inflammation microscopically in the setting of otherwise endoscopically normal-appearing tissue [24, 25]. Recent reports suggest that CLE can predict histology with a sensitivity of 94%, specificity of 81%, positive predictive value of 82%, and negative predictive value of 94% [26]. In assessing activity of disease, CLE was first demonstrated to be able to detect the loss of intestinal barrier function at sites of cell shedding. A simple, dichotomous grading system predicted IBD relapse over a 12-month period [27]. Studied features of intestinal mucosal barrier dysfunction include (Fig. 5.1a–d) fluorescein leak, which is a fluorescein plume entering the lumen from between two enterocytes, representing loss of apposition between two cells; cell-junction enhancement, which is a buildup of fluorescein between two epithelial cells, representing impaired tight-junction proteins before breakage of the final basal tight junction releasing the fluorescein into

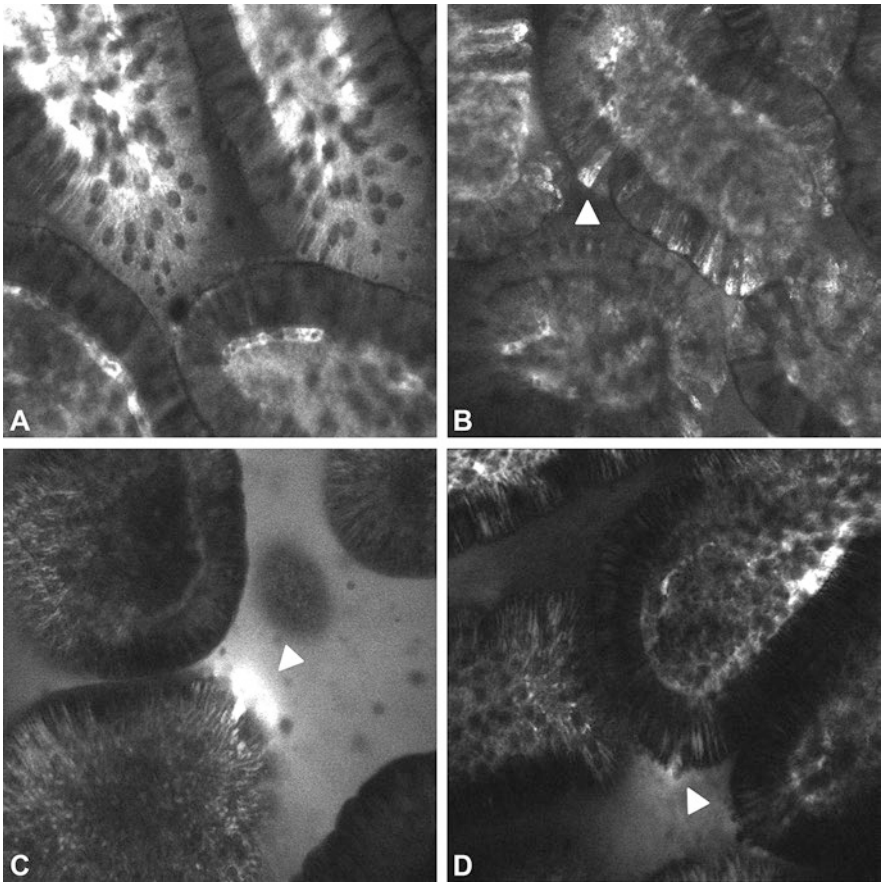

Fig. 5.1 Endoscopic confocal laser endomicroscopic features of increased intestinal permeability. Control (**a**), cell-junction enhancement (**b**), fluorescein leak (**c**), cell dropout (**d**) (Reprinted from Gastrointestinal Endoscopy, 83(4), Chang J, Ip M, Yang M. et al., *The learning curve, interobserver, and intraobserver agreement of endoscopic confocal laser endomicroscopy in the assessment of mucosal barrier defects*, pp. 785–791, 2016, with permission from Elsevier)

the lumen from between two enterocytes; and cell dropout, which is shedding of an apoptotic enterocyte into the luminal space. These findings are functional features, which do not have histopathologic equivalents. The presence of these findings was also demonstrated to potentially guide therapy, as Leong et al. reported that medical therapy escalation resulted in reversal of the findings of leaky gut in three patients with IBD [25].

In 2014, Lim et al. scored CLE images of the duodenum in 35 patients (15 CD, 10 UC, and 10 controls) for the number of epithelial gaps, cell shedding, and the degree of fluorescein leakage into the intestinal lumen [24]. In all cases, macroscopic endoscopic appearances of the duodenum were normal, and conventional histological analysis showed a mild nonspecific duodenitis in 7 of 15 patients with

CD while patients with UC had a histologically normal duodenum. However, in both UC and CD groups there were significantly more epithelial gaps, epithelial cell shedding, and leakage of fluorescein into the duodenal lumen than in controls, suggesting disease activity otherwise not apparent on conventional endoscopy or histology.

CLE may aid in the diagnosis of IBD-associated dysplasia by increasing the yield of biopsy and reducing the need for random biopsy examinations. This was demonstrated in a randomized trial of 161 patients with long-standing UC in which combined chromoscopy with CLE detected 4.75-fold more neoplasia than conventional colonoscopy with 50% few biopsy specimens ($p = 0.008$) [28]. In this study, the presence of neoplasia could be predicted by endomicroscopy with high accuracy (sensitivity 95%, specificity 98%, and accuracy 98%).

While conventional CLE utilizes intravenous fluorescein, a recent report demonstrated the use of fluorescent antibodies to membrane-bound TNF (mTNF) as a predictive marker of response to anti-TNF biologic therapy. Atreya et al. administered topical antibody to 25 patients with CD, which led to detection of intestinal $mTNF^+$ immune cells during CLE [29]. Patients with high numbers of $mTNF^+$ cells showed significantly higher short-term response rates (92%) at week 12 upon subsequent anti-TNF therapy as compared to patients with low amounts of $mTNF^+$ cells (15%). This clinical response in the former patients was sustained over a follow-up period of 1 year and was associated with mucosal healing observed in follow-up endoscopy suggesting that molecular imaging with fluorescent antibodies has the potential to predict therapeutic responses to biological treatment and can be used for personalized medicine in CD.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a noninvasive technology that provides real-time, cross-sectional imaging of tissue using infrared light waves (750–1300 nm). The long wavelength of infrared light has decreased absorption and allows for detection of backscattered or reflected light off of structural tissues. OCT has been used to image biologic tissues since the 1980s; however, its clinical utility has predominantly arisen in ophthalmology, cardiology, and dermatology. Although OCT has had increased use in the gastrointestinal tract, including Barrett's esophagus and IBD, the currently only commercially available OCT system is the Nvision VLE Imaging System (Nine Point Medical, Bedford, MA, USA), which is designed specifically for the esophagus using a through-the-scope balloon. Research use, however, has expanded into IBD and, in particular, colonic disease using through-the-scope probes to image the gut wall at a depth of 2.5–3.5 mm with a 10-μ spatial resolution.

Probe-based through-the-scope OCT has been evaluated in the small bowel and colon with normal colon revealing the presence of a regular, uniform crypt pattern in the epithelium with increased optical transmission through the crypt lumens [30]. Preliminary OCT studies in UC documented large subsurface voids, ulcerations,

and loss of crypt pattern, suggesting this modality could allow for optical biopsies akin to histology. Familiari et al. assessed this theory by comparing OCT images to histology in 27 patients with UC. Three OCT patterns were identified in patients with UC: mucosal backscattering alteration, delimited dark areas, and layered colonic wall. In the colon of affected segments of active and UC in remission, these patterns showed a good correspondence with the histology. The assessed sensitivity and specificity of OCT in normal segments of patients with UC was 100% and 69%, respectively [31].

OCT, taking advantage of the modality's ability to image the muscularis mucosa, submucosa, and muscularis propria, has also been used to assess for transmural inflammation and differentiating UC from CD [32, 33]. In an ex vivo study, colectomy specimens from patients with a preoperative diagnosis of CD (n, 24) or UC (n, 24) were studied with a through-the-scope OCT probe [32]. A disrupted layered structure on OCT, a characteristic feature of transmural disease, was identified in 96% of patients with CD and in eight patients who had a pre-operative diagnosis of UC but a diagnosis change to CD after histologic evaluation of the colectomy specimens. Of the 16 patients with UC, all had superficial inflammation, while 13 (81%) had an intact layered structure on OCT. Thus, the sensitivity and specificity for OCT to detect transmural disease were 86% and 91%, respectively. This study was subsequently validated in vivo by the same group in 40 patients with CD and 30 patients with UC (Fig. 5.2a–c) [33]. Using the clinical diagnosis of CD or UC as the gold standard, the disrupted layered structure on OCT indicative of transmural inflammation had a diagnostic sensitivity and specificity of 90.0% (95% CI: 78.0–96.5%) and 83.3% (95% CI: 67.3–93.3%) for CD, respectively.

While safe, feasible, and reliable in preliminary investigations, the main limitation of OCT imaging is the increased procedure times, including real-time image interpretation versus delayed/post-procedure image interpretation and image interpretation learning curve. Further studies are needed to evaluate the efficacy of OCT in IBD, and OCT probes for the colon are not currently commercially available.

Over-the-Scope Attachments

Advancements in endoscopic technology have not been limited to the endoscope and the endoscopy systems/software themselves, as emerging technologies have now included distal attachment devices for increased colonic mucosal field of view, such as Endocuff (Arc Medical Design Limited, Leeds, England) and transparent caps in addition to the Third Eye (Avantis Medical Systems, San Jose, CA, USA) panoramic device, or devices designed for large defect, perforation, and fistula repair including over-the-scope clips (OTSC®) such as OVESCO (Ovesco Endoscopy USA, Cary, NC, USA) or endoscopic suturing devices such as the Overstitch™ endoscopic suturing system (Apollo Endosurgery, Austin, TX, USA). Despite the excitement with these new over-the-scope devices, there have been no prospective studies evaluating the safety or efficacy of use in the IBD population.

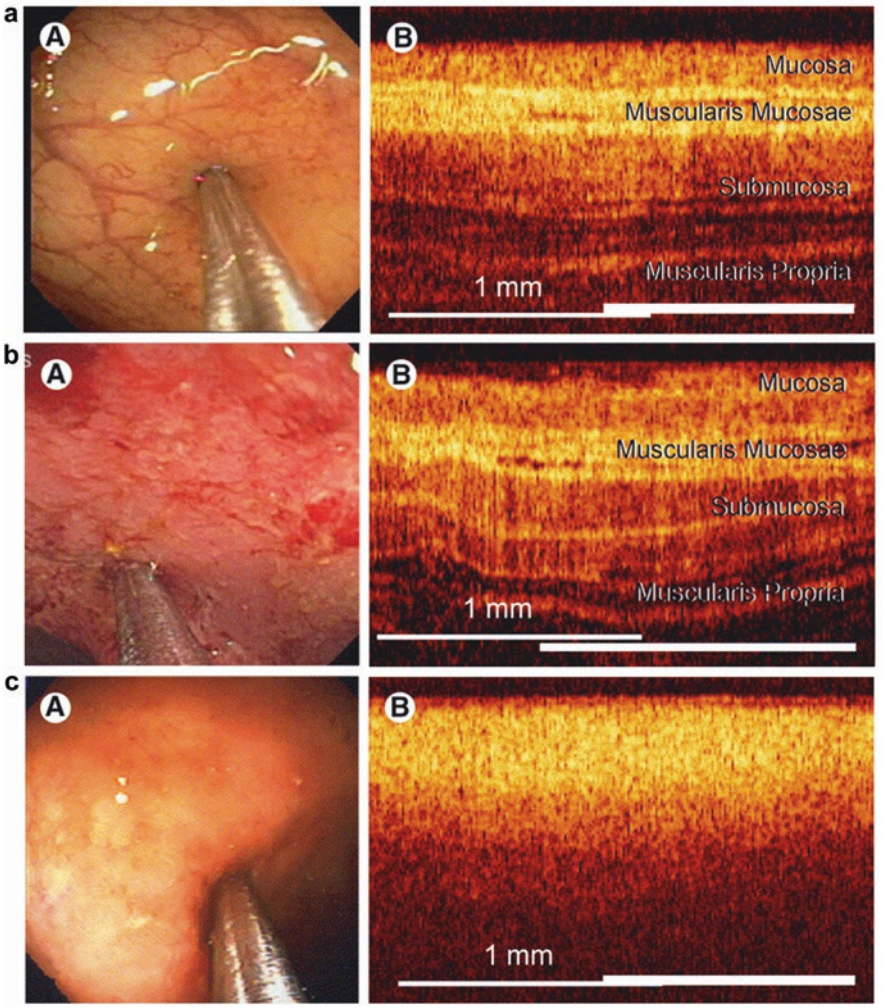

Fig. 5.2 (**a**) (*a*) Endoscopy and (*b*) in vivo optical coherence tomography (OCT) imaging via colonoscopy of the normal colon. (**b**) Endoscopy and optical coherence tomography (OCT) imaging of ulcerative colitis. (*a*) Nodular mucosa on endoscopy. (*b*) The layered structure shown on OCT imaging. (**c**) Endoscopy and optical coherence tomography (OCT) imaging of Crohn's disease. (*a*) Nodular mucosa on endoscopy, similar to that in ulcerative colitis. (*b*) Disrupted layered structure on OCT imaging (Reprinted from Clinical Gastroenterology and Hepatology, 2(12), Shen B, Zuccaro G, Gramlich TL. et al., In vivo *colonoscopic optical coherence tomography for transmural inflammation in inflammatory bowel disease*, pp. 1080–1087, 2004, with permission from Elsevier)

Small Bowel Enteroscopy

It has been reported that up to 30% of patients with CD will have only small bowel disease [34]. Although cross-sectional, noninvasive CT and MR imaging with enterography protocols have reduced the need for diagnostic deep enteroscopy, the need to access the small intestine remains for tissue acquisition for histopathological diagnosis of small bowel CD and therapeutic interventions. Enteroscopy to evaluate the small bowel can be completed using push enteroscopy, device-assisted enteroscopy, or intraoperative endoscopy. Device-assisted enteroscopy began with double-balloon enteroscopy (DBE) and was originally introduced in 2001 by Yamamoto and Fuji Photo Optical Incorporated Company (currently Fujifilm Corporation, Montvale, NJ) [35]. DBE was followed by single-balloon enteroscopy (SBE; Center Valley, PA, USA) in 2006 [36], rotational enteroscopy in 2007, and most recently, an on-demand through-the-scope device that consists of a disposable anchoring balloon known as NaviAid AB (SMART Medical Systems Ltd., Ra'anana, Israel).

Overtube-Assisted Enteroscopy

DBE provided the first minimally invasive, stable, and reliable detailed examination of the small intestine with the ability to target specific areas for examination or intervention. In DBE, the small intestine is pleated onto an overtube by pulling the enteroscope-overtube apparatus while the balloons grip the small bowel. Stepwise advancement deep into the small bowel is accomplished by alternating endoscope advancement while the overtube balloon grips the intestine, and overtube advancement while the endoscope balloon grips the intestine.

DBE has been demonstrated to provide diagnosis in suspected CD with several small studies reporting the diagnostic yield for DBE in suspected CD to range between 30% and 59.4% [37–39]. One study with 23 of 40 patients undergoing DBE for small bowel pathology were subsequently diagnosed with CD, DBE identified strictures in 61%, multiple aphthous ulcers in 42%, longitudinal ulcers in 39%, cobblestone appearance in 22%, and inflammatory pseudopolyps in 22% [37]. The CD lesions were distributed in the ileum only in 61%, in both the jejunum and ileum in 26%, in the jejunum only in 9%, and in the duodenum only in 4%. The ECCO (European Crohn's and Colitis Organisation) recommends that DBE not be the first-line procedure in the evaluation of suspected small bowel CD [34]. In the setting of no obstructive symptoms, the consensus guidelines recommend capsule endoscopy be complementary to DBE, as the findings may help direct the route of intubation.

In addition to diagnostic indications, DBE has been demonstrated to guide therapy as well as provide therapeutic interventions in patients with small bowel CD. Mensink et al. reported the use of DBE, followed by step-up therapy in patients with small bowel lesions. Thirty-five patients showed small bowel lesions and

almost half were in small bowel locations that could not be assessed by conventional endoscopy. At 1-year follow-up, step-up therapy led to clinical remission in 23/26 (88%) [40]. Several small studies reporting the use of DBE to dilate CD-associated small intestinal strictures have noted a short-term success rate of 72% [41, 42]. Long-term success (one dilation without future need for surgery or repeat dilation) was achieved by balloon dilatation in 56–75% of patients [41–43]. Technical failure was significantly more common in long-segment strictures (>3 cm), and in other studies, long-strictures >5 cm were excluded with a general consensus that long-segment stricture dilation increases the risk of perforation. Complications were reported to range from 0% [43] to 8–9% [41, 42] of dilations and included hemorrhage, acute pancreatitis, and one case of delayed perforation.

Single-Balloon Enteroscopy (SBE)

SBE was developed after the introduction of DBE and offers the advantages of being less expensive, less technically challenging with a shorter learning curve [44]. However, these benefits are offset by a significantly decreased likelihood of total enteroscopy relative to DBE. [45] The utility of SBE in IBD was first demonstrated in the pediatric population with a specific focus on the diagnostic yield in 20 patients with high clinical suspicion compared to cross-sectional magnetic resonance enterography (MRE) [46]. SBE identified active small bowel disease out of the reach of standard endoscopy in 60% of patients and active disease in the setting of negative MRE in 15%. SBE was subsequently used to define disease activity to guide therapy by introducing or changing biological therapy and to provide therapeutics with successful dilations of small bowel strictures [47]. Depending on the location of disease and intent of the procedure, SBE can be used with similar diagnostic and therapeutic outcomes to DBE, particularly when total enteroscopy is not required.

NaviAid AB

The NaviAid AB device is an on-demand single-balloon device that is advanced through-the-scope working channel and uses a pressure-sensitive automated insufflation balloon as an anchor to provide the leverage to advance the endoscope deeper into the small intestine (Fig. 5.3a, b). Rubin et al. reported the initial experience of using the NaviAid through-the-scope single-balloon device to augment deep ileal intubation in six patients with known or suspected CD [48]. Technical success was achieved in all six procedures with an incremental ileal intubation of 15–60 cm beyond the intubation extent of the colonoscope alone. The procedure was well tolerated without complications and in all patients, clarification of disease activity and diagnosis was achieved. This report was followed by a 2015 multicenter, retrospective study using a NaviAid AB balloon system for small bowel evaluation [49]. In total 98 patients were included (anterograde, $n = 65$; retrograde, $n = 33$). The

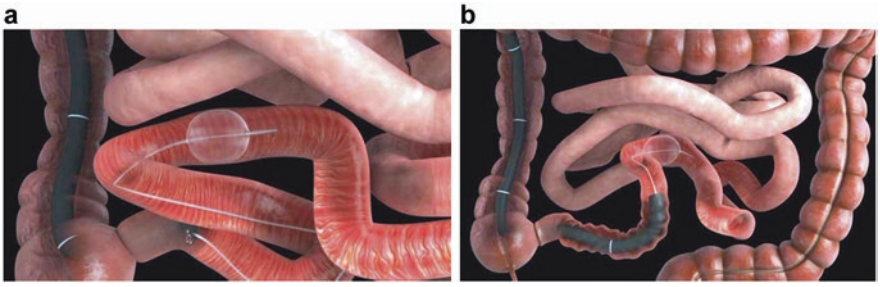

Fig. 5.3 (**a**) Once the endoscope has intubated the small intestine, the through-the-scope balloon catheter is inserted through the tool channel, advanced ahead of the endoscope to the desired position, and the balloon is inflated. (**b**) Once the balloon is inflated, anchoring the bowel, the endoscope is advanced by pushing it forward while pulling the catheter back (Reprinted from Gastrointestinal Endoscopy, 82(5), Ali R, Wild D, Shieh F. et al., *Deep enteroscopy with a conventional colonoscope: initial multicenter study by using a through-the-scope balloon catheter system*, pp. 855–860, 2015, with permission from Elsevier)

cumulative diagnostic yield was 44% with small bowel CD, a finding in only 1%. Although the average depth of insertion was less than that in DBE (158 cm distal to the pylorus in anterograde procedures and 89 cm proximal to the ileocecal valve in retrograde procedures), the total reported procedure times were reduced relative to DBE (anterograde and retrograde procedures were 17.6 minutes and 23 minutes, respectively). Further prospective studies in the IBD population are needed; however, generally the NaviAid AB system appears to be a safe technique that facilitates on-demand deep small bowel intubation with standard equipment.

Rotational Enteroscopy

In 2007, rotational enteroscopy was developed as a simpler and faster alternative method to perform deep enteroscopy. RE pleats the small intestine in a clockwise rotation using a specialized overtube with a raised helix at the distal end, which mimics the motion of a corkscrew. There are two different overtubes available for antegrade (Endo-Ease Discovery SB; Olympus America, Center Valley, PA, USA) or retrograde (Endo-Ease Vista; Olympus) procedures (Fig. 5.4a, b). The spiral overtubes are shorter than standard DBE overtubes (118 cm vs. 145 cm long) with 4.5–5.5 mm soft raised spiral helices. The advantages of RE include the ability to disengage the overtube/endoscope and completely withdraw the endoscope while maintaining the position in the small bowel with the overtube as well as the lack of need to purchase a dedicated system as the overtubes can be used with ordinary enteroscopes or pediatric colonoscopes. However, similar to DBE, RE requires two operators to perform.

No studies have been designed to specifically evaluate the technical performance, diagnostic and therapeutic yields, and safety RE in IBD. However, multiple studies have evaluated the diagnostic yield in small bowel disease, including

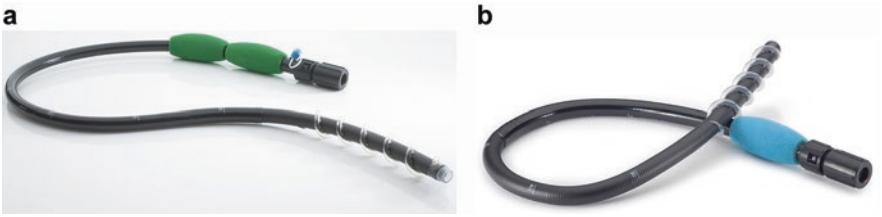

Fig. 5.4 (**a**) The anterograde Spirus EndoEase Discovery SB overtube utilized primarily for anterograde deep enteroscopy. (**b**) The retrograde Spirus EndoEase Vista overtube is shorter and wider compared to the anterograde overtube (With permission from Springer. Endoscopy in Inflammatory Bowel Disease, *Spiral Enteroscopy: Technique, Diagnostic and Therapeutic Yield and Application in Small Bowel Crohn's Disease*, 2014, pp. 129–133. Chiorean, M. Original copyright notice as given in the publication in which the material was originally published)

Crohn's disease [50]. Although the general consensus is that it is safe and feasible in CD, some experts have raised theoretical concerns with patients with intestinal strictures (particularly when less than 10 mm, greater than 2 cm in length, acutely angled or ulcerated) as the overtube external diameter is larger (14.5–17.4 mm vs. 12.2–13.2 mm) and more rigid than DBE [51, 52].

DBE Versus RE

In comparing the depths of small intestinal insertion of DBE and RE, Messer et al. reported a small, single-center prospective, randomized, comparative study comparing DBE and SE [53]. The rate of complete enteroscopies with DBE was 12 times the rate achieved with SE (8% in the SE group and 92% in the DBE group; $p = 0.002$), and the estimated depth of insertion was also significantly greater in the DBE group than in the SE group for both the upper and lower examinations. However, the DBE procedure times were significantly longer. The RE group had one perforation of the terminal ileum in a lower examination. These findings supporting DBE over RE are countered by prior prospective and retrospective comparison studies that did not show a significant difference in depth of insertion when using similar techniques to estimate depth of small intestinal intubation [54]. However, the American Society for Gastrointestinal Endoscopy recommends DBE as the most effective deep enteroscopy technique for achieving total enteroscopy [55].

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) uses a transducer on the tip of the endoscope to produce high-frequency sound waves to provide continuous, real-time images of the intramural gastrointestinal tract and organs and adjacent structures that otherwise

would not be visible. The radial-array echoendoscope was the first echoendoscope developed and provides a 360-degree view in a plane perpendicular to the long axis of the echoendoscope. The radial-array EUS is used only for diagnostic purposes. The advent of the curved-linear array echoendoscope containing an elevator and therapeutic channel allowed for the passage of aspiration needles, guidewires, and stents under direct endosonographic visualization. The most recent advancement has been the development of an Olympus forward-viewing echoendoscope with an elevator that shifts the orientation of endoscopic and ultrasound views from oblique to forward.

EUS in the IBD population has been used to assess disease activity, differentiating CD and UC and the assessment of CD-associated perianal complications including perianal fistulae. In one study assessing the ability to differentiate active CD versus UC, EUS was able to differentiate the two disease entities with a sensitivity of 92% by assessing differences in mucosal (greater in UC)–submucosal (greater in CD) thickness and total wall thickness and lymph nodes (present in 74% of patients with CD and not present in patients with UC) [56].

While EUS has been demonstrated to have an accuracy of 91% in assessing perianal fistula anatomy in patients with CD [57], a recent meta-analysis reported that pelvic MRI may be superior [58] and recent ECCO guidelines favor pelvic MRI as the diagnostic modality of choice for this indication [59].

Capsule Endoscopy

Capsule endoscopy (CE) allows for evaluation of the bowel mucosa and has recently been suggested by ECCO to be a potential initial diagnostic modality for patients with high suspicion but negative ileocolonoscopy and no obstructive symptoms [60].

To date, CE has been predominantly used in the small bowel for mucosal assessment in patients with established or suspected CD (Fig. 5.5a–d). A recent meta-analysis reported the sensitivity and specificity of terminal ileal CD to be not significantly different by CE as compared to MRE with standard ileocolonoscopy as reference. However, subtle small bowel lesions may be easier to identify using CE, as lesions in the proximal small bowel were identified in 18 patients as compared to 2 patients with MRE ($p < 0.05$) [61].

Data assessing response to therapy and evaluating for mucosal healing is limited with one published prospective, multicenter study assessing CE pre- and post-therapy in inflammatory CD. Post-therapy CE was able to detect a significant decrease in the number of large ulcers, but no significant change in the number of aphthous ulcers or percentage of time with visible lesions [62]. A recent abstract published in 2013 described CE in patients with CD before and after treatment with anti-TNF biologic therapy with corticosteroids or thiopurines. Treatment resulted in a significant reduction in the Lewis score after a median of 32 weeks (range 11–55) of anti-TNF therapy with just over 80% of patients having only mild mucosal

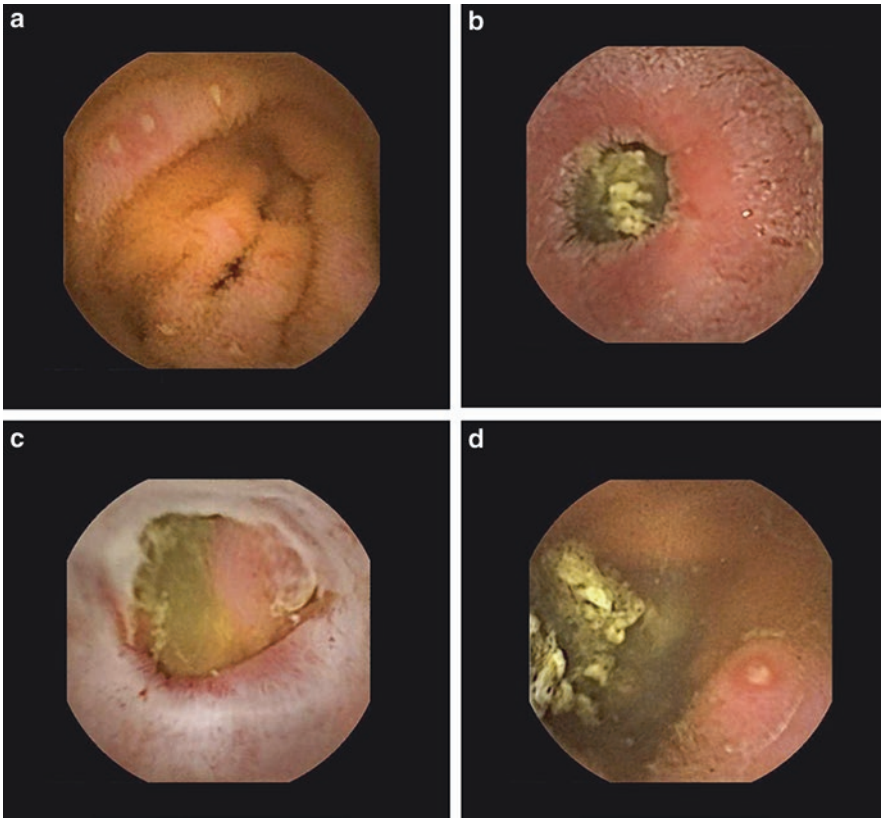

Fig. 5.5 Wireless video capsule endoscopy images of patients with small intestinal Crohn's disease with features including (**a**) multiple aphthous ulcerations, (**b**) small bowel stricture without ulceration, (**c**) small bowel stricture with ulceration, and (**d**) postoperative recurrent Rutgeerts score i1 aphthous ulceration (Images courtesy of David T. Rubin, MD)

inflammation or normal findings [63]. CE has also been demonstrated to help guide management with one study of 50 consecutive patients with CD; the activity of disease documented by CE resulted in a change in management in 44% (n = 22) cases [64].

Recently, two-camera colonic capsules have been developed for evaluating colonic mucosa including potential use for disease monitoring in colonic IBD. Initial studies using first-generation capsules have been inconsistent as compared to conventional colonoscopy [65, 66]. A recent clinical feasibility study utilizing a second-generation colonic capsule with higher frame rate demonstrated a strong correlation with findings of conventional colonoscopy [67].

Currently CE technology is limited by its inability to sample tissue, but the predominant concern limiting use to date is capsule retention, which has been reported to 1–2% of patients with suspected CD but up to 13% of patients with known CD [68]. Patency capsules can be used to help prevent capsule retention; however, in our

practice, the benefits of assessing transmural and extramural disease in addition to the high rate of patients excluded from CE after CT or MRI (reported 27–40%) [69] favor the use of MRE in assessing response to therapy.

Conclusions

With the continued development of new endoscopic imaging technology, through-the-scope and over-the-scope devices, this new and improved multimodality instrument has effectively replaced the standard issue endoscope of the past. These advances have been demonstrated to have a significant impact across gastrointestinal disease, including the management of IBD. However, the excitement with novel technology must be balanced by an emphasis an academic rigor into studying the efficacy and safety of these advances. The vast majority of the above studies have been completed in small cohorts in a nonrandomized controlled fashion. In the future, with continued research into these technologies, the management and surveillance of IBD will likely continue to evolve.

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Chapter 6
Radiology Redefined

Emily Ward and Aytekin Oto

Introduction

Inflammatory bowel disease (IBD) affects approximately 1.4 million people in North America. Because of its tendency to present in younger patients and episodic course, patients often undergo numerous imaging studies [1]. Incorporating imaging into the management of these patients is important and can be challenging for clinicians. Multiple imaging studies can be employed for the diagnosis of IBD, assessment of response to therapy and disease activity, and detection of complications. These imaging studies include small bowel follow through examination, enteroclysis, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Over time, computed tomographic enterography (CTE) and magnetic resonance enterography (MRE) have become the modalities of choice due to their outstanding image quality, lack of need for bowel preparation, and ability to diagnose extraintestinal complications of the disease [2]. MRE does not utilize ionizing radiation and can employ cine imaging to evaluate peristalsis, conferring additional advantages on MRI as an imaging modality.

When Do We Need Imaging?

When a patient presents with clinically suspected IBD, imaging can be used to confirm the diagnosis. Most guidelines suggest that endoscopy should remain the basis of diagnosis [3, 4]. Performing a small bowel evaluation with one of the aforementioned diagnostic tools is explicitly recommended, however, by the European Crohn's

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and Colitis Organization (ECCO) guidelines [4] to establish the diagnosis of Crohn's disease, irrespective of the findings by ileocolonoscopy. Imaging techniques can also help guide initial treatment options, evaluate for risk of complications, and help determine prognosis [5–9]. There is less consensus regarding indications and appropriate scheduling for follow-up of patients with episodic disease activity. The American College of Radiology's (ACR) Appropriateness Criteria can provide guidance regarding when imaging is appropriate (https://acsearch.acr.org/list).

In the acute initial presentation with suspected Crohn's disease in an adult, CT of the abdomen and pelvis with intravenous contrast and CTE are listed as being 'usually appropriate', with MRE listed as 'may be appropriate' given that it may not be well tolerated in the acute setting. MRE may be an option if the patient cannot receive the intravenous iodinated contrast for CT. In the nonacute or indolent presentation, both CTE and MRE are felt to be equally appropriate but only one should be performed. In the acute initial presentation of a child with suspected Crohn's disease, both CTE and MRE are felt to be 'usually appropriate', with MR receiving a higher score given the lack of radiation.

For an acute exacerbation in an adult with known Crohn's disease, CTE, CT abdomen and pelvis and MRE are all felt to be usually appropriate. For a child with an acute exacerbation of known Crohn's disease, MRE, CTE, and CT abdomen and pelvis are all listed as usually appropriate. MRE receives a higher score, again due to the lack of ionizing radiation.

For surveillance or evaluation of mild symptoms in an adult or child with known Crohn's disease, MRE and CTE are listed as 'usually appropriate' with MRE receiving a slightly higher score again primarily due to the lack of ionizing radiation.

Imaging of Patients with IBD

For many years, the imaging reference standard for IBD has been barium fluoroscopy. Enteroclysis and small bowel follow through were employed for evaluation of the small bowel and barium enema for evaluation of the large bowel. These imaging modalities, for the most part, assessed the bowel mucosa and caliber. Fluoroscopy is insensitive for the detection of transmural and extraluminal disease. CTE and MRE are both capable of diagnosing and surveying IBD in a sensitive and a specific manner. CT benefits from better spatial resolution, fewer motion artifacts, increased availability, lower cost, and shorter examination times [10]. Claustrophobia is also less of a problem due to the wider bore of the CT gantry. The major disadvantage with CTE (which is a particular problem in younger patients) is that it employs ionizing radiation. In addition to being radiation-free, MRE provides better contrast resolution and superior evaluation of perianal disease [2]. It also provides a number of different ways of distinguishing between acute and chronic disease which can impact greatly on management. Dynamic cine imaging also allows real-time evaluation of bowel peristalsis – a feature which is not available with CTE. For these reasons, MRE appears to be the superior choice for imaging these patients.

MR Enterography

MR Enterography Technique

Adequate small bowel distention is a prerequisite for optimal small bowel imaging, regardless of the preferred imaging modality. The optimal contrast agent should provide adequate distention of the small bowel and be well tolerated by the patients. The most commonly used oral contrast is low-concentration barium (VoLumen®, E-Z-EM, Westbury, NY), which is also used as an oral contrast agent in CTE and has been shown to provide reasonable distention during MRE [11]. Before starting MRE, a spasmolytic is usually administered to reduce bowel peristalsis. Glucagon is given as a single dose of 1 mg intravenously or intramuscular immediately before the onset of imaging or as a split dose with half of the dose administered before the acquisition of contrast-enhanced sequences. A basic MRE protocol includes T2-weighted imaging and contrast-enhanced T1-weighted images.

Advanced MR Enterography Techniques

3T Imaging

The higher field strength results in better signal-to-noise ratio (SNR) with the possibility of acquiring images at higher spatial resolution and/or with shorter scan times, which are particularly advantageous in MRE.

Dynamic Contrast-Enhanced MRI

Increased bowel wall enhancement is an established finding indicative of active inflammation in patients with CD [12–16]. Using standard post-contrast sequences, enhancement is evaluated as a snapshot in time. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is the acquisition of serial MRI images before, during, and after the administration of an MR contrast agent. Using this technique, it is possible to evaluate the enhancement as a function of time and calculate quantitative parameters to evaluate perfusion [17–22].

Diffusion-Weighted Imaging

Advances in MRI technology have made diffusion-weighted imaging (DWI) much more plausible in body imaging. It has long been recognized that certain inflammatory processes may cause restricted diffusion. While this phenomenon is challenging to explain and is likely multifactorial, it has nevertheless led to an emerging interest in using DWI as a quantifiable indicator of inflammation in the abdomen.

Inflamed bowel segments have more restricted diffusion compared to normal bowel segments, which can be assessed qualitatively (increased signal intensity on DWI) and quantitatively (decreased ADC values) [23]. This study among others suggests an evolving role for DWI in inflammatory bowel disease.

Motility and Cinematographic Techniques

Dynamic cine sequence can be used to visually evaluate small bowel peristalsis, identifying areas of altered motility, specifically focal areas of paralysis or hypomotility. Using these cine MR sequences, Froehlich et al. detected more specific findings for Crohn's disease than standard MRE [24].

MRI Findings of Crohn's Disease

MR is a powerful tool in assessing luminal and extraluminal findings of Crohn's disease. Certain findings, such as degree of wall thickening, wall edema, and contrast-enhancement patterns, have been shown to be independent markers of disease activity and severity [7, 25]; however, interpretation of disease status should ideally be made based on the constellation of multiple findings rather than a single variable.

Bowel Wall Thickening

Wall thickness normally measures 1–3 mm in distended small bowel and generally ranges between 5 and 10 mm in bowel affected by Crohn's disease [16] (Fig. 6.1a, b). Wall thickening is the most consistent imaging finding of Crohn's disease and

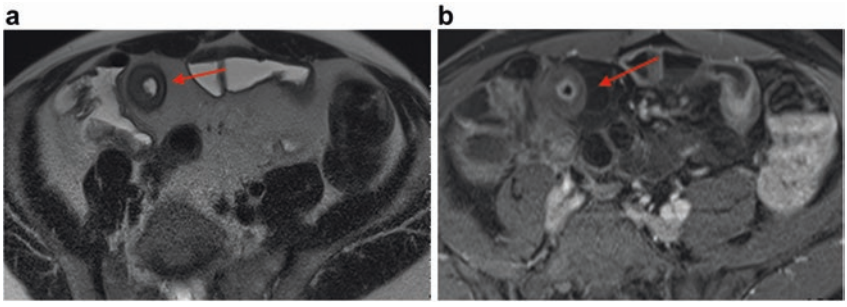

Fig. 6.1 (**a**) Axial half-Fourier acquisition single-shot turbo spin-echo sequence demonstrates abnormal T2 signal within the bowel wall (*arrow*) signifying underlying mural edema. (**b**) Early (70 s) post-contrast T1-weighted image demonstrates marked wall thickening within the abnormal small bowel loop (*arrow*). We can identify the stratified wall enhancement consisting of the strongly enhancing mucosa, a poorly enhancing edematous submucosa, and an enhancing serosa

has been shown to correlate with the presence and severity of disease [7, 25–27]. A cutoff thickness of 6 mm has been proposed to distinguish active and inactive disease [13]. Although thickness decreases during remission, inactive yet pathologic bowel is likely to be thicker compared to completely normal bowel [13, 16].

T2-Weighted Imaging Findings

Actively inflamed bowel wall is edematous and will appear as increased intramural T2 signal (Fig. 6.1a); this finding has been shown to correlate with severity of inflammation [7, 13, 25]. Low T2 signal is suggestive of chronic disease, which can be a helpful feature in interpreting the significance of thickened bowel wall [28] (Fig. 6.2a).

Bowel Wall Enhancement

Bowel wall enhancement plays an important role in determining disease severity and may be one of the earliest signs of disease activity [28]. Studies have shown that, compared to normal bowel, diseased bowel wall demonstrates early and intense uptake of contrast that increases over time until a plateau is reached [17–20]. A difference in enhancement pattern and dynamics is observed between active disease

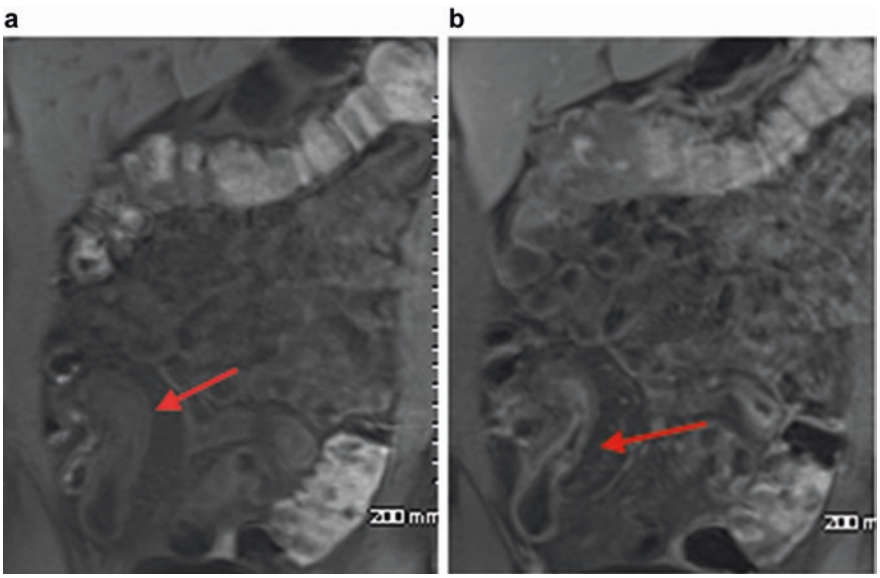

Fig. 6.2 (**a**) Coronal noncontrast T1-weighted image demonstrates an abnormally thickened segment of terminal ileum (*arrow*). (**b**) Coronal T1-weighted image obtained at 70 s demonstrates a stratified enhancement pattern of the actively inflamed bowel wall

and inactive disease [18, 21, 22] with a significant decrease in enhancement being observed during the transition from active disease to remission [16].

Enhancement can be assessed during several phases after injection of the contrast agent. The optimal scan delay time has still not been determined. Peak wall enhancement in normal volunteers was found to be 60–70 s (portal venous phase) [29]. However, Zappa et al. found that differentiating inactive and active disease was best achieved by the level of enhancement on delayed phase images [13]. Several enhancement patterns have been described and vary depending on inflammatory activity. A layered pattern of enhancement, termed mural stratification, has been shown to correlate with disease activity [25, 30]. The layers are formed by a strongly enhancing mucosa; a poorly enhancing, edematous submucosa; and an enhancing serosa (Fig. 6.2b). Koh et al. showed the stratification enhancement pattern to be highly specific for active inflammation and only present in pathologically proven actively diseased bowel segments [26]. Homogenous enhancement is less specific. Although intense homogenous enhancement can represent active transmural inflammation, less intense, homogenous enhancement is often seen in chronic disease without acute inflammation [18, 25] (Fig. 6.3b, c). In such cases, correlation with other findings, such as intramural T2 intensity or inflammation of adjacent mesentery, is helpful in interpretation.

Judging enhancement intensity remains largely subjective and can be done by comparing the abnormally enhancing segment to an adjacent normal loop. Emerging dynamic enhancement techniques show promise in quantifying enhancement and to determine inflammation activity [31].

Mucosal Findings

While mucosal hallmarks of CD, such as ulcerations, pseudopolyps, and cobblestoning, have been well described with fluoroscopy studies, the inferior spatial resolution of MR has not been able to reliably show these changes.

Motility

Rapid MRI techniques have enabled acquiring cine sequences which depict bowel motility and can therefore confirm fixed stenosis and segmental dilatation and detect adhesions. Abnormally decreased or increased peristalsis may be an early sign of involvement by Crohn's disease and can potentially help identify affected segments which do not yet show other signs of inflammation [24].

Mesenteric Findings

Inflammation of mesentery surrounding an actively inflamed bowel loop may be seen in some patients. Inflamed, edematous mesentery will show enhancement and increased T2 signal, most apparent on fat-suppressed sequences.

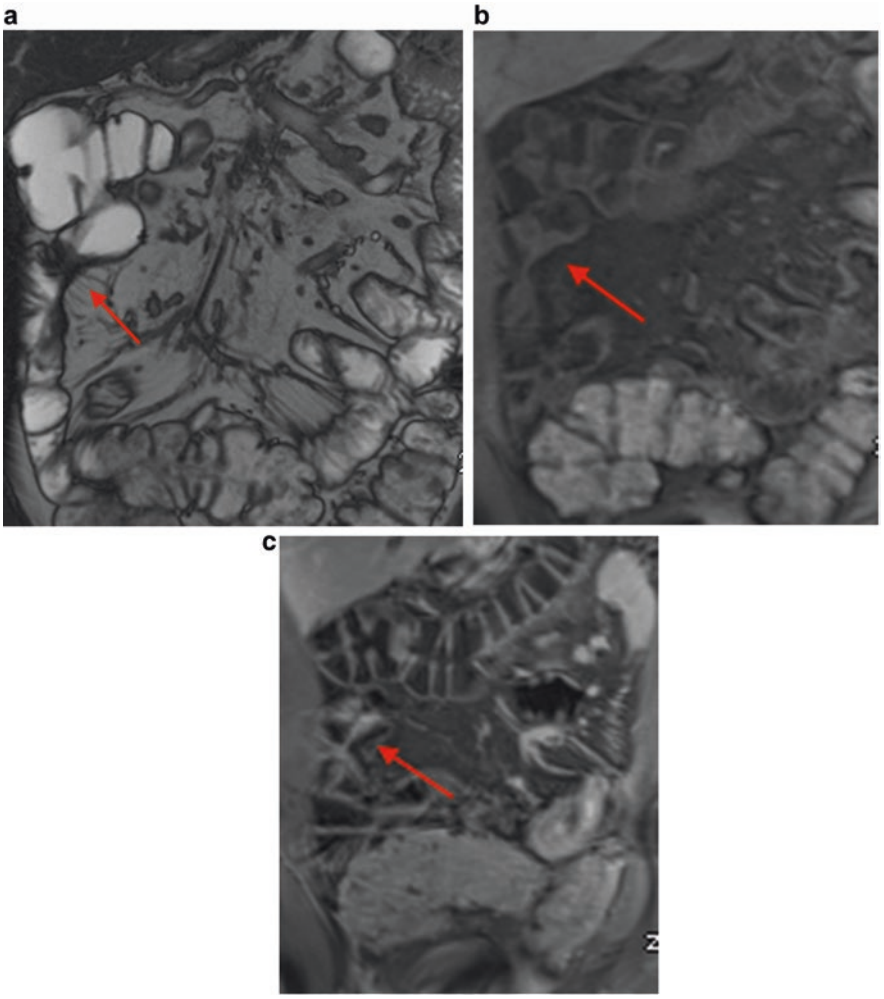

Fig. 6.3 (**a**) Coronal fast imaging with steady-state free precession demonstrates low T2 signal within the wall of a short segment chronic stricture involving distal ileum consistent with underlying fibrosis. (**b**) Coronal noncontrast T1-weighted image shows mild wall thickening of the same segment consistent with chronic disease. (**c**) Coronal post-contrast T1-weighted image demonstrates homogeneous enhancement within the abnormal strictured segment consistent with fibrosis. Note the absence of stratified enhancement which would suggest active inflammation

Increased mesenteric blood flow resulting in engorgement of vasculature, known as the comb sign, has mostly been reported in active disease [13, 27, 32]. Fatty proliferation around involved bowel loops ("creeping fat"), usually affecting the mesenteric border, can lead to separation of bowel loops and is a specific finding of chronic CD [33]. Enlarged mesenteric lymph nodes can be seen in active and chronic disease, and their presence alone is not indicative of activity. Nodal enhancement and edema are however suggestive of active disease [14, 34].

Complications

Strictures in CD are associated with wall thickening and can cause upstream bowel dilation and obstruction. MRE has been shown to perform well in depicting mural stenosis, strictures, and obstruction [30, 35]. Chronic, fibrotic strictures will have low signal on T1 and T2 sequences and may demonstrate low to moderate homogenous or inhomogeneous enhancement (Fig. 6.3a–c).

Progression of transmural ulceration into the surrounding mesentery results in blind ending tracks (sinus tracks) or abnormal communications with adjacent bowel loops, organs, or skin (fistulas). Fistulas are well visualized on MR and appear as linear high T2 signal tracts with associated enhancement of the tract and surrounding mesentery [13, 27, 36] (Fig. 6.3b). Extension of ulceration into the mesentery may also result in the formation of collections of inflammatory tissue (phlegmons) or walled-off collections of puss (abscesses). Patients with CD are also at increased risk for small bowel adenocarcinomas. Since malignancy will typically present as a stricture and wall thickening, it can be difficult to differentiate from a benign stricture. Malignancy is more likely to be associated with focal or segmental mural thickening and mass lesions, whereas benign disease will have more generalized and diffuse thickening and absence of mass [28].

Perianal Disease

The high soft tissue contrast of MR makes it the preferred method in detecting, classifying, and following perianal fistulas and abscesses [37–40]. Fistulas appear as bright T2 signal tracts coursing through the perianal space, ischiorectal fossa, and subcutaneous fat. As for internal fistulas, DWI and contrast-enhanced sequences are useful adjuncts to T2 sequences for perianal fistula diagnosis [41].

Pitfalls

Several pitfalls of MR imaging in IBD need to be considered. The jejunum normally enhances more intensely compared to ileum; this should not mistakenly be interpreted as jejunal disease. In cases of suspected jejunal disease, other features such as wall thickening, enhancement pattern, and mesenteric inflammation can be used to more accurately determine disease extent.

Under distension of bowel loops is a major pitfall that can give the false impression of wall thickening and increased enhancement, especially in collapsed terminal ileum. Additionally, collapsed bowel loops can conceal mucosal findings, such as ulcerations, as well as early strictures. Delayed imaging, to allow further progression of oral contrast, as well as dynamic imaging may be helpful in avoiding this pitfall.

Wall thickening can be a marker of active disease, but it is also seen in chronic, fibrotic disease. Associated intramural T2 hyperintense signal or stratified wall

enhancement may be helpful in deciding if active or inactive disease is present (Fig. 6.2a, b). Increased wall enhancement can also be seen in the setting of inactive disease and should be interpreted in the context of the pattern in which it occurs.

Patients with Crohn's disease often have a history of prior bowel surgery due to obstructing strictures or severe disease. Stricturoplasty, and other post-surgical changes, may simulate pathology such as strictures or malignancy. Post-stricturoplasty changes will often have a lobulated appearance, and reviewing a concerning segment in multiple planes may be helpful [42].

Evaluation of Response to Treatment

MRI also has a promising role in evaluating response to treatment. Studies of response to TNF alpha inhibitors in patients with perianal disease are beginning to define the role of imaging in monitoring therapy. Savoye-Collet et al. have demonstrated a significant change in MRI findings such as hyperintensity on T2-weighted images and hyperenhancement in patients who responded to the treatment as opposed to patients who did not [43]. Ng et al. showed that resolution of perianal fistulas was variable and slower than clinical healing, but, once the healing was seen on MRI, the fistula was likely to remain healed [44]. The application of the advanced quantitative imaging techniques such as DWI, DCE-MRI, quantitative motility, and magnetization transfer in monitoring and quantifying the response to treatments such as TNF alpha inhibitors is an area open for exploration that may transform the role of MRE in CD.

Potential Impact of MR Enterography on Patient Management

Apart from assessing for diseased bowel, MRE may have a major impact on patient management by assessing disease activity. Recently, Rimola et al. validated MRI variables, including wall thickness, relative contrast enhancement, and presence of edema and ulcers as independent predictors of disease severity and developed a quantitative index based on these variables for diagnosis of active disease for use in research studies. The index had a sensitivity and specificity of 87% and 87% [8]. Similarly, Steward et al. showed significant correlation between the MRI activity index and biopsy scores of acute inflammation [45]. The MRI activity index factored in mural thickness and mural T2 signal which were the two factors that best predicted biopsy scores of acute inflammation. Sempere et al. showed that a clinical transition from the active disease phase to remission was associated with a significant decrease in thickness and contrast enhancement of the affected bowel wall [16]. While these studies strongly suggest that MRI can assess disease activity, the clinical applications of these findings remain unclear. This is probably due to the lack of standardized criteria for assessing disease activity on MRI and the lack of a widely accepted algorithm for clinical decision making based on imaging findings.

In general, findings suggestive of active disease should warrant a trial of medical therapy, whereas fibrostenotic disease with no significant evidence of active inflammation can be an indicator for surgical intervention. To add to the complexity of the situation, several authors have suggested that inflammation and fibrosis commonly overlap on histopathology. This is further compounded by the limitation of current imaging protocols in distinguishing inflammation and fibrosis [13, 46]. For this reason, evolving quantitative techniques such as DWI, DCE-MRI, quantitative motility, and magnetization transfer may hold the key for developing reproducible criteria for assessing the disease and directing management. Larger studies of these techniques will have to be performed to clarify their clinical role.

Comparison of MR Enterography with Other Imaging Techniques

There appears to be regional variation in the choice between MRE and CTE. In the majority of Europe, MRI is the preferred modality [47] In the UK, however, only 24 of 63 surveyed departments offered MRI of the small bowel [48]. Similarly, in the USA, the use of CT appears to be more prevalent [47]. The main advantage of MRE compared to CT is the lack of ionizing radiation. There are multiple reasons that make the issue of radiation of much relevance in CD evaluation. First, a large portion of the affected patients are young in age, increasing the risk of late effects due to their longer life expectancy [49]. This is in addition to the increased vulnerability of pediatric patients to the effects of radiation [50]. Second, the need for repeated examination can result in a large cumulative dose. Third, patients with CD already have background risk of neoplasia. Fourth, those patients are co-exposed to potentially synergistic agents as part of their medical treatment, which further increases the risk of neoplasia [51]. Ultrasound has gained popularity as an imaging tool in these patients due to its lack of need for ionizing radiation. It has increasingly been employed in the pediatric population for this reason. MRE can be difficult in children due to claustrophobia and also the need for general anesthetic during the study to ensure the patient remains still for the duration of the examination. Fluoroscopy has been used less over the past decade with the advent of CTE and MRE; however, for isolated cases, it can still provide useful information.

CT Enterography

CTE is tailored to detect bowel wall abnormalities, through the use of large volume neutral enteric contrast and thin slice technique. Currently, routine CT evaluation of Crohn's disease includes assessment of bowel wall thickening, perienteric and pericolonic mesenteric inflammation; lymph node size and number; extraluminal collections (fistulae, abscesses, sinuses); and extraintestinal complications [52]. As already discussed, although CT has proved to be an effective imaging modality for Crohn's disease, one significant limitation is its associated patient exposure to

ionizing radiation. Epidemiological studies suggest a nonzero radiation-induced cancer risk at exposure levels as low as 75 mSv, which are often exceeded in patients diagnosed with Crohn's disease during childhood [51, 53, 54]. For these reasons, MDCT is avoided by most pediatric radiologists. However, iterative reconstruction algorithms in CTE have shown that a decrease of effective doses to less than 2 mSv is possible with considerably lower image quality but without missing clinically significant diagnostic information [55, 56]. The feasibility and integration into daily clinical practice of these low-dose techniques require further investigation and standardization.

CTE is nonetheless the preferred imaging technique for evaluating IBD in some centers because of certain advantages over MRI: shorter examination time, convenient procedure, greater availability, increased radiologist familiarity and experience in interpreting findings, high spatial resolution, fewer motion artifacts, less need for sedation, lower cost, and availability for patients with implanted MR-sensitive devices [57].

CT findings to look for include bowel wall thickening greater than 3 mm in a distended loop, mural hyperenhancement and segmental hyperenhancement compared with adjacent loops, mural stratification due to intramural edema (Fig. 6.4a, b), increased attenuation of the mesenteric fat due to edema and engorgement of the vasa recta (comb sign), chronic fibrostenosing disease (strictures) without mural hyperenhancement or other signs of active inflammation, sacculations (as the inflammation typically involves the mesenteric border of the bowel loops, so with fibrosis, shortening and structuring of the mesenteric side ensues leading to compensatory dilatation of the antimesenteric wall), fibrofatty proliferation, sinus tracts and fistulas, abscesses, treatment response (decrease in mural hyperenhancement and bowel wall thickening), inflammatory pseudopolyps, pneumatosis [58].

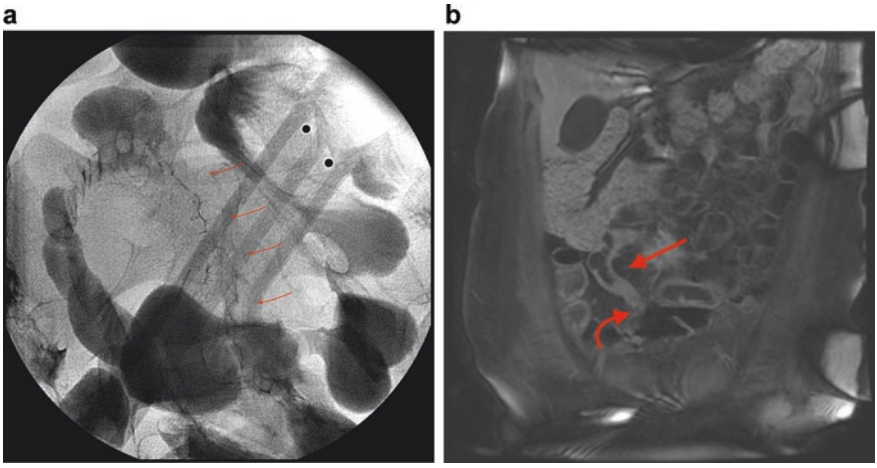

Fig. 6.4 Axial (**a**) and coronal (**b**) post-contrast CTE images demonstrate abnormal mural thickening and stratification of a segment of distal ileum (*arrows*) in a patient with active inflammation and IBD

Ultrasound

Transabdominal ultrasound (TUS) and small intestine contrast ultrasound (SICUS) are radiation-free, low-cost, and easy-to-use radiographic techniques with high availability and good tolerance by children. They can be performed with little preparation and without sedation. Fasting 4 h before the examination is helpful. The use of oral and/or IV contrast agents remains controversial but has been shown to be a safe practice that increases diagnostic accuracy [59]. In patients with suspected CD, the sensitivity and specificity of both methods in detecting small bowel lesions are shown to be 75% and 100% for TUS and 100% and 100% for SICUS, while in patients with proven CD, the sensitivity and specificity can reach 76% and 100% for TUS and 96% and 100% for SICUS, respectively [60]. Another advantage of US is the real-time evaluation of bowel wall for both anatomic and functional abnormalities. Sensitivity is reported to be significantly lower for less accessible locations such as rectum (14.2%) and duodenum/jejunum (28.6%) [6, 61]. Ultrasound findings to look for are the following: bowel wall thickening greater than 3 mm; modification or loss of normal stratification; bowel stiffness: noncompressible and hypoperistatic loops; strictures with prestenotic dilatation; ulcers in the bowel wall; fistulas; abscesses; and inflammatory mesentery which includes free fluid and enlarged hyperemic lymph nodes. Color or power Doppler imaging of the vascularity of thickened wall segments has been proved useful in the distinction between remission and active disease, as normal bowel wall does not show much vascularity [58]. Ultrasound elasticity, although not in routine clinical employment in bowel wall assessment, represents a promising real-time objective diagnostic tool in the detection and measurement of fibrosis in IBD. So far, it has been shown that it can accurately differentiate inflammatory from fibrotic bowel in rat models of IBD [62].

Among the disadvantages of US are the facts that the examination is operator dependent and not reproducible and that it is difficult to examine the whole GI tract, with additional difficulties in overweight children and in cases of overlying bowel gas. Localization of disease is difficult away from the terminal ileum, and mucosal detail and entero-enteral/colic fistula cannot be demonstrated.

Fluoroscopy

Because of its ability to depict fine mucosal detail, the double-contrast barium study is a valuable technique for diagnosing ulcerative colitis and Crohn's disease even in patients with early disease. Barium can be used to outline the large bowel and small bowel. During a barium enema, it is important to reflux barium into the terminal ileum to assess the ileocolic junction. Traditionally, the use of barium either by small bowel follow through, or using enteroclysis have been used to evaluate the

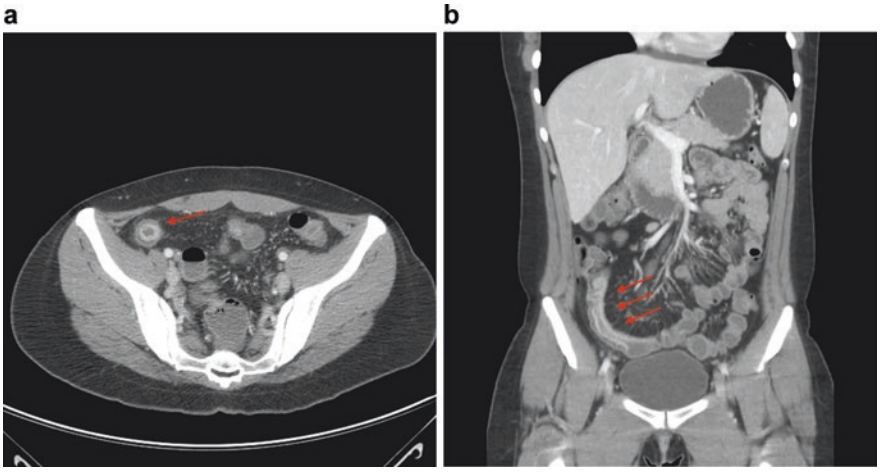

Fig. 6.5 (**a**) Small bowel follow through demonstrates mucosal irregularity in an area of strictured terminal ileum (*arrow*). (**b**) The stricture was confirmed with MRE study a few days later (*arrow*). The MRE also showed and area of fistualation (*curved arrow*) to an adjacent small bowel loop which was not demonstrated on the small bowel study

mucosa of the small bowel and map the small bowel. The limitations have been the use of radiation in young patients and the lack of extraluminal information. Barium however does demonstrate the luminal mucosa in detail with the ability to demonstrate fine ulceration and strictures (Fig. 6.5a). Fistulas can be demonstrated when filled with contrast. Overlapping small bowel loops especially in the pelvis can however be a challenge.

The enteroclysis technique is uncomfortable and poorly tolerated by patients. Until recently, the small bowel follow through has been the most common modality and sometimes the only available method of evaluating the small bowel and is relatively well tolerated. The accuracy varies depending on technique and can be optimized using compression, spot views, and frequent fluoroscopy.

Extraintestinal Manifestations

Extraintestinal manifestations of Crohn's disease can also be evaluated with CT or MR imaging: sclerosing cholangitis, cholelithiasis, liver abscess, portal vein thrombosis, pancreatitis, hydronephrosis caused by ureteral involvement, nephrolithiasis, IBD-related arthropathy (progressive ankylosing spondylitis and sacroiliitis), osteoporosis, peritoneal pseudocysts, and cutaneous manifestations [58].

Summary

Multiple imaging studies can be employed for the diagnosis of IBD and also to assess response to therapy and disease activity and to evaluate for complications, each with its own advantages and disadvantages. MRE is playing an increasing role in the evaluation of IBD, with performance at least comparable to, and in some areas better than, other small bowel imaging modalities which expose the patients to radiation. Advanced sequences improve the diagnostic performance of MR. Clinician and Radiologist input is essential to determine the appropriate modality for as well as timing of any imaging of these patients to aid with accurate diagnosis and appropriate management.

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Chapter 7
Prevention of Colorectal Cancer in Inflammatory Bowel Disease Using Advanced Technologies

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Introduction

The risk of colorectal cancer (CRC) among patients with inflammatory bowel disease (IBD) has been well described. The increased risk has been attributed to chronic mucosal inflammation, associated with early disease onset, increased disease duration, extensive mucosal involvement, and concomitant primary sclerosing cholangitis (PSC). Because of this risk, prevention strategies have been recommended and the primary approach to such prevention has been colonoscopic assessment of the mucosa in search of precancerous or early-stage cancerous lesions. Recent developments of advanced visualization techniques such as high-definition colonoscopes and dye-spray chromoendoscopy have provided new options for our approach to prevention. Due to the fact that we now have better visualization

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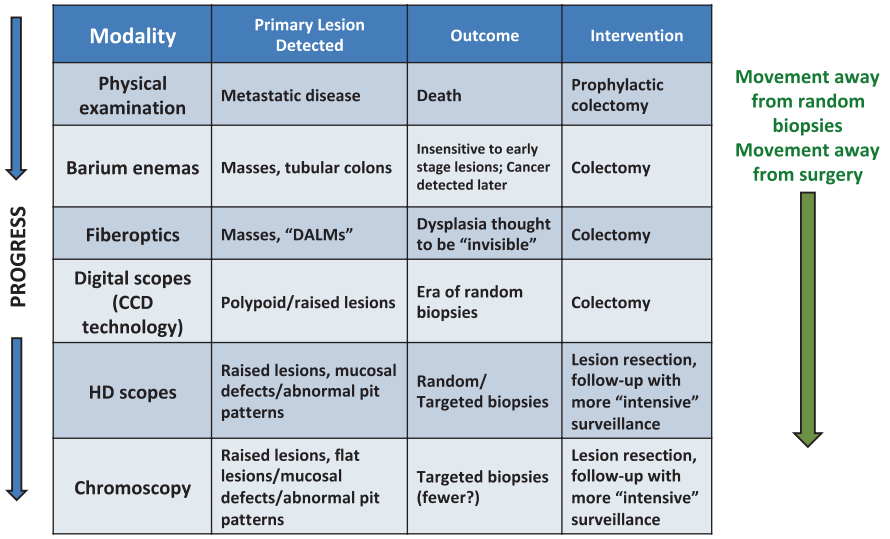

Modality	Primary Lesion Detected	Outcome	Intervention
Physical examination	Metastatic disease	Death	Prophylactic colectomy
Barium enemas	Masses, tubular colons	Insensitive to early stage lesions; Cancer detected later	Colectomy
Fiberoptics	Masses, "DALMs"	Dysplasia thought to be "invisible"	Colectomy
Digital scopes (CCD technology)	Polypoid/raised lesions	Era of random biopsies	Colectomy
HD scopes	Raised lesions, mucosal defects/abnormal pit patterns	Random/ Targeted biopsies	Lesion resection, follow-up with more "intensive" surveillance
Chromoscopy	Raised lesions, flat lesions/mucosal defects/abnormal pit patterns	Targeted biopsies (fewer?)	Lesion resection, follow-up with more "intensive" surveillance

Fig. 7.1 Evolution of cancer prevention in IBD. As time and technology have progressed, there has been a movement away from empiric treatments, a need for random biopsies, and total colectomy

techniques, the approach has shifted away from random nontargeted sampling biopsies and total proctocolectomy in the setting of neoplasia and towards targeted biopsies, active surveillance, and segmental resections if surgery is needed.

In this chapter we describe the evolving evidence related to cancer prevention in chronic colitis, with an emphasis on newer technologies and how they have changed the approach to detection and follow-up of neoplasia. We propose a rational approach to the incorporation of selective chromoendoscopy and outline the evidence gaps for future study and guideline development (Fig. 7.1).

Risks of Neoplasia in Ulcerative Colitis and Crohn's Disease

Ulcerative Colitis

Although ulcerative colitis (UC) patients are believed to be at an increased risk of CRC, it appears that the risk has been declining. Multiple surveillance studies from the UK, Denmark, Sweden, and Canada demonstrate updated incidence rates (IR) of CRC among IBD patients that range from similar to the general non-IBD population to as high as 10.8% at 40 years from symptom onset [1–3]. Despite continuing to show an overall increased risk of CRC, the most recent 40-year surveillance experience at St. Mark's Hospital in the UK demonstrated decreasing rates of both advanced CRC and interval CRC, with cumulative incidence of CRC to be 0.1% in the first

decade since the UC symptom onset, followed by 2.9%, 6.7%, and 10.0% by second, third, and fourth decade, respectively [4]. A variety of reasons for this apparent decrease in CRC incidence have been proposed. It may be that this change represents simply a more accurate measure of the rate of cancer (better designed and performed studies) or a result of improved effectiveness of surveillance colonoscopy. Improved medical control of inflammation and primary chemoprotection may also be a contributing factor; however, such studies have not been performed yet. It is also possible that the diminished incidence of CRC is due to removal of the highest risk medically resistant patients because they have had effective surgical intervention.

Risk factors for dysplasia and CRC in chronic UC may be divided into those that are "immutable" or, in other words, inherent to the disease, and those that may be modifiable, which are primarily related to control of inflammation. The immutable risks include family history of CRC [5–8], diagnosis of PSC [9], longer duration of disease, younger age of diagnosis [10, 11], and greater extent of involved colonic mucosa. Prior studies have identified a 10–15-fold increase of CRC in patients with pancolitis, 2–3-fold increased risk in patients with left-sided colitis, and no significant increased risk when the disease is confined to the rectum [10].

The potentially modifiable risk factors include degree of inflammation over time, the presence of pseudopolyps, which may represent the effect of severe inflammation that has healed, and backwash ileitis, which may represent a more extensive and active form of panulcerative colitis [12]. Although higher degree of inflammation is associated with increased risks of CRC, the converse has not yet been shown (controlling inflammation OR treating to mucosal healing) [11, 13, 14]. The challenge of proving this point lies in the lack of understanding whether the severity of inflammation sets the risk early in the disease course and whether that risk can indeed be successfully modified later. In the absence of evidence to the contrary, it is reasonable, for multiple reasons, to recommend active medical therapy to control inflammation.

Concomitant PSC has been confirmed to be a potent independent risk factor for CRC, but the pathogenetic reasons are unknown. A meta-analysis by Soetikno et al. describes an odds ratio of CRC of 4.09 (95% CI, 2.89–5.76) when compared to UC patients without PSC [9]. Given the associated higher rates of right-sided CRC in this IBD group, carcinogenic bile acid is believed to possibly play a role [15, 16]. Another suggested cause is thought to be related to the well-described rate of subclinical disease in this patient population, which may lead to long exposure to active inflammation and a delayed diagnosis [17, 18]. Due to this increased risk, it is recommended to perform surveillance annually in this unique high-risk subset of UC patients, and in patients without a known diagnosis of colitis who are diagnosed first with PSC, immediate colonoscopy is advised.

The presence of prior dysplasia or a stricture is also associated with increased risk of neoplasia in UC [19–21]. In the past, if any dysplasia was identified, even if it was unifocal low-grade dysplasia (LGD), proctocolectomy was recommended [19, 22] due to concern for the presence of synchronous unidentified adenocarcinoma. In recent years, improvement in optical technologies and higher detection rates of neoplasia has led to the appreciation that not all dysplasia requires surgical

Table 7.1 Risks of neoplasia in colitis: those that are unchangeable and those that are potentially modifiable with treatment of inflammation

Immutable	Modifiable (potentially)
Male sex	Increased inflammatory activity
Longer duration of disease	Backwash ileitis
Greater extent of colonic involvement	Pseudopolyps
Family history of CRC	Prior dysplasia
Younger age of diagnosis	Mass/stricture
PSC	

removal of the colon. There is an emerging change in practice and more comfort with endoscopic resection and "active surveillance" after the finding of some types of dysplasia [23]. This is described in greater detail below (Table 7.1).

Crohn's Disease

Measuring the risk of CRC in Crohn's disease (CD) poses several challenges relating to the patchy nature of the disease and difficulty in controlling disease extent due to the fact that many patients do not have colonic involvement. Despite these challenges, several studies have been able to adjust for disease location and offer estimates of CRC risk in colonic CD.

A meta-analysis by Jess et al. [24] estimated an overall standardized incidence ratio (SIR) for CRC in CD of 1.9 (95% CI: 1.4–2.5). As would be expected, the risk was significantly higher for colonic and rectal CD than for pure ileal and ileocolonic disease (SIR = 4.3; 95% CI: 2.0–9.4 for colonic; SIR = 2.6; 95% CI: 0.8–8.2 for ileocolonic; and SIR = 0.9; 95% CI: 0.2–4.1 for pure ileal disease) [24].

Additional studies of CRC risk in CD have identified many of the same risk factors for CRC as UC patients, including younger age at diagnosis, greater extent of colonic involvement, and longer disease duration [25–28].

In addition, it appears that bypassed segments of bowel [29] and perianal fistulae [30] in CD are also sites of increased risk for neoplastic transformation and warrant heightened vigilance. Furthermore, bowel strictures in CD may harbor dysplasia or cancer [31] and should be carefully biopsied and resected if a scope cannot traverse them. Unlike UC, however, strictures in CD may be benign given the transmural inflammation of this condition [32].

Limitations to Assessment of Risk of CRC in IBD

The risks for cancer in IBD have been determined from a large number of studies of various designs and statistical power. However, there have been significant challenges to accurate assessment, including different definitions of disease extent

(endoscopic vs. histologic) and inability to control for confounding variables (due to absence of these variables in the datasets or lack of knowledge about the risks). For example, the knowledge that the degree of inflammation is an independent risk for dysplasia and CRC is a recent discovery, and therefore, control of this essential variable is missing from all the prior studies of risk and studies of chemoprevention. Therefore, interpretation of the risks outlined above must take into considerations these limitations [33].

Guidelines

A number of guidelines have been published over the past decade in the USA and the UK to assist gastroenterologists in their approach to surveillance of dysplasia and cancer in IBD [21, 34–37]. We summarize the existing guidelines here, but acknowledge that the state of the science has advanced beyond these guidelines [38], so include them for the sake of thoroughness for the reader and as a point of historical reference, followed by our discussion of advances and changes that are expected to be incorporated into future guidelines. There is a separate section on the recently published SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients) consensus paper.

According to the current guidelines, the initial screening colonoscopy in all UC patients should be performed 8–10 years after onset of symptoms [21]. The purpose of this initial screening exam is to identify dysplasia or cancer, if present, as well as to evaluate possible reclassification of disease extent. The extent of disease in a given UC patient should be considered the greatest extent of involvement documented on either gross or histologic exam at the time of diagnosis of UC or at initial screening colonoscopy (but recognize that studies of extent of colitis and risk of CRC were all based on barium or endoscopic extent and not histologic assessments). Patients with CD of the colon should be managed in an identical manner as UC patients of comparable extent of colonic involvement. CD patients with at least one-third of their colon involved are considered to have extensive colitis. Patients with left-sided or extensive colitis (UC or CD) who have a negative screening examination should continue periodic surveillance at an interval of every 1–2 years. The exceptions are patients with colitis and coexistent PSC, in whom annual surveillance should begin at the time of PSC diagnosis. Because of the traditional understanding of dysplasia occurring in flat mucosa, a systematic approach to mucosal sampling has been recommended, which involves four quadrant random biopsies at 10-cm increments throughout the colon in addition to targeted biopsies of suspiciously abnormal mucosa. Although this practice is changing, the existing guidelines still recommend the approach.

All abnormal biopsies' results should be confirmed through independent review by a second pathologist. A finding of indefinite dysplasia should prompt accelerated surveillance with a repeat exam in 3–6 months. Management of LGD is a subject of debate among experts with no clear consensus on optimal management (see below).

In the setting of LGD, physicians should initiate an informed discussion with their patients regarding the risks and benefits of immediate surgery versus heightened colonoscopic surveillance. An accelerated program of surveillance colonoscopy every 3–6 months should be pursued. Endoscopically discreet polyps may be removed as they would be in non-IBD patients, but if the polypoid lesion contains dysplasia, the management and follow-up recommendations will depend on the grade of dysplasia, the number of dysplastic lesions, as well as other risk factors for CRC. As described above, available evidence suggests that complete removal of polypoid dysplasia may be safely followed, albeit with more intense surveillance [23, 39–41].

Outcomes of Dysplasia

In the past, it was observed that precancerous dysplasia was a specific risk factor for concurrent adenocarcinoma. In addition, dysplasia was often invisible by barium radiography and early-technology endoscopes. Therefore, identification of dysplasia was based only on pathologic review of randomly obtained biopsies. There was a fundamental principle of "field abnormalities" related to the idea that if one area of the chronically inflamed epithelium became dysplastic, other areas were at equal risk, and, therefore, were likely to harbor invisible dysplasia as well. This was borne out from early observational and mostly retrospective studies. Most concerning was the identification of concurrent adenocarcinoma in patients who had dysplasia identified.

The finding of LGD was associated with a risk of a synchronous (concurrent) adenocarcinoma at the time of proctocolectomy of 19% [19]. This risk was deemed unacceptable, and therefore, the recommendation for proctocolectomy when LGD was identified was developed. A study from Mount Sinai Hospital in New York City, published by Ullman and colleagues in 2003, demonstrated that of 46 patients with flat LGD, who did not undergo immediate proctocolectomy, seven patients subsequently developed CRC. Importantly, five of seven were stage II or higher by the time they had their surgery [22]. These findings led to the conclusion that even for unifocal LGD surveillance was an insufficiently safe practice. The limitations to this study, however, included its retrospective design, small numbers, and biased population of patients who either refused colectomy when it was recommended or who has other features that led to their physician delaying a surgical approach. Despite the findings in the Ullman and Bernstein studies as well as others, there was ongoing confusion in the field about the approach to LGD. The approach to high-grade dysplasia HGD, however, has been less controversial or confusing. In earlier studies, it was associated with as high as 42% likelihood of a concurrent adenocarcinoma at the time of immediate proctocolectomy [19].

In addition, studies from the St. Mark's Hospital in the UK and from the University of Chicago have demonstrated that, despite historical teachings and descriptions, most dysplasia in ulcerative colitis is visible [4, 42, 43]. Of interest in these retrospective analyses was that most of those colonoscopies were done with standard definition colonoscopes. In the University of Chicago experience, cancer

was never missed [43]. These findings challenged the old descriptions of invisible dysplasia and ushered in an era in which improved technology was recognized as changing the approach to prevention.

Subsequent to the Ullman/Mt. Sinai study, there have been analyses of patients who had dysplasia and did not undergo immediate proctocolectomy. In a study by Pekow et al., the outcome of LGD was distinguished based on whether it was in flat mucosa or a raised discreet lesion. The raised LGD, which, in most cases, had been removed completely endoscopically, was associated with a significantly lower likelihood of progressing to advanced neoplasia of HGD or cancer than in patients with dysplasia in flat lesions [44]. One of the interpretations of these findings is that raised neoplasia may behave more similarly to the sporadic adenoma-type polypoid neoplasia than flat lesions, which may, in fact, be colitis-associated and be progressing along a different molecular or genetic pathway [45].

Most recently, the understanding that advances in endoscopic technology enable better visualization has challenged the terminology of "invisible" neoplasia. Because new technology enables more visualization than ever before, surveillance can be performed more accurately. The concepts of synchronous "hidden" lesions and concurrent adenocarcinoma are removed from the modern assessments. Krugliak Cleveland et al., at the University of Chicago, described that patients who had LGD found with high-definition colonoscopy never had a missed synchronous adenocarcinoma [46]. Additional studies have supported these findings [47]. Therefore, in the current era, careful colonoscopy with advanced technologies has eliminated or at least virtually eliminated the principle of a "missed" concurrent adenocarcinoma in the presence of LGD. In contrast, the approach to HGD has not changed very much, although an endoscopically resectable lesion with HGD may, in some patients, eliminate the need for colonic resection [48].

One of the challenges that continues to plague the field of cancer prevention in IBD is the appreciation that dysplastic lesions be adequately described and characterized. In fact, colonoscopy reports and communication among gastroenterologists and surgeons is not standardized, and this has led to confusion in follow-up and subsequent efforts to develop a standard approach of reporting [49, 50].

Movement Away from the Random Biopsy Paradigm

Because of previous concerns about finding dysplasia that was not visible endoscopically, a strategy of systematic mucosal sampling had been advocated. In a retrospective analysis, it was found that at least 33 biopsies are required to detect dysplasia with 90% sensitivity and 64 biopsies are needed to achieve 95% sensitivity [51, 52]. Although consensus guidelines incorporate this finding and recommend 30–40 biopsies, subsequent follow-up of such a practice has revealed that this is both highly inefficient [53] and not being performed by most gastroenterologists. In a survey of 300 gastroenterologists, more than half indicated that they routinely obtained less than the number of recommended biopsies [54]. In addition, in

numerous reviews of prior random biopsy schemes, the yield of random biopsies was so low as to make it an impractical approach. In one study of 167 patients who underwent 466 surveillance colonoscopies, only 24 of 11,772 random biopsies detected neoplasia. This was a 0.2% per biopsy yield. The authors concluded that random biopsies were not efficient and suggested that given advancing technologies and visibility such an approach is impractical [55].

Movement Away from Proctocolectomy

An additional area that is evolving is performing less extensive surgical resections in patients with dysplasia. This has been advocated due to the less-than-ideal outcomes of many patients with ileal-pouch-anal anastomoses (IPAA) and with the appreciation that appropriate imaging and active surveillance is safe in specific patient types. Therefore, in a patient who may have a poor functional outcome from an IPAA, or is not a candidate for an IPAA due to the diagnosis of CD, their age, or body mass, a subtotal colectomy is reasonable if the patient does not have dysplasia in the distal colon, the surgical expert feels that it is technically feasible, the patient is in stable clinical and endoscopic remission from their IBD, and the patient and practitioner are willing and able to perform ongoing active surveillance of the remaining segments of bowel. It is likely that the quality of life of such patients is significantly better than those who receive temporary ileostomies, permanent ileostomies, or malfunctioning IPAAs [56]. Our review of patients who underwent subtotal colectomy with sigmoid or ileorectal anastomosis identified no patients who had cancer, and of those who had recurrence of dysplasia, the lesions were all low-grade and easily identified [57].

Advanced Technologies for the Optical Detection of Neoplasia

Detection rate of neoplasia depends on the quality of the surveillance examination, including the quality of the colonic preparation, technique and experience of the endoscopist, the optical technology used, as well as the quality of the pathologic review. Most academic centers and many community-based practices are currently using high-definition colonoscopes. The high-definition scopes have enabled more careful evaluation and visualization of the mucosa and challenged the status quo in our use of random biopsies and follow-up. Second, a variety of optical and digital enhancements have been proposed.

A specific advancement is narrow band imaging, the electronic filtering of specific wavelengths in order to better visualize the mucosa. The most common type of narrow band imaging is the elimination of red wavelengths to blunt the interference of blood vessels with visualization of the epithelial mucosa. Although narrow band imaging has been associated with increased detection of polypoid neoplasia in the

non-IBD population, there are at least four studies in chronic colitis that have failed to demonstrate a benefit of narrow band imaging over white light [58–61]. Therefore, despite the ease of flipping a switch for narrow band imaging in the colon of patients with colitis, it is not currently advocated as a routine approach to colonic neoplasia detection in chronic colitis.

On the other hand, there have been numerous studies of dye-spray chromoendoscopy, which have demonstrated superiority of detection of dysplasia compared to that with white light. The majority of these studies to date have been with standard-definition colonoscopes. In a meta-analysis of randomized control trials comparing the incremental yield of dysplasia detection between dye-spray chromoendoscopy with methylene blue or indigo carmine compared to white light endoscopy, the overall analysis favored dye-spray chromoendoscopy with a 6% incremental yield and a confidence interval of 3–9%. This included seven studies of tandem imaging [23]. There are several studies that have further examined the utility of high-definition colonoscopy in IBD dysplasia detection. A study by Subramanian and colleagues demonstrated that high-definition colonoscopy with white light identifies more dysplasia than standard definition colonoscopy [62].

In a study by Mohammed and colleagues, more dysplasia was detected per patient with high-definition chromoendoscopy compared to high-definition white light, but the number of overall lesions was quite small with six lesions in five patients compared to 14 lesions in 11 patients [63]. In an additional study by Deepak and colleagues, there was a greater proportion of flat lesions visualized with chromoendoscopy and high-definition scopes when compared to high definition with white light [64]. In 95 patients chromoendoscopy after a white light exam identified 40 new lesions in 30 of the patients. All of these studies are challenged by small numbers of patients and sometimes surprising yields of neoplasia in such small numbers, suggesting that these are the high risk patient populations and extrapolation to the general population is quite challenging. In two additional presentations high-definition white light did not miss cancer in patients with LGD, and subsequent studies have demonstrated that surveillance biopsies surrounding dysplastic lesions did not miss additional dysplasia, and therefore, had no additional predictive value, suggesting that the previous recommendation (AGA technical review) to obtain biopsies around polypoid or dysplastic lesions was no longer necessary [46, 65]. In a large retrospective study by Mooiweer et al. of 440 colonoscopies in 401 patients, chromoendoscopy had a 10% dysplasia detection rate with a 95% confidence interval of 6–14% while white light endoscopy had an 11% dysplasia detection rate with a 95% confidence interval of 9–13%. The neoplasia detection rate was similar in both groups and not statistically significantly different. This suggested that chromoendoscopy was not incrementally better than high-definition colonoscopy alone [47] (Fig. 7.2).

Two studies have looked at chromoendoscopy after white light colonoscopy for dysplasia to answer the question of whether chromoendoscopy is of appropriate utility as a follow-up procedure after a white light exam identified dysplasia. Deepak and colleagues described a retrospective analysis of 95 patients in whom 72 index lesions were found with white light and then underwent up to two additional chromoendoscopy follow-up examinations. The conclusion from this study was that

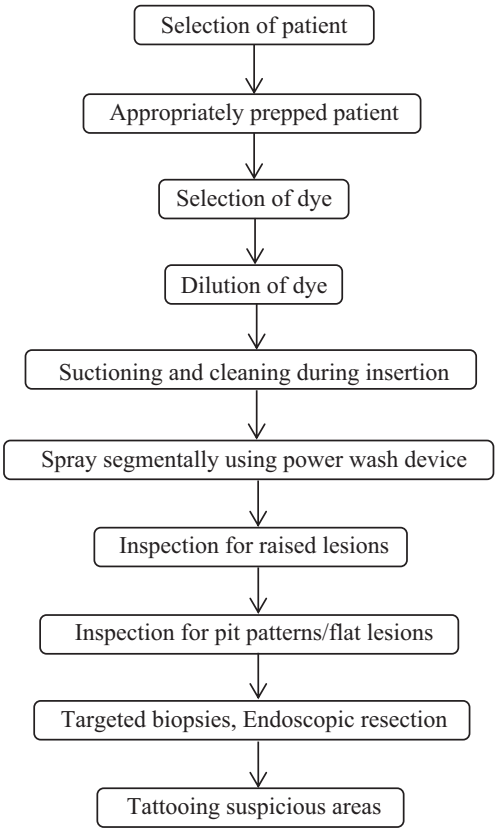

Fig. 7.2 A suggested approach to chromoendoscopy [86]

chromoendoscopy frequently identified additional lesions after a white light screening exam [64]. A study performed at our institution in 37 patients had 28 additional lesions identified during chromoendoscopy in follow-up and had a similar conclusion to the Deepak study [50].

One of the tandem studies comparing white light to chromoendoscopy described their follow-up in a recent publication. Marion and colleagues from Mount Sinai described the 102 patients in their original series who underwent chromoendoscopy. Ten of them had a colectomy due to unresectable LGD, and no CRCs were identified. Their conclusion was that using chromoendoscopy was safe and effective and following these patients was appropriate given that there was no loss of chance in identifying high-risk patients who finally went to surgery later [66, 67]. The limitation to their study was the small number of patients and limited follow-up, but it certainly adds important information to these discussions.

On the whole, the ongoing debate about whether chromoendoscopy should be performed as standard for surveillance in patients with chronic colitis has not been settled. It appears that with the addition of high-definition colonoscopy, chromoendoscopy does not add substantial incremental benefit. What is not sufficiently

Table 7.2 Suggested individualized approach to surveillance and cancer prevention: combination of patient and disease-related factors with dysplasia-related factors can assist in stratification of risk for cancer, surveillance intervals, and need for surgery

Patient/disease-related factors	Dysplasia-related factors
PSC	Grade Indefinite vs. low-grade vs. high-grade
Family history of CRC	Morphology Flat vs. polypoid "Invisible" vs. raised
Duration of disease	Field effect/synchronicity Unifocal vs. multifocal
Extent of disease	Longitudinal follow-up? Dysplasia on a single exam vs. metachronous lesions on serial exams
Sex	
Willingness and ability to follow recommendations	

addressed in any of these studies is the learning curve or the expertise of the endoscopist and how that plays an additional role in the use of high-definition white light or high definition with augmented imaging (Table 7.2).

SCENIC Consensus

The SCENIC consensus statements published in multiple society journals simultaneously in 2015 were developed by an international group of gastroenterology, surgery, pathology, and patient representatives who analyzed all available data in a number of systematic reviews and meta-analyses and developed specific recommendations based on the evidence and their opinions [23, 68]. The findings and recommendations of SCENIC included the following: high-definition colonoscopy is recommended over standard definition; patients with endoscopically resectable dysplastic lesions can be followed rather than go to surgery; dye-spray chromoendoscopy should be used when standard definition scopes are used; and that a second opinion from an expert pathologist is required when dysplasia is identified.

The group was undecided about whether random biopsies might be avoided, but there was active discussion about whether appropriate imaging and technology could eventually eliminate this practice. The issue of chromoendoscopy as standard of care for surveillance when high-definition scopes are used remained incompletely answered.

Table 7.3 Unanswered questions about chromoendoscopy in cancer prevention of IBD

Does chromoendoscopy change clinically meaningful outcomes?
Which patients benefit from chromoendoscopy? Should it be performed in all patients and all exams?
Does chromoendoscopy with high-definition scopes increase detection yield compared to high-definition scopes alone?
Which dye should be used?
What type of training in technique and pit pattern recognition is necessary?
How should quality chromoendoscopy be defined?
How many chromoendoscopic exams should be performed to achieve competency?

Our Recommendations for Colorectal Cancer Prevention in IBD: A Practical Approach

The field is moving toward an individualized approach to risk and dysplasia detection. We advocate a compounded risk factor analysis that includes disease type, duration and previous inflammatory activity, and the type of dysplasia identified (flat, raised, unifocal, or multifocal as well as grade and metachronicity over time). Combining all these risks into a discussion with the patient can lead to a more informed decision about active surveillance, surgical approach, and risk management (Table 7.3).

Although not entirely clear, specific high-risk patients may benefit from active surveillance using chromoendoscopy such as patients with PSC and pancolitis. Another group to consider is those with previous dysplasia identified by white light as described in the Deepak and Rubin studies above. Perhaps limited dye-spray chromoendoscopy can be used around lesions that are identified by white light during colonoscopy to better visualize the lesion and define it for endoscopic removal or labeling. It is important to acknowledge that consensus in the field around this "selective chromo" approach has not been reached, and there remain a number of unanswered questions and an undefined training pathway or competency for the best approach to chromoendoscopy in IBD.

If using high-definition colonoscopy equipment, we believe that in a patient with a clean colon and complete mucosal healing there may not need to be random biopsies, other than to assess for disease extent (histologically) or histologic disease activity. Despite our recommendation, it is notable that this has not yet been widely adopted and that a learning curve for the identification of subtle but clinically relevant dysplastic lesions is still in development by the American Society of Gastrointestinal Endoscopy and other groups [69].

How to Perform Chromoendoscopy: Practical Advice

There are general recommendations for the performance of effective chromoendoscopy. First is the identification of an appropriate patient (see Table 7.3 and above comments). It is important that the colon be completely clean, and although different

types of preps are advocated, we use a split-dose polyethylene glycol prep when possible. A sodium-phosphate prep such as the tablet formulation is also possible and actually provides a very nice and dryer catharsis but is not used often due to concerns about electrolyte abnormalities [70]. Next, unlike typical colonoscopies in which suctioning and cleaning is done during withdrawal, we advocate suctioning during insertion so that retained fluid does not impair or dilute effective dye spray throughout the colon. After reaching the cecum (or ileum if assessment is needed), we have our assistants switch the power wash device to a preprepared bottle of dye. Choice of dye varies by institution and endoscopist, but we prefer methylene blue due to its cytoplasmic absorptive properties. Indigo carmine is a surface dye and tends to pool more often and requires more spraying and patient positioning in order to use it. Sometimes choice of dye is influenced by availability and national shortages, however. The "recipe" for our methylene blue is two 10 mL vials of 10 mg/ mL (1%) mixed into 250 cc of sterile irrigation fluid (this is 0.37% concentration).

The Food and Drug Administration has issued a safety warning for methylene blue related to certain psychiatric medications, including selective serotonin reuptake inhibitor drugs [71]. However, this is relevant only when methylene blue is used intravenously, and there are no data to suggest that this is a risk with the dye-spray and diluted methylene blue. In addition, concerns have been previously raised about the carcinogenic risk with methylene blue, but there are insufficient data in humans to limit our use at this time [72–74].

During withdrawal of the scope, segmental exams are performed, first with white light, then with limited power wash spraying of the colonic mucosa. The spray is aimed at the "top" of the colon, so that gravity can assist with passive distribution of the dye and even absorption. This also limits pooling and is more efficient. Raised and flat lesions are easily identified initially. Recognition of abnormal pit/crypt patterns occurs next, and is definitely a more difficult part of this examination, given the large surface area of the colon and the lack of a defined training pathway to learn about this. Targeted biopsies and endoscopic resection are performed subsequently. Bleeding can obscure interpretation of the dye spray, so it is critical to inspect the entire segment before obtaining biopsies and attempting resections. It is important to tattoo any areas that are not easily re-identifiable or where there may be specific concerns, in order to find them again on a future examination [75].

In usual fashion, the colon is decompressed during withdrawal, and in recovery, the patient should be informed that they will see blue in the toilet for a few days and have green-tinged urine for about 24 h [76].

Upcoming Technologies

There are a number of upcoming technologies that may add to our approach to surveillance and cancer prevention in patients with chronic colitis. Laser endomicroscopy enables in vivo histologic analysis. Given the high magnification and sensitivity of such an approach, it must be partnered with high-definition scopes and

chromoendoscopy to identify suspicious lesions prior to the use of the laser endomicroscopy and targeted biopsies. In a prior study, chromoendoscopy-guided laser endomicroscopy had a higher sensitivity and specificity than chromoendoscopy alone for detection of dysplasia (Buchner and colleagues) [77]. More recently, its use in CD was not particularly helpful [78]. Further analysis and careful application of this technology is required.

Flexible spectral imaging color enhancement is another tool with similar utility to chromoendoscopy. This enables image display in 1 of 10 preset wavelengths in real time. It is similar to narrow band imaging but offers more resolution and improved ability to assess structural and vascular patterns on the surface of polyps over white light. In a non-IBD study, this technology was able to distinguish between adenomas and hyperplasia or normal tissue with a high degree of sensitivity [61, 79]. However, this has not been sufficiently studied in the IBD setting.

An additional technology called "virtual chromoendoscopy" has been described. Such digital chromoendoscopy was not better than dye-spray chromoendoscopy in 75 patients who were assessed using high-definition white light, dye-spray, and the digital chromoendoscopy approach [80].

An additional technology of interest would be molecular beacons, in which intravenously administered antibodies would target specific labels on dysplastic cells which would lead these cells to fluoresce or be highlighted in other ways during chromoendoscopy or standard colonoscopy or black light or other techniques [81]. While this is an exciting possibility for the future, studies have not been completed in order to advocate its use at the current time.

Evidence Gaps and Future Studies

Although we have made good progress, there is clearly much room for improvement in our understanding of the neoplastic risks in patients with IBD. A variety of approaches are being explored, although none are likely to change our current practice at this time. In the non-IBD population, using the Paris classification for polypoid lesions is advocated [82]. The use of the Paris classification to better characterize the morphology of raised, flat, and depressed lesions in IBD has not been described or validated, but may have a role in the future. Using such standardized terminology may enable better understanding of prognostic value of specific types of dysplastic lesions in the colon. In addition, the ongoing studies of high-definition scopes with or without optical enhancements will clarify further whether it is truly safe and appropriate to perform active surveillance rather than recommend immediate surgery.

There has been much interest in the identification of biomarkers that are associated with dysplasia or early-stage cancer development. Some have been in peripheral blood and others have been in tissue. Unfortunately, none have been sufficiently sensitive or specific to warrant their use in this field [83, 84]. In addition, despite the positive studies in patients with sporadic polyps and cancer, an array of fecal DNA and molecular markers has not been sufficiently sensitive for use in IBD [85].

The additional area of great interest in the field is the adequate control of inflammation through appropriate use of medical management. Given the acknowledgment that chronic inflammation is the underlying cause for most neoplastic transformation, appropriate control of the disease both symptomatically and by mucosal healing is gaining recognition as a primary goal of management which is expected to reduce the likelihood of downstream neoplastic changes. Incorporation of treatments to achieve the target of mucosal healing should be part of a cancer-prevention strategy but has not yet replaced the need for careful surveillance colonoscopies.

Conclusions

The future of cancer prevention in IBD continues to rely on the predominant strategy of identification of neoplastic lesions using direct visualization. While there is hope in future technologies, including fecal markers, the current approach relies on identifying at-risk patients and carefully performing colonoscopies. High-definition colonoscopy with white light remains the standard approach at the current time. While chromoendoscopy is recommended when standard-definition scopes are used, its utility in high-definition scopes and even with high-risk-patient types has not been fully clarified. In addition, in the absence of further training protocols and learning curves as well as competency requirements, dye-spray chromoendoscopy is not yet ready for standard of care utilization.

Understanding an individual patient's risk for dysplasia and knowing the options for active surveillance or surgery when dysplasia is found is important for the practitioner and patient alike. It is now fully appreciated that most dysplasia is visible and that patients with endoscopically resectable dysplastic lesions do not require surgery. Instead, approaches to minimize interventions and minimize surgical approaches have begun to gain acceptance and are supported by some early evidence.

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Chapter 8
Pathological Diagnosis of Inflammatory Bowel Disease

Le Shen and Christopher R. Weber

Key Points

- Pathology is essential to the management of inflammatory bowel disease (IBD).
- The pathologist currently relies almost entirely on conventional gross and microscopic examination of hematoxylin and eosin stained tissue.
  - Key histologic features and the pattern of disease help to differentiate between ulcerative colitis (UC), Crohn's disease (CD), and other disease processes.
  - Assessment of severity of inflammation, or disease activity, helps guide therapy.
  - Due to the increased risk of cancer in patients with IBD, it is important to evaluate for dysplasia in all biopsies from IBD patients.
- Genetics will likely play an important role in IBD diagnosis and management in the near future.

Inflammatory bowel disease (IBD) is associated with long-term morbidity and mortality in 1.6 million Americans. Treatment of IBD requires a multidisciplinary approach which relies heavily on pathology. The pathologist helps to subclassify IBD as ulcerative colitis (UC) or Crohn's disease (CD) according to the pattern of inflammation present. Pathological assessment of disease activity is also important in guiding and evaluating response to therapy. Finally, since IBD is associated with an increased risk of developing cancer, it is critical that the pathologist assess for the presence of dysplasia in all biopsies from patients with IBD. Despite the increasing use of molecular approaches by the modern pathologist, diagnosis and evaluation of

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IBD is achieved principally through microscopic examination of hematoxylin and eosin (H&E) stained tissue and gross examination of surgically resected specimens. However, as our understanding of IBD increases, there is likely to be an ever-increasing role of genetics in IBD diagnosis and assessment.

Histopathological Assessment of IBD

Pathological assessment of tissue from patients with IBD is performed by routine examination of hematoxylin and eosin stained slides as well as gross examination of surgical specimens. In most cases, there are four important questions that the pathologist needs to answer. First, since IBD is a chronic disease process, the pathologist needs to determine if there is histological evidence of a chronic injury, and, in doing so, rules out self-limited disease processes. Second, in order to define disease activity, the acute, "active" inflammatory infiltrate is quantified. Third, the pathologist assesses for gross or microscopic features which can be used to differentiate between UC, CD, or some other form of chronic injury. Finally, since there is an increased risk of adenocarcinoma in patients with IBD, the pathologist always assesses for the presence or absence of dysplasia.

Establishing the Presence of Chronic Injury

A critical question that the pathologist must consider when evaluating the histopathology of a patient with suspected IBD is whether the hallmark histologic features of chronic injury are present. Chronic injury occurs secondary to relapsing and remitting inflammation which occurring over months to years, not days to weeks. In the absence of chronic injury, an acute, often self-limited process such as infectious colitis or acute NSAID injury is more likely. Three principle features of chronic injury are architectural distortion, basal lymphoid hyperplasia, and metaplastic epithelial changes.

Architecture In normal colon and small intestine, crypts are spaced evenly and extend to the muscularis mucosae (Fig. 8.1), and small intestinal villi are long and slender. The presence of branched crypts, loss of some crypts (i.e., crypt dropout), or blunted or misshapen villi are features of architectural distortion and are indicative of long-term chronic injury.

Metaplasia When one type of well-differentiated cell is replaced by another cell type, this is known as metaplasia and is another feature of chronic injury. The two types which are most commonly observed in the lower GI tract are paneth cell and pyloric metaplasia. Paneth cells normally reside throughout the small intestine and in colonic mucosa close to the ileocecal valve, but the mucosa distal to the splenic flexure should have none (Fig. 8.2) [1]. Similarly, the presence of pyloric glands, normally restricted to gastric epithelium, in the colon or small intestine indicates a chronic disease process (Fig. 8.3).

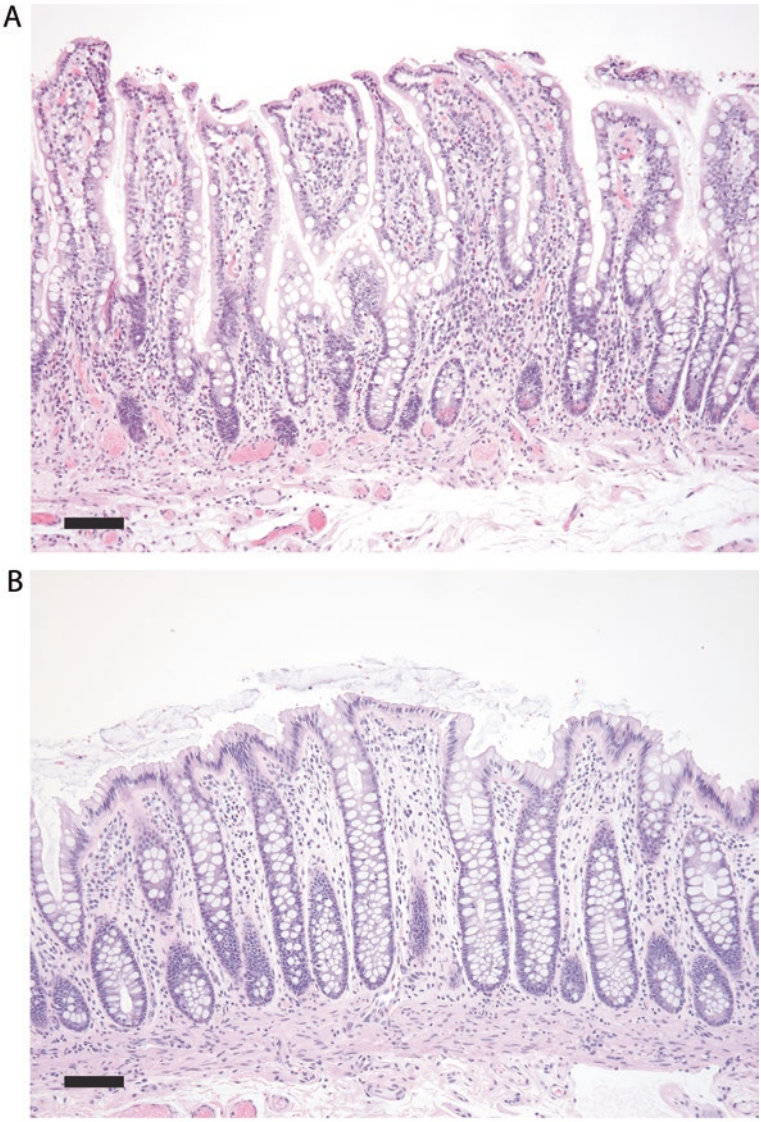

Fig. 8.1 Hematoxylin and eosin staining of normal mucosa reveals normal architecture with long and slender villi in the small intestine (**a**) and evenly spaced crypts which extend to the muscularis mucosa in the colon (**b**). Scale bar 100 μm. The histology in this figure should serve as a reference of comparison for the other figures

Basal Lymphoid Hyperplasia The presence of increased numbers of lymphocytes and/or plasma cells in the basal portion of the lamina propria, where they form a band-like infiltrate, is known as basal lymphoid hyperplasia (i.e., Fig. 8.4b, c vs. Fig. 8.1b). Increased numbers of eosinophils and mast cells may also be occasionally observed in the lamina propria in this location. In contrast, the presence of neutrophils would be more in line with an acute process than a chronic process.

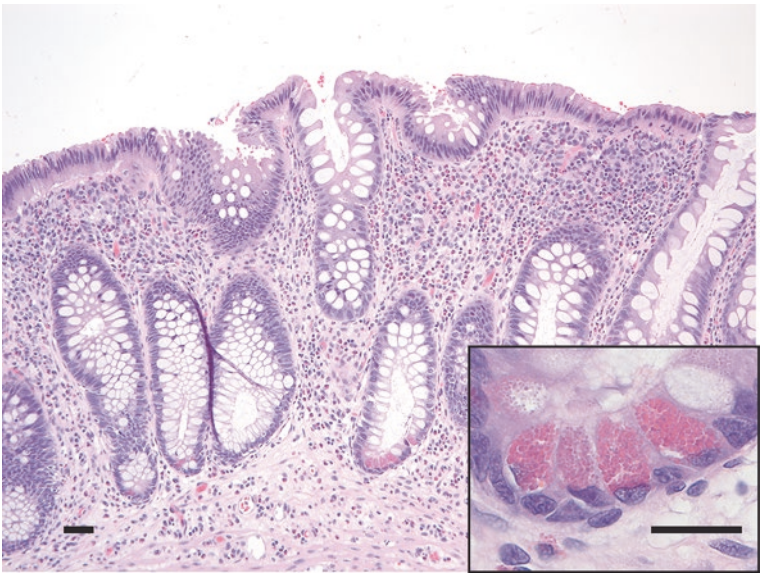

Fig. 8.2 Architectural distortion and the presence of paneth cells in the left colon (*highlighted* in the *inset*) are indicative of chronic injury in this biopsy of a patient with ulcerative colitis. Scale bar 50 μm

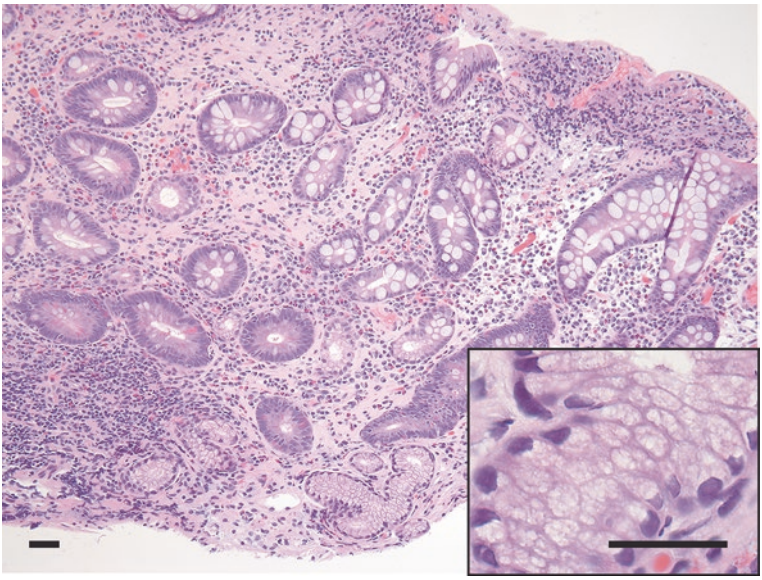

Fig. 8.3 Pyloric gland metaplasia (*highlighted* in the *inset*) appears histologically similar to gastric pyloric glands and is a nonspecific indicator of chronic injury that is often seen in patients with IBD. Scale bar 50 μm

The pathologist uses words such as "patchy," "focal," and "diffuse" to describe the distribution of chronic injury within a single biopsy or across biopsies from the same region. This becomes important when differentiating between UC and CD.

Once chronic injury is identified, it is essential to make clinical–pathologic correlations since the presence of chronic injury does not establish the diagnosis of IBD. Other chronic disease processes need to be ruled out. Similarly, the absence of chronic injury in an individual with long-term well-managed disease does not exclude IBD. In such circumstances historic pathology reports prior to therapy are more informative.

Grading Disease Activity

Disease activity refers to the presence of neutrophils within the epithelium. By definition, IBD occurs on a background of chronic injury; however, activity can occur without evidence of chronic injury. Therefore, a diagnosis of "chronic active colitis" describes the histologic findings of intraepithelial neutrophils superimposed on features of chronic injury. This diagnosis differs from "active colitis," which is present in acute self-limited inflammatory processes devoid of chronic injury. Knowledge of disease severity is important clinically, and many pathologists use scales such as the one below to quantify activity (Fig. 8.4).

1. Quiescent: Features of chronic injury such as architectural distortion or metaplastic changes are present, but intraepithelial neutrophils are not observed (Fig. 8.4a).
2. Mildly active: Scattered neutrophils are seen within the epithelium (Fig. 8.4b).
3. Moderately active: Neutrophils have migrated across the epithelium to collect within crypts and form microabscesses referred to as "crypt abscesses" (Fig. 8.4c). Crypt rupture and destruction can also be observed.
4. Severely active: Crypt abscesses have evolved into erosions and/or ulcerations (Fig. 8.4d).

In the pathological diagnosis, words such as "patchy," "focal," and "diffuse" should be avoided when describing the distribution of active disease, since those words are used to reflect the distribution of the overall disease process.

Defining the Cause of Chronic Injury

Once the diagnosis of chronic disease is established, the next important step is to consider the etiology of the chronic injury. Many non-IBD causes can usually be ruled out from the clinical history. For example, a history of radiation or certain medications such as chemotherapeutic agents or chronic NSAID use may be associated with chronic injury. Some causes of chronic injury, such as mucosal prolapse

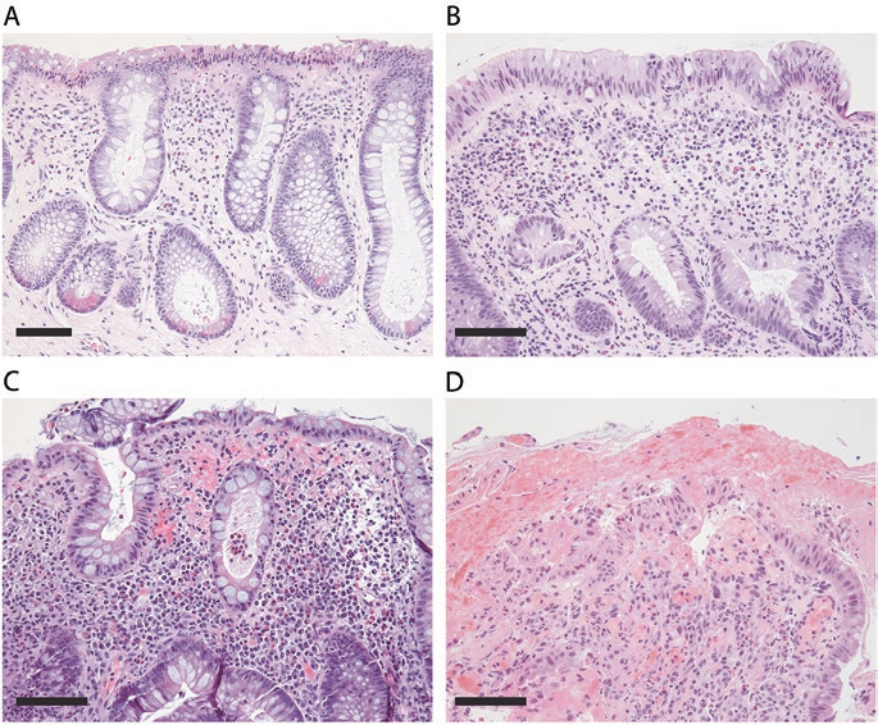

Fig. 8.4 Disease activity is quantified as quiescent (**a**), mildly active (**b**), moderately active (**c**), and severely active (**d**) according to the prominence of the neutrophilic infiltrate and presence or absence of ulcerations. Scale bar 100 μm

or diverticular disease, are usually straightforward to recognize based on the endoscopic appearance. Parasitic infections, such as *Entamoeba histolytica*, can produce deep ulcerations resembling CD and must be considered if a patient provides an appropriate travel history. Ischemia should also be included on the differential diagnosis of segmental chronic injury but can usually be identified by typical histological features of withered or attenuated surface epithelium. Behçet's disease, collagen vascular disorders, and chronic infections are other diseases which may be confused with IBD on the basis of chronic injury. Thus, whenever one is evaluating a patient with suspected IBD, it is essential to start with a broad differential diagnosis. Once the diagnosis of IBD is favored, it is important for therapeutic reasons to subclassify disease as CD or UC. This is achieved through careful gross and histological examination of the pattern of inflammation.

Gross Appearance

UC characteristically starts in the rectum and extends proximally in a continuous manner, sparing the small intestine. On endoscopic or gross examination, involved mucosa appears red, granular, and friable. Areas of hemorrhage and ulceration are

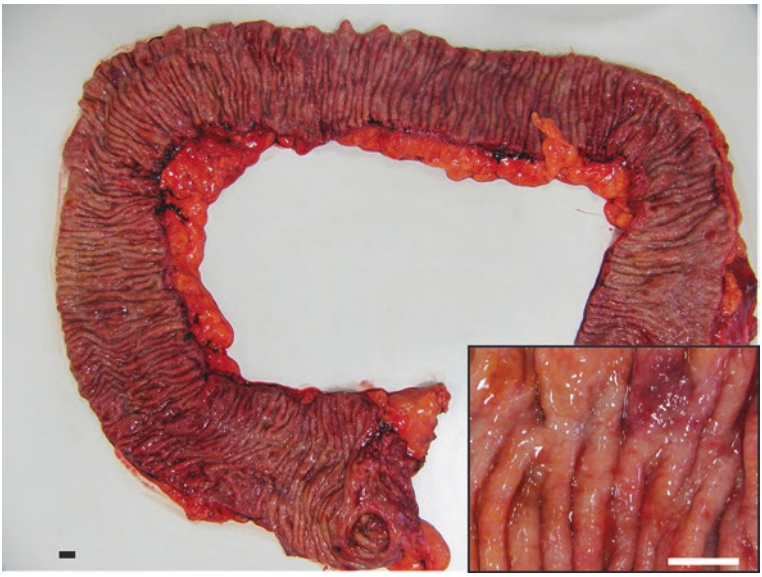

Fig. 8.5 Colectomy specimen from a patient with ulcerative colitis lies flat and demonstrates no strictures. Scale bar 1 cm

present in severe cases. Since inflammation in UC is nontransmural, serosal surface appears smooth and glistening. Additionally, since strictures are absent in UC, specimens usually lie flat when opened (Fig. 8.5).

In contrast to UC, CD may be discontinuous and can involve any segment of the GI tract, from the oral cavity to the anus. Gross examination of the mucosa often reveals a segmental or patchy distribution of disease. Mucosa sometimes has a "cobblestone" appearance due to alternating areas of ulceration and intervening preserved mucosa. Larger intervening areas of normal mucosa are often referred to as "skip lesions." Since inflammation is transmural, the serosa can be involved and often displays "creeping fat" or "fat wrapping" due to fibrous adhesions and increased fat deposition (Fig. 8.6a). Further, when the resection specimens are opened, affected areas do not lay flat as with UC, due to fibrosis and stricture formation (Fig. 8.6b). Fistula tracts and serosal abscess cavities are frequently observed in patients with CD.

Continuous distribution and superficial disease are hallmarks of UC. Occasionally, however, UC may have some features which may be confused with CD. For example, backwash ileitis is the term used to describe mild active distal ileal involvement by UC. The inflammation resolves following total colectomy and is believed to be caused by proximal extension of colonic disease through an incompetent ileocecal valve. The diagnosis is reserved for cases of severe UC pancolitis and when ileitis is mild.

Cecal red patch [2–4] describes UC localized to the appendix and periappendiceal mucosa and can be observed in up to one-third of patients with UC. Histologically, these biopsies resemble mildly active UC (i.e., evidence of chronic injury and intraepithelial neutrophils), and it is important not to misinterpret these patches as "skip lesions." Similarly, pediatric IBD patients may occasionally present with rec-

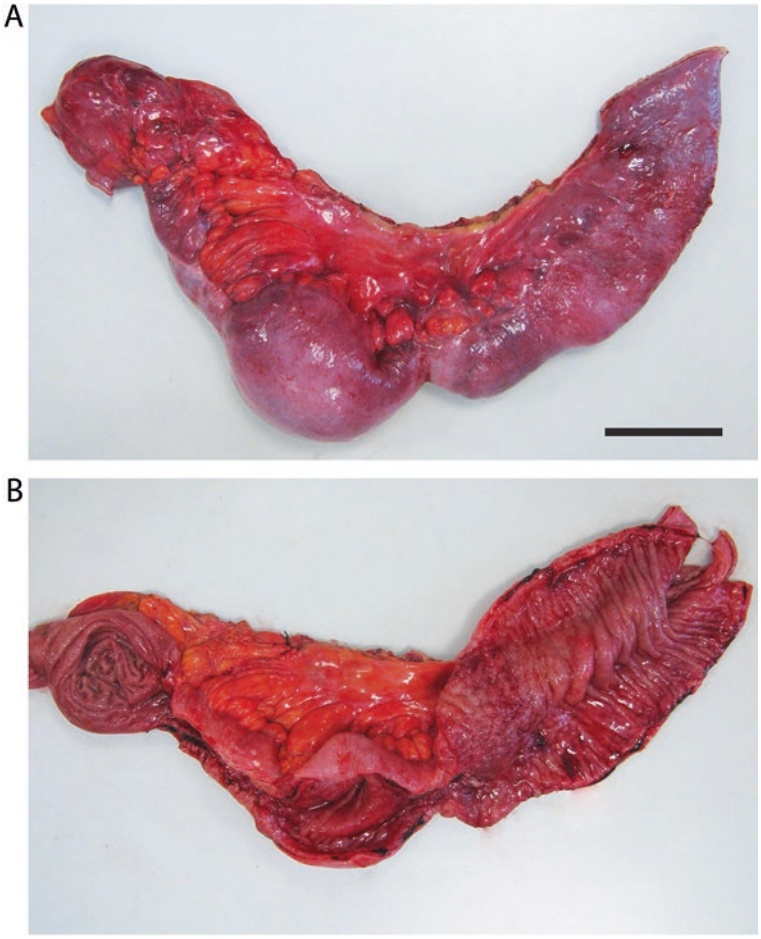

Fig. 8.6 Segmental resection of portion of small bowel from a Crohn's disease patient demonstrates fat wrapping (**a**) and does not lie flat due to transmural inflammation, fibrosis, and stricture formation (**b**). Scale bar 5 cm

tal sparing, and this should not be taken as evidence confirming a diagnosis of CD [5, 6]. This unconventional distribution of disease is considered a normal variant in the pediatric UC population. Finally, long-term therapy in UC patients may sometimes result in a patchy distribution of disease or rectal sparing and does not reflect the true underlying disease process.

Microscopic Appearance

The same patterns differentiating UC from CD at the gross, whole-organ level, also apply to observations at the microscopic level. For example, chronic injury in the upper GI tract or small bowel is consistent with CD. Similarly, patchy or focal disease favors CD. In contrast, continuous involvement in the colon, extending proximally from the rectum favors UC. For this reason, it is important for the gastroenterologist to sample areas that appear normal as well as abnormal so that the pathologist can fully appreciate grossly appreciable skip lesions.

Histologic analysis of resection specimens often shows deep or transmural inflammation in CD specimens and largely superficial inflammation with UC. The histologic correlate of stricturizing CD is a thickened fibrotic stroma. Ulcerations are typically deep and knife-like and may eventually lead to the formation of fistulas extending through the serosa and into pericolonic fibroadipose tissue. In contrast, UC demonstrates little fibrosis, and ulcers are typically shallow and broad-based (Fig. 8.7).

One of the most important microscopic features used to differentiate between CD and UC is the presence of aggregates of histiocytes known as granulomas (Fig. 8.8). Granulomas are present in many, but not all, patients with CD and are seldom associated with UC. Granulomatous inflammation can sometimes form independent of IBD as a reaction to entrapped foreign material. Careful histological inspection of multiple levels can usually exclude this possibility. Granulomas in the GI tract may also occasionally be explained by sarcoidosis or tuberculosis. However, once these possibilities are excluded, compact, well-formed granulomas are virtually diagnostic of CD, and the presence or absence of granulomas is always mentioned in the pathology report.

Assessing for Dysplasia: Flat and Otherwise

IBD is linked to an increased risk of colorectal carcinoma. Endoscopic screening typically is recommended every 1–2 years, starting 8–10 years after disease onset, to assess for dysplasia, the precursor lesion for carcinoma [7]. IBD dysplasia may present with an endoscopically apparent lesion or mass or may be flat. Since the latter can be difficult to detect, the guidelines are to perform random 4-quadrant biopsies every 10 cm. However, with the advent of newer endoscopic imaging approaches, targeted biopsies of visible lesions are becoming the norm.

Identification of IBD-associated dysplasia greatly increases the subsequent risk of developing colorectal carcinoma. Therefore, the presence of high-grade dysplasia or multifocal low-grade dysplasia requires very aggressive follow-up and frequently results in surgical intervention [8]. In contrast, the presence of sporadic non-IBD-associated adenomas can also occur in patients with IBD. Because of the management of these sporadic lesions is far more conservative, it is important to determine if the area of dysplasia is arising within a region of bowel involved by IBD or if it is

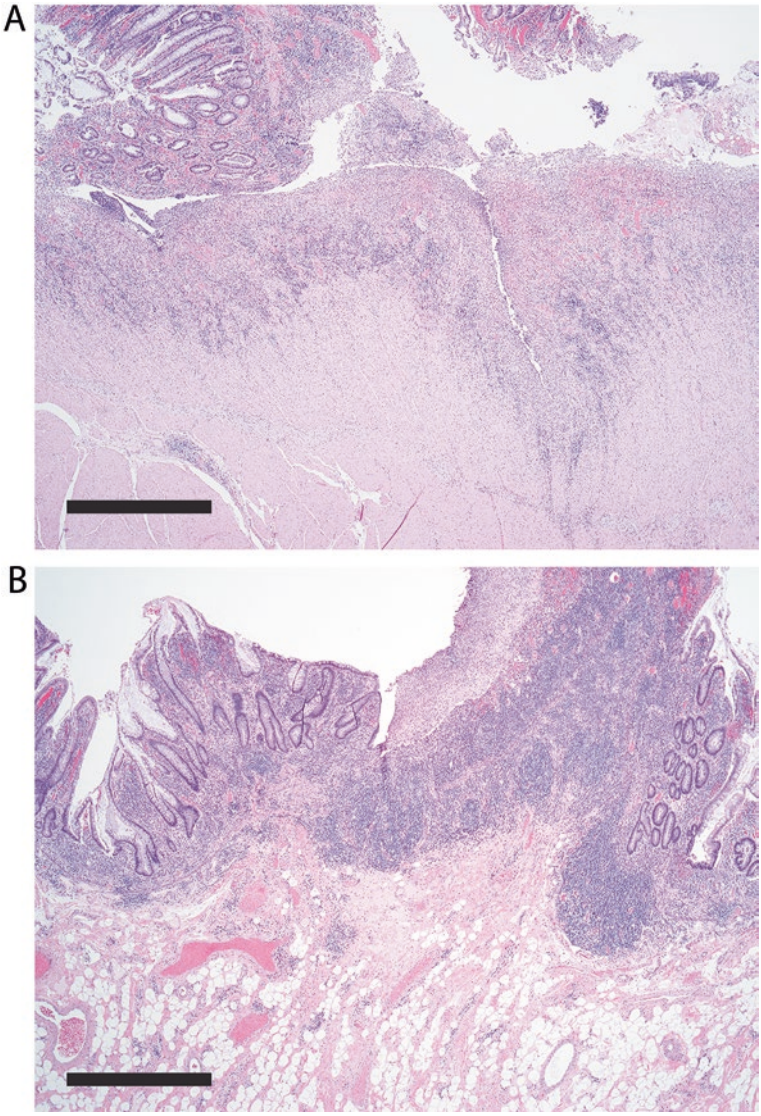

Fig. 8.7 Low-power hematoxylin and eosin stain demonstrates deep knife-like fissuring ulcers in patients with Crohn's disease (**a**). These ulcers often extend into the muscularis propria and form the basis of fistula tract formation. In ulcerative colitis, ulcerations are typically broad based and superficial (**b**). Scale bar 1 mm

arising within a background of normal colonic mucosa. The later would favor the diagnosis of sporadic adenoma which can be treated by simple polypectomy.

Dysplasia is categorized as either low- (Fig. 8.9a) or high-grade (Fig. 8.9b) based on histologic features. Both low- and high-grade dysplasia demonstrate lack of epithe-

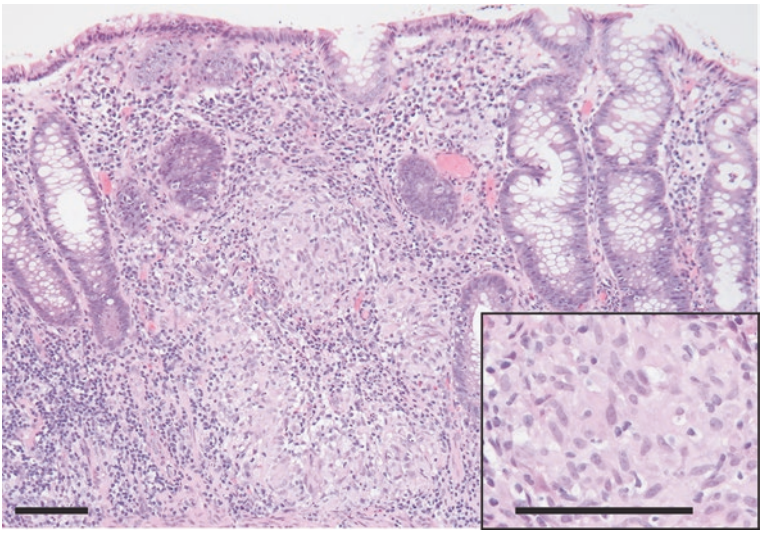

Fig. 8.8 Well-formed granulomas are present in the lamina propria of this colon biopsy from a patient with Crohn's disease. Scale bar 100 μm

lial maturation as cells move toward the surface. In low-grade dysplasia, epithelial cells are tall and pseudostratified, with hyperchromatic and elongated nuclei, but nuclei remain basally oriented. In contrast, in high-grade dysplasia, epithelial polarity is lost which can result in glands growing back-to-back without the intervening stroma. Nuclei of high-grade dysplasia also appear pleomorphic and may have bizarre mitotic figures. The diagnosis of dysplasia in patients with active IBD can be particularly challenging because areas of inflammation may have marked regenerative features. In such cases, a third category of "indefinite for dysplasia" (Fig. 8.9c) is sometimes used to communicate to the clinician that a firm diagnosis of dysplasia cannot be made.

Role of Genetics in the Assessment of IBD

Genetic Studies of IBD Pathogenesis

It has been widely suggested that IBD development is controlled by genetic factors, luminal microbiota, environmental factors, and immune responses. Interactions of these factors contribute to persistent infection of certain pathogens, dysbiosis, defective mucosal barrier, or aberrant immune regulation, which, in turn, promotes IBD initiation and progression [9]. Early epidemiology studies suggested a genetic component of IBD pathogenesis, and the first IBD-associated gene, NOD2, was identified by genetic linkage analysis [10, 11]. With the progressive advance of genome-wide association studies

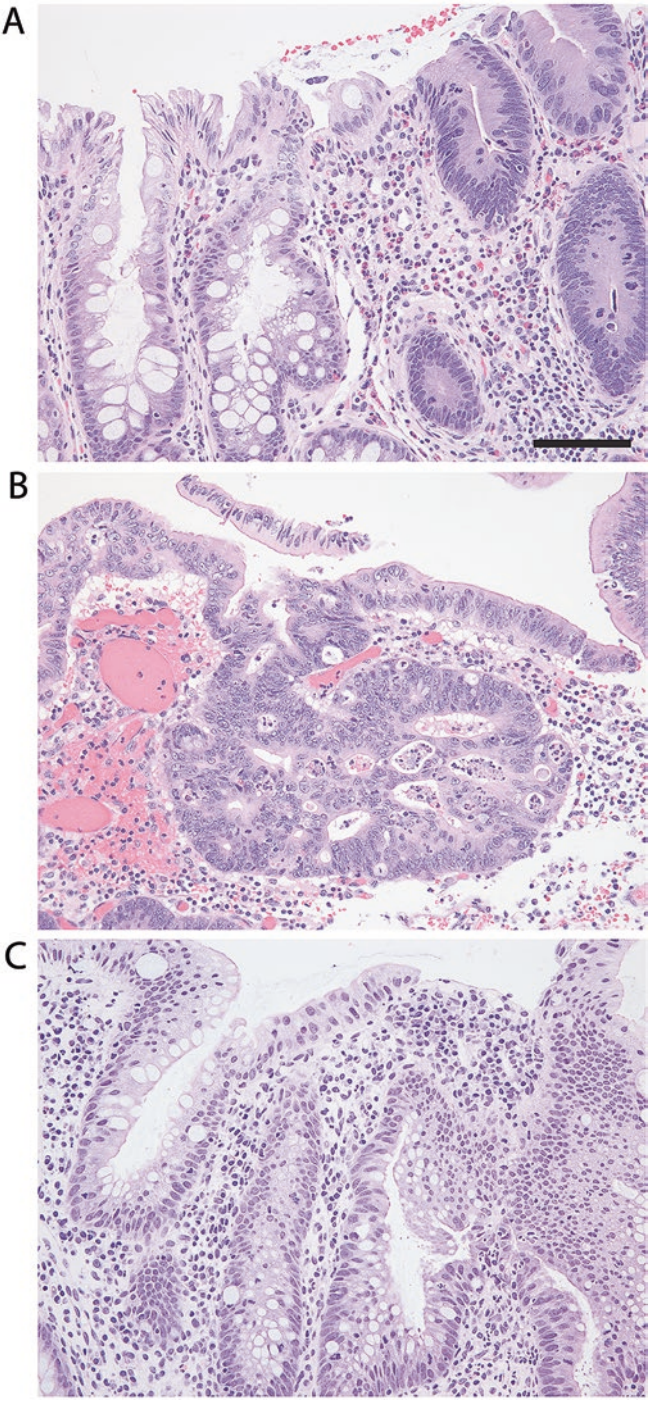

Fig. 8.9 Pathologists assess for the presence of dysplasia in all biopsies. Low-grade dysplasia is characterized by nuclear hyperchromasia and stratification but nuclei remain basally oriented (**a**). High-grade dysplasia is characterized by highly atypical nuclear features, loss of nuclear polarity, and may demonstrate a cribriform architecture (**b**). In patients with active IBD, it is sometimes difficult to differentiate between reactive atypia and dysplasia, and in such circumstances, the term, "indefinite for dysplasia," may be used by the pathologist (**c**). This requires close follow-up and rebiopsy of the affected area. Scale bar 100 μm

(GWAS), more than 200 IBD loci have been identified based on disease-associated single-nucleotide polymorphism (SNP) sites by studying large populations of patients of European, Asian, and African American origin [12–14]. At the same time, efforts have been directed at understanding how these genetic variants are associated with disease. Some of the loci have functional significances. For example, loss of function NOD2 missense mutations have an impaired ability to activate NFκB signaling, ATG16L1 T300A mutation has defective autophagy response, which is associated with IBD phenotype [15, 16]. In contrast, loss of function IL23R E381Q mutation is protective [17, 18]. Despite these disease-associated coding sequence changes, at most of these GWAS-identified loci, the maximal associated SNPs are located at noncoding regions. It has been postulated that these loci affect IBD through modulating gene expression [19, 20]. Thus, the GWAS data has been combined with datasets that probes gene expression and its regulation, including expression quantitative trait loci (eQTL) data, intestinal expression data, and epigenetic chromatin immunoprecipitation-sequencing (ChIP-Seq) data, to understand the contribution of individual genes to IBD [21].

With increasing affordability of direct sequencing, efforts have been directed at identifying rare transcript variants that significantly contribute to diseases. Whole exosome sequencing studies of very-early-onset (VEO) IBD patients, a group of patients with more severe disease and more prominent family history, have so far identified about 50 rare mutations [22, 23]. These mutations, such as IL10R mutations, may display Mendelian-like transmission with high IBD penetrance [24]. These very early onset IBD patients often also present features of other known monogenetic diseases. Conversely, many monogenic disease patients also have IBD-like pathogenesis. These findings highlight that single-gene disorders may also predispose to complex disorders and indicate that Mendelian and complex disorders could share genetic footprints, and common genetic variants of IBD, which are identifiable by GWAS studies, may interact with rare Mendelian variants discovered by direct sequencing to contribute to IBD development [25].

Clinical Applications of Genetic Testing

Because the widely accepted genetic contribution to IBD, it has been postulated that genetic testing could be used for IBD diagnosis and guide treatment. Although a large amount of knowledge has been generated in IBD genetics studies, genetic testing has not significantly affected IBD clinical practice. McGovern et al. have shown that because of low-background prevalence of IBD and moderate genotype risks of IBD-associated loci, genetic testing would be a poor method for IBD diagnosis [25]. Such difficulty is exemplified by the finding that although 10–20% of the general population has common variations of NOD2, a gene with highest effect size in IBD, less than 5% of these individuals have or will develop CD. Although one study has suggested that adding genetic data of four IBD-associated loci and inflammatory marker data to serological marker alone slightly increased the ability of the assay to distinguish IBD and non-IBD individuals, the contribution of genetic testing to such increased

detection is not clear [26]. Nevertheless, with the advance of genetic testing methods, including whole genome and exosome sequencing, combination of genetic testing with other biomarker testing could provide diagnostic values in the future.

In contrast to the difficulty of genetic screening to identify patients based on common variants of IBD-associated loci, direct sequencing panels are offered to VEO-IBD patients and their family members. These panels detect mutations implicated with VEO-IBD based on exosome sequencing studies, and results of such tests are used to identify mutation associated with VEO-IBD patients or IBD-like diseases to make molecular diagnosis of disease and to identify mutation carriers for genetic counseling; testing results may also allow for genotype-specific interventions and experimental therapies. For example, a conventional therapy resistant pediatric patient was found to have homozygous loss of function IL-10R mutation [24]. Subsequent studies assigned the defect to hematopoietic cells, and bone marrow transplant caused disease remission [27–29].

In additional to disease diagnosis, genetic testing may also be used to predict treatment effectiveness and adverse effects. Testing for thiopurine methyltransferase variants prior to thiopurine treatment has been used clinically to reduce the risk of bone marrow toxicity [30–32]. Furthermore, genetic testing may also be used to predict disease prognosis. For example, a genome-wide association approach has identified 46 SNPs that can be used to identify UC patients who are refractory to regular medical treatments [33].

Although we are still at the beginning of genetic studies of IBD, these studies have already suggested that IBD diagnosis, prognosis, and therapy can be impacted by genetic testing of patients. Further investigation will not only identify how genetic factors impact IBD pathogenesis, it will help us have better diagnosis and treatment in the precision medicine era.

Summary

The pathologist plays a key role in the management of IBD. Presently, the pathological diagnosis is established by careful gross examination of surgical specimens as well as microscopic examination of hematoxylin and eosin stained tissue sections. The severity of inflammation is determined by the degree of neutrophilic inflammation. Additionally, the pathologist always assesses for the presence of dysplasia. The gastroenterologist and surgeons rely heavily on this information in establishing the most efficacious therapeutic approaches and in considering surgical management. In the future, as our understanding of IBD genetics increases, and as the cost of genetic testing decreases, it is likely that there will be an ever-increasing role of genetic and molecular testing to help guide and optimize therapy for patients with IBD.

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Chapter 9
Tricks of the Trade: Treating Your Patient with Mild to Moderate Inflammatory Bowel Disease

Fernando Velayos

Education is what remains after one has forgotten what one has learned in school
-Albert Einstein

Introduction

It is common to write a chapter describing medications for treating inflammatory bowel disease (IBD); it is unique to write a chapter on tricks of the trade. A trick of the trade is an idiomatic expression that relates to the special skills and knowledge that professional workers learn from experience. These skills and knowledge result in effective and even clever methods for doing a job better or faster. This chapter is not meant to be exhaustive or the final word, but rather practical and useful. This approach, in fact, is a trick of the trade for writing a chapter. Similar to the other "tricks" or "tips" described in this chapter, it is based on lessons learned from observing effective mentors, teachers, friends, and peers who provide outstanding care for patients with inflammatory bowel disease.

Identifying the Patient with Mild to Moderate IBD

For decades, the cornerstone of IBD treatment has been to choose therapy based on the severity of disease. While a logical strategy, the main challenge with this approach has been deciding on which parameter to define severity. Severity can be defined

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based on symptoms, colonoscopic criteria, histological criteria, impact of symptoms on quality of life, or even risk for progression and complications. Unfortunately these different criteria do not always correlate. Moreover, scoring systems used in clinical trials to define severity often are not practical, thus the severity scales used in trials compared to what is used in real life are often different.

As a result, treatment algorithms have been based on what is accessible to the patient and physician: severity of symptoms, physical exam, vitals, and occasionally labs. The problem with these four traditional categories of severity, mild, moderate, severe, and fulminant, is that the individual components of each category can sometimes be found in the same patient. Thus, these categories are not mutually exclusive and can lead to misclassification. To address this, these four categories have been grouped into three groups that provide a range of severity that unfortunately also overlap: mild-moderate, moderate-severe, severe-fulminant. Even then, these ranges do not fully describe severity as additional modifiers can be added. For example, a mild-moderate and moderate-severe patient can each be categorized as steroid dependent, but they may look very different clinically.

One tip is to define mild-moderate IBD using the algorithms recently published in two American Gastroenterological Association (AGA) clinical pathways: one for UC [1] and one for Crohn's [2]. Patients are stratified not based on disease severity per se but rather on the presence or absence of factors associated with either a low or moderate/high risk of disease progression and complications (Fig. 9.1). The premise

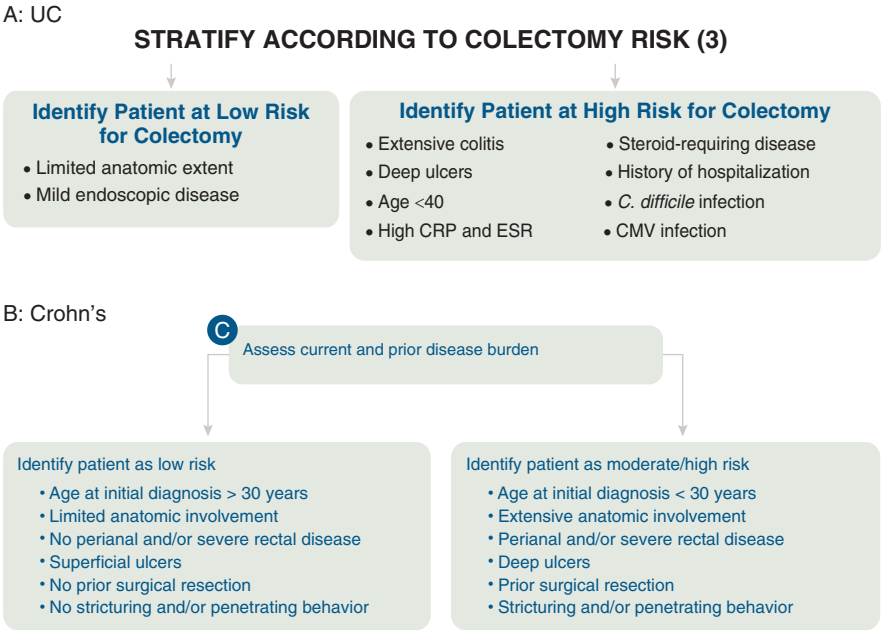

Fig. 9.1 AGA Criteria for defining patient patients as low risk of complications and progression for UC (**a**) and Crohn's (**b**)

is that IBD is an aggressive disease but there are patients who have a mild phenotype and often do not need anything more than mesalamine or an occasional pulse of steroids or initiation of an immunomodulator at diagnosis to control symptoms. This strategy of defining disease based on the risk of complications and progression helps clarify the objective of therapy (prevent complications and progression). It also de facto highlights that the remaining patients, combined into a moderate/high-risk group, are in fact not at low risk, and should be treated more aggressively,

FDA Therapies Used to Treat Mild-Moderate IBD

FDA approved therapies for mild-moderate inflammatory bowel disease are mesalamine (ulcerative colitis), ileal release budesonide (Crohn's), colonic release budesonide (ulcerative colitis), and budesonide foam (ulcerative colitis up to 40 cm). Thiopurines, methotrexate, and corticosteroids are not formally FDA approved for the treatment of IBD as their use predates the more modern approval process for medication use. Patients on thiopurines (UC, Crohn's) and methotrexate (Crohn's) typically are considered to be moderate-severe; however, there is an option in the AGA Crohn's pathway to start these therapies at diagnosis in low-risk patients [2]. Traditional corticosteroids also indicate a more moderate-severe patient. However, in a patient with quite mild disease or where corticosteroids are used at diagnosis, sometimes one waits until the need for the second course of steroids within a 12-month period to start a steroid sparing agent. Details on how to use these therapies to treat mild-moderate (low-risk) IBD are seen in Fig. 9.2.

With regard to tips for using mesalamine agents, the recommended dose for inducing remission in mild-moderate UC ranges between 2 and 4.8 g per day. Studies have not shown much difference between 2.4 and 4.8 g per day; however, subgroup analyses suggest that patients with moderate disease may benefit from the 4.8 g/day dose [3, 4]. The median time to symptomatic remission is 10–37 days, so that if patients do not have a symptomatic response by 4–8 weeks after starting therapy, they should be evaluated to determine the need to modify therapy [3]. Maintenance doses should be at least 2 g/day. Patients with more active disease may benefit from a higher maintenance dose of 4.8 g/day [3].

With regard to budesonide, the two oral formulations differ in the location of their release and therefore the disease indication. The ph and time dependent (ileal release) formulation is approved for mild-moderate ileal/right-sided Crohn's at a dose of 9 mg per day for up to 8 weeks [5]. A recurring episode can be treated with a repeat 8-week course of treatment. If disease is in remission after treatment, the label allows for the treatment to be continued at 6 mg once daily for up to 3 months. This continuation for an additional 3 months is optional and rarely done. The MMX (colon release) formulation is approved for mild-moderate ulcerative colitis at a dose of 9 mg per day for up to 8 weeks [5]. Budesonide foam was recently approved by FDA for use in mild-moderate distal ulcerative colitis up to 40 cm. The approved dose is 2 mg bid for 2 weeks and then daily for another 4 weeks [6].

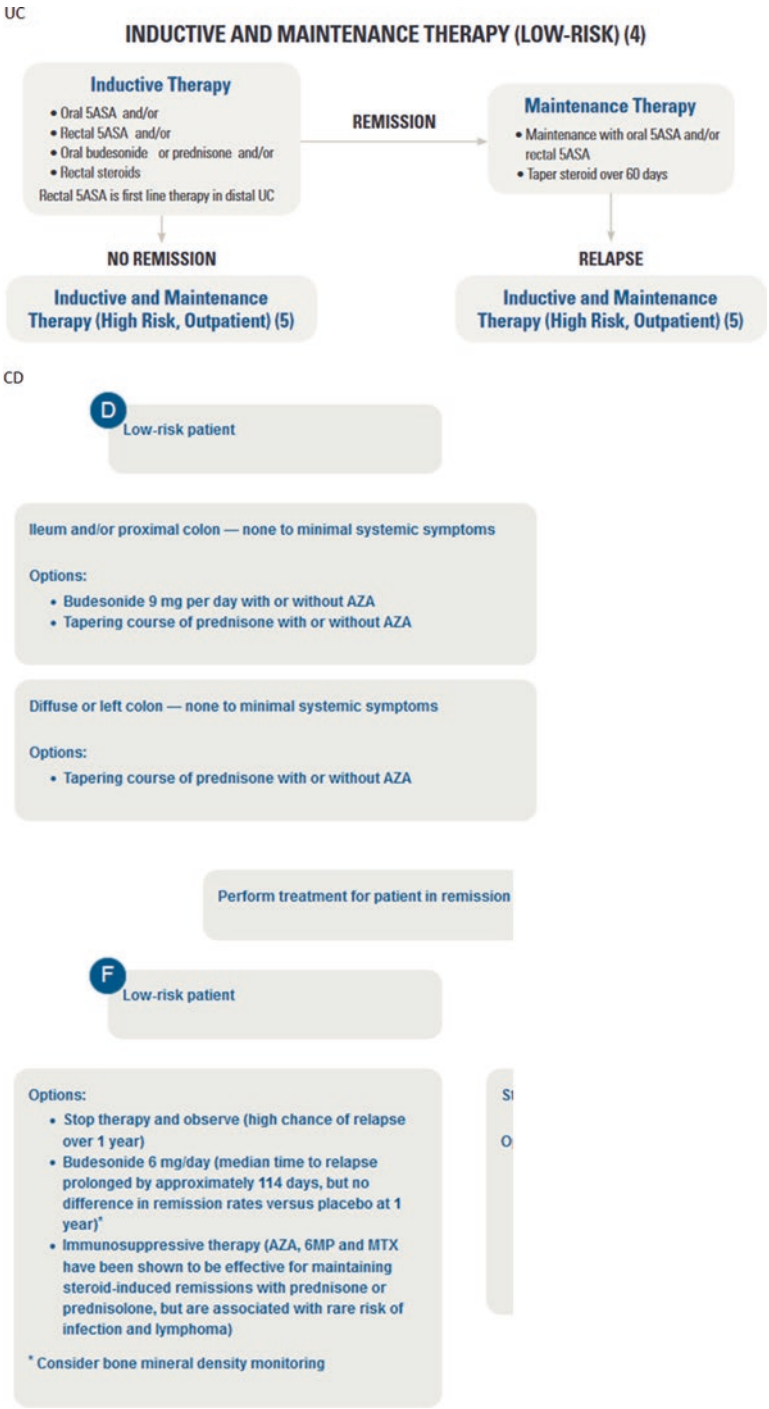

Fig. 9.2 Treatment options for low-risk patients with UC and Crohn's

Control of Rectal Inflammation

Whether a patient has ulcerative colitis or Crohn's and whether the disease is limited or extensive, immediate control of rectal inflammation serves to relieve some of the most bothersome symptoms of IBD (tenesmus, urgency, rectal bleeding, and incontinence). A well-publicized study, now decades old, highlighted the efficacy of adding rectal mesalamine therapy to oral mesalamine in patients with distal ulcerative colitis [7]. In a randomized control trial, patients with distal disease who received oral and rectal mesalamine had a greater reduction in bleeding and total disease activity index than topical therapy and oral therapy alone.

What has been less publicized is that this observation is not limited to distal disease. In a controlled trial, patients with mild to moderately active pancolonic UC who received 8 weeks of oral mesalamine (4 g/day) plus 4 weeks of mesalamine enema (1 g/day) did better than those who received the same dose of oral mesalamine alone [8, 9]. Patients who received combination therapy had greater rates of remission (64% vs. 43%, $p = 0.030$), quicker cessation of bleeding ($p = 0.003$), and important favorable trends in several quality of life domains, specifically anxiety/depression ($p = 0.049$) [9].

The issue of course that the suppositories and enemas are often not easily accepted by patients, especially at the first office visit, when they are trying to understand their disease and the doctor is trying to establish a good doctor-patient relationship. That being said, awareness and discussion of the available data and tips for its use can help to at least begin to help in this process.

With regard to tips, it is important to do your best to control rectal inflammation early by adding rectal mesalamine independent of disease extent if distal inflammation is present. For more significant symptoms, rectal steroids can be used, although trials have not shown they perform better than rectal mesalamine. Use of rectal therapy requires significant education and walking a patient through the process and sharing some of the data above so that they understand the reasons for the choice. Print and review with the patient the instructions for how to insert the enema or suppository. It helps to let them know that they may not be able to hold in the contents of an enema, especially at the beginning due to the inflammation itself. Let them know this is expected and will improve and does not reflect on their capacity. Patients should be encouraged that even if they can only keep the contents in for a very brief period, once they have done, they are done for the evening. Additionally, patients should be counseled to deliver the enemas at night before going to bed. As in the above trial, it can be useful for patient acceptability to know that the rectal therapy is a time-limited component of induction therapy (in above trial 4 weeks). To avoid surprise and build trust, it is also helpful to warn patients that a month's worth of enemas will need to be carried home in a large bag.

Addressing Minor but Recurring Rectal Symptoms

Some patients with mild-moderate UC have a few mild flares over the course of a year and are already on maximal oral mesalamine therapy. They either do not want to escalate therapy or may not meet criteria to escalate therapy. One tip for these patients is to consider adding weekend rectal mesalamine therapy to their oral regimen. In a controlled trial, patients with pancolonic UC who just achieved remission were randomized to receive either 3/day of oral mesalamine plus 1.5 g mesalamine enema on the weekend or oral mesalamine alone [10]. The trial was stopped early due a significant benefit in the weekend mesalamine group. Patients who added weekend mesalamine to oral therapy had fewer relapses (18.2%) compared to the oral mesalamine alone group (76.9%).

Simplifying the Maintenance Mesalamine Regimen

Not all mesalamine formulations have a once daily indication, yet it is believed that taking medication once per day should improve compliance and outcomes. Given that choice of mesalamine medication is not always under control of the physician, several studies have evaluated whether there are worse outcomes if these multiple dose per day mesalamine formulations are given once per day once a patient is in remission.

The main tip is that regardless of mesalamine formulation, use mesalamine in the maintenance phase once per day instead of multiple times per day [3]. Two randomized controlled trials demonstrated equivalence between the once daily vs. multiple dose per day dosing [11, 12] whereas another showed greater sustained remission for the once daily regimen over the twice per day (70.9% vs. 58.9%, $p = 0.02$) [13]. A meta-analysis confirmed the once per day dosing is at least equivalent to the multiple dose per day regimens for maintaining remission [14]. Such simplification of the regimen can help improve adherence and risk of relapse.

Mesalamine and Mild-Moderate Crohn's

For at least a decade, authors have argued against the use of mesalamine to treat Crohn's [15]. Few understand the nuance and history behind this recommendation, and might even be confused since there are still patients with very mild Crohn's who are on mesalamine and who appear to be doing well. In addition, older guidelines supported the use of a related 5-ASA, sulfasalazine, for induction of mild Crohn's based on data from the National Cooperative Crohn's Disease Study (NCCDS) [16]. In the NCCDS, 4–6 g/day of sulfasalazine resulted in greater induction of clinical remission (43%) compared to placebo (30%) but was not effective in maintaining clinical remission [17].

Use of mesalamine for mild-moderate Crohn's became widespread after a positive randomized controlled trial published in 1993 showed that 4 g/day of Pentasa was superior to placebo for the treatment of active Crohn's [18]. Patients with isolated small bowel Crohn's as well ileocolonic Crohn's were enrolled in this trial. Remission occurred in 43% in the mesalamine group and 18% in the placebo group ($p < 0.0017$). To put the available therapies in context, this was the era of the randomized controlled trials for the new "sulfa-free" mesalamines. Traditional corticosteroids were available and immunomodulators were just beginning to have widespread use. There were no FDA approved biologics for the treatment of Crohn's. The ability to have data to justify using a non-steroid, non-immunomodulator to treat mild-moderate Crohn's disease was quite welcome.

Although there was never FDA approval to use Pentasa for Crohn's, there was biologic plausibility for suggesting the results of the study were true. Pentasa is the only mesalamine formulation that is released throughout the small intestine. The others are ph dependent, for which release in the ileum is possible but variable, or require bacteria found only in the colon for release of the active compound, so they are not released in the small bowel at all.

The enthusiasm for using Pentasa for Crohn's was tempered once it was discovered that two similar trials, conducted around the same time, had negative results and were never published at their completion. It was not until 2004 when these two trials along with the original positive study were published as a meta-analysis. Although the results showed that pooling of all three studies resulted in a statistically significant 43 point reduction in the Crohn's Disease Activity Index with use of Pentasa [19], the accompanying editorial highlighted that this difference was below the threshold of what a typical clinician could detect. As a result, the editorial concluded that the totality of the data did not support the use of mesalamine for Crohn's disease [15].

The main tip is to not use mesalamine to treat mild ileal Crohn's disease. Based on the AGA Crohn's clinical pathway, these patients can be treated with a single tapering course of budesonide or prednisone with or without azathioprine and then observed (Fig. 9.2). The newer AGA Crohn's pathway no longer includes use of 4–6 g/day of sulfasalazine for treating mild Crohn's of the colon [20]. These patients can also be treated with a single tapering course of prednisone with or without AZA and then observed.

Use of Non-traditional Steroids to Treat Mild Flares

Oral budesonide is a synthetic corticosteroid that is an attractive alternative to traditional corticosteroids due to its limited systemic bioavailability and fewer side effects compared to conventional corticosteroids.

The first tip is to use budesonide instead of traditional corticosteroids when possible to treat a mild flare [3]. A recent meta-analysis of 14 studies examining ileal release budesonide confirmed that it is more effective than placebo for inducing

remission in mild-moderate Crohn's [21]. It was, however, less effective than traditional steroids, but was associated with a lower likelihood of adverse events and adrenal suppression [21]. Similar favorable evidence and safety profile supports its use over placebo for inducing remission in mild-moderate ulcerative colitis [22].

Another tip, which addresses a situation which is fortunately less common now, is to make sure that the patient is given the correct formulation of budesonide, especially if they are not improving. It is easy for the pharmacy to fill "9 mg of budesonide for IBD." The ileal release formulation consists of three 3 mg tablets and then colonic release formulation consists of a single 9 mg tablet.

A final tip is to understand that budesonide is still a corticosteroid. Although it may be favorable to use instead of traditional corticosteroids, there can still be corticosteroid-related side effects, especially with long-term use. Use of two full courses of budesonide (each course 4–8 weeks) in a given year should prompt reassessment as to whether a steroid sparing agent (immunomodulator or biologic therapy) should be used, similar to what would be recommended for a traditional corticosteroid. Budesonide is not recommended as a maintenance agent for either UC or Crohn's [5]. In Crohn's, there are minor benefits in terms of CDAI and longer time to relapse but these were offset by higher treatment related adverse event rates and frequent adrenal suppression that occurred with long-term treatment [23].

Steroid Tapers

There is no standardized or approved way to start or taper steroids; therefore a variety of patterns have been observed. The first is the "rapid on and off." Patients are started on 40 mg and then tapered "quickly" to 0 mg within 2 weeks to a month. Although this does provide quick relief and technically minimizes exposure to steroids, patients often relapse and go through several cycles of these without sustained relief. The second pattern observed is the opposite, the "high dose (60 mg) with slow taper." This strategy does provide sustained improvement, but often with significant corticosteroid exposure and side effects. The third is the "low and slow." Fearing use of steroids, patients are started on perhaps 20 mg of steroids and when improvement is minimal, the dose is slowly titrated up to 40 mg. This strategy often results in inadequate disease control and prolonged steroid exposure. A variation on all these tapers is the "autopilot taper." Patients can be started on any dose with any frequency of taper, but the premise is that the tapering occurs on a fixed schedule whether the symptoms are resolved or not. Patients often are frustrated as they are symptomatic and experience steroid side effects.

Several facts are known about dosing of corticosteroids. First, the efficacy of 60 mg of prednisone is only marginally greater than 40 mg but side effects are much greater. Second, most of the prednisone side effects occur at doses greater than 20 mg. Thus, one tip when treating flares with oral corticosteroids is to start at a full dose, 40 mg, and then taper to 30 mg and then 20 mg within the first 10–14 days if symptoms are adequately controlled. Within this time period, the appropriate testing

and initiation of a steroid sparing agent can begin. Then a slower taper over the next 30–45 days is coordinated with the patient based on the initiation and response to a steroid sparing agent. Patients unable to fully taper after 60 days are considered steroid dependent and additional evaluation and possible change of therapy is undertaken.

Conclusion

The mild-moderate patient with IBD can be challenging, but for different reasons than the moderate-severe patient. Ways to improve care consists of first defining this group narrowly to include mostly patients at low risk for complications and progression. The main FDA approved therapies used in the group is mesalamine (ulcerative colitis) and budesonide. Azathioprine can be added after the first course of steroids at diagnosis in Crohn's patients, but mild patients can also be observed after treatment. Whenever possible, remember to control rectal inflammation while starting other treatments. Convert multiple dose per day maintenance regimens of mesalamine to once per day. Use newer non-traditional steroids in place of prednisone for mild flares. Remember to look for signs your patient is changing from a patient with mild-moderate disease to one of greater severity. Clues include use of any steroid more than twice in any 12-month time period and inability to wean off prednisone after 60 days. Be mindful of erratic steroid tapers which may make it more difficult to wean off steroids or that promote unnecessary steroid side effects. While not exhaustive, following these rules should improve the treatment of patients with mild-moderate IBD.

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Chapter 10
Tricks of the Trade: Treating Your Patient with Moderate-to-Severe IBD

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When Treating Patients with IBD Who Have Active Symptoms, Document the Presence of Active Disease

Appropriate management of inflammatory bowel disease (IBD) first requires objective evidence of active inflammation. Symptoms may suggest disease activity but are usually nonspecific. Diarrhea and abdominal discomfort, two of the most common symptoms in patients with active Crohn's disease (CD) and ulcerative colitis (UC), are not specific for IBD but may overlap with typical presentations of numerous other gastrointestinal disorders including lactose deficiency, irritable bowel syndrome, celiac disease, CMV colitis, *Clostridium difficile* colitis, and infections from enteric pathogens. Excluding alternative etiologies and confirmation of active IBD require laboratory evaluation and objective documentation of appropriately active disease findings on upper endoscopy, colonoscopy, and small bowel imaging.

Demonstration that a patient has objective evidence of inflammation in their bowel has important implications for predicting therapeutic response, as highlighted by the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) study group [1]. The SONIC trial was a randomized, double-blind

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trial that evaluated the efficacy of infliximab monotherapy, azathioprine (AZA) monotherapy, or the two drugs combined in immunomodulator-naïve patients with moderate-to-severe Crohn's disease. Patients were eligible based on age and their Crohn's Disease Activity Index (CDAI), which utilizes subjective criteria such as patient-reported stool counts and symptoms [2]. Ileocolonoscopy was performed at baseline and again at 26 weeks for those patients found to have mucosal ulcers. The primary endpoint was the rate of corticosteroid-free clinical remission, which was defined by a CDAI score of less than 150 and no administration of systemic corticosteroids for 3 weeks. While the study concluded that therapy with infliximab resulted in significantly higher rates of corticosteroid-free clinical remission than AZA monotherapy, a post hoc analysis found that patients with elevated C-reactive protein (CRP), mucosal lesions, or a combination of both at baseline endoscopy had the best clinical response. Furthermore, there was no significant difference in the three therapy groups for subjects without these findings, suggesting that patients without objective evidence of mucosal inflammation are less likely to respond to immunomodulatory therapies.

After active disease is endoscopically confirmed, disease activity should be followed. The costs of invasive monitoring and the once prevailing view that clinical response is more relevant than endoscopic findings led to the development of several clinical disease activity indices. The CDAI, mentioned previously, is the most broadly utilized index in clinical trials of CD. It correlates the physician's evaluation of clinical status to eight variables, including hematocrit, body weight, extraintestinal manifestations, need for antidiarrheal medication, presence of an abdominal mass, general well-being, abdominal pain severity, and liquid stool counts [2]. The calculation requires a 7-day diary of patient-reported symptoms, and the final score relates to the severity of disease activity. However, the CDAI has been shown to be poorly correlated to endoscopic disease activity and is plagued by subjectivity and patient recall bias [3]. The ACCENT I trial, which evaluated infliximab as a long-term treatment regimen in Crohn's, showed that at 10 weeks, only 36% of patients with confirmed mucosal healing (MH) were in remission as calculated by the CDAI [4]. Conversely, 40% of those in clinical remission per the CDAI did not demonstrate endoscopic remission. The Harvey Bradshaw Index (HBI) is a simplification of the CDAI, using only five of its eight independent variables and no laboratory data [5]. While lauded for its simplicity relative to the CDAI, it too correlates poorly with the severity of endoscopic disease [6, 7]. The CDAI, although used in clinical trials in the past, has been cumbersome and not well accepted for use in clinical practice.

Recognizing the limitations of scoring systems that omit endoscopic assessment in CD, the French GETAID group developed the Crohn's Disease Endoscopic Index of Severity (CDEIS) [8]. The group evaluated the importance of mucosal lesions and the percentage involvement of the colon. The resulting CDEIS incorporates superficial and deep ulcerations, lesion surface area, and the number of colonic segments involved. The index was found to have relatively minimal interobserver variability, and lesion surface area assessment measured on a visual analog scale was highly reproducible. The tool is frequently used as an

endoscopic severity index in clinical trials. However, it requires careful training and is too difficult and cumbersome to employ clinically.

Fortunately in 2004, Daperno and coworkers proposed the Simplified Endoscopic Severity Index for Crohn's Disease (SES-CD) [9]. The SES-CD evaluates the size and penetration of ulcerations and also has strong interobserver agreement. Additionally, it is well correlated with the CDEIS, but does not require such precise measurements of lesion surface area [10]. Therefore, for routine clinical practice, the SES-CD may be the endoscopic index of choice to follow disease activity in CD. The SES-CD however is not a useful index for patients who have undergone ileocecal resection when assessing their risk for disease recurrence postoperatively.

In Crohn's patients who have undergone ileocecal resection, the Rutgeerts endoscopic score, which incorporates endoscopic lesions in the neoterminal ileum, is routinely used in randomized controlled trials (RCTs) and is the clinician's gold standard assessment tool for postoperative recurrence [11]. It grades the mucosa of the distal ileum from a range of i0 (no lesions) to i4 (diffuse inflammation with nodules, large ulcers, and/or narrowing). Patients with a score of i3 or i4 within 12 months of ileocecal resection have a higher rate of disease recurrence and more aggressive disease course than those with lesions of lesser severity. Therefore, patients should undergo ileocolonoscopy within 6–12 months after resection for risk stratification and to determine the need for additional therapy.

In UC, several indices have been developed to assess disease activity, many of which incorporate endoscopic evaluation. The role of endoscopic findings in UC has been appreciated for decades, and Truelove and Witts developed the first endoscopic score to evaluate UC activity in 1955 [12]. Today, the Mayo score prevails in clinical trials to describe disease activity [13]. It incorporates stool frequency, rectal bleeding, physician global assessment, and flexible sigmoidoscopy findings, known as the Mayo endoscopic subscore. This score ranges from 0 to 3. A score of 0 represents normal mucosa, 1 represents mild disease and friability, 2 represents moderate disease and market erythema and friability, and 3 represents severe disease with diffuse ulcerations and spontaneous bleeding. The main challenges with this scoring system however are the overlap between scores, particularly 1 and 2, the inability to discriminate superficial from deep ulcerations, and the evaluation of only the most severely affected mucosa with no consideration of disease extension. Additionally, interobserver agreement was recently found to be modest [14].

To address the need for increased interobserver agreement, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was developed in 2012 [15]. The UCEIS is a validated index for UC endoscopic severity that incorporates a more detailed description of mucosal inflammation than the Mayo subscore. It is therefore felt to be more clinically useful by reducing variability between observers, though an improvement in interobserver agreement has yet to be established (see Table 10.1) [16].

More recently, Lobaton and colleagues recalculated and expanded the Mayo endoscopic subscore to include the evaluation of disease extension as the Modified Mayo Endoscopic Score (MMES) [17]. They multiplied the sum of Mayo scores in five colonic segments by the total extension of inflammation and divided the product by the number of actively inflamed segments (Mayo subscore >0). The

Table 10.1 Commonly used disease activity indices in IBD

Disease index	Disease	Independent variables	Score interpretation	Advantages	Disadvantages
Crohn's Disease Severity Index (CDAI) [2]	CD	Number of liquid/soft stools Abdominal pain General well-being Extraintestinal manifestations Antidiarrheal use Abdominal mass Hematocrit	Remission: <150 Severe: >450	Does not require endoscopy Extensively used in clinical trials	Subjective Relies on patient recall or diary over 7 days Correlates poorly with endoscopic findings Cumbersome for everyday practice
Harvey Bradshaw Index (HBI) [5]	CD	Number of liquid/soft stools Abdominal pain General well-being Extraintestinal manifestations	Remission: <5 Mild: 5–7 Moderate: 8–16 Severe: >16	Does not require endoscopy Does not require laboratory testing Fewer variables than the CDAI	Subjective Correlates poorly with endoscopic findings
Crohn's Disease Endoscopic Index of Severity (CDEIS) [8]	CD	Deep ulcerations Superficial ulcerations Surface area affected by disease Surface area with ulcerations	Range 0–44 (higher = more severe)	Reliable and reproducible	Elaborate and time consuming Requires visual analog scale Cumbersome for everyday practice Not useful after ileocecal resection
Simplified Endoscopic Severity Index for Crohn's Disease (SES-CD) [9]	CD	Presence and size of ulcers Extent of affected surface Extent of ulcerated surface Presence and type of narrowings	Remission: <2 Mild: 3–6 Moderate: 7–15 Severe: >15	Reliable and reproducible Correlates well with CDEIS and is less cumbersome	Still perhaps too cumbersome for everyday practice Not useful after ileocecal resection

Rutgeerts Score [11]	CD	Aphthous lesions Ulcers Inflammation Nodules Stenosis	Low recurrence risk: i0–i1 Intermediate: i2 High: i3–4	Extensively used in clinical trials Gold standard assessment for postoperative recurrence Cutoffs validated for recurrence	Only utility is after ileocecal resection
Mayo Score [13]	UC	Stool frequency Rectal bleeding Physician global assessment Endoscopic subscore: erythema, vascular patterns, friability, bleeding, ulcerations, and erosions	Overall range 0–12 (higher = more severe) Endoscopic subscore: Normal: 0 Mild: 1 Moderate: 2 Severe: 3	Combines clinical and endoscopic components Extensively used in clinical trials	Subjective Overlap between endoscopic subscore ratings
Modified Mayo Endoscopic Score [17]	UC	Sum of Mayo endoscopic subscore in five colonic segments × disease extent/ number of segment with active inflammation		Accounts for disease extension Has potential for use in clinical practice	Newly developed and requires further validation
Ulcerative Colitis Endoscopic Index of Severity [15]	UC	Vascular pattern Bleeding Lesions and ulcerations	Range 3–11 (higher = more severe)	Validated Does not require full colonoscopy High interobserver agreement	Does not consider disease extension No cutoff values for disease severity Unclear delineation between superficial and deep ulcers

MMES was shown to correlate significantly with fecal calprotectin (FC; $r = 0.73$) and clinical index ($r = 0.54$). It has potential for use in both clinical practice and research but will require further validation in clinical trials. A summary of the most commonly used clinical and endoscopic disease activity indices in IBD can be found in Table 10.1.

Employ a "Treat-to-Target" Strategy in Clinical Practice

With confirmation of disease activity, every gastroenterologist should identify a treatment target and a strategy to reach it. Management of rheumatoid arthritis (RA), another chronic disease characterized by ongoing inflammation, exemplifies the benefits of a treat-to-target approach. Newer biologic therapies including tumor necrosis factor (TNF) antagonists have allowed clinicians to achieve lower levels of disease activity in RA than ever before. The advent of feasible disease remission has prompted trials of drug combinations of TNF antagonists with older agents like methotrexate and newer approaches such as early therapy that have sought to suppress inflammation to the greatest degree [18]. This reflects a treat-to-target strategy that relies on regular assessment of disease activity and subsequent adjustments to the therapeutic plan to reduce disease activity further.

In RA, specific treatment targets such as the Disease Activity Score (DAS) rely on patient-reported outcomes as well as objective data. The traditional targets of therapy in IBD have similarly centered on patient symptoms, but it is now known that the correlation between symptoms and mucosal inflammation is poor. Patients may have no symptoms with the presence of active histological disease and vice versa [7, 19]. Consequently, a symptom-based treatment strategy undertreats a significant proportion of patients and predisposes many to the detriments of ongoing inflammation, including disease progression and dysplasia.

There is growing evidence that targeting mucosal healing (MH) in IBD leads to more favorable outcomes such as sustained remission and reduced rate of steroid use, hospitalization, and surgery [20–22]. MH is evaluated by endoscopy and is typically defined by the absence of mucosal ulceration. A Scandinavian prospective cohort study first established the importance of MH in 2007 [19]. Over 5 years, 227 CD patients were evaluated, and 141 were reevaluated by endoscopy up to 2 years after diagnosis. Of these, 38% demonstrated MH. After a 5-year follow-up period, the presence of MH was associated with significantly less endoscopic inflammation and steroid use. In a follow-up study of the step-up/top-down trial by D'Haens et al. [23], MH was defined as a SES-CD of 0 [22]. Patients that achieved this score 2 years into the trial had significantly more steroid-free remission at years 3 and 4.

The benefits of MH are similarly represented in UC. In the prospective Inflammatory Bowel South-Eastern Norway (IBSEN) study, about 50% of UC patients had MH 1 year after diagnosis [20]. Subsequent colectomy rates were significantly lower when compared to patients without MH. Additionally, the time to MH appears to have prognostic significance. Ferrante and colleagues conducted a

single-center cohort of UC patients treated with infliximab, where early MH negatively predicted colectomy [24]. Patients with early MH, defined by a Mayo endoscopic subscore of 0 or 1 at week 4 or 10 after infliximab initiation, had a significantly lower 5-year colectomy rate. Post hoc analysis of the Active Ulcerative Colitis (ACT) trials similarly showed that patients with a Mayo endoscopic subscore of 0 or 1 at 8 weeks had significantly lower colectomy rates after 1 year [25].

While the above studies underscore the utility of MH as a therapeutic target, several drawbacks exist. Most obvious is the lack of a universal definition for MH and the variability in its interpretation. In clinical trials, MH was typically defined using various endoscopic scoring systems including the Mayo endoscopic subscore (for patients with UC) and the SES-CD (or patients with CD); however, these indices were created only for the purpose of describing and quantifying disease severity, not for establishing disease remission. Additionally, using MH exclusively ignores important aspects of the disease in UC and CD that are not identified endoscopically. Healed mucosa seen only macroscopically in UC may harbor active histological disease and inflammation, which predisposes these patients to dysplasia and malignancy [26]. Similarly, CD often involves extracolonic segments that are not easily accessed (i.e., small intestinal disease), and exclusive attention to mucosal ulceration ignores the transmural disease that may be appreciated only by MR enterography. Also, from a practical perspective, patients may not be amenable to routine invasive monitoring, particularly when their symptoms are well controlled.

Reasonable alternates to invasive strategies include biomarkers of disease activity, such as the fecal calprotectin (FC) and C-reactive protein (CRP). Calprotectin is found primarily in neutrophils, and when the bowel is inflamed, neutrophil infiltration rises and the cells are then shed into the feces [27]. Therefore, the FC can reflect the severity of inflammation in IBD [28]. Multiple studies have shown the association between FC and both endoscopic and microscopic bowel inflammation [29–31]. A prospective study by Guidi et al. demonstrated that FC also has predictive functions in active IBD and can fulfill a noninvasive treat-to-target strategy [32]. They enrolled 63 IBD patients who received anti-TNF induction therapy. An FC $\leq$ 121 μg/g after therapy predicted mucosal healing, which occurred in 22% of patients, with a negative predictive value (NPV) of 90%. In UC patients with colonoscopic evidence of mucosal healing (defined by Mayo endoscopic subscore of 0 or 1), FC has been shown to correlate with active histological inflammation. Patients with histologically active disease had a significantly higher median FC (278 vs. 68 μg/g, $p = 0.002$) than patients with normal microscopic findings [33].

To facilitate a treat-to-target strategy, after remission in UC is achieved, FC can be used to modify therapy before clinical relapse ensues. After total colectomy and creation of an ileal pouch anal anastomosis (IPAA), FC has been significantly elevated 2 months before the clinical onset of pouchitis [34]. Additionally, DeVos and colleagues demonstrated that two consecutive FC >300 μg/g 1 month apart in UC patients treated with infliximab predicted relapse with 61.5% sensitivity and 100% specificity [35]. In a study by Falvey et al., the investigators sought to identify a relationship between biomarkers and endoscopic inflammation to establish potential

thresholds for IBD disease activity. Endoscopically active disease was assessed in 81 UC patients who submitted stool samples for FC just prior to their bowel prep [36]. Receiver operating curve (ROC) analysis determined that FC > 125 μg/g predicted endoscopic activity with 74% sensitivity and 80% specificity. Unfortunately, no threshold could be calculated to predict endoscopic remission.

Similar success for FC has been documented in CD. FC predicted endoscopic relapse after ileocecal resection in a post hoc analysis of the Post-Operative Crohn's Endoscopic Recurrence (POCER) trial [37]. Levels of FC were measured in 135 patients and decreased from 1347 to 166 μg/g 6 months after surgery and was significantly elevated (275 vs. 72 μg/g) in patients with endoscopic evidence of relapse (defined by Rutgeerts score ≥2) compared to those in remission. FC > 100 μg/g predicted endoscopic recurrence with 89% sensitivity, 59% specificity, and an NPV of 91%. Conversely, FC < 51 μg/g in patients with remission at 6 months predicted sustained remission with an NPV of 79%. Falvey and coworkers also assessed FC thresholds in CD and determined that FC > 125 μg/g predicted endoscopic inflammation with a sensitivity and specificity of 71% each [36]. But similar to the study's results in UC, no threshold could reliably predict mucosal healing. Larger-scale studies are desired to establish universal FC thresholds in CD and UC to predict both endoscopically active disease and mucosal healing. However, given that FC is often normal in patients with confirmed active disease, endoscopy will likely remain the clinician's test of choice to document mucosal healing. The use of FC in a treat-to-target strategy should not replace endoscopic evaluation.

While the CRP has also been associated with endoscopically active IBD, interpatient variability has precluded the establishment of universal thresholds for clinicians to target and adjust therapy [36, 38]. However, the CRP has some utility in predicting disease severity and morbidity. In a prospective UC cohort, elevated CRP was significantly associated with hospitalization [39]. Crohn's patients with "silent disease," or those with clinical remission but elevated CRP, had significantly more hospitalizations than those in remission with normal CRP levels [40]. Additionally, a Hungarian cohort study found that elevated high-sensitivity CRP was associated with relapse after 3 and 12 months in CD patients previously in remission [41]. Evidence also suggests that normalized CRP levels are associated with a favorable disease course. CRP < 10 mg/L 12 weeks after therapy with adalimumab was associated with endoscopic remission after 1 year in a multicenter Crohn's cohort [42]. Similarly, in a CD cohort treated with infliximab, early normalization of CRP was associated with sustained remission [43]. Furthermore, CRP levels measured after induction in these patients were correlated with the degree of MH.

Given the diversity of phenotypes and patient preferences in IBD, flexibility in therapeutic approach is essential. However, our general treat-to-target strategy centers on endoscopic evidence for disease activity or MH with interim measurements of serum and fecal biomarkers that may help predict disease recurrence (Fig. 10.1). Once a diagnosis is made, disease extent and prognostic factors should be considered when deciding the intensity of induction therapy. High-risk patients with severe and extensive inflammation should be treated both early and aggressively

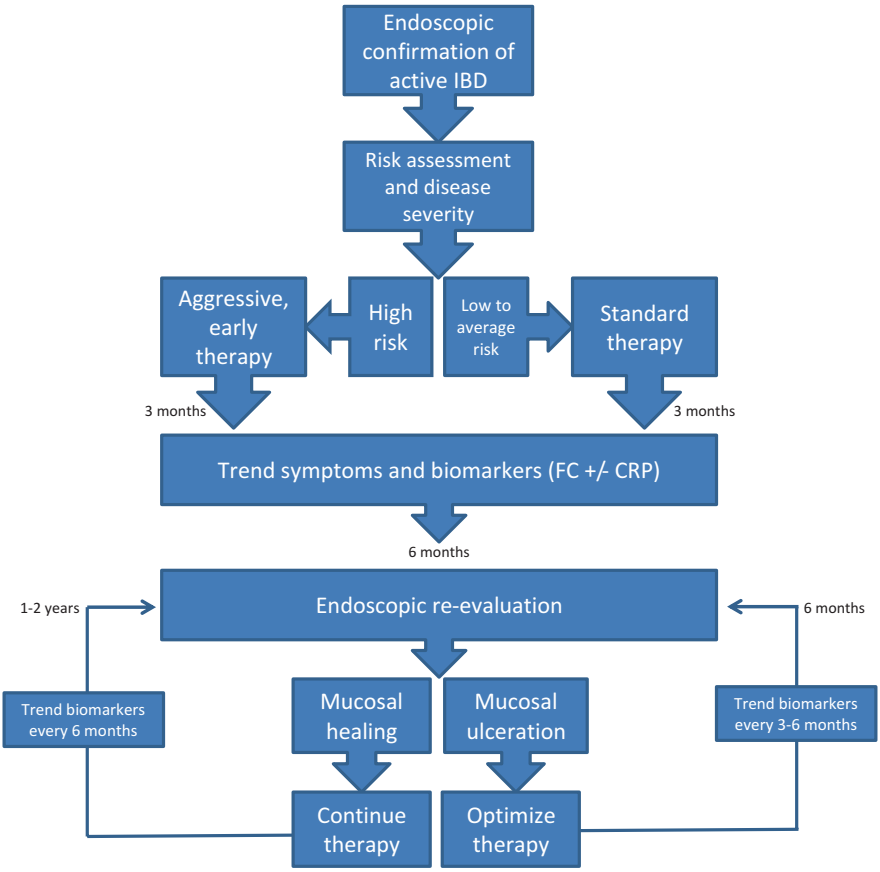

Fig. 10.1 A proposed treat-to-target strategy in IBD

with MH as a therapeutic target. While no widely accepted definition for MH exists, the absence of mucosal ulceration is a reasonable assumption. In the SONIC trial, 44% of patients who received early effective therapy achieved MH (defined by the absence of mucosal ulceration) [1]. Moreover, the step-up/top-down trial demonstrated that 73% of patients with CD who were assigned to early dual therapy achieved MH within 2 years. However, for patients with only mild inflammation endoscopically, the risks of aggressive therapy will likely outweigh the benefits.

After risk stratification and initiating treatment in a step-down fashion, endoscopy should guide therapeutic adjustments to achieve MH. While prospective data supporting this approach is limited, a retrospective study by Bouguen and colleagues demonstrated that when endoscopic ulceration was present after a diagnosis of UC, subsequent treatment alterations over time were significantly associated with both MH (defined by Mayo endoscopic subscore of 0) and histological healing [44]. In a related study in CD, modifications to medical therapy after early endoscopic reevaluation (<26 weeks)

had revealed persistent ulceration were also strongly associated with MH [45]. While the literature available to guide endoscopic intervals is scarce, we suggest reevaluation after 6 months of initial therapy in both UC and CD. In patients with abnormal FC and/or CRP at diagnosis, levels should be checked after 3 months of therapy and twice yearly thereafter. Once the target of MH is achieved, de-escalation of therapy can be considered after at least one full year of remission. However, at this time there is inadequate data to recommend discontinuation of therapy after any duration of stable remission. In patients who refuse repeated endoscopies, the clinician should avoid pure reliance on biomarkers and may consider imaging modalities such as MR enterography or CT colonography in patients with CD and UC, respectively [46]. Thoughtful communication between the gastroenterologist and patient is essential at diagnosis to establish expectations and the most effective management plan.

Measure Therapeutic Drug Levels for Proactive Monitoring and for Patients with Secondary Loss of Response

CD and UC are chronic, systemic, and inflammatory conditions that are treated by blunting or modulating the immune response. Therapy traditionally consisted of systemic glucocorticoids and 5-aminosalicylate compounds. The detriments of long-term steroid use led to trials evaluating the efficacy of immunomodulators such as 6-mercaptopurine (6-MP) and AZA, both of which effectively maintain remission in many CD and UC patients and are widely utilized to this day [47, 48]. More recently, anti-TNF therapies including infliximab, adalimumab, certolizumab pegol, and golimumab have proven effective in IBD treatment and have transformed our expectations for disease remission [4, 49–54]. Recently, anti-integrin agents have been added as tools to treat patients with UC (vedolizumab) and CD (vedolizumab and natalizumab).

As TNF antagonists have become a mainstay of therapy in moderate-to-severe IBD, the importance of therapeutic drug monitoring has become apparent. In severe IBD, combined therapy with an anti-TNF agent and an immunomodulator is an effective induction strategy in part due to the synergistic effects that help reduce immunogenicity [55]. A similar mechanism justifies the maintenance of adequate serum drug levels, which helps minimize the generation of antidrug antibodies (ADAs) that promote early drug clearance. Baert and colleagues conducted one of the first studies that underscored the impact of immunogenicity on long-term drug efficacy. They demonstrated lower titers of anti-infliximab antibodies and increased duration of response to episodic dosing when drug levels were above 12 μg/mL at 4 weeks [56]. Further work has corroborated that low serum drug levels are associated with an increased risk for immunogenicity with both infliximab and adalimumab [57–59].

The clinical benefits of adequate drug concentrations have been confirmed by multiple studies that measured anti-TNF trough levels (TLs). TLs have been shown to correlate inversely with CRP and endoscopic scores and positively with MH and

remission [60, 61]. In a post hoc analysis of the ACCENT I trial, TLs of 3.5 μg/mL or greater 14 weeks after infliximab induction predicted remission through week 54 [62]. Similarly in the SONIC trial, infliximab TLs greater than 1.0 μg/mL were associated with increased remission rates (72.8 vs. 58.2%) at 30 weeks [1]. Undetectable infliximab levels have been associated with higher colectomy rates in UC, but detectable drug levels were associated with increased rates of MH [49, 63]. Increased remission rates with higher TLs of adalimumab have also been appreciated in an Israeli cohort study [64]. A more recent cross-sectional analysis by Ungar et al. investigated the influence of therapeutic drug levels on MH in 145 patients receiving either infliximab or adalimumab therapy. Patients demonstrating MH had more than twice the drug levels for both infliximab and adalimumab compared to those with inflammation. The authors also identified optimal therapeutic windows; infliximab and adalimumab levels greater than 5 and 7.1 μg/mL, respectively, were most predictive for MH, while there was no added benefit above 8 and 12 μg/mL [65].

In clinical practice, there are two scenarios in which therapeutic drug monitoring may be considered. Individuals who initially respond to the biologic agent but over time lose the response are known to have a secondary loss of response (LOR). Drug monitoring is also used proactively, which may entail drug dose escalation or lowering and measurement of trough levels and antibodies. If the presence of a strongly positive antibody is detected in a patient, then different biologic agents may be considered.

One of the most difficult aspects of IBD management is secondary LOR to previously effective therapy. In the ACCENT I trial, less than 40% of patients initially responsive to infliximab therapy maintained remission at 54 weeks [4]. Other study groups have estimated an annual LOR risk of 13% per patient-year with infliximab [66]. The presence of ADAs may contribute to this LOR. Since the work of Baert and colleagues, two episodic dosing trials have found a reduction in response duration in those who developed anti-infliximab antibodies [67, 68]. However, two scheduled dosing trials have not identified adverse outcomes with positive ADA titers [4, 69]. Interestingly, the Active Ulcerative Colitis (ACT) trials found an improved drug response in patients with positive anti-infliximab antibodies. The data for antibodies against adalimumab and certolizumab is similarly conflicting.

In practice, coupling serum TL drug concentrations with antibody titers can help guide management in patients with secondary LOR (Fig. 10.2). During an IBD flare with documented inflammation (i.e., active disease), if antibody titers are negative and TLs of the drug are therapeutic, the physician should consider switching to an entirely new class of medication [70]. If the drug is subtherapeutic, the dose or frequency of administration should be increased. If high antibody titers are detected, switching to another anti-TNF or an anti-integrin is recommended. If only low titers are present, the same agent can be used with the addition of an antimetabolite such as AZA, which may restore the clinical response by eradicating ADAs [71]. Switching therapeutic mechanisms to an anti-integrin is another option. The available clinical data supports this strategy. In a retrospective study of therapeutic

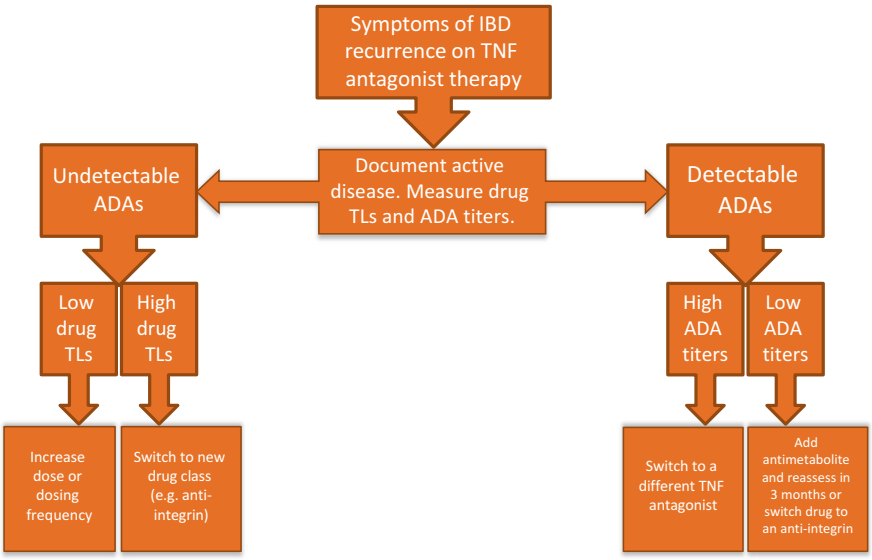

Fig. 10.2 Proposed use of anti-TNF trough levels (TLs) and antidrug antibodies (ADAs) during an IBD flare

infliximab monitoring, 83% of patients with subtherapeutic drug levels responded to dose escalation compared to a 33% response rate after switching to a different TNF antagonist. In patients with ADAs, 92% responded to switching anti-TNF agents compared to a 17% response rate with dose escalation [72].

A strategy to minimize LOR involves monitoring serum drug concentrations proactively. Drug levels are measured at prespecified time points followed by titration of the dose to achieve target concentrations. The benefits of this strategy were demonstrated by the *T*rough Level *A*dapted Infli*XI*mab *T*reatment (TAXIT) study group [73]. Higher rates of clinical remission were achieved when a threshold TL of 3–7 μg/mL was actively targeted. The study also demonstrated an economic benefit to this approach, as patients with TLs of ≥7 μg/mL could be safely dose de-escalated without affecting remission rates. After a successful dose optimization, there was no added benefit to continuing concentration-based dosing over clinically based dosing for the remainder of the first year of therapy [74]. In a recent cross-sectional study, Vaughn and colleagues investigated the impact of proactive drug concentration monitoring and titration of infliximab dosing to a target in patients with clinical remission. Patients who underwent proactive monitoring had a greater likelihood of remaining on infliximab therapy compared to controls (HR = 0.3, 95% CI 0.1–0.6), and those with a TL > 5 μg/mL saw the greatest benefit [75].

Measuring serum drug concentrations to guide therapy has also proven to be cost effective. Velayos and colleagues utilized a Markov model to compare simulated outcomes for a testing-based strategy vs. empirical dose escalation in Crohn's patients with LOR to infliximab [76]. The testing-based strategy had similar

quality-adjusted life-years and remission rates, but was significantly less expensive ($31,870 vs. $37,266) than empirical dose escalation over a 1-year period. Therefore, for both clinical and economic benefits, clinicians should consider incorporating drug concentration measurements into their therapeutic decision-making process.

When Treating Patients with Biologic Therapy, Optimize Therapy

The goals of therapy in IBD have focused on the achievement and maintenance of disease remission through treatment optimization. Traditionally, symptomatic remission was pursued using a "step-up" strategy involving medication and dose escalation as the severity of disease progressed. This strategy involves the use of the least effective and least potentially toxic medications initially, and if not beneficial, more aggressive and effective therapies with potentially greater toxicity are initiated. With the advent of biologic therapy, an effort to achieve resolution of both clinical symptoms and endoscopic inflammation is the focus of therapeutic intervention. The use of prognostication to predict which patients have the highest probability of aggressive disease has led to earlier introduction of biologic therapy in the medical therapeutic armamentarium. Since many patients do not initially respond to standard dosing, adjustments are needed to achieve optimized dosing.

The growing diversity of biologic agents alone has facilitated therapy optimization and remission even in severe disease. The TNF antagonists currently approved by the FDA for CD include infliximab, adalimumab, and certolizumab pegol, while those for UC include infliximab, adalimumab, and golimumab. All of the TNF antagonists have comparable clinical response rates, but switching between them is one potential optimization strategy after LOR [77]. Alternatives to anti-TNF therapy include the anti-integrin agents natalizumab (humanized monoclonal anti-alpha-4 integrin) and vedolizumab (humanized monoclonal anti-alpha-4-beta-7 integrin). However, use of natalizumab is restricted due to an increased risk for JC virus-associated progressive multifocal leukoencephalopathy (PML). The data for therapy optimization, however, is primarily based on the data from infliximab since this agent has been on the market for the longest of all biologics (FDA approved in 1998).

Optimization of therapy begins with an assessment of the risk of disease progression and assessment of the disease severity when considering the use of combination therapy (anti-TNF and immunomodulator). Certain clinical factors portend a higher risk of having complicated disease (poor prognosis), including early onset disease, early steroid requirement, perianal involvement, and severity of endoscopic inflammation [78]. Patients with these risk factors merit a "top-down" approach with early initiation of both a biologic and an antimetabolite. A randomized controlled trial by D'Haens et al. demonstrated that early treatment with dual therapy – infliximab and AZA – in patients with CD (who had no prior exposure to immunomodulators or biologic therapy) was associated with higher rates of MH compared to those receiving biologics later in their disease course [23]. The SONIC

trial also found a dual therapeutic approach in CD to be the most efficacious for steroid-free remission and MH [1]. Most recently, Khanna and colleagues conducted a cluster randomized trial to compare early combined immunosuppression with a conventional step-up approach in CD [79]. While there was no difference in remission rates as prior studies had shown, the risk of surgery, hospital admission, and disease-related complications was significantly lower with no increase in drug-related adverse events in patients receiving early combined therapy.

In UC, the benefits of combination therapy were also investigated in patients with frequent relapse and steroid dependence. Prior treatment guidelines have recommended a "step-up" approach in UC patients with antimetabolite monotherapy prior to a trial of a biologic agent [80]. The validity of this strategy was challenged by the UC SUCCESS trial [81]. Patients with moderate-to-severe UC who were refractory to steroids and naïve to TNF antagonists were treated with AZA monotherapy, infliximab monotherapy, or dual therapy. Those in the dual therapy group had significantly higher rates of corticosteroid-free remission at 16 weeks than patients receiving either monotherapy. Combined therapy also demonstrated significantly more MH than AZA monotherapy, further supporting a top-down approach for these high-risk patients.

In addition to implementing a "top-down" approach in high-risk patients, the clinician should have a strategy to optimize those with an inadequate initial response or secondary LOR to biologic therapy. Scheduled maintenance biologic dosing is preferred to episodic dosing to minimize immunogenicity, but is not 100% effective in preventing ADAs and subsequent LOR [72]. As discussed previously, therapeutic drug monitoring and ADA titers can be helpful in this regard (Fig. 10.2).

Dose escalation is appropriate in situations of negative ADAs and low drug levels, and the available data is most helpful for titrations of infliximab and adalimumab. With infliximab, dosing can be increased from 5 to 10 mg/kg every 4–8 weeks. The ACCENT I trial demonstrated an 80% response rate to this dose escalation in CD patients and the ACCENT II study showed a 50% response in more severe, fistulizing disease [82, 83]. Evidence also supports escalation of adalimumab from 40 mg every other week to weekly. In the CLASSIC II trial, 204 CD patients who were not in remission at weeks 0 and 4 after adalimumab induction entered an open-label cohort with 40 mg adalimumab given every other week [84]. With subsequent disease flares, doses could be escalated to 40 mg weekly. Forty-six percent of patients who completed 56 weeks of therapy required escalation to weekly dosing, among which 42% achieved clinical remission. In a post hoc analysis of the ULTRA 2 trial for UC, 29% of primary nonresponders to adalimumab demonstrated MH by week 52 with weekly dosing [85]. Similarly, weekly adalimumab led to clinical response and MH in 45% of patients with secondary LOR.

More data is needed to support dose escalation for the newer TNF antagonists – specifically certolizumab pegol and golimumab – given the lack of prospective, controlled blinded data. With certolizumab, the WELCOME and PRECISE 4 trials showed that reinduction doses or a single additional dose led to a maintained

clinical response in 50–60% of CD patients with relapse [86, 87]. For golimumab, higher drug levels were associated with greater clinical response in the PURSUIT-SC trial, suggesting a potential benefit to dose escalation that should prompt further investigation [54]. Recent data suggests there may be similar benefit for shortening the dosing frequency for patients with secondary LOR receiving vedolizumab for the treatment of IBD [88].

The diversity of patient and clinical factors in IBD presents challenges to therapeutic decision-making. However, the available data should provide a framework for achieving disease remission in a spectrum of disease manifestations. The greatest benefits are seen when a combination of biologic and antimetabolite therapy is initiated early in severe disease, and following drug levels and ADAs can positively influence dosing and medication adjustments to maintain MH. Future advancements in drug development and monitoring, individualized diagnostics, and risk stratification will promote a more robust approach to therapy optimization.

Dose Appropriately and Use the Correct Induction and Maintenance Doses

For treating IBD patients with active disease, we will review several clinical scenarios that require careful dosing considerations. First, it is important to give appropriate loading doses and appropriate maintenance dosing. Use of approved loading and maintenance doses are based upon pharmacokinetics and modeling. The standard induction and maintenance regimens for approved biologics are listed in Table 10.2.

(a) Prior to initiation of biologics and immunomodulators, vaccinate and screen for future potential infectious complications appropriately.

Table 10.2 Loading doses for biologics and immunomodulators

Biologic	Indication	Loading dose	Maintenance dose
Infliximab	CD, UC	5 mg/kg IV week 0, 2, 6	5 mg/kg IV every 8 weeks
Adalimumab	CD, UC	160 mg sc week 0; 80 mg sc week 2, 40 mg sc week 4	40 mg sc every 2 weeks
Certolizumab pegol	CD	400 mg sc week 0, 2, 4	400 mg sc every 4 weeks
Golimumab	UC	200 mg sc week 0, 100 mg sc week 2	100 mg every 4 weeks
Vedolizumab	CD, UC	300 mg IV week 0, 2, 6	300 mg IV every 8 weeks
Immunomodulator	**Indication**	**Dose**	**–**
Azathioprine	CD, UC	2.5 mg/kg/day	–
6-Mecaptopurine	CD, UC	1.5 mg/kg/day	–
Methotrexate	CD	25 mg sc/im/week	–

Table 10.3 Recommended testing and vaccination prior to initiation of therapy with immunomodulators and biologic agents

Infectious agent	Test	Treatment recommendation
HBV	HBcore Ab, HBsurface Ag, HBsurface Ab	Tenofovir, entecavir
Mycobacterium tuberculosis	Quantiferon TB Gold	INH
HIV	P24 antigen and antibody, PCR	N/A
Varicella	History, PCR	Two doses of varicella vaccine, repeat X 1
Human papilloma virus	Serology IgA, IgG	Bi/quadrivalent vaccine for both gender
Pneumococcus PCV13	N/A	Single vaccination
Influenza	N/A	Annual vaccination in autumn

It is well known that the use of immunomodulators and biologic therapy increases the risk of developing viral, fungal, parasitic, or bacterial infections (Table 10.3). Use of azathioprine/6-MP has been linked to an increased risk for viral infections, whereas biologic agents primarily increase the rate of fungal or mycobacterial infections [89].

Elderly patients with IBD are at an even greater risk for infectious complications. Specifically, patients over the age of 65 years have a 3- to 20-fold increased likelihood of developing urinary tract infection and community-acquired pneumonia while on immunomodulator therapy when compared to subjects 25 years and younger [90]. This argument also applies to elderly patients receiving biologics, as this population is more likely to develop severe infections and have an even higher mortality, making age an independent risk factor for hospitalization [91].

Prior to the initiation of immunosuppressive medications, all patients must be tested for hepatitis B (HBc antibody, HBs antigen, HBs antibody). In addition, vaccination is recommended for all HBc antibody-negative or hepatitis B surface antibody-negative individuals. HBs antigen-positive individuals who require immunosuppressive therapy for CD or UC should receive either entecavir or tenofovir 2 weeks prior to initiating immunosuppressive therapy. Reactivation of HBV in HBs antigen-positive patients has been shown to result in liver dysfunction ranging from 25 to 36% [92, 93]. Fulminant hepatic failure has also been described in this population. Currently, it is suggested that nucleotide/nucleoside analogs should be continued for a total of 12 months after completion of therapy for IBD in patients with a high viral load (HBV DNA > 2000 IU/mL) [94, 95]. The most recent suggestion is to continue nucleotide/nucleoside analogs until reaching endpoints that apply to immunocompetent patients [94, 95].

Besides HBV, serious consideration has to be given to latent Mycobacterium tuberculosis (TB) infection. TB should be excluded prior to the treatment of IBD in all patients with testing that includes an interferon-γ release assay, chest X-ray, and tuberculin skin test. This practice is mandatory, since it has been well recognized that TB reactivation can lead to serious complications and even death in patients treated with anti-TNF medications [96, 97]. Tuberculin skin test results have to be

interpreted with caution, as false-positive results (injection site induration ≥5 mm at 48 h) occur in patients that have received immunization with Bacillus Calmette–Guerin in the past, whereas false-negative findings are associated with active treatment with steroids, immunomodulators, and even active IBD by itself.

Treatment for latent tuberculosis consists of isoniazid and vitamin B6 [98]. Studies on the length of therapy with isoniazid have shown that medication for 9 months is associated with 90% protection, and treatment for 6 months resulted in 60–80% protection from tuberculosis reactivation [99]. Only a fraction of patients on isoniazid will develop liver biochemical abnormalities, and these should be monitored periodically. For patients with IBD and latent tuberculosis, a delay of at least 2 months for treatment prior to initiation of anti-TNF medications has been recommended [100].

Infection of immunocompromised IBD patients with varicella zoster virus (VZV) is a potentially fatal complication in up to one out of four subjects, resulting in disseminated intravascular coagulopathy, encephalitis, and/or hepatitis [101, 102]. In addition, postherpetic neuralgia is more severe in IBD patients treated with immunomodulatory medications with evidence of systemic dissemination in more than 20% [102, 103]. Therefore, IBD subjects without a definite history of chickenpox or varicella zoster should be tested for VZV-specific IgG and if negative, receive two doses of the VZV vaccine at least 3 weeks prior to initiation of biologic therapy [104].

Recommendations for the live zoster vaccine are more complex. In contrast to VZV, immunization with the zoster vaccine can be given while on immunosuppressive therapy, according the United States Center for Disease Control, as long as current medical therapy does not exceed the following dosing schedules: azathioprine ≤3 mg/kg, 6-mercaptopurine ≤1.5 mg/kg, methotrexate ≤0.4 mg/kg [105]. The zoster vaccine appears to be safe even in IBD patients on anti-TNF therapy [106]; however, it is not currently suggested to be given to patients on current anti-TNF therapy.

Female patients with IBD being treated with immunosuppressive medications should receive an annual pelvic examination. The screening for cervical cancer and its precursors in immunocompromised patients is now a standard recommendation. In addition to and regardless of medical therapy, the quadrivalent vaccine directed against human papilloma virus (HPV) L1-virus-like particles should be given to sexually active women and men from 11 to 26 years of age (Advisory committee on immunization practices CDC 2013).

(b) Optimize therapy – dose escalate when appropriate.

Patients who have persistent clinically significant inflammation despite biologic (anti-TNF or anti-integrin) therapy with therapeutic drug levels are considered as a therapeutic primary failure. However, patients initially responding who lose their response over time (termed secondary loss of response) should be considered for dose escalation before switching to an alternative agent. In general, the concept involves targeting higher biologic trough levels of the prescribed biologic agent. Table 10.4 summarizes relevant studies of dose escalation and factors that influence response and remission to biologic agents.

Table 10.4 Dose escalation and factors that influence response and remission to biologics

Study	Endpoint	Result	Remarks
ACCENT I (2002) [4] Maintenance of remission for CD	Rate of remission at week 30	Placebo 21%, IFX 5 mg/kg 39%*, IFX 10 mg/kg 45%*	*: Statistically significant in comparison to placebo 28.5% of patients developed worsening symptoms on IFX
	Median time to loss of response at week 54 (CDAI decrease >70 points, or 25% reduction total score)	Placebo 19 weeks, IFX 5 mg/kg 38 weeks*, IFX 10 mg/kg > 54 weeks*	
	Discontinuation of steroids at week 54	Placebo 9%, combined IFX 5/10 mg/kg 29%*	
GAIN (2007) [107] Adalimumab for the treatment of CD patients who failed IFX	Rate of remission at week 4 (CDAI decrease >70 points)	Placebo 7% vs. adalimumab 21%*	*: Statistically significant in comparison to placebo Switching to adalimumab after failure of IFX does not result in regain of anti-TNF responsiveness
PRECISE 4 (2010) [86] Dose escalation in CD patients with secondary failure to certolizumab	Rate of response at week 4	Group A (reintroduction dosing) 63%, group B (maintenance dosing) 65%	
	Rate of response at week 54	Group A (reintroduction dosing) 55%, group B (maintenance dosing) 59%	Addition of a single dose of certolizumab results in regain of anti-TNF responsiveness
Identification of variables that influence IFX dose intensification in CD (2007) [108]	Rate of event-free (flare) at month 30 time period from first infusion	Interval decrease 69%, dose increase 49%, interval decrease and dose increase 46%	Patients becoming symptomatic with IFX every 8 weeks should be tried on an increased infusion frequency schedule, first

Adalimumab dose intensification in CD patients with secondary loss of response (2013) [109]	Change in CDAI at months 3 and 12 while on adalimumab every week	Rate of patients with a decrease in CDAI >100 64% at 3 months, and 57% at 12 months	After secondary loss of response, dose escalation with weekly adalimumab injections induces response and remission
Effect of serum albumin concentration on the effectiveness of vedolizumab in patients with CD (2016) [88]	Assessment of Harvey Bradshaw Index score at weeks 0 and 14, subdivided by quartile serum albumin concentration	Response to vedolizumab was independent of albumin serum concentration	Vedolizumab might provide an alternative first choice of biologic in patients with below normal serum albumin concentrations

(c) Check TPMT prior to treatment with antimetabolite therapy. Consider the toxicities associated with thiopurine use.

Thiopurine methyltransferase (TPMT) genotype or phenotype (i.e., enzyme activity) testing prior to initiating immunomodulatory therapy with AZA or 6-MP can help to predict drug response and is now standard of practice [110–112]. In the general population and in patients with IBD, enzyme activity in Caucasians is divided into low (0.3%), intermediate (11%), and normal levels (89%). In general, patients with intermediate enzyme activity are started on a lower dose of 6-mercaptopurine and azathioprine, as opposed to patients with normal TPMT activity, usually receiving a regular maximal dose at 1.5 mg/kg and 2.5 mg/kg, respectively. The rare patient with a low TPMT enzyme activity should not receive immunomodulatory therapy with AZA or 6-MP due to increased toxicities.

Thiopurines for the maintenance of remission are not tolerated by approximately 20% of patients beyond 1 month. Most commonly encountered side effects including headache, diarrhea, nausea, vomiting, abdominal pain, and fatigue [113]. Complications encountered for the duration of thiopurine treatment include myelosuppression with ensuing leukopenia in about 5% of patients, even after patients stop medication for 6 months [114, 115]. In addition, 2.3% of patients may develop pancreatitis, and more rarely, hepatitis may occur.

A more recent concern is the increased risk for lymphoma with thiopurine use. Kotlyar and colleagues conducted a meta-analysis to determine how this risk varied with patient age and gender and found that the risk was greatest in individuals older than 50 and men younger than 30 [116]. Weighing the risks and benefits of antimetabolite therapy therefore merits further attention in individuals from either of these groups.

(d) Prior to conception, it is important to ensure the mother is in remission.

Pregnancy in patients with IBD poses a special challenge to the mother, fetus, and provider. Besides general recommendations, including adequate nutrition, supplemental folate and vitamin D, and smoking cessation, specific attention has to be paid to medical therapy for induction and maintenance of remission. Prognostically, female patients that conceive during a flare of IBD have an approximately 70% chance of continued or worsening activity of intestinal inflammation during pregnancy [117–119]. Therefore, it is of paramount importance to achieve clinical remission prior to considering pregnancy. Continuation of appropriate medication during pregnancy is currently the standard to consider for patients in remission.

(e) Anti-TNF therapy is perceived to be safe in pregnancy to the mother and fetus. However, there is limited data for the safety of anti-integrin therapy.

Anti-TNF agents are used for induction and maintenance of remission during pregnancy and are considered low risk to the fetus and mother [120]. Transplacental traffic of IgG1 increases and accumulates in the fetus with gestational age [121], and the increase in anti-TNF medications might lead to modification and suppression of

the fetal enteric immune system, as clearance of anti-TNFs has been shown to take between 2 and 7 months to become undetectable postpartum. Infliximab, adalimumab, golimumab, and vedolizumab are composed of IgG1 Fc segments and cross transplacentally, whereas certolizumab pegol is IgG4 and has low transplacental transfer. To this date, preterm birth, infections, or developmental differences have not been identified in comparison to unexposed infants [122]. Biologic agents can be safely sustained for the first two trimesters until weeks 24–26, but due to a lack of prospective trial data, firm recommendations whether to stop, decrease the dose, or maintain the medication at full strength depend on the individual provider and the patient. However, prior to any decision, disease activity should be assessed [123].

Vedolizumab has limited data available in abstract form only [124]. A small study showed that of 16 documented exposures to vedolizumab during pregnancy, nine resulted in live births, two in spontaneous abortions, two in elective abortions, and three were lost to follow-up.

(f) AZA and 6-MP use during pregnancy is not associated with any systematic birth defect but has been associated with infants who are premature or small for gestational age.

AZA and 6-MP are categorized as class D drugs in pregnancy, as there is positive evidence of human fetal risk, based on adverse reaction data from investigational and marketing experience, as well as human studies. However, potential benefits may warrant use of the drug in pregnant women despite the potential risks, as there is no systematic birth defect that has been described with its use. A recent meta-analysis [125] has demonstrated that thiopurine exposure in women with IBD was not associated with low birth weight or congenital abnormalities, but was associated with preterm birth. Exposure in men at the time of conception was not associated with congenital abnormalities.

Data from the PIANO registry noted that adverse outcomes for women and their newborn were not significantly different from control populations, but this study noted a few exceptions to this finding [126]. First, besides an increased rate of spontaneous abortions and Cesarean sections, infants born to mothers with IBD were more likely to deliver early and require postpartum intensive care. Second, mothers treated with anti-TNF agents for UC had a fivefold increased rate of spontaneous abortion, which was not the case for CD pregnancies. Third, combination therapy with anti-TNF and immunomodulatory agents resulted in postpartum complications of any kind, adjusted for disease activity.

Additionally, 6-thioguanine nucleotide (6-TGN), a metabolite of 6-MP and AZA, is detectable in newborns of mothers treated with immunomodulators and usually mirrors the mother's 6-TGN serum concentrations. In contrast, 6-methylmercaptopurine nucleotide (6-MMP) does not traverse the placental barrier and is not found in fetal peripheral blood. Despite these findings, increased congenital abnormalities have not been described [125, 127, 128]. Among providers there is agreement to not start immunomodulators during pregnancy out of concern for bone marrow suppression and pancreatitis.

(g) For infants born to mothers on anti-TNF therapy, avoidance of live vaccines for 6 months after birth is suggested. Certolizumab pegol crosses the placenta in very low concentrations.

Experts from the United States Centers for Disease Control and Prevention, Public Health Agent of Canada, European Crohn's and Colitis Organization, and World Congress of Gastroenterology, all currently recommend that infants exposed to biologics in utero should receive the same nonlive vaccines given to unexposed individuals. However, live attenuated vaccines, like rotavirus, intranasal influenza, and BCG, should not be given until 6 months of age. This recommendation is based upon the observation that biologics for the treatment of the mother's inflammatory bowel disease in some cases are not cleared by the infant until that time, raising the concern for disseminated infections. If concern regarding a lack of clearance of biologics in infants beyond 6 months exists, serum titers can be obtained to guide the administration of live attenuated vaccines.

Therefore, it is advisable to weigh risks and benefits carefully, tailored to each individual pregnancy, taking into consideration the past and present behavior and severity of disease, as well as successful and unsuccessful medications used to maintain remission. A multidisciplinary approach is advisable, managing these complex patients with advice from obstetrics, nutrition, pharmacy, and possibly surgery.

(h) Serum albumin is one of the most important predictors of response to biologic therapy.

When evaluating patients in the office or hospital setting, it is important to assess the response that an individual patient may have to medical therapy. Biomarkers that enable practitioners to successfully predict a patient's response to biologic agents are now beginning to emerge. Serum albumin concentration is one of the most well-studied biomarkers for this purpose. Combining data from two study populations with over 700 UC subjects, patients with a normal range of serum albumin demonstrated a lower clearance rate, longer half-life, and significantly higher serum trough levels of infliximab, translating into a more favorable clinical response rate to therapy [129]. In particular, a retrospective pharmacokinetic analysis of two Phase III trials by the same group (REACH, ACCENT I) found that low serum albumin was associated with significantly increased infliximab clearance [130]. Interestingly, even within the range from high (4.8 mg/dL) to low-normal (3.1 mg/dL) albumin levels, infliximab clearance increased by approximately 45%, speculating that a normal albumin concentration improves the function of the neonatal Fc receptor, ergo recycling infliximab more efficiently, and accounting for more than 80% of infliximab efficacy. When investigating CD patients with a loss of response to anti-TNF therapy at 5 mg/kg, after a dose adjustment to 10 mg/kg, remission rates at 40 weeks were significantly higher in subjects with trough infliximab concentrations $\geq$1 μg/mL and albumin levels $\geq$3.5 g/dL [131].

While treating with certolizumab pegol, univariant analysis short-term recurrence is significantly higher in patients with an albumin concentration below

3.5 mg/dL [132]. Further, multivariant analysis has shown that for every unit increase in albumin and single percent of hematocrit, the probability of losing remission at a given time is reduced (HR 0.944 and HR 0.736, respectively). In reverse, when data was subjected to logistic regression analysis, maintenance of remission with certolizumab was shown to be associated with, among others, a normal serum albumin concentration (OR 1.07, 95% CI 1.01–1.13). These findings suggest that serum albumin concentrations should be closely monitored for the prediction of long-term outcome in UC and CD, and dose escalation should be considered in patients with low serum albumin.

Promote Medication Adherence in All Patients

While successful IBD management requires a thoughtful and personalized treatment approach, suboptimal medication adherence remains a significant and often overlooked barrier to remission. Nonadherence occurs in greater than 30% of IBD patients, and as many as 60% of adults do not take their oral 5-ASA medications consistently [133, 134]. This lack of adherence increases the risk of IBD flares by more than fivefold while also escalating healthcare costs [135]. Unfortunately, recognition of nonadherence is challenging, and evidence for the use of disease characteristics and demographics to screen for nonadherence is lacking [136, 137]. The clinician's efforts should therefore focus on methods to promote medication adherence in all patients.

Current evidence supports the use of education and dose simplification to maximize adherence. Gastroenterologists should aim to expand their patients' knowledge regarding IBD and associated symptoms, purpose and mechanisms of specific medications, potential adverse effects of therapy, and the consequences of nonadherence. The most commonly reported reasons for intentional treatment discontinuation are adverse effects and symptom resolution (removing the perceived need for therapy), which may reflect a fundamental misunderstanding of the disease process [138]. Many patients outwardly express a desire to learn more about their disease and endorse fear related to knowledge deficits [139, 140]. Prior studies have demonstrated that disease-specific education can mitigate these concerns and bolster adherence [141–143]. An RCT by Waters et al. corroborated that formal IBD education successfully improves patient knowledge, perceived knowledge, and satisfaction [144]. While underpowered, the study also found a nonsignificant reduction in nonadherence in the patient education group. In a recent cohort study, Selinger and colleagues investigated modifiable risk factors associated with nonadherence to IBD therapy. The belief of necessity of medication was associated with significantly better adherence, suggesting a valuable role for a patient's understanding of specific treatments and their functions.

Simplification of the dosing regimen has also been shown to improve medication adherence in adults. Kane et al. randomized UC patients to either conventional mesalamine dosing (two or three times daily) or once-daily dosing. At 3 months,

once-daily dosing resulted in full adherence, while conventional dosing yielded only 70% adherence [145]. Further work by Dignass and colleagues found the remission rate of UC to be higher with once-daily compared to twice-daily mesalamine [146]. Additionally, both once- and twice-daily MMX mesalamine effectively induced clinical and endoscopic remission when compared to placebo in patients with mild to moderate UC, affirming that simplified dosing is also a therapeutically sound option [147]. This strategy may be most beneficial in cases of accidental nonadherence due to the complexity of treatment regimens.

Several more specialized adherence strategies may be considered based on patient preferences and characteristics. In pediatric populations, cognitive behavioral therapy (CBT) aimed at problem solving has been effective. Greenley and colleagues found that two family-centered problem-solving training sessions improved adherence by 18% among patients who were previously nonadherent to oral medication [148]. For more challenging cases, a multifaceted and tailored approach that combines education, behavioral therapy, and support may be preferred. Moshkovska et al. demonstrated significantly greater adherence to mesalamine in UC patients who underwent motivational training, education, and three additional patient-chosen tactics including simplified dosing, pill organizers, and various medication alarms and reminders [149]. Given the many potentially effective interventions, it is worthwhile for every gastroenterologist to discuss adherence in the clinic and identify any modifiable barriers prior to optimizing therapy.

Prognosticate to Predict Which Patients Will Have the Highest Probability of Having Aggressive Disease. Treat Aggressive Disease Aggressively

One of the most important challenges in IBD management is identifying high-risk patients to whom a top-down therapeutic approach should be applied. The risk of structural bowel damage leading to intestinal resection in CD is nearly 80%, and 10% of UC patients will have a colectomy within 10 years of diagnosis [150, 151]. Implementing early aggressive therapy that combines a thiopurine and TNF antagonist can reduce the incidence of these tragic outcomes in select patients [1]. But those destined for a more benign disease course may instead suffer from the complications of unnecessary immunosuppression if their risk is incorrectly stratified. There is therefore an obvious need for reliable predictors of disease course and severity to be applied in clinical practice.

In CD, clinical findings at diagnosis can predict disease severity. Wolters et al. found that age <40 years and the presence of upper gastrointestinal lesions on endoscopy predicted recurrence, while Solbert and colleagues identified age <40 years, perianal fistulas and abscesses, and involvement of the terminal ileum as predictive factors for surgery within 10 years of diagnosis [152, 153]. The need for steroids in treating the first IBD flare also predicted disabling disease (e.g., steroid dependence, hospitalization, surgery, disabling symptoms) within 5 years of diagnosis in a

referral center cohort [154]. Smoking has been established as a risk factor for transient worsening in CD, while nonsmoking status and higher educational level were independently associated with a nonsevere 15-year course in a 600-patient cohort [148, 155]. For postoperative CD recurrence, smoking is associated with a twofold increased risk that grows further according to the number of cigarettes smoked daily [156].

Serologic factors can also provide useful prognostic information in CD. Several studies have assessed serum markers, and antibodies against *Saccharomyces cerevisiae* antibody (ASCA), *Escherichia coli* outer-membrane porin C (OmpC), anti-CD-related bacterial sequence (anti-I2), and CBir1 flagellin (CBir1) are associated with early disease onset, penetrating disease, and need for early surgical intervention [157–159]. ASCA may also predict pouchitis after ileal-anal anastomosis [160]. Unlike in UC, perinuclear antineutrophil cytoplasmic antibody (p-ANCA) has been associated with less severe disease and fewer small bowel complications in CD [158, 161].

The utility of genetic predisposition is more limited in prognosis, given that a family history of CD (which increased risk for CD) does not predict disease severity [162]. However, a select few genetic polymorphisms may help predict clinical outcomes. The NOD2 polymorphism has been associated with an increased risk for stricture, early surgical intervention, and postoperative recurrence [163]. Additionally, multidrug resistant 1 (MDR1), migration inhibitory factor (MIF), and TNF genetic polymorphisms may help predict steroid refractory disease [164–166]. More recent work has identified apoptosis gene polymorphisms that may help predict anti-TNF responsiveness in CD [167].

In UC, clinical predictors for disease severity were evaluated in population-based cohorts. Female gender and young age at diagnosis were associated with frequent relapses in two studies, and significant systemic symptoms such as fever and weight loss increased the risk for colectomy in a Danish cohort [168–170]. The data for smoking, however, is somewhat more conflicting; one cohort study associated smoking with reduced relapses, while others have found a less active disease course in nonsmokers [155, 169]. Nonetheless, smoking is never advised in IBD patients.

Less data exists for serologic and genetic markers for disease severity in UC. However, multiple studies, including a recent prospective Australian cohort, have associated colectomy with elevated CRP at diagnosis [171]. And while genetic factors are not yet applied in clinical practice, Iliev and colleagues found that a haplotype of the gene CLEC7A predicts treatment-refractory UC and shorter time to colectomy [172].

A global assessment of prognostic factors should be used to guide therapy in IBD. Siegel and colleagues recently developed a Web-based tool that combines clinical, serologic, and genetic variables to predict outcomes that can help providers make personalized treatment decisions in CD [173]. The variables incorporated into the model are readily available through standard IBD evaluation and include the location of disease in the bowel, ASCA, CBir1, ANCA, and NOD2 frameshift mutation. These characteristics are inputted in an online interface that then calculates and plots the patient's percentage risk for complications

against time. This is the first validated predictive model that facilitates shared decision-making between the patient and the provider that will hopefully see extensive use by gastroenterologists in the coming years. With additional prospective data on predictors of disease course, we hope that similar models will be developed for practical use in UC as well.

Conclusions

We hope that this chapter provides a helpful framework for approaching patients with moderate-to-severe IBD. While no single therapeutic plan can benefit all patients, we feel that a general strategy that involves documenting active disease, treating to objective targets, optimizing therapy, and promoting adherence will lead to the best outcomes. High-risk patients now warrant a top-down approach, and achieving mucosal healing has become a feasible goal in the biologic era. With the growing diversity of immunomodulatory agents and improvement in our prognostic capabilities, we hope to be able to tailor therapy with even greater precision to individual patients' needs.

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Chapter 11
IBD Therapies: Coming Attractions

Joel Pekow

Abbreviations

IBD	Inflammatory Bowel Disease
UC	Ulcerative colitis
JAK	(Janus Kinase)
STAT	(signal transducer and activator of transcription)
(TYK2)	Tyrosine Kinase 2
(IL)	Interleukin
TNF	Tumor Necrosis Factor
CDAI	Crohn's disease activity index
PDE4	(phosphodiesterase 4)
cAMP	(cyclic adenosine monophosphate)
FDA	Food and Drug Administration
ICAM-1	(intracellular adhesion molecule 1)
VCAM-1	(vascular cell adhesion molecule 1)
MAdCAM-1	(mucosal vascular addressin cell adhesion molecule 1)
(CCR-9)	C-C chemokine receptor 9
(CCL25)	Chemokine ligand 25
(IP-10)	Interferon-γ-inducible protein 10
(FFA2)	Free fatty acid receptor 2
(S1PR)	Sphingosine-1-phosphate receptor
(TGFβ1)	Transforming growth factor β1
CRP	c-reactive protein
(CCL-11)	Eotaxin-1
(MMP9)	Matrix metalloproteinase 9

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Introduction

Since FDA approval of infliximab in 1998 for the treatment of Crohn's disease, five additional biologic therapies have been approved for either Crohn's disease or ulcerative colitis. These new therapies have improved rates of mucosal healing and outcomes for patients with inflammatory bowel disease (IBD). Despite these advances, overall remission rates with these agents continue to be suboptimal. As such, research aimed at optimizing response rates to currently available treatments through developing tools for prediction of response and achieving therapeutic drug levels continues to be important. In addition, there is a great need to develop new therapies targeting novel mechanisms of action. This chapter will focus on therapies currently in development for the treatment of Crohn's disease and ulcerative colitis. In the first section, the emphasis will be on therapies currently in clinical trials for IBD that are FDA approved for other indications (Prêt-à-Porter). The second section will review other treatments currently in development. Although many of these therapies are being studied in other diseases, they are not yet FDA approved for other indications.

Prêt-à-Porter

Tofacitinib

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway directs intracellular signaling following the binding of numerous cytokines to their respective transmembrane receptors. This intracellular signaling cascade ultimately results in transcriptional regulation. Through this mechanism, the JAK/STAT pathway is a key mediator of inflammatory cytokines on cell-specific inflammation-associated gene transcription [1, 2]. There are four JAK proteins (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]). Tofacitinib is an oral selective inhibitor of Janus kinase (JAK) 1 and 3 with reduced inhibition of JAK2 and TYK2. Tofacitinib 5 mg bid is currently FDA approved for patients with moderate to severe rheumatoid arthritis, as clinical trials have demonstrated superiority of tofacitinib to methotrexate and adalimumab in this population [3–5]. More recently, tofacitinib was found to be effective in the treatment of plaque psoriasis in phase III studies [6, 7]. In these clinical trials, tofacitinib treatment has been associated with a decrease in neutrophil counts, increases in low- and high-density lipoprotein cholesterol levels, and mild increases in serum creatinine in a minority of patients [4, 8]. Although the risk of infectious complications and death was not reported higher than with other biologics in one analysis, increased rates of herpes zoster have been reported in clinical trials compared to those receiving placebo [9, 10].

In a phase II trial comparing treatment with tofacitinib 0.5, 3, 10, and 15 mg bid in 194 patients with moderate to severe ulcerative colitis, 32% ($p = 0.39$), 48% ($p = 0.55$), 61% ($p = 0.1$), and 78% ($p < 0.001$), respectively, achieved a clinic response compared to placebo (42%). Clinical remission was seen in 13% ($p = 0.76$), 33%

($p = 0.01$), 48% ($p < 0.001$), and 41% ($p< 0.001$), respectively, compared to placebo (10%). As has been reported with the use of tofacitinib in clinical trials for other indications, a dose-dependent increase in LDL and HDL cholesterol was seen in this study. In addition, three subjects in the study who were on 10 or 15 mg doses developed absolute neutrophil counts <1500 cells/mm^3 [11]. Phase III studies examining the efficacy of tofacitinib 10 mg bid vs. placebo in the induction of remission (OCTAVE) and 5 mg bid vs. 10 mg bid vs. placebo in the maintenance of remission in UC (OCTAVE Sustain) supported the therapeutic benefit of the medication seen in earlier phase studies although have yet to be published in a peer reviewed journal.

A phase II study was also conducted in 139 subjects with moderate to severe Crohn's disease comparing treatment with 1, 5, or 15 mg bid to placebo. No differences in clinical remission or response were observed at week 4; however, subjects who received 15 mg bid did have reductions in C-reactive protein and fecal calprotectin [12]. It is worth noting that the placebo response rate was 47.1% in this study. A larger phase II study to investigate tofacitinib 5 mg bid and 10 mg bid compared to placebo for induction and maintenance therapy in moderate to severe Crohn's disease was recently completed although results have not been reported (NCT01393626 and NCT01393899).

Ustekinumab

Ustekinumab is an IgG1 monoclonal antibody which targets the p40 subunit common to both interleukin (IL)-12 and IL-23, thus inhibiting binding to the receptor, IL-12β1. Randomized, placebo-controlled studies have demonstrated the effectiveness of ustekinumab in the treatment of plaque psoriasis and psoriatic arthritis, leading to FDA approval of the drug for those indications [13–15]. As IL-12 and IL-23 are known to be integral to the T-cell response and single nucleotide polymorphisms of several genes in the IL-12/IL-23 pathway are associated with Crohn's disease, there has been great interest in targeting this pathway in IBD [16, 17]. A phase IIa multicenter, double-blinded, placebo-controlled crossover study examined ustekinumab in patients with active Crohn's disease. One hundred and four were given either subcutaneous ustekinumab 90 mg at weeks 0–3 and placebo at weeks 8–11, placebo at weeks 0–3 and subcutaneous ustekinumab at weeks 8–11, intravenous ustekinumab 4.5 mg/kg at week 0 and placebo at week 8, or IV placebo at week 0 and intravenous ustekinumab 4.5 mg/kg at week 8. Twenty-seven primary or secondary non-responders to anti-TNF agents were also randomized to receive open label ustekinumab either subcutaneous 90 mg at weeks 0–3 or a single dose of 4.5 mg/kg given intravenously. Although the study did not reach the primary end point of a CDAI decrease of ≥70 at week 8, response rates at 4 and 6 weeks were significantly higher in the combined group of subjects treated with ustekinumab. The study also indicated increased rates of response in patients previously treated with anti-TNF therapy [18]. A subsequent phase IIb trial was conducted in 526 patients with Crohn's disease resistant to anti-TNF therapy. These subjects were randomized to receive 1, 3, or 6 mg/kg of intravenous ustekinumab or placebo [19]. Patients who responded to induction therapy at week 6 were

further randomized to receive 90 mg of subcutaneous ustekinumab or placebo at weeks 8 and 16 with primary outcome measured at week 22. The proportion of patients who achieved the primary end point of ≥100 point decrease in CDAI at week 6 were 36.6%, 34.1%, 39.7%, and 23.5% for the 1, 3, 6 mg/kg, and placebo doses, respectively ($p = 0.005$ for 6 mg/kg compared to placebo). However, there were not differences in clinical remission between the 6 mg/kg group and placebo at week 6 ($p = 0.68$). Maintenance therapy with ustekinumab 90 mg resulted in an increased rate of clinical remission at week 22 than placebo (41.7% vs. 27.4%, $p = 0.03$). Serious adverse events were uncommon in this study, and infectious complications were similar between groups.

A phase III trial examining induction treatment with 6 mg/kg intravenous vs. 130 mg intravenous vs. placebo was recently completed in 628 patients with moderate to severe Crohn's disease. Clinical response as defined by a CDAI decrease >100 or a CDAI score <150 at week 6 was seen in 52% of patients receiving 130 mg and 56% of patients receiving 6 mg/kg as compared to 28% of patients receiving placebo ($p < 0.001$). Clinical remission, defined as a CDAI score <150, was observed in 18% of patients receiving placebo compared to 29% ($p = 0.007$) of patients receiving 130 mg and 35% of patients receiving 6 mg/kg ($p < 0.001$)(add reference Feagen BG N Engl J Med 2016;17:1946-1960.). A maintenance of remission trial comparing 90 mg subcutaneous dosing at different intervals to placebo in patients who achieved remission to induction dosing demonstrate efficacy with 90 mg every 8 weeks and every 12 weeks at week 44. (add reference Feagen BG N Engl J Med 2016;17:1946-1960.) Further supporting the potential benefit of ustekinumab in patients with Crohn's disease, recent publication evaluating 122 patients with Crohn's disease refractory to anti-TNF therapy in Europe reported that 65% of patients receiving subcutaneous ustekinumab reported benefit [20].

Apremilast

Apremilast is an oral small molecule inhibitor of phosphodiesterase 4 (PDE4). On immune cells, PDE4 is the dominant phosphodiesterase expressed and is known to regulate cyclic adenosine monophosphate (cAMP) through hydrolysis. As cAMP controls several proinflammatory cytokines, apremilast results in modulation of proinflammatory and anti-inflammatory mediators, including decreasing TNFα and IL-23, while increasing IL-10. In clinical trials, apremilast demonstrated benefit in psoriatic arthritis and was subsequently FDA approved [21]. Serious adverse events in patients receiving apremilast in clinical trials for psoriasis, psoriatic arthritis, rheumatoid arthritis, and Behçet's disease have been rare [21–23]. A phase II study examining 30, 40 mg bid, and placebo in patients with ulcerative colitis is ongoing (NCT02289417) (Table 11.1).

Table 11.1 Therapies being investigated in inflammatory bowel disease that are currently FDA approved for other indications

Name	Mechanism	Route	Current FDA-approved indication	IBD indication studied	Current phase of trial in IBD
Tofacitinib	Inhibitor of JAK1/3 > JAK2	PO	Rheumatoid Arthritis	UC CD	UC-Phase III CD-Phase II
Ustekinumab	Monoclonal antibody to p40 common to IL-12 and IL-23	IV/SC	Plaque Psoriasis Psoriatic Arthritis	CD	Phase III completed
Apremilast	Inhibitor of phosphodiesterase 4	PO	Psoriatic Arthritis	UC	Phase III

Work in Progress

Therapies That Target Inflammatory Cell Adhesion and Migration

Secondary adhesion molecules expressed on lymphocytes, termed integrins, facilitate migration of lymphocytes to tissues through an interaction with receptors expressed on the vascular endothelium. The integrins that participate in this process include: $\alpha_2\beta_2$ which is present on neutrophils and binds to ICAM-1 (intercellular adhesion molecule 1), $\alpha_4\beta_1$ which is expressed on most leukocytes and targets VCAM-1 (vascular cell adhesion molecule 1), $\alpha_4\beta_7$ which is located on gut-specific lymphocytes and binds to MAdCAM-1 (mucosal vascular addressin cell adhesion molecule 1), and $\alpha_E\beta_7$ which is expressed on intraepithelial lymphocytes and binds to E-cadherin on epithelial cells [24–26]. Inflammatory cells expressing β_7 containing integrins together with the C-C chemokine receptor 9 (CCR-9) interacting with chemokine (C-C motif) ligand 25 (CCL25) facilitates their homing to the gut [27, 28]. Multiple pharmacological agents have been developed to target integrins or their receptors in order to inhibit the trafficking of lymphocytes to inflammation in the gut. The first two therapies approved by the FDA targeting this pathway were natalizumab in 2006 for the treatment of Crohn's disease, a monoclonal antibody targeting α4 integrin, and vedolizumab in 2013 for the treatment of Crohn's disease and ulcerative colitis, a monoclonal antibody against $\alpha_4\beta_7$. In addition to natalizumab and vedolizumab, several biologic agents targeting adhesion molecules are in development.

Etrolizumab

Etrolizumab is a humanized monoclonal antibody that targets $\alpha_4\beta_7$ and $\alpha_E\beta_7$. A phase II trial comparing etrolizumab 100 mg dosed at weeks 0, 4, and 8 vs. a 420 mg loading dose followed by 300 mg at weeks 2, 4, and 8 vs. placebo demonstrated

significantly increased remission rates in patients with moderate to severe UC at week 10 (0% placebo, 21% etrolizumab 100 mg [p = 0.004], 10% etrolizumab 300 mg [p = 0.048]). In this study, the percentage of patients with endoscopic remission and a Mayo bleeding subscore of 0 was 0% in placebo-treated patients compared to 10% of patients receiving 100 mg (p = 0.16) of etrolizumab and 8% of patients receiving 300 mg of the medication (p = 0.19) [29]. A subsequent analysis using subjects from this study demonstrated that pretreatment increased levels of α_E and Granzyme A in the colonic mucosa were associated with a response [30]. Phase III trials examining the efficacy of induction and maintenance of remission with etrolizumab in both UC (NCT02165215, NCT02171429, NCT02163759, NCT02136069, NCT02100696) and Crohn's (NCT02394028) disease are currently ongoing.

AMG 181

AMG 181 is a monoclonal antibody that binds to $\alpha_4\beta_7$; it has been developed as a subcutaneous therapy [31]. The antibody is being evaluated in phase II trials in patients with moderate to severe Crohn's disease and ulcerative colitis (NCT01696396, NCT01694485).

PF-00547659

PF-00547659 is a monoclonal antibody targeting MAdCAM-1 [32]. A phase II randomized, double-blind, placebo-controlled trial including 80 patients with ulcerative colitis who had a Mayo score ≥6 at enrollment did not demonstrate statistically significant differences in clinical response, clinical remission, or endoscopic remission. However, there was a trend toward improvement in all three parameters and significant reductions in fecal calprotectin [33]. As such, larger phase II trials in Crohn's disease and ulcerative colitis with this monoclonal antibody were conducted. Three hundred and fifty-seven patients with UC who had a total Mayo score >=6 and a Mayo endoscopy subscore ≥2 were randomized to subcutaneous dosing of 7.5, 22.5, 75, 225 mg or placebo given every 4 weeks for 3 doses in the TURANDOT study. After 12 weeks, a significantly higher percentage of patients who were taking 7.5 mg (11.3%), 22.5 mg (16.7%), and 75 mg (15.5%) achieved clinical remission compared to placebo (2.7%). In the group receiving 22.5 mg, 27.8% of patients achieved mucosal healing compared to 8.2% of patients receiving placebo [34]. A similar study, the OPERA trial, was conducted in 267 subjects with moderate to severe Crohn's disease who had failed or were intolerant to anti-TNF therapy or immunosuppressants. In this study, there were no differences in response or remission rates between any of the treatment groups (22.5, 75, 225 mg) or placebo. It is worth noting, however, that the placebo response rate in the trial was 59%, and a post-hoc analysis of subjects with a CRP >18 revealed an increase in percentage of patients in remission of all three treatment groups compared to placebo (22.5 mg – 37.5%, 75 mg – 24%, 225 mg – 39%, placebo – 14%) [35].

Vercirnon

CCX282-B (GSK1605786A) is an oral selective antagonist of CCR9. In the phase IIb PROTECT-1 trial, CCX282-B demonstrated efficacy in clinical response after 12 weeks induction and at week 36 in patients with Crohn's disease taking 500 mg daily compared to placebo [36]. A larger randomized phase III trial, SHIELD-1, in patients with Crohn's disease who had a Crohn's disease activity index (CDAI) of 220–450 and either endoscopically confirmed disease or elevation in both CRP and fecal calprotectin, however, did not demonstrate a benefit in clinical response from the compound [37].

BMS-936557 (Eldelumab)

BMS-936557 is a monoclonal antibody to interferon-γ-inducible protein 10 (IP-10), which is a chemokine integral to inflammatory and epithelial cell migration. A phase II randomized study of 10 mg/kg of BMS-936557 given intravenously every other week in patients with active UC did not demonstrate differences in clinical response at day 57, however, subjects with a higher steady-state concentration of the drug were significantly more likely to achieve clinical response and histological improvement [38]. A phase II study examining induction and maintenance of remission of BMS-93557 in subjects with moderate to severe Crohn's disease was recently completed and presented at Digestive Disease Week in 2015. In the study, subjects with active Crohn's disease were randomized 1:1:1 to placebo, 10, or 20 mg/kg IV. Drug was delivered on days 1 and 8 and every other week for a total of 11 weeks. There was a trend toward efficacy in clinical end points and endoscopic improvement. Clinical remission and response were (20/35%), (22.5/47.5%), and (29.3/41.5%) with placebo, 10, and 20 mg/kg, respectively. In addition, the investigators reported higher remission and response rates in anti-TNF naïve patients. Serious adverse events occurred in 5%, 7.5%, 9.8% in subjects treated with placebo, 10 mg/kg, 20 mg/kg, respectively. The majority of these serious adverse events were infusion related [39]. Further investigations of this therapy in IBD have not been announced.

GLPG0974

GLPG0974 is a selective antagonist of the free fatty acid receptor 2 (FFA2) [40]. Inhibition of FFA2 results in decrease in neutrophil activation and migration. GLPG0974 was studied in a phase IIa study of mild to moderately active UC at a dose of 200 mg bid for 4 weeks. Although no differences were seen in clinical response, remission, or mucosal healing at week 4, there was a significant decrease in myeloperoxidase-staining cells in the lamina propria and fecal calprotectin in the group treated with GLPG0974, suggesting a decrease in neutrophil activation and migration [41]. Further studies examining the effectiveness of this treatment in IBD have not been announced.

Sphingosine-1-Phosphate Receptor Modulators

Sphingosine-1-phosphate is a bioactive lipid mediator which is a ligand for the G-protein-coupled sphingosine-1-phosphate receptors (S1PR). There are five S1PRs which function as cell surface receptors to mediate extracellular signaling. Of these receptors, it is believed that S1P interaction with S1PR1 is needed for the egress of lymphocytes from the thymus and lymph nodes. Modulators of these receptors result in internalization, phosphorylation, or ubiquination of the receptor ultimately leading to the prevention of the inflammatory cell egress from lymph tissue. The first medication targeting this pathway was fingolimod, which is a non-specific S1PR agonist, is a FDA approved for the treatment of multiple sclerosis. As side effects have been associated with this medication, including bradycardia, which are thought to be mediated through S1PR3, there has been an interest in developing S1PR1 specific blockade. Three S1PR1 modulators are in development for IBD: Ozanamid, APD-334, and MT-1303.

Ozanamid

Ozanamid (RPC1063) is an oral agent which is a modulator of S1PR1. In a phase II randomized control trial of 197 patients with moderate to severe UC (TOUCHSTONE), 8 weeks of induction treatment resulted in increased rates of remission (placebo – 6.2%, 0.5 mg – 13.8%, 1 mg – 16.4%) as well as mucosal improvement (placebo – 12.3%, 0.5 mg – 27.7%, 1 mg – 34.3%) [42]. A follow-up study examining those who achieved a clinical response to induction treatment demonstrated significantly increased rates of remission, response, as well as mucosal improvement after an additional 24 weeks of therapy with 1 mg daily [43]. A phase III trial has been started looking at the efficacy of the compound in patients with moderate to severe UC (NCT02435992), and phase II trials are ongoing in patients with moderate to severe Crohn's disease (NCT02531113). Two additional S1PR1 modulators are being studied in phase II trials: MT-1303 in Crohn's disease (NCT02378688) and APD-334 [44] in ulcerative colitis (NCT02447302) (Table 11.2).

Blockade of Proinflammatory Cytokines

Therapies Targeting IL-23 Signaling

AMG-139 (MEDI2070) and BI655066

Given the success of ustekinumab in targeting the IL-23 pathway in Crohn's disease and psoriasis, there has been an interest in developing other agents selectively inhibiting this pathway. AMG-139 is a human IgG_2 antibody which binds to the p19 subunit of IL-23. A phase IIa study comparing MEDI2070 to placebo in 121 subjects with

Table 11.2 Therapies for inflammatory bowel disease which have not been FDA approved for other indications currently being investigated in clinical trials

Name	Mechanism	Route	Indication	Current phase of trial in IBD
Therapies targeting inflammatory cell migration and adhesion				
Etrolizumab	Monoclonal antibody to $\alpha_4\beta_7$ and $\alpha_E\beta_7$	SC	UC CD	Phase III
AMG 181	Monoclonal antibody to $\alpha_4\beta_7$	SC	UC CD	Phase II
PF-00547659	Monoclonal antibody to MAdCAM-1	SC	UC CD	Phase II completed
Vercirnon (CCX282-B)	Selective antagonist of CCR9	PO	CD	Phase III completed
Eldelumab (BMS-936557)	Monoclonal antibody to interferon-ϒ-inducible protein 10	IV	UC CD	Phase II completed
GLPG0974	Selective antagonist of the free fatty acid receptor 2	PO	UC	Phase II completed
Sphingosine-1-phosphate receptor modulators				
Ozanamid (RPC1063)	Modulator of sphinogsine-1-phosphate receptor 1	PO	UC CD	Phase III Phase II
MT-1303	Modulator of sphinogsine-1-phosphate receptor 1	PO	CD	Phase II
APD-334	Modulator of sphinogsine-1-phosphate receptor 1	PO	UC	Phase II
Therapies targeting proinflammatory cytokines				
AMG-139 (MEDI2070)	Monoclonal antibody to p19 subunit of IL-23	IV/SC	CD	Phase II
BI655066	Monoclonal antibody to p19 subunit of IL-23	IV/SC	CD	Phase II
Tralokinumab (CAT-354)	Monoclonal antibody to IL-13	SC	UC	Phase IIB completed
Anrukinzumab	Monoclonal antibody to IL-13	IV	UC	Phase IIA completed
QAX576	Monoclonal antibody to IL-13	IV	CD (Fistulizing)	Phase II completed
NNC0144-0006	Monoclonal antibody to IL-21	IV	CD	Phase II completed
PF-04236921	Monoclonal antibody to IL-6	SC	CD	Phase II completed
AVX-470	Polyclonal antibody to TNFα	PO	UC	Phase I completed
HMPL-004	Extract of *Andrographis paniculata*	PO	UC	Phase III completed
Blockade of pathways mediating cytokine production				
Mongerson *(GED-0131)*	Antisense oligonucleotide to SMAD7	PO	UC CD	UC-Phase II CD-Phase III

(continued)

Table 11.2 (continued)

Name	Mechanism	Route	Indication	Current phase of trial in IBD
Laquinimod	Immunomodulator	PO	CD	Phase II completed
Vidofludimus (4SC-101)	Inhibitor of dihdyroorotate dehydrogenase	PO	UC CD	Phase IIa completed
Peficitinib (ASP015K)	Selective inhibitor of JAK3 > JAK1/JAK2	PO	UC	Phase II
Filgotinib	Selective inhibitor of JAK1 > JAK2	PO	CD	Phase II
ABT-494	Selective inhibitor of JAK1 > JAK2	PO	CD	Phase II
Miscellaneous therapies				
Masitinib	Tyrosine kinase inhibitor	PO	CD	Phase IIb
Bertilimumab	Monoclonal antibody to eotaxin-1	IV	UC	Phase II
GS-5745	Monoclonal antibody to matrix metalloproteinase 9	SC	UC CD	Phase II/III
LT-02	Modified-released phosphatidylcholine	PO	UC	Phase III

active Crohn's disease (CDAI ≤450 and ≥220 with either a CRP ≥5 mg/L or a fecal calprotectin ≥250 mcg/g). At week 8, clinical remission was seen in 27.1% of patients treated with AMG-139 vs. 15% with placebo (p = 0.1) and clinical response was observed in 45.8% vs. 25% (p = 0.017) [45]. A second larger phase II study in Crohn's disease is currently underway (NCT02574637). Similarly, BI 65066 is an IgG_1 monoclonal antibody directed against the p19 subunit of IL-23. In early phase trials, it has demonstrated effectiveness in plaque psoriasis [46] and is currently being investigated in a phase II study of patients with moderate to severe Crohn's disease (NCT02031276).

Therapies Targeting IL-13

Tralokinumab

Tralokinumab (CAT-354) is a human IgG4 monoclonal antibody targeting IL-13. Expression of IL-13 is increased in the mucosa of patients with active ulcerative colitis, and neutralization of the cytokine has been demonstrated to improve inflammation in murine models [47, 48]. Tralokinumab is currently also being evaluated in clinical trials for asthma and pulmonary fibrosis. A phase IIb randomized placebo control study examined tralokinumab 300 mg every 2 weeks for 12 weeks vs. placebo in 80 subjects with ulcerative colitis and a total Mayo score ≥6. There was no difference in the primary end point of a treatment response (33% vs. 38%, p = 0.4). However, more patients in the treatment group achieved clinical remission (6% vs. 18%, p = 0.03), and there was a trend toward an increase in the percentage

of patients who had mucosal healing (20% vs. 32%, $p = 0.1$). In an exploratory analysis, the investigators were unable to identify subgroups of patients more likely to benefit from treatment [49].

Anrukinzumab

Similar to Tralokinumab, Anrukinzumab is a humanized monoclonal IgG1 antibody to IL-13 [50]. Anrukinzumab was evaluated in a phase IIa randomized control trial where 84 patients with moderate ulcerative colitis were treated with 200, 400, 600 mg IV or placebo for 5 infusions over 14 weeks. The primary end point of the study, which was a fold change in fecal calprotectin from baseline, was not reached. In addition, there were no changes noted between treatment and placebo in clinical response or clinical remission, despite an increase in total, including bound, IL-13 [51].

QAX576

Previous data also indicates that IL-13 is up-regulated in fistulas from patients with Crohn's disease fistulas and up-regulation of IL-13 in intestinal epithelial cells is associated with an increased expression of genes associated with cell invasion [52]. As such, there has been an interest in investigating the role of IL-13 blockade in fistulizing Crohn's disease. A third monoclonal antibody to IL-13, QAX576, was investigated in a recent phase II trial, and results for this trial are pending.

IL-21 Pathway Blockade

NNC0114-0006

ATR-107 is a monoclonal antibody targeting the IL-21 receptor. Binding of the antibody inhibits IL-21 induced phosphorylation of STAT3 [53]. Phase I studies demonstrated that a single dose of the medication given intravenously could occupy the receptor for at least 42 days [54]. In this study, 76% of healthy subjects, however, developed antidrug antibodies and further investigation into the effectiveness of the antibody in IBD has not been pursued further. However, a phase II trial examining a second IL-21 antibody, NNC0114-0006, in active Crohn's disease was recently completed although results have not been released.

IL-6 Signaling Blockade

IL-6 binds to both membrane-bound and soluble IL-6 receptor (IL6R). The IL-6/IL6R complex then attaches to the transmembrane glycoprotein, gp130, activating several intracellular pathways involved in inflammation, including JAK1-STAT3. IL-6 is increased in the mucosa of patients with Crohn's disease with active inflammation, and blocking IL-6 signaling attenuates murine colitis [55–57].

Tocilizumab

Tocilizumab is an FDA-approved humanized antibody to the IL-6 receptor which has demonstrated efficacy in rheumatoid arthritis, juvenile arthritis, and Castleman's disease [58–61]. In 2004, a randomized placebo-controlled trial in 36 patients with active Crohn's demonstrated that 80% of the patients randomized to treatment with 8 mg/kg of the monoclonal antibody had a clinical response at 12 weeks compared to 31% of those who received placebo ($p = 0.02$) [62]. However, only 2 of 10 patients treated with tocilizumab in this study went into remission, and there were no differences in endoscopic or histologic appearance between the groups.

PF-04236921

Although tocilizumab has not been studied further in Crohn's disease, a second monoclonal antibody, PF-04236921, which binds and neutralizes the IL-6 ligand, was subsequently developed. A phase II trial of PF-04236921 in patients with Crohn's disease who have failed anti-TNF therapy (ANDANTE) compared doses 10, 50, and 200 mg given subcutaneously on days 1 and 28 to placebo in 247 subjects. At week 12, the primary end point, which was a decrease in CDAI score of 70 points, was achieved in 28% of patients receiving placebo ($n = 69$), 35.2% of patients receiving 10 mg ($n = 65$; $p = 0.26$), 47.4% of patients receiving 50 mg ($n = 71$; $p = 0.04$), and 51.7% of patients receiving 200 mg ($n = 40$; $p = 0.14$) [clinicaltrials.gov]. It is worth noting that in this study 2 subjects had gastrointestinal perforations, 4 subjects had gastrointestinal abscesses on treatment, and an additional 3 patients had abscesses after completing treatment.

Miscellaneous Therapy Targeting Proinflammatory Cytokines

AVX-470

AVX-470 is an oral anti-TNF antibody that is generated by purifying immunoglobulin from the colostrum of cows immunized with recombinant human TNF. In vitro studies have demonstrated a similar specificity and neutralizing capability as infliximab, and the compound has been effective in murine models of colitis [63]. A phase Ib study with this compound was conducted in 36 patients with active ulcerative colitis who received one of three doses of the drug or placebo. Although this study has not been published in a peer-reviewed journal, the results were presented at the United European Gastroenterology Week in 2014 [64]. In addition, they did see an increase in bovine IgG in the colonic mucosa, indicating that the drug may penetrate the colonic mucosa. The investigators also reported on dose-related improvement in clinical and endoscopic activity. Drug-related serious adverse events were not reported in this study. Phase II studies investigating this compound are being designed.

HMPL-004

Andrographis paniculata (*A. paniculata*) is an herbal remedy used to treat upper respiratory tract infections [65]. The extract of *A. paniculata* (HMPL-004) has demonstrated its inhibitory activity against TNFα, IL-1β, and NF-κβ in vitro [66, 67]. In patients with mild to moderate ulcerative colitis, a randomized, double-blind study comparing HMPL-004 to slow release mesalamine demonstrated equivalence in clinical and endoscopic remission [68]. A subsequent placebo-controlled trial comparing HMPL-004 1200, 1800 mg, and placebo in patients with mild to moderate UC treated for 8 weeks demonstrated an increase in response in those treated with 1800 mg but no difference in rates of clinical remission [69]. Phase III trials were subsequently initiated although terminated in 2014 following an interim analysis.

Blockade of Pathways That Mediate Cytokine Production

Mongersen

Transforming growth factor β1 (TGFβ1) is a secreted protein that is important in cellular proliferation and differentiation. It is known to have anti-inflammatory properties through inhibition of T-cell proliferation and differentiation resulting in a decrease in proinflammatory cytokines. SMAD7, which is increased in the tissue of patients with Crohn's disease, inhibits TGFβ1 signaling [70]. An oral antisense oligonucleotide, Mongersen (GED-0301), was developed which binds SMAD7 and undergoes a pH dependent release in the terminal ileum and right colon. A phase I study demonstrated that blockade of SMAD7 with Mongersen resulted in reduced cytokine expressing CCR9-positive T cells [71]. A follow-up Phase II double-blind randomized control trial examined 10, 40, or 160 mg of Mongersen or placebo daily for 2 weeks in subjects with Crohn's disease of the ileum and/or right colon [72]. The primary end point was a CDAI of less than 150 at day 15 with maintenance of remission for at least 2 weeks. Patients who received 40 and 160 mg achieved the primary end point in 55% and 65% of subjects, respectively, compared to 10% of patients receiving placebo. The rate of clinical response was 37% in those receiving 10 mg, 58% in those receiving 40 mg, and 72% in those receiving 160 mg, compared to 17% of patients receiving placebo. Remission was maintained in the majority of patients up to day 84 even though they had not received the drug after day 14. Of consideration is the fact that the trial used CDAI scores for enrollment and assessing outcomes and the investigators did not perform an assessment of mucosal healing. Phase III trials are currently underway investigating the medication in subjects with active Crohn's disease (NCT02596893, NCT02596893), and a phase II trial was started in subjects with ulcerative colitis (NCT02601300).

Laquinimod

Laquinimod is an oral immunomodulator with high bioavailability that is being evaluated in patients with multiple sclerosis, Huntington's disease, lupus nephritis, as well as Crohn's disease. It targets antigen presenting cells, decreases proinflammatory cytokines, increases anti-inflammatory cytokines, and inhibits leukocyte migration [73, 74]. Laquinimod was studied in a phase II trial of patients with Crohn's disease who had a CDAI 220-450 with either a CRP >5 mg/L or ulcerations on colonoscopy [75]. In this study, 180 patients were randomized to receive 0.5, 1, 1.5, or 2 mg daily for 8 weeks. The 0.5 mg dose demonstrated 48.3% remission compared to 15.9% of placebo. Subjects taking the other doses did not have significantly higher response or remission rates compared to placebo. Although there was not a consistent decrease in CRP in patients treated with Laquinimod, subjects with elevated CRP at baseline who received the drug had a higher rate of CRP normalization than placebo (36% vs. 5%). Similarly, there was not a consistent Laquinomod treatment effect on fecal calprotectin, although subjects who received any dose of Laquinomod were more likely to have at least a 50% decrease or a concentration of <250 μg/g. Adverse events were similar between the groups [75]. Phase III studies investigating the compound in patients with Crohn's disease have not been announced.

Vidofludimus

Vidofludimus, 4SC-101, is an immunosuppressive drug which inhibits dihydroorotate dehydrogenase, a key enzyme in pyrimidine biosynthesis. In animal models, the drug inhibited lymphocyte proliferation, IL-17 production by lymphocytes, and resulted in improvement in colitis [76]. An open label study of vidofludimus was conducted in 34 patients with steroid dependent ulcerative colitis and Crohn's disease. In this study, 57.1% of patients with Crohn's disease and 50% of patients with UC were in steroid free remission at week 12 [77]. A phase IIb study in patients with Crohn's disease is being planned.

JAK Inhibitors

Peficitinib

Peficitinib (ASP015K, JNJ-54781532) is a JAK inhibitor which has selectivity for JAK3 over JAK1 and JAK2. In a phase IIa randomized control trial in patients with moderate to severe psoriasis comparing twice daily (10, 25, 50, 100 mg) or once daily 50 mg to placebo, peficitinib demonstrated dose-dependent efficacy in both clinical and histological response [78]. The small molecule inhibitor is also being studied in rheumatoid arthritis, and a phase II study comparing peficitinib 25, 75,

150 mg daily and 75 mg bid compared to placebo is ongoing in patients with moderate to severe ulcerative colitis (NCT01959282).

Filgotinib

Filgotinib (GLPG0634) is a JAK inhibitor selective for JAK1 and JAK2, reported to be ~30-fold more selective for JAK1 over JAK2 [79]. In preclinical models, filgotinib inhibited a Th1 and Th2 response and resulted in improvement in collagen-induced arthritis models [80]. The efficacy of filgotinib as an add-on to methotrexate vs. methotrexate alone was studied in 594 patients with moderate to severe rheumatoid arthritis in the DARWIN 1 phase IIb study. A phase II study comparing filgotinib 100, 200 mg, and placebo for 20 weeks was also conducted in 175 patients with Crohn's disease with an endoscopic evidence of ulcerations (FITZROY). Following a 10-week interim analysis, the company released a press statement in December 2015 stating that subjects randomized to 200 mg ($n = 128$) had improvement in clinical remission (48% vs. 23%, $p = 0.007$) and response (60% vs. 41%, $p = 0.04$) compared to placebo ($n = 44$). Results of the full analysis have not been presented.

ABT-494

ABT-494 is also a highly selective inhibitor of JAK1 greater than JAK2. Similar to filgotinib, ABT-494 demonstrated improvement as an oral therapy in early phase trials of rheumatoid arthritis. It is currently being studied in a phase II trial in subjects with moderate to severe Crohn's disease who have failed or are intolerant to anti-TNF therapy (NCT02365649).

Miscellaneous Therapies

Masitinib

Masitinib is a selective oral tyrosine kinase inhibitor that targets the c-kit receptor [81]. Through this mechanism, masitnib inhibits mast cell activation which is observed in several inflammatory conditions, including IBD. Initial research focused on the treatment effect of the medication in gastrointestinal stromal tumors, although there has been an interest in investigating masitnib in inflammatory disorders. Studies have been conducted examining the effectiveness of the medication in asthma, multiple sclerosis, Alzheimer's disease, rheumatoid arthritis, and psoriasis. In addition, a 12-week phase IIb trial is ongoing in patients with moderate Crohn's disease unresponsive to immunosuppressive drugs or anti-TNF agents (EudraCT # 2012-004222-25).

Bertilimumab

Bertilimumab is a monoclonal antibody to eotaxin-1 (CCL-11) and currently under investigation for the treatment of ulcerative colitis. Eotaxin-1 is important in eosinophil function and known to be increased in the mucosa of patients with active ulcerative colitis [82]. Furthermore, inhibition of CCL-11 resulted in improvement in disease activity in a murine model of colitis [83]. A phase II study is ongoing comparing 7 mg/kg of bertolimumab to placebo in 90 subjects with moderate to severe UC (NCT01671956).

GS-5745

GS-5745 is a monoclonal antibody directed against matrix metalloproteinase 9 (MMP9). Expression of MMP9 is elevated in gastrointestinal tumors and inflammatory bowel disease. MMP-9 promotes release of TNFα and TGFβ, potentiates IL-8, and activates IL-1β. In addition, MMP-9 proteolyzes collagen IV and laminin of the basement membrane, resulting in the loss of the mucosal epithelial barrier. Because of this dual role in propagating inflammation, there has been significant interest in inhibiting MMP in IBD. In the past, broad-spectrum MMP inhibitors have been developed although not utilized clinically secondary toxicity with the development of musculoskeletal syndrome. In contrast, GS-5745 is a selective MMP-9 inhibitor that demonstrated efficacy in a murine model of colitis without the toxicity seen in non-selective MMP inhibitors [84]. A phase Ib trial of GS-5745 in 74 patients with moderate to severely active UC compared multiple ascending IV doses and a single subcutaneous dose. Overall, the combined response rate was 43%, remission rate 14%, and mucosal healing 33% compared to 13%, 0%, and 25% respectively for placebo. As a proof of principle regarding the effectiveness of the antibody to neutralize MMP9, there was a decrease in serum, tissue, and stool MMP9 in all patients and to a greater degree in responders. Adverse events were reported to be comparable to placebo [85]. A phase II/III trial of GS-5745 in patients with moderate to severe UC, however, was terminated early as the medication did not achieve clinical efficacy at a prespecified interim analysis Clinical trials of GS-5745 are ongoing in gastric cancer, rheumatoid arthritis, and COPD.

Modified Release Phosphatidylcholine

Phosphatidylcholine (PC) is a protective component of colonic mucous [86]. Patients with active ulcerative colitis have decreased phosphatidylcholine [87, 88]. Several previous studies have demonstrated efficacy of a delayed release PC containing 30% PC in active ulcerative colitis [89–91]. Subsequently, LT-02 was designed to contain >94% PC. LT-02 was recently investigated in a 12-week European randomized control trial in patients with active ulcerative colitis refractory to mesalamine. In this study, the mean simple clinical colitis activity index

decrease from baseline was higher in the group receiving the highest dose (3.2 gm/day) compared to placebo ($p = 0.03$), which was the primary end point of the study. Mucosal healing was seen in 32.5% of placebo vs. 42.7% LT-02 ($p = 0.09$). Histologic remission occurred in 20% of subjects receiving placebo compared to 40.5% of subjects receiving LT-02 ($p = 0.02$) [92]. Phase III studies comparing LT-02 to placebo (NCT02142725) and mesalamine (NCT02280629) are ongoing.

Conclusion

Although the majority of the agents presented in this chapter will not reach the clinical arena due to a lack of efficacy or safety concerns, it is anticipated that there will be several new therapeutic options in IBD treatment in the coming years. Given the heterogeneity in disease phenotype and treatment response, the availability of new therapies targeting alternative pathways involved in inflammation is likely to greatly improve the care of patients with IBD. As overall treatment responses to currently available therapies as well as those in development continues to be modest, however, there will be a great need for research involving currently available therapies as well as newly approved agents focused on optimizing response through both targeting therapeutic drug levels and developing tools to predict treatment response.

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Chapter 12
The Different Drummer: Non-traditional Therapeutic Approaches

Eugene F. Yen

Introduction

The use of complementary and alternative medications (CAM) therapy is common in chronic conditions, and IBD is no exception, with up to 60% of patients reporting current or past CAM usage in the management of their IBD [1]. Reasons for the use are multifactorial, but include a search for "optimal therapy," side effects of conventional therapy, and lack of success of conventional treatment [2]. Despite the ubiquitous nature of CAM therapies, providers often lack the knowledge on the existing data and thus are often less inclined to trust their efficacy.

The aim of this review is to present the existing data on CAM therapies, including probiotics, helminths, herbs, and mind-body practices. In addition, more recent studies on cannabis and fecal microbiota transplantation will be discussed. While there is considerable data, albeit limited in larger controlled studies, providers nonetheless should be educated on the existing evidence on CAM therapy to better engage patients on all of their treatment choices as they pertain to conventional and complementary therapies.

Probiotics

One of the proposed pathways of IBD pathogenesis is represented by an imbalanced immune response to microbes, a concept also known as "dysbiosis." However, it is not known if dysbiosis is a cause or a consequence of having a particular disease. Thus, probiotics have been proposed as a solution for this microbial imbalance.

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The true mechanisms for probiotics are unknown. While probiotics to date have not been proven to significantly alter the dysbiosis in IBD, probiotics have been shown to influence the composition of gut bacteria. In addition, probiotics have been proposed to improve gut barrier function, affect motility and pain perception, and influence local immune response [3].

Results for the few probiotic studies in ulcerative colitis (UC) have been heterogeneous, and the mechanisms for probiotics were different for each individual probiotic product. For example, VSL#3 is a probiotic that has a combination of three *Bifidobacterium* species, four *Lactobacillus* species, and *Streptococcus thermophiles*, and in vivo models have shown potential therapeutic benefit via modulation of dendritic cell function by increasing regulatory cytokines and lowering pro-inflammatory cytokines and toll-like receptor (TLR) expression. In VSL#3-treated patients, TLR-2 and IL-12p40 expression decreased, and IL-10 production increased, similar to the action of corticosteroids [4]. Further, probiotics have been have shown to modulate secretion of mucous and chloride and affect the integrity of tight junctions, in addition to reducing apoptosis of epithelial cells [5].

The majority of studies involving probiotics and ulcerative colitis took a mild-to-moderate disease cohort, with the comparator usually being mesalamine or placebo. The largest studies were for VSL#3. Tursi and colleagues evaluated rates of induction of remission in patients with VSL#3 at 900 billion bacteria daily (one VSL#3 DS packet) vs. mesalamine 2.4 g daily vs. combination VSL#3 and balsalazide 2.25 g daily. Combination VSL#3 and balsalazide was statistically superior to either therapy alone, and time to remission was also faster in the combination group. This analysis was limited by smaller sample size (30 per arm), but combination therapy also showed improvement in both endoscopic and histologic scores over mesalamine alone [6].

Subsequently, higher dose VSL#3 (3600 billion bacteria – four VSL#3 DS packets daily) vs. placebo studies included patients with mild-to-moderate UC and concomitant use of aminosalicylates or thiopurines. Both studies reported a decrease in the UCDAI in >50% of patients in the VSL#3 arm. While one study showed improvements in remission over placebo [7], the other did not reach statistical significance, perhaps due to the study's 32% placebo rate and the relatively short duration of the study (8 weeks) [8].

VSL#3 was also studied in a subset of patients with pouchitis, which found VSL#3, but not *Lactobacillus GG*, to be effective in the maintenance of remission in pouchitis. However, these trials were limited by small sample sizes and limited duration of follow-up, from 3 to 12 months [9–12].

Multiple studies were conducted using single strain *Escherichia coli Nissle* 1917 (ECN 1917), which is a non-pathogenic *E. coli* strain. In a placebo-controlled trial of rectally administered ECN 1917 in distal UC, there were significant differences in response in the per-protocol analysis only in the ECN 1917 group [13]. Three randomized trials showed no significant difference between ECN 1917 and mesalamine for maintenance of remission [14–16]. However, a Cochrane review of these studies did not feel that there was significant evidence of efficacy in maintenance of remission in probiotics, due to the small numbers, lack of blinding in some studies,

and the high risk for bias [17]. Systematic reviews from the Cochrane group reported that probiotics were not more effective than placebo in inducing remission of patients with active ulcerative colitis [18]. However, given the above data, there would possibly be some role of certain probiotics as adjunct to standard therapy. However, the effect of probiotics in more extensive or severe disease is unknown.

In summary, probiotics have limited role in inducing remission, but may have some potential for ECN 1917 in maintenance of remission, and perhaps VSL# for maintenance of remission in pouchitis or as an adjunct to therapy in active ulcerative colitis. In pediatric populations, VSL#3 and ECN 1917 are a potential treatment choice for mild UC in patients who do not tolerate mesalamine, or as an adjuvant therapy in those not responding to mesalamine alone.

In contrast to ulcerative colitis, the vast majority of placebo-controlled studies in Crohn's disease have shown no significant improvements with probiotics in the setting of induction or maintenance of remission in Crohn's disease and post-operative prophylaxis after surgical resection [19–22]. However, in a recent randomized controlled trial involving VSL#3 in patients with ileocolonic resection, there were similar rates of recurrence of severe endoscopic disease, but patients receiving VSL#3 had reduced mucosal inflammatory cytokine levels when compared to those receiving placebo [23].

Fecal Microbiota Transplantation

Similar to proposed mechanisms for probiotics, fecal microbiota transplantation (FMT) has been proposed as potential therapy for the microbial dysbiosis in IBD. The success of FMT is well reported in the setting of recurrent *Clostridium difficile* infection from both case series and randomized trials [24, 25]. Interest in FMT as possible therapy for IBD has grown rapidly, as initial case reports and small case series have suggested that FMT may have a positive effect [26].

Over the past 2 years, two randomized trials for FMT have been reported evaluating the efficacy in ulcerative colitis. In the first study, Moayyedi et al. conducted a randomized trial in patients with mild-to-moderate ulcerative colitis. Seventy-five subjects received weekly FMT or placebo (water) via retention enema for 6 weeks. The primary end point was remission based on the Mayo score as well as endoscopic parameters. Initially, this study was presented as a negative study in abstract form, with the trial's data safety and monitoring boards recommending discontinuing the study during an interim analysis due to likely futility in reaching their primary end point. However, when 22 additional subjects were enrolled, the end point was met. Overall, the authors found that subjects achieve remission in 9/38 (24%) who received FMT vs. 2/37 who received placebo ($p = 0.03$). Interestingly, the final 22 patients received the same donor, suggesting that donor selection may be more important in the setting of ulcerative colitis [27].

In the second study, Rossen and colleagues took 50 patients with mild-to-moderately active UC, and randomized them to donor stool or autologous (placebo)

FMT, this time via nasoduodenal tube at baseline and then 3 weeks later. This study was terminated at interim analysis due to futility, as there were no differences in clinical and endoscopic remission between the two groups in both the intention-to-treat and per-protocol analyses [28]. Microbiome analysis in both studies showed an increased diversity in FMT-treated subjects who responded compared to controls.

The literature on FMT in Crohn's disease is limited to smaller case series, with results varying for both pediatric and adult groups, but randomized control trials are lacking. However, microbiome analysis also showed an expansion in bacterial diversity in patients with active CD after FMT [29, 30]. In one study, Vermeire and colleagues saw no significant improvement in endoscopy or clinical scores in a subset of six patients with Crohn's disease receiving FMT. However, the donor richness and the extent of transferred phylotypes to the recipient were associated with FMT success [31]. While promising, IBD flares and infections have been described after FMT [32]. Based on our current data, further studies are ongoing to determine the optimal frequency, donor selection, and mode of delivery for FMT in IBD. Finally, FMT is restricted for use only in clinical trials, of which there are several currently ongoing. In addition, in the USA, an investigational new drug (IND) application must currently be obtained from the U.S. Food and Drug Administration to use FMT in any condition other than recurrent *C. difficile* infection.

Herbals and Botanicals

Herbal therapies are one of the most common forms of CAM used in the management of IBD, accounting for up to 58% of all CAM use [33, 34]. While there have been numerous small reports of herbal therapies in IBD, there is limited evidence regarding the safety and efficacy of these products, and results have been inconsistent. For example, in one systematic review of herbals in IBD, there were over 1000 abstracts from 1947 to 2013. However, only 21 were randomized controlled studies, some of which will be reviewed in this section [35].

Boswellia serrata is a plant that is native to India and Pakistan, and produces Indian frankincense, a common remedy used in the treatment of arthritis. Studies have reported on its natural anti-inflammatory properties, and thus there has been interest in the management of IBD. The first study by Gerhardt and colleagues took 102 patients randomized to either *Boswellia serrata* or mesalazine in a double blind manner for 8 weeks. In a per-protocol analysis there was no difference in disease activity, measured via Crohn's disease activity index (CDAI) [36]. In patients in remission from Crohn's disease, a second study by Holtmeier and colleagues randomized 82 patients to boswellia extract vs. placebo, and after 12 months, there were no significant differences regarding maintenance of remission or time to relapse [37].

Artemisia absinthium, also known as absinthe wormwood, is a plant that is a main ingredient in the spirit absinthe. In in vitro studies, suppression of pro-inflammatory cytokines such as tumor necrosis factor alpha was reported with wormwood extract, later confirmed in a small study of Crohn's patients showing

decreased CDAI scores and TNF-alpha serum levels [38]. The same group compared wormwood to placebo in 40 patients with Crohn's disease on a corticosteroid taper, and steroids were forced to taper to off by 10 weeks, at which point wormwood was also discontinued. Patients were followed to 20 weeks, and at the end of the study period, the intervention group reported improved mood and quality of life, and 10% of patients in the wormwood group had to restart steroids for flare of symptoms, compared to 80% of patients who received placebo. While promising, these studies were limited by their short observational period, non-randomization, and missed blinding [39].

Andrographis paniculata, also known as Indian Echinacea, is a plant known for its bitter taste, and its extract, known as HMPL-004, is found to inhibit TNF-alpha and prevents colitis in animal models. In an 8-week randomized trial comparing HMPL-004 with mesalamine, 120 patients with active ulcerative colitis were assessed every 2 weeks with endoscopic and clinical symptoms. Both groups equally showed improvements both clinically and endoscopically [40]. In another trial with the same authors, 224 patients were randomized to placebo vs. 1200 or 1800 mg HMPL-004, in addition to mesalamine, for active ulcerative colitis. After 8 weeks, both groups who received HMPL-004 had higher rates of response compared to placebo. Thus, the authors suggested that *Andrographis paniculata* could potentially serve as an alternative to mesalamine in mild-to-moderate ulcerative colitis [41].

Curcumin is the bright yellow compound derived from turmeric, a commonly used spice in curries and South Asian cuisine. In vitro studies have shown curcumin's effects of decreased levels of pro-inflammatory cytokines, increased antioxidant activity, and other inflammatory mediators such as NF-kβ. In addition, it has been one of the most popular herbs tested for a variety of clinical disorders, including IBD, cancer, arthritis, and Alzheimer's disease. In one study of ulcerative colitis patients in remission, 89 patients were randomized to curcumin vs. placebo over a 6-month period, and recurrence rates, endoscopy scores, and clinical activity were all improved in curcumin-treated patients vs. placebo [42]. Similarly, in a study comparing curcumin enema vs. placebo, in addition to oral mesalamine, in mild-to-moderate ulcerative colitis, there were improvements in disease activity and remission rate, which were not statistically significant in the intention-to-treat population [43]. Finally, a recent study took 50 patients with mild-to-moderate ulcerative colitis, not responding to 2 weeks of oral or topical mesalamine, and randomized them to curcumin vs. placebo. In this study, clinical response and endoscopic remission were statistically improved in the curcumin group by week 4 [44].

Cannabis

The cannabis plant has nearly 500 different chemical compounds isolated, the most relevant being the phytocannabinoids, which are in the plant's flowering buds. Tetrahydrocannabinol (THC) is primarily responsible for the psychoactive effects of marijuana, but there is increased interest in cannabidiol (CBD), which has less psychoactive effects and has potentially demonstrated anti-inflammatory properties [45].

Smaller studies have reported improvements with marijuana with regard to quality of life, disease activity in Crohn's disease using the Harvey–Bradshaw index, and need for surgery and other medications [46, 47]. The same group also conducted a small randomized placebo-controlled trial of 21 Crohn's patients who did not respond to steroids, immunomodulators, or anti-TNFs. The primary end point of the study (complete remission with a CDAI <150) was not met; however, 10/11 patients who received marijuana had a clinical response, with 3/10 able to wean off steroids. But endoscopic healing was not evaluated, and there was no change in C-reactive protein c-reactive protein pre- and post-marijuana therapy [48].

In patients with IBD, over 50% have used marijuana for management of their IBD symptoms, which helped patients with abdominal pain, nausea, and poor appetite. Patients felt that marijuana was relatively less helpful in treating diarrhea, despite animal studies that show that cannabinoids delay GI transit [49]. However, use of cannabis >6 months was also a predictor for requiring surgery for Crohn's disease, even after correcting for demographics, smoking, and biologic use, suggesting a potential effect of worsening of Crohn's disease with marijuana use [50].

As restrictions for the use of both recreational and medical marijuana have loosened over the past decade, so too has their acceptance by the general public and patients with IBD. An increased number of patients have turned to marijuana as potential therapy for their IBD. As practitioners, there are both scientific and legal aspects of certifying use of marijuana in IBD, which is poorly understood. In the USA, state medical marijuana laws vary, and Crohn's disease may be on the list of approved conditions for medical marijuana, in which patients can apply to legally obtain marijuana. As marijuana still carries Schedule I status (no accepted medical use with high potential for abuse), there is a general prohibition for physicians to write a prescription for marijuana, but instead they are usually instructed to certify the medical necessity for marijuana. However, there are legal considerations for clinicians who consider medical marijuana that will depend on state and federal regulations [51].

Helminths

Helminths are parasites that are rather common, especially in the developing world where organisms can be spread via contaminated water, soil, or food. Prior to sanitation efforts in the early twentieth century, colonization of helminths was nearly universal, and given their ability to colonize in a host, helminths have been postulated to interact with both the innate and adoptive immunity to modulate inflammation. Thus, part of the "hygiene hypothesis" involves a theory that living in extremely clean environments had largely rid our exposure to potential parasites, which in turn could predispose us to immune diseases in increased numbers. For example, in patients with multiple sclerosis (MS), the rise of MS cases was correlated to deceased numbers of *Trichuris triciura,* and helminth infection during the course of a patient's course with MS was associated with fewer disease exacerbations [52].

The two classes of helminths that can inhabit the human body are nematodes (roundworms) and the platyhelminths (flatworms), which include trematodes (flukes) and cestodes, and can live in the bloodstream, biliary system, intestines, and airways. Similarly, there are helminths that come from both domesticated and wild animals, which usually fail to colonize in the human and less commonly lead to human disease, including *Trichuris suis.* Given a helminth's ability to colonize and evade a host's immune system, helminths have been studied for their immune regulatory properties. It has been postulated that helminths can regulate multiple pathways, including influencing mucous production and barrier function of epithelial cells, release factors such as TGF-β that can down-regulate inflammation, and interact with the existing microbiota to affect mucosal response [53].

Based on the promising findings of helminth infections on animal models of colitis, small clinical studies have been performed looking at the efficacy of helminths in IBD. In a randomized trial of 54 patients with ulcerative colitis, the efficacy and safety of *Trichuris suis* ova vs. placebo was examined over a 12-week period, as measured by the ulcerative colitis disease activity index (UCDAI). At 12 weeks, clinical improvement was seen in 13/30 (43.3%) in the *T. suis* group vs. 4/24 (16.7%) in the placebo group ($p = 0.04$). The mean UCDAI score was lower in the *T. suis* group (6.1 +/− 0.61) compared to the placebo group (7.5 +/− 0.66) after 12 weeks of treatment. Adverse events were few in both groups, and not thought to be related to study treatment [54].

Current worm-based studies are ongoing in Crohn's disease, while others are under development at several pharmaceutical companies. As discussed, there is continuing development of worms as preventative therapies in multiple sclerosis, asthma, and food allergy. While this field holds great potential, there are still risks with helminths, so the interest in such therapies must proceed with caution.

Mind-Body Practices

Psychological stress has long been tied to IBD activity, as perceived stress and negative mood have been tied to disease flare-ups [55]. Indeed, in one study involving ulcerative colitis patients, it was acute perceived stress which was predictive of disease flare-up in 12 months, more so than mucosal healing [56]. Thus, there have been numerous attempts to investigate mindfulness-based interventions in the setting of IBD. In one study, patients with ulcerative colitis were randomized to usual care vs. a 10-week training program involving stress management training, psychoeducational elements, and self-care strategies. At 3 months, there were benefits in quality of life, physical and emotional scores, but no discernible effects were seen between the two groups at 12 months [57]. In addition, the comprehensive lifestyle modification approach did not have any effects on clinical disease, results that were duplicated in other studies looking at mindfulness-based interventions. However, the quality of life was improved in subjects who received these interventions, illustrating a potential multimodal treatment approach to care in IBD [58, 59].

Gut-directed hypnotherapy is a form of hypnosis that uses suggestions specific to the improved function of the gastrointestinal tract, and has been effective in irritable bowel syndrome. Keefer and colleagues reported on a study involving 54 patients with ulcerative colitis randomized to 7-week gut-directed hypnotherapy vs. control, which after 52 weeks showed significant improvements in maintaining clinical remission [60].

Acupuncture and moxibustion are traditional Chinese therapies that are used separately or in combination. Moxibustion involves the act of burning dried mugwort, or moxa, on parts of the body with the intention of improving circulation at key points for a desired benefit. Traditional Chinese medicine textbooks describe a condition similar to IBD ("damp-hot diarrhea"), which has been purported to be responsive to certain acupuncture trigger points. Two randomized studies by Joos and colleagues were performed, one for Crohn's disease and the other for ulcerative colitis. In the Crohn's trial, 51 patients were randomized to acupuncture vs. sham acupuncture, and the patients who had acupuncture had a 90-point decrease in CDAI scores, compared to a 40-point decrease in the control group. However, at 12 weeks, there were no significant differences in the general well-being and quality of life. This study was also notable for excluding patients on immunomodulators or biologics, suggesting a milder disease cohort [61]. Similarly, the same authors performed a randomized trial in 29 mild-to-moderate ulcerative colitis patients, which showed modest benefits in both sham and traditional acupuncture/moxibustion, but no differences in the quality of life, general well-being, and serum markers of inflammation [62]. In general, studies involving acupuncture have had major methodological deficiencies, including insufficient description of end points and randomization process, missing power calculations, and the high risk of bias. While promising, further more rigorous studies are needed.

Conclusion

There is widespread agreement that inflammatory bowel disease is a complex disorder, driven by multiple factors, including immune dysregulation, microbial dysbiosis, and genetic factors. Thus, treatment of IBD has evolved to target mediators of inflammation. In this review, multiple CAM therapies have been reviewed with mechanisms potentially similar to those conventional pharmacologic agents.

Currently available agents and their indications for use are discussed in other chapters in this book, and much like conventional agents, treatment decisions for CAM therapy should apply to the appropriate type and severity of IBD. For example, it should be noted that the majority of limited studies using CAM therapy used a mild IBD patient cohort or used mesalamine as comparator agents, so those with severe disease may not response to such therapies. Finally, mind-body interventions, particularly stress and lifestyle modification and potentially gut-directed hypnotherapy, illustrate the potential of health psychologists as added members of a treatment team.

In conclusion, CAM therapies will always have a place in the care of IBD patients, with or without the involvement of clinicians. As health care consumers, patients can pick and choose on the type of therapy that they will accept for their IBD, and knowledge of all aspects of these choices, including CAM therapies, will serve to better educate our patients. As providers, it is our responsibility to recognize current CAM use and also to know the available evidence that currently exists, however limited, and to encourage further studies needed to inform these decisions.

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Chapter 13
The Biosimilar Revolution: Coming to an IBD Patient Near You?

Sudarshan Paramsothy, David T. Rubin, and Remo Panaccione

Introduction

Biologics can be defined as "a medicinal product or vaccine that consists of, or has been produced by the use of living organisms" [1]. The initial approval of the first biologic, infliximab (Remicade, Janssen Pharmaceuticals, Malvern, PA), for the treatment of moderate to severe Crohn's disease (CD) in the USA in August of 1998 ushered in a new era of therapeutics in inflammatory bowel disease (IBD). Since that time other biologics have entered the market, including several other anti-TNFs (adalimumab, certolizumab pegol, and golimumab), anti-integrins (natalizumab and vedolizumab), and most recently, anti-IL12/23 (ustekinumab). These agents

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have transformed how we treat both adult and pediatric CD and ulcerative colitis (UC). However, this has come with a substantial increase in the direct medical costs of treating these diseases, which has concerned many stakeholders around the globe. Biologics account for 64% of total expenses in CD and 31% in UC [2].

Biosimilars are defined as biologic medicines that enter the market after an original reference product (originator) whose data exclusivity has expired and whose similarity to the reference medicine exhibits "no clinically meaningful differences in terms of quality, safety and efficacy" [3]. They are also known in other jurisdictions as a follow-on, imitator biologic, or subsequent entry biologics (SEBs). Their entry into the marketplace comes with hope of reducing the cost of treating patients with immune-mediated diseases. Theoretically, biosimilars of monoclonal antibodies could reduce the price by 25–40%, a considerable difference adding "value" to the treatment [4]. Many biosimilars have been approved in Europe in various disease states. In August 2013, The European Medicines Agency (EMA) approved CT-P13 for the treatment of IBD, and after a lengthy delay, the Federal Drug Agency (FDA) of the USA followed suit in April 2016, thus ushering in the era of biosimilars in inflammatory bowel disease.

In this chapter, we will discuss how biosimilars are approved, the clinical data that have led to the approval of CT-P13 in IBD, and the controversies and unanswered questions that remain.

What Are Biosimilars and How Are Biosimilars Approved?

It is important to understand that biosimilars are not generics. The chemical structure of a biosimilar drug, in contrast to generic drugs, is not an identical copy of the original reference drug [5]. There are many important differences between biosimilars and generics [6]. Generics are synthetic chemical compounds, also known as small molecules. Biosimilars are typically very large, complex proteins or analogous products, about 400 times larger than a synthetic chemical compound or its generic. Generics are chemically synthesized, whereas biosimilars are grown in living cells or cell lines. Generics can usually be copied exactly, whereas biosimilars cannot be exactly copied and are subject to manufacturing variance. Therefore, a generic is typically the identical molecule as the reference agent, whereas a biosimilar is a different molecule than the reference agent. A generic is not immunogenic, whereas a biosimilar is immunogenic. A generic is therapeutically equivalent, whereas a biosimilar is not necessarily therapeutically equivalent, but it is highly similar.

Due to their unique structure and manufacturing process, the approval of biosimilar agents has required new regulatory processes, which continue to evolve. Global regulatory authorities agree that biosimilars must be similar to the original molecule with respect to *quality, safety, and efficacy.* This is achieved by demonstrating that the new drug is "equivalent" to a product with existing approval in terms of dosing and administration in the final clinical studies [7]. Assessment of biosimilar applications is carried out according to specific guidelines and steps that

differ from the traditional drug approval process in which the most pivotal step is the demonstration of efficacy and safety in well-designed phase III randomized placebo-controlled or comparator trials.

The FDA guidance pathway for biosimilar approval involves a stepwise approach requiring that a manufacturer demonstrates biosimilarity to the original compound using comparisons of structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical efficacy, safety, and immunogenicity. An extensive structural and functional characterization serves as the foundation of a biosimilar development program. A fingerprint-like analysis reduces the possibility of otherwise undetected structural differences and may lead to a more selective and targeted approach for clinical testing. Differences in certain posttranslational changes or excipients might not preclude a determination of biosimilarity if they do not result in any meaningful clinical differences. Once these standards are fulfilled, there may be an application to go forward in clinical studies.

Fulfillment of these criteria provides the totality of evidence that may lead to FDA approval [8]. From a biosimilar study design perspective, the FDA recommends a calculation of a 90% confidence interval (CI) for the ratio between the means of the parameters studied to be tested. However, an appropriate limit for the CI may range between 80% and 25% of the ratios comparing the reference and biosimilar product [9]. In assessing the "totality of the evidence," the FDA does not require an approach to "independently establish the efficacy and safety of the biosimilar," but rather "a demonstration of the biosimilarity between the proposed product and a reference product." The relative weight that the FDA places on the development program of the original biological product, as part of the traditional pathway, required for an originator drug approval, the 351(a), compared with the abbreviated program, the 351(k) pathway, for a biosimilar is therefore quite different.

Clinical Data for CT-P13

The clinical data that led to the approval of CT-P13 by the FDA come from randomized controlled trials performed in rheumatoid arthritis (RA) and ankylosing spondylitis (AS). There have been no randomized controlled trials in IBD. The indications were extrapolated to IBD (see below).

The PLANETAS trial was a phase I, double-blind multicenter study in anti–TNF-naïve patients with active AS. Two hundred and fifty patients were randomized 1:1 to receive CT-P13 (n = 125) or Remicade (n = 125) dosed at 5 mg/kg at weeks 0, 2, and 6 and then every 8 weeks up to week 30 [10]. No concomitant disease-modifying antirheumatic drugs, including methotrexate, were allowed throughout the study. The PLANETAS study differed from the typical dose-ranging phase I studies, where the aim is to identify the optimal dosing regimen. In this study, the primary aim of the PLANETAS trial was to establish pK equivalence between CT-P13 and Remicade, with a secondary aim to demonstrate similar efficacy and

safety. Steady-state pK data, based on area under the curve (AUC) and Cmax values, trough levels, and medication half-life were essentially equivalent for CT-P13-treated and Remicade-treated patients at all measured time points postinfusions. Clinical response rates at weeks 14 and 30 were 63% and 71% for CT-P13 versus 65% and 72% for Remicade, respectively, with similar changes in baseline activity scores and quality-of-life scores at weeks 14 and 30. Of note, these response rates are similar to week 24. In the PLANETAS study, antidrug antibodies (ADA) occurred in 9% and 27% of CT-P13-treated patients comparable with 11% and 23% of Remicade-treated patients at weeks 14 and 30, respectively, with the presence of ADA negatively influencing the pK of both agents. Treatment-emergent adverse event rate at week 30 was 65% for CT-P13 versus 64% for Remicade.

In the subsequent open-label extension study, patients treated with CT-P13 could continue treatment with CT-P13 (n = 88) and Remicade-treated patients were switched to CT-P13 (n = 86) at week 54 and followed for an additional 48 weeks. Notable findings included similar partial remission rates at weeks 78 and 102 between CT-P13-treated patients who continued therapy (70% and 81%) and patients switched from Remicade to CT-P13 at week 54 (77% and 77%, respectively). However, treatment-emergent adverse event rates were higher for the switch group (Remicade to CT-P13, 71%) compared with patients treated with CT-P13 with continued treatment (49%). ADA were present in 22% and 25% of continued CT-P13-treated patients at weeks 54 and 102, respectively, compared to 26% at week 54 and 31% at week 102 for the CT-P13-switched group [11].

The PLANETRA trial was a phase III, randomized, double-blind, multicenter parallel-group study of CT-P13 in patients with RA with active disease despite treatment with a minimum of 3 months of methotrexate at various above 12.5 mg weekly [12].

Eligible patients with RA were randomized 1:1 to receive CT-P13 (n = 302) or Remicade (n = 304) dosed at 3 mg/kg at weeks 0, 2, and 6 and then every 8 weeks until the end of the study at week 30. The primary aim of the PLANETRA trial was to demonstrate therapeutic equivalence between the two treatment groups defined as 95% CI of treatment response within an upper and lower margin of 15% at week 30. At week 30, response rates were similar for CT-P13-treated patients (60.9%) and Remicade-treated patients (58.6%), thus falling within the prespecified equivalence margin. All other secondary clinical end points including clinical disease activity indices, quality-of-life assessments, and C-reactive protein values were similar between the two treatment groups at week 30. Adverse event profiles (CT-P13, 60.1%; Remicade,60.8%) at week 30 and pK data profiles (AUC and Cmax values) measured after each infusion were also equivalent between the two treatment groups. At week 30, 25.8% of CT-P13-treated patients and 25.4% of Remicade-treated patients developed ADA using electro-chemiluminescent-immunoassay (ECLIA)–based assays for ADA detection. Among patients continuing with the PLANETRA study to week 54, remission and response rates, pK profiles, and adverse event rates were again comparable between the two treatment groups.

In the open-label extension study, beginning at week 54, PLANETRA study patients treated with CT-P13 could continue with scheduled 3 mg/kg dosing every 8 weeks (n = 158) or Remicade-treated patients could switch to CT-P13 at the same

dosing and interval for an additional 48 weeks (n = 144). Clinical efficacy and adverse event rates were comparable between the continued versus switched groups, with the proportions of CT-P13-treated patients with ADA also similar between the patients who continued CT-P13 (49.1% at week 54, 46.4% at week 102) and the patients who switched from Remicade to CT-P13 (49.3% at week 54, 49.6% at week 102) [13].

Current Controversies

Does the Manufacturing Process Matter?

The production of biologic agents is different from typical pharmaceuticals in that they are derived from a natural source, often a unique cell line. The complex biological processes involved in their production are more sensitive to manufacturing conditions with the potential for posttranslational modifications and other variations. As such, it is not possible to ensure even within a biologic agent that every product is an exactly identical or standardized replica. Therefore, batch-to-batch variation exists but is controlled within very defined internal and regulatory parameters. Furthermore, even among the originator biologic agents, there can be additional subtle changes over time resulting from altered manufacturing processes. Approval of biosimilars is based on evidence that the product is highly similar and has no clinically meaningful differences from the originator in the parameters of purity along with safety and effectiveness as demonstrated by randomized controlled trials [14]. However, these differences in manufacturing processes and the inability to precisely control the biosimilar products have been used as an argument against extrapolation across indications and switching (see below).

Extrapolation

A controversial area in the biosimilar regulatory and approval process is the principle of extrapolation. Extrapolation is the philosophy that clinical studies of biosimilars can be performed in one disease state or sensitive population group and then inferred to work in other disease indications for which the reference biologic is approved and licensed. This is dependent on sufficient scientific justification including but not limited to mechanism of action [15]. As such, there is no requirement to independently perform trials in each of the reference biologic indications to then obtain approval of the biosimilar across all the same indications. Rather, such approval can be granted based on the principal of clinical experience with the reference biologic and presumed identical mechanism of action due to “totality of evidence” of biosimilarity [15].

This is of particular relevance for inflammatory bowel disease, as the anti-TNF alpha biosimilars currently approved and utilized for IBD across the world were done so without independent trials in IBD patients, rather presumed effective for IBD patients based on trials in rheumatological conditions. Some have argued that differences between IBD and other conditions with respect to immunogenicity and other aspects mean equivalence studies may not translate across conditions [16], and that comparative noninferiority randomized controlled trials (RCTs) should be specifically performed in IBD patients. Conversely, others argue that the principal of extrapolation is already in place for changes in manufacturing protocols for originator biologics, and that the requirements for biosimilars are more stringent in that they require clinical trials.

Due to the abbreviated phase III clinical testing and extrapolation, structured prospective phase IV postmarketing surveillance takes on greater importance (and could be argued should be mandatory), as often this is the first time disease-specific data for the biosimilar is obtained.

Substitution Versus Nonmedical Switching and Interchangeability

There is a theoretical concern that changing from an originator biologic to a biosimilar for an extrapolated indication may result in not only altered efficacy and safety but also the potential for increased immunogenicity and development of antidrug antibodies. Therapeutic substitution is the situation where a patient, usually with stable controlled disease, is transitioned from a reference or originator biologic to a biosimilar in a physician-controlled process. This usually involves a one-time single transition in circumstances where there is supporting clinical data.

The greater worry among clinicians with biosimilars, however, relates to the possibility of nonmedical switching (automatic substitution) by insurance providers or governmental funding sources for economic reasons without physician and patient approval or notification. Regulations governing nonmedical switching vary globally; in the USA, pharmacy-level substitution of a biosimilar with the originator biologic is only permissible if the biosimilar is formally designated as "interchangeable" for the particular indication by the FDA. "Interchangeability" is a higher standard than "biosimilarity", and implies the ability to safely change back and forth between the originator biologic and biosimilar; such designation is dependent on the pharmaceutical companies conducting switching studies in which patients alternate between the originator biologic and biosimilar with no loss of efficacy or safety compared to continued use of the originator biologic [15].

It is important to appreciate that biosimilars should not be considered an additional or new therapeutic strategy to the originator biologic and are unlikely to be effective in circumstances where the originator biologic failed or when antidrug antibodies have developed. The clinical setting where biosimilars will likely be of greatest value is in the de novo commencement of biologic therapy, and potentially the stabilized responder once substitution or interchangeability has been established.

Real-World Data in IBD

The policy of extrapolation has meant there have not been any randomized controlled trials of the new biosimilar anti-TNF alpha agents in IBD published to date, as they are not a requirement for regulatory approval.

A recent systematic review of anti-TNF alpha biosimilar agents identified 19 studies, of which only 5 were phase III RCTs in RA (none in IBD) with 8 phase I studies (7 in healthy individuals), and 6 observational studies [17]. They found that the pK, clinical efficacy, and adverse event data supported the comparability of biosimilar and originator products. Only four small cohort studies were identified that switched from originator biologic to biosimilar, though these suggested similar remission maintenance rates.

In 2016, several conference abstracts reporting the preliminary clinical experiences of IBD specialty centers (primarily European) with infliximab biosimilars were reported. To date the observational data appears encouraging, though it is only short term. Overall, infliximab biosimilars appeared to have equivalent efficacy and safety to Remicade in the de novo induction setting for anti–TNF-naïve IBD patients (Tables 13.1 and 13.2). As one would expect, some suggested lower remission and response rates and higher infusion reaction rates in patients with prior anti-TNF alpha exposure. While these data to date appear to justify the policy of extrapolation, there remains insufficient evidence regarding interchangeability and the immunogenic consequences of switching. Available data for switching involves limited follow-up duration, and almost exclusively involves a single "switch" (Tables 13.1 and Table 13.3). The largest cohort to date by Fiorino et al. [23] suggested that while biosimilar therapy is safe and effective, there was a fivefold increase in loss of response (12.2% vs. 2.3% $p = 0.001$) in patients who were switched. Subtle post-translational modifications unique to the biosimilars relative to the originator biologic may be sufficient to lead to antidrug antibody formation with associated loss of response and drug reactions upon switching, especially if multiple switches back and forth between agents occur [50]. Longer term observational and investigator-initiated biosimilar trial data specific to IBD are still required, with a particular emphasis on the immunogenic sequelae of switching to establish the validity of interchangeability, such as the just completed NOR-SWITCH study [51]. This was a phase IV, multi-indication (IBD – Crohn's disease, ulcerative colitis; inflammatory arthritis – rheumatoid arthritis; psoriatic arthritis, ankylosing spondylitis; psoriasis), multicenter, prospective, double-blind, noninferiority randomized controlled trial of nonmedical biosimilar switching conducted by the Norwegian government, presented in abstract form at UEGW 2016 [49]. The noninferiority margin was set at 15%. A total of 481 patients were recruited across 40 centers, who had been on stable treatment with Remicade for at least 6 months. In this study, the primary outcome was disease worsening at 12 months, which was noted in 53/202 (26.2%) of Remicade-treated patients compared to 61/206 (29.6%) of the CT-P13-switched patients, with no significant difference between the two arms. When looking specifically at IBD patients, disease worsening was noted in 21.2% of Remicade-treated and 36.5% (difference of 14.3%) of CT-P13-treated CD patients

Table 13.1 Studies of biosimilar CT-P13 in IBD: Induction (new starts) and maintenance (switching)

Study	Population	Follow-up	Efficacy	Safety
Park SH 2015 Korea *Full Text* [18]	95 CD: 51 naïve 44 switched 78 UC: 62 naïve 16 switched	Week 30	Clinical remission: Mod-severe CD = 59% naïve; 80.6% switched Fistulizing CD = 50% naïve; 50% switched UC = 37% naïve; 45.5% switched Mucosal healing: 69% naïve; 67% switched	No unexpected adverse events (5 severe adverse events)
Kang 2015 Korea *Full Text* [19]	8 CD: 3 naïve 5 switched 9 UC: 5 naïve 4 switched	Week 8 (induction)	Clinical remission: CD = 2/3 naïve; 4/5 switched UC = 5/5 naïve; 4/4 switched	1 adverse event
Jung 2015 Korea *Full Text* [20]	59 CD: 32 naïve 27 switched 51 UC: 42 naïve 9 switched	Week 54	Clinical remission: CD = 75% naïve; 93% switched UC = 50% naïve; 67% switched Mucosal healing: 67% in UC naïve	5 adverse events in naïve
Gecse 2016 Hungary *Full Text* [21] *and Updated Abstract* [22]	184 CD: 25% nonnaïve 107 UC: 14% nonnaïve	Week 54	Clinical remission: CD = 47% UC = 53% Decreased remission rates when associated with prior anti-TNF exposure Decreased CRP	7.2% infusion reactions overall
Fiorino 2016 Italy *Abstract* [23]	223 CD: 105 naïve 67 prior biologics 52 switch 174 UC: 112 naïve 20 prior biologics 42 switch	6 months	Clinical response (CD + UC): 92% naïve 84% prior biologics 94% switched Loss of response in 12% of switched patients (fivefold greater than overall cohort)	8.3% severe adverse events 5.3% infusion reactions
Guerra Veloz 2016 Spain *Abstract* [24, 25]	75 CD: 71 switched 40 UC: 31 switched	6 months	No difference between group in remission and group not in remission at start of study	Mild adverse events: 6.6% in CD; 5% in UC
Carvalho Lourenço 2016 Portugal *Abstract* [26]	19 CD: CT-P13 41 CD: IFX-R	Week 24	Significant decrease in HBI and CRP compared with baseline in both groups	No infusion reactions with CT-P13

(continued)

Table 13.1 (continued)

Study	Population	Follow-up	Efficacy	Safety
Hlavaty 2016 Slovakia *Abstract* [27]	19 CD 6 UC	Week 14 for induction, Every 8 weeks for maintenance	Clinical remission (CD + UC) = 84%	4 adverse events overall
Hamanaka 2016 Japan *Abstract* [28]	8 CD 12 UC *14 naïve*	Week 22	Clinical remission: CD = 100% UC = 80%	1 infusion reaction
Murphy 2015 Ireland *Abstract* [29]	14 IBD: CT-P13 22 IBD: IFX-R	Not reported	Higher surgery rate and hospital readmission rate; higher likelihood of steroid augmentation; and no decrease in CRP with CT-P13	Not reported

CD Crohn's disease, *UC* ulcerative colitis, *CRP* C-reactive protein, *CT-P13* infliximab biosimilar, *IFX-R* infliximab-Remicade, *HBI* Harvey-Bradshaw Index, *IBD* inflammatory bowel disease Used with permission from Millennium Medical Publishing, from Paramsothy et al. [30]

Table 13.2 Studies of biosimilar CT-P13 in IBD: Induction (new starts) only

Study	Population	Follow-up	Efficacy	Safety
Jahnsen 2015 Norway *Full Text* [31]	46 CD: 33 naïve 13 prior biologics (IFX, ADA, GOL) 32 UC: 27 naïve 5 prior biologics (IFX, ADA, GOL)	Week 14	Clinical remission: CD = 79% UC = 56% Significant reduction in CRP and calprotectin	No unexpected adverse events
Keil 2016 Czech *Full Text* [32]	30 CD 22 UC *(all anti-TNF naïve)*	Week 14	Clinical remission: CD = 50% UC = 41% Decreased CRP	4 adverse events overall
Farkas 2015–2016 Hungary, Czech *Full Texts* [33, 34]	63 UC 18 CD	Week 14 (UC) Week 8 (CD)	Clinical remission: UC = 47.6% CD = 50% Mucosal healing: UC = 47.6%	New antidrug antibodies in 7 UC naïve patients
Malickova 2016 Czech *Abstract* [35]	60 IBD: CT-P13 (*all anti-TNF naïve*) 71 IBD: IFX-R	Week 14	Not assessed	No difference in antidrug antibodies or other autoantibodies

(continued)

Table 13.2 (continued)

Study	Population	Follow-up	Efficacy	Safety
Sieczkowska 2016 Poland *Abstract* [36]	36 CD: 17 naïve (*Pediatric*)	Week 14	Clinical remission = 72% Decrease in mean PCDAI	1 allergic reaction
Muhammed 2016 UK *Abstract* [37]	CD: 18 CT-P13 14 IFX-R UC: 6 CT-P13 3 IFX-R (*Pediatric*)	Not specified	No significant difference in clinical efficacy	No significant difference in infusion reactions
Bortlik 2016 Czech *Abstract* [38]	79 CD 25 UC	Week 22	Complete or partial response: CD = 89.6% UC = 78.3% Mucosal healing: UC = 50%	20 adverse events New antidrug antibodies in 10% patients
Kaniewska 2016 Poland *Abstract* [39]	77 CD: IFX-R 52 CD: CT-P13 47 CD: ADA	12 months then 6 months post cessation	No difference in clinical response, CDAI, calprotectin, or relapse rate	No difference in allergic reaction rates among IFX-R and CT-P13
Kaniewska 2016 Poland *Abstract* [40]	32 UC: IFX-R 35 UC: CT-P13	Induction therapy (3 doses) & 6 months follow-up	No significant difference in: Clinical response Endoscopic remission	No difference in adverse events
Turk 2016 Croatia *Abstract* [41]	25 UC 19 CD 2 unclassified	8 months	Clinical & laboratory remission = 79% Mucosal healing = 32% of patients in remission	No severe adverse events

CD Crohn's disease, *UC* ulcerative colitis, *IFX* infliximab, *ADA* adalimumab, *GOL* golimumab, *CRP* C-reactive protein, *IBD* inflammatory bowel disease, *CT-P13*: infliximab biosimilar, *IFX-R* infliximab-Remicade, *PCDAI* Pediatric Crohn's Disease Activity Index, *CDAI* Crohn's Disease Activity Index Used with permission from Millennium Medical Publishing, from Paramsothy et al. [30]

(n = 155), while for UC the respective values were 9.1% and 11.9% (difference 2.8%) (n = 93), with the adjusted treatment differences within the prespecified non-inferiority margin. No difference was identified in the detection of antidrug antibodies (Remicade 7.1% vs. CT-P13 7.9%), through drug levels, and frequency of adverse events including infusion reactions.

Table 13.3 Studies of biosimilar CT-P13 in IBD: maintenance (switching) only

Study	Population	Follow-up	Efficacy	Safety
Smits 2016 The Netherlands *Full text* [42] *and Abstract* [43]	57 CD 24 UC 2 unclassified (*all switched from IFX-R to CT-P13*)	Week 16	No change in median disease score, fecal calprotectin, or CRP Increased median infliximab trough levels	No severe adverse events New antidrug antibodies in 2 patients
Sieczkowska 2016 Poland *Full Text* [44] *and Abstract* [45]	32 CD 7 UC (*Pediatric*) (*all switched from IFX-R to CT-P13*)	8 months (CD) 5 months (UC)	Clinical remission: CD = 88% UC = 57%	No significant difference adverse events Antidrug antibodies in 4 patients
Bettey 2016 UK *Abstract* [46]	134 IBD (*all switched from IFX-R to CT-P13*)	Week 16	No change in drug persistence	No difference in incidence rate of side-effects
Kolar 2016 Czech *Abstract* [47]	56 CD 18 UC (*all switched from IFX-R to CT-P13*)	Week 24	No difference in CRP, calprotectin, disease activity, or infliximab trough levels	No infusion reactions No difference in antidrug antibodies
Díaz Hernández 2016 Spain *Abstract* [48]	62 CD 10 UC (*all switched from IFX-R to CT-P13*)	6 months	Clinical remission = 86%	No unexpected adverse events
Jørgensen 2016 Norway *Abstract* [49]	155 CD 93 UC 91 SpA 77 RA 30 PsA 35 Ps (481 patients) (*all switched from IFX-R to CT-P13*)	Week 52	Noninferiority in disease worsening: Among all patients: 26.2% (IFX) vs. 29.6% (CT-P13) CD: 21.2% (IFX) vs. 36.5% (CT-P13) UC: 9.1% (IFX) vs. 11.9% (CT-P13)	No difference in detection of antidrug antibodies, trough drug levels, and frequency of adverse events

CD Crohn's disease, *UC* ulcerative colitis, *IFX-R* infliximab-Remicade, *CT-P13*: infliximab biosimilar, *CRP* C-reactive protein, *IBD* inflammatory bowel disease, *SpA* spondylarthritis, *RA* rheumatoid arthritis, *PsA* psoriatic arthritis, *Ps* psoriasis Used with permission from Millennium Medical Publishing, from Paramsothy et al. [30]

Unanswered Questions and Future Directions

The emergence of biosimilar agents presents unique challenges and opportunities in the care of IBD patients, for whom biologics are currently the most effective therapies available. There is concern regarding the abbreviated regulatory process, extrapolation, and risks of nonmedical switching. This is reflected in the position

statements of several IBD society bodies across the world, including the Crohn's and Colitis Foundation of America (CCFA) and the European Crohn's and Colitis Organisation (ECCO) [52–57]. ECCO calls for direct testing and specific evidence of efficacy and safety in IBD populations. The CCFA statement mandates the need for comprehensive human testing and voices concerns regarding immunogenicity risk and the need for this to be clearly defined in product information. They also state that for interchangeability status, evidence that switching does not lead to immunogenicity be provided. CCFA furthermore advocates that prescriber notification of any substitution be mandatory, with ability to prevent substitution if deemed necessary along with unique medication name/ID number to prevent confusion between the originator and biosimilar.

That said, the cohort data available to date are encouraging with regard to the bioequivalence of these agents in the de novo setting and short-term single switch studies, though interchangeability has not been adequately established. Ongoing postmarketing studies and IBD specific trials, with emphasis on interchangeability and long-term outcomes and bioequivalence data, are crucial to clearly define the safety, efficacy, and immunogenicity profiles of these agents in IBD and guide future regulatory processes.

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Chapter 14
Nutrition Matters in IBD

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Abbreviations

BMI	Body mass index
CCFA	Crohn's and Colitis Foundation of America
CD	Crohn's disease
CDC	Centers for Disease Control
CMC	Carboxymethyl cellulose
EEN	Exclusive enteral nutrition
EN	Enteral nutrition
FODMAP	Fermentable, oligo-, di-, monosaccharide, and polyols
GI	Gastrointestinal
GRAS	Generally recognized as safe
HOS	High-output stoma
IBD	Inflammatory bowel disease
IBD-AID	Inflammatory bowel disease-anti-inflammatory diet
IBS	Irritable bowel syndrome
mmol/l	Millimole per liter
MUAC	Mid-upper arm muscle circumference
MUST	Malnutrition universal screening tool

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NGT	Nasogastric tube
NPO	Nothing by mouth
ORS	Oral rehydration solution
PEN	Partial enteral nutrition
PN	Parenteral nutrition
PO	By mouth
RDN	Registered dietitian nutritionist
SBS	Short-bowel syndrome
SCD	Specific carbohydrate diet
SCFA	Short-chain fatty acids
SD	Standard deviation
TNF-α	Tumor necrosis factor-alpha
UC	Ulcerative colitis

Nutrition and Epidemiology of IBD

There is a growing interest in how diet patterns play a role in the development of inflammatory bowel disease (IBD). Diet refers to actual foods consumed and food choices which incorporate lifestyle and patterns of eating [1]. Nutrition is the absorption of food and nourishment to support life. The role of the "Western diet" cannot be excluded; however, current evidence is insufficient to point to specific nutrients or foods in the development of IBD [2]. Studies in Japan have linked higher consumption of sweets to an increased risk of both ulcerative colitis (UC) and Crohn's disease (CD) [3]. Dietary intake in Asia has shifted to favor the Western diet, with an increase in refined sugars, fast food, and reduction in fruits, vegetables, and fiber [4, 5]. Immigrants who move to Western countries have heightened inflammatory state with shifts from minimally processed to highly processed foods [6].

The Western diet is unbalanced in fats, favoring omega-6 fatty acids. An optimal ratio of omega-6 to omega-3 should be 4:1 or less; however, Western diets reflect 15–20:1 [7]. High intake of omega-6 may increase the risk of UC, while omega-3 fatty acids may be protective [8, 9]. A study at the University of Chicago found mice fed on a high-saturated-milk-fat diet showed changes in bile acid composition leading to an increase in colonic inflammation versus a high-polyunsaturated-fat diet [10]. Imbalance in fatty acids and lack of fruit and vegetable intake are associated with increased risk of CD in children [11]. A recent study found correlation between increased dietary fiber from fruits and a reduced risk of CD but not UC [12]. A population-based, case-control study in Stockholm found an increase in the relative risk of CD and UC in those who consumed fast food more than twice a week [13]. Further studies on diet patterns and the Western diet are warranted.

Diet and the Microbiome

There are nearly 100 trillion bacterial species in the human body, which is ten times the number of cells in the body [14]. Gut microbiota, or the microbiome, has been termed the "second genome" and is subject to environmental stressors, with diet as a major factor in "Westernization" worldwide [6]. Prior to modernization, diet was limited to wild plant and animal foods. Today, convenience foods encompass refined grains, vegetable oils, saturated fats, and added sugars. Diet has the ability to change the function and composition of microbiota and may be the most realistic method to modify gut bacteria [15]. A recent study found that within 24 h of commencing a high-fat, low-fiber diet, the microbiome changed significantly compared to being on a low-fat, high-fiber diet [16]. In both mice and humans, an animal-based diet has been found to increase fecal bile acid concentrations versus a plant-based diet [17, 18]. It is unknown if specific macronutrients or micronutrients alter the induction or maintenance of remission in IBD [19]. It has been reported that individuals with IBD have a significantly high carbohydrate intake compared to healthy controls [20]. More studies are needed to determine the types and quantities of carbohydrates that promote short-chain fatty acids (SCFA) and which may be detrimental in IBD [21]. Current studies are exploring how diet can shift the microbiome to determine an evidence-based diet for IBD [22].

Dietary Intake and Nutritional Status in IBD

Diet and nutrition are important pieces of the puzzle in the management of IBD patients. Nutritional status may be overlooked if clinicians fail to routinely check vitamin levels or are unaware of the potential risk of nutrient deficiencies. Patients are especially vested in how to alter their disease by dietary modifications and often ask physicians what diet recommendations are most optimal. There is limited evidence on diet for IBD, and patients may instead search the Internet, which furthers confusion and misinformation. Current recommendations suggest a healthy and varied diet [23, 24]. Physicians and nurses do not have time or expertise to focus on nutrition education or counseling. Registered Dietitian Nutritionists (RDNs) are instrumental in nutrition assessment and education. Consulting an RDN ensures a personalized approach is utilized with respect to location and extent of disease and food avoidances or aversions [25]. Up to 90% of IBD patients believe dietary counseling and education are an integral part of management, yet only 20% receive adequate information on diet, risk of deficiencies, or nutrient-dense food choices [26].

Food choice and nutrition status have a profound impact on IBD patients. The simple act of eating may exacerbate symptoms, which could compound into lifelong food aversions and avoidances. Patients may avoid foods for decades that troubled them once during a flare. Up to 40% of patients believe certain foods affect flares, and 50% believe IBD changes the pleasure of eating [27]. A food frequency survey by Crohn's and Colitis Foundation of America (CCFA) of over 6000 IBD patients on self-reported associations between food intake and IBD revealed which

foods were believed to improve or worsen symptoms [28]. Foods reported to reduce symptoms included yogurt, rice, bananas, while vegetables, fruits, nuts, fried foods, milk, red meat, soda, popcorn, coffee, and beans were reported to exacerbate symptoms [28]. Nutritional deficiencies and weight loss may occur when multiple food groups are avoided over extended periods of time.

Overlap of IBS in IBD

A common challenge in patients with IBD is the increased prevalence of irritable bowel syndrome (IBS). There is paucity in the literature on treating IBD patients who experience IBS. Clinicians tend to extract recommendations for IBS to treat this population [29]. These symptoms may mimic those of IBD. Often, clinicians work up patients who report such debilitating symptoms, and find IBD is quiescent. IBS is a functional disorder that often correlates with a decrease in quality of life and physical functioning while increasing anxiety in many IBD patients [29].

Types of Dietary Fiber

It is important for clinicians and patients to understand the difference between soluble and insoluble fiber. Soluble fiber dissolves in water and forms a gel-like substance in the gut, slowing down transit time and gastric emptying, and minimizing diarrhea. Insoluble fiber draws water into the gastrointestinal (GI) tract and speeds up transit time. It has long been considered that insoluble fibers from skins, seeds, and high-fiber foods are risky as they may cause obstructions in those with stricturing disease and exacerbate gastrointestinal symptoms. It is imperative that clinicians educate patients on the types of fiber and what is acceptable depending on the extent of disease to allow a varied and personalized diet.

Oral Diets in IBD

Diet plays a small role in the published guidelines for IBD. Access to high-quality dietary information is lacking in the management of IBD [30, 31]. This may send the wrong message that diet is not an important component in the management of IBD [1]. Progress for dietary therapies in IBD has been slow, and information provided to patients is often outdated and inconsistent [1, 32]. Patients are typically instructed to avoid or limit foods that cause gastrointestinal distress or aggravate symptoms. Overly aggressive diet restrictions may negatively impact patients and should be considered when determining diet recommendations. Future studies should lay the groundwork for standardized nutrition therapy guidelines in IBD [33] and specify differences in recommendations between CD and UC.

Low-Fiber and Low-Residue Diet

In a randomized trial, patients on a low-residue diet did not have any difference in outcomes in hospitalization, obstructions, or surgery than those transitioned to a normal diet with gradual reintroduction of fiber. The authors note the prospect of lifting dietary restrictions, as it provides an appetizing and nutritious diet, without symptomatic deterioration or precipitation of intestinal obstruction in CD [34]. Despite this, a low-fiber diet remains commonly recommended in IBD dietary guidelines. A recent review of randomized controlled trials found limited evidence to restrict or supplement fiber in IBD [35].

The Specific Carbohydrate Diet (SCD)

The SCD was developed in the 1920s by Dr. Sidney Haas to treat celiac disease. Elaine Gottschall popularized the diet in the 1950s with the book *Breaking the Vicious Cycle* [36]. The SCD restricts carbohydrate intake to allow only monosaccharides which require minimal digestion. Both disaccharides and most polyols are excluded [36]. Fresh fruits, some vegetables, fresh meat, poultry, fish, and eggs are allowed. The diet only permits homemade yogurt that is fermented for 24 h to eliminate all lactose. This is a grain-free, lactose-free, and sucrose-free diet, thought to reduce the poorly digested carbohydrates in the diet while reducing bacterial fermentation [37, 38]. A case series report of patients with moderate to severe disease following the SCD note those patients were able to discontinue immunosuppressive medications, although all subjects were in remission at the time of the study [37]. A recent study found the SCD beneficially increased microbial diversity, while the low-residue diet decreased microbial diversity in patients with CD [39]. Diet modification may provide a means of altering gut microbiota to not only minimize symptoms but also induce mucosal healing. This may be a low-cost adjunct to medical management, but patient education level and time to cook and prepare food are important factors to consider. Long-term adherence to this restricted diet may create nutrient deficiencies and unintended weight loss.

The Inflammatory Bowel Disease Anti-inflammatory Diet (IBD-AID)

The IBD-AID is derived from the SCD and is an updated version of the nutritional regimen. It was developed by the University of Massachusetts Medical Center to optimize nutrition and minimize GI symptoms in patients with IBD [40]. There are five components of the diet regimen. It emphasizes modification of carbohydrates just as SCD: avoiding lactose and refined and processed carbohydrates. Emphasis is placed on addition of probiotics and prebiotics to aid in restoring the intestinal flora. Unlike the SCD, focus is on the types of fats: saturated and trans fats are avoided,

while emphasis is on monounsaturated and polyunsaturated fats. Contrary to SCD, it considers the overall dietary pattern to determine risks of nutrient deficiencies and identify food intolerances. The IBD-AID focuses on modifying textures of foods, and allows fiber-rich foods that are blended, ground, and cooked. Rather than avoiding all grains, it allows oatmeal. The initial study found that 100% of patients following the diet were able to discontinue at least one IBD medication and experienced a reduction in symptoms [40]. A small follow-up prospective study utilizing IBD-AID found patients were able to follow the diet, as avoiding foods was relatively easy to incorporate into their lifestyle. On the contrary, inclusion of unfamiliar foods like kimchi, miso, or sauerkraut was challenging and may create a barrier to maintaining the diet in some individuals [41]. Further prospective studies are needed to determine the use of IBD-AID as an adjunct to medical management of IBD.

The Gluten-Free Diet

A CCFA survey of over 1600 patients found 65% of those on a gluten-free diet found a reduction in symptoms of IBD, and 38% reported a decrease in the severity of flares [42]. It is unknown whether this is due to inflammatory response or symptom management and quality of life. This is a patient-reported outcomes survey and is not correlated with serological testing to support the use of a gluten-free diet to reduce IBD flares [42]. This therapeutic approach may be feasible in patients whose functional symptoms respond to a gluten-free diet, though symptoms do not correlate with disease activity. Further prospective studies are warranted to determine who would benefit from the diet and how it could be utilized in a clinical setting. It is of utmost importance to rule out celiac disease in patients prior to embarking on a gluten-free diet. A recent study found the incidence of both IBD and celiac disease was 3.2%, significantly higher than the suspected 1% of the population with celiac disease alone [43].

The Low-FODMAP Diet (Fermentable, Oligo-, Di-, Monosaccharides, and Polyols)

Benefit of the low-FODMAP diet has been found in irritable bowel syndrome (IBS) as it reduces carbohydrates that produce gas, bloating, and diarrhea. The low-FODMAP diet minimizes the osmotic load, which reduces multiple IBS symptoms. Historically, lactose was the most commonly known FODMAP which patients and clinicians were aware should be limited to avoid gas or bloating upon consumption. The low-FODMAP diet has proven effective for reducing ileostomy output; however, there are no direct benefits known yet for IBD [44]. It has been found to increase the quality of life by reducing symptoms of IBS which may overlap in IBD [45]. Studies are limited in IBD on low-FODMAP diets; it is anticipated that it may

be easier to follow than SCD as it allows a greater variety in the diet [33]. This is a restrictive diet that may increase risk of nutrient deficiencies if a patient remains on the elimination diet phase without reintroducing foods back to the diet. Long-term adherence may not prove beneficial, as it restricts sources of soluble fibers which act as a fuel source to SCFAs. Not all patients are good candidates for the diet if they have a history of eating disorders, are underweight or are unable to shop or cook for themselves. The benefit of a restricted diet must outweigh the risks, especially in the IBD patient.

Nutrition Screening and Assessment of the IBD Patient

Inflammation of the GI tract, its associated abnormal metabolic state, and/or symptoms such as diarrhea, pain, and nausea can lead to reduced oral intake which can cause impaired nutrition status in IBD patients [23, 46, 47]. Pharmacological and surgical treatment may impair digestion and absorption of nutrients due to drug–nutrient interactions and reduced absorptive area of the intestine secondary to surgical resections [48].

Nutrition screening identifies patients who are malnourished or at risk for malnutrition to determine if a detailed nutrition assessment is indicated [49]. In the United States, nutrition screening is required by the Joint Commission within 24 h of hospital admission [49]. In the clinic setting, nutrition screening is not a requirement; however, self-screening for IBD patients using the malnutrition universal screening tool (MUST) has been shown to be valid, easy to use, and if adopted, is likely to increase malnutrition screening in the busy outpatient setting [23, 50].

A comprehensive nutrition assessment should be completed for patients who are malnourished or at risk of malnutrition. Medical, nutrition, and medication histories, physical examination, anthropometrics, laboratory data, food/nutrient intake, and functional assessment are incorporated to identify nutrition problems [49, 51]. This assessment leads to recommendations for nutrition interventions to improve nutrition status of the patient [49]. Nutrition intervention has been associated with reduced hospital admissions, improved nutrition status, nutrient intake, physical function, and quality of life [49].

Historically, serum acute-phase proteins, including albumin and prealbumin, have been used as indicators of nutrition status [46]. However, acute-phase proteins do not consistently or predictably change with weight loss, calorie restriction, or nitrogen balance and appear to better reflect the severity of the inflammatory response [51]. In addition, they do not specifically indicate malnutrition or typically respond to nutrition interventions in the setting of active inflammatory response and are not advised in isolation as an indicator of malnutrition [51].

Malnutrition

Malnutrition is more common in patients with CD [52]. Protein-energy malnutrition has been estimated to occur in 20–85% of patients with CD [52, 53]. Malnutrition has been linked to decreased quality of life, adverse outcomes, and increased complications after surgery including increased susceptibility to infection and poor wound healing [23, 46, 52, 54].

Factors that may lead to malnutrition in IBD patients include [46, 47, 52, 53] the following:

- Decreased oral intake
- Anorexia
- Increased nutrient needs related to the catabolic effect of systemic inflammation
- Malabsorption due to chronic inflammation, bowel resection, or bypass
- Maldigestion
- Increased intestinal losses
- Disease activity
- Surgical resections
- Medications

Dysbiosis and altered mucosal immune response to luminal bacterial antigens lead to chronic inflammation seen in IBD [23]. Inflammation is increasingly recognized as an underlying risk factor for malnutrition and may contribute to suboptimal response to nutrition intervention and increased risk of mortality [51]. Determining the presence of inflammation is crucial in accurately classifying the etiology and severity of malnutrition [55]. There is no single "parameter" that indicates inflammation; therefore, decreased acute-phase proteins, elevated C-reactive protein level, marked negative nitrogen balance, and existence of wound or incisional infection may be useful in determining the presence of inflammation and its severity [56].

Gathering data to diagnose malnutrition requires review of the medical record, verbal discussion with the patient and/or caregiver, and completion of a physical assessment [56]. Identification of two or more of the following criteria is recommended for the diagnosis of adult malnutrition, with its severity further defined via specific thresholds [51, 56]:

- Insufficient energy intake
- Weight loss
- Loss of muscle mass
- Loss of subcutaneous fat
- Localized or generalized fluid accumulation that may sometimes mask weight loss
- Diminished functional status as measure by hand grip strength

Specific thresholds for the six characteristics listed above can be obtained from The Academy of Nutrition and Dietetics/The American Society for Parenteral and Enteral Nutrition Consensus Malnutrition Characteristics: Application in Practice document [56].

Nutrition Support in the IBD Patient

Enteral Nutrition

Enteral nutrition (EN) can play a role in the treatment of IBD patients with malnutrition or who are at risk of malnutrition [19, 57]. EN may be used for patients with functional GI tracts who cannot maintain adequate oral intake to maintain or restore nutritional status [19, 33, 57]. EN is the preferred method of feeding when nutrition support is needed [57]. EN physiologically delivers nutrients into the GI tract, has stimulatory effects on GI structure and function, is more cost-effective, and is associated with fewer complications than parenteral nutrition (PN) [33].

Polymeric enteral formulas contain intact proteins and require digestion by gastric, intestinal, and pancreatic enzymes, in contrast to elemental formulas which contain free amino acids and require minimal to no digestion [33, 48]. There is no difference between using elemental, semielemental, or polymeric formula in IBD patients [33, 58].

Exclusive Enteral Nutrition

An area that has generated much interest is the use of exclusive enteral nutrition (EEN) as a primary therapy for IBD, reducing reliance on pharmacologic immunosuppressants [33]. EEN refers to the use of EN to provide 100% of the nutrient needs and requires avoidance of all foods for several weeks [33, 48]. The dose and duration of EEN depend upon clinical parameters such as nutrition status and decrease in disease activity [57]. As symptoms improve, patients may be allowed some food intake and EN may be reduced with the increase in oral nutrition [57]. It is hypothesized that EEN may promote mucosal healing in the GI tract by favorably altering the GI microbiota, reducing intestinal permeability, enhancing barrier defense and adaptation, and promoting a reduction of proinflammatory cytokines [19, 33, 48, 57]. There is evidence to support EEN as a primary therapy to induce and maintain remission in adults and children with active CD, but not in UC [19, 57]. It is most frequently used as primary therapy for children with CD as it promotes growth, may improve bone health, and has minimal side effects compared to steroids [19, 57, 59, 60].

Use of EEN at pediatric centers in western European countries is standard practice with 62% of gastroenterologists reporting frequent use [61]. EEN is not as commonly used in North American pediatric centers with 30% of Canadian and only 4% of American gastroenterologists reporting frequent use [61]. Main barriers reported by North American physicians included lack of practice guidelines and concerns about patient compliance [61]. A major drawback of EEN is that it requires many patients to place a nasogastric tube (NGT) each evening or keep it in all day [62]. Oral consumption of enteral formula on an exclusive basis as an induction therapy for pediatric CD

might be as effective as continuous enteral feeding and an option to avoid nightly NGT placement. However, more research is needed [48, 63]. Partial enteral nutrition (PEN) which provides EN in addition to a normal diet has been investigated as an option that may be more acceptable, but has not been found effective in inducing remission [64]. Success has been reported using PEN as a maintenance therapy such as overnight feedings with a normal diet or nasogastric feeding for 1 of every 4 months [62].

EEN is not used as often as a primary therapy for adult patients with CD partially due to compliance issues [19]. In addition, EEN may be more effective in children than adults [48]. Some studies on EEN found it to be as effective as steroid therapy in inducing remission [48]. In contrast, a Cochrane systematic review found steroid therapy to be more effective than EEN in inducing remission in adult patients with active CD [48, 65]. When taking into consideration potential adverse effects of pharmacologic treatment, EEN is safer and can be used as a therapeutic method [48, 65]. North American clinical guidelines recommend use of EN in adults as an adjunctive therapy to support nutritional status rather than as a primary therapy [48, 65]. Other counties have varying guidelines regarding use of EEN in the management of IBD [48].

Parenteral Nutrition

Historically, parenteral nutrition (PN) was used to rest the bowel to promote mucosal healing; however, this practice is no longer supported by the literature [33]. PN should be reserved for patients who are at risk of malnutrition, have a nonfunctioning GI tract, lack enteral access, or show intolerance to EN [33]. It may be needed for patients who require stoma creation proximally in the gastrointestinal tract such as a jejunostomy [66].

Indications for the use of parenteral nutrition include [57] the following:

- Bowel obstruction
- Short-bowel syndrome
- Severe malabsorption
- Fluid and electrolyte needs that cannot be met with EN
- Severe dysmotility
- EN intolerance with inability to maintain adequate PO intake
- High-output intestinal fistulas
- IBD-related surgery in the perioperative period
- High-output stomas

Perioperative Nutrition

In emergency situations or when medical therapy has failed, surgery may be necessary [47]. Surgery rates are on the decline; however, it is estimated that 10% of UC and 50% of CD patients will require surgery within ten years of disease onset [47].

Ideally, assessment of nutrition status should be a part of the preoperative evaluation for elective surgery patients and goal-directed nutrition therapy should be implemented [67]. Malnutrition is a serious clinical problem seen in IBD patients and is associated with poor surgical outcomes [23, 67]. Surgery induces a stress response which has a catabolic effect on the body's substrate stores [47]. Optimization of the metabolic state prior to major surgery leads to improved outcomes and reduced length of hospital stay [67, 68]. Preoperative fasting is associated with insulin resistance, hyperglycemia, the need for exogenously administered insulin, and failure to achieve an anabolic state and should be avoided [23, 67]. Carbohydrate loading prior to surgery is associated with improved insulin sensitivity, decreased preoperative thirst, hunger, and anxiety, and may lead to earlier return of bowel function, shorter length of stay, and improved muscle strength in colorectal surgery patients [67]. Improved clinical outcomes have been associated with short courses of immune-modulating formulas that contain combinations of arginine, omega-3 fatty acids, and other nutrients [67]. Immune-modulating nutrients play a key role in metabolic pathways that promote reduction of the metabolic response to stress and improve wound healing and immune function [67]. The use of preoperative immunosuppressive agents may increase the incidence of postoperative complications [69]. One study found that use of EEN for perioperative optimization in CD patients prolonged the immunosuppressant-free interval, reduced the risk of urgent surgery and reoperation, and decreased complications after surgery [69]. Use of EEN prior to surgery has been associated with reduced risk of septic complications after surgery [23]. While PN should not be the first choice of nutrition support during the perioperative period, it may be advised when the GI tract is not functional or intact [47]. A recent review of the literature concluded that when necessary, perioperative PN may reduce postoperative complications and improve disease severity and nutrition status in adults with IBD [47].

Nutritional Considerations for Ostomy Patients

The amount of intestine remaining after surgery will determine nutritional needs based on absorptive capacity [66]. It is important for clinicians to be aware of the type of stoma, how it was formed, and the length of the remaining proximal bowel [66, 70]. Individualized dietary advice should take food preferences and sociocultural influences into consideration [66].

Nutritional Management of Colostomy Patients

Colostomy output is generally formed to semiformed and ranges from 200 to 600 ml/day [70]. Dehydration is rarely a concern except when minimal colon remains [70]. The more distal the colostomy, the thicker the output, as there is more

Table 14.1 Foods of concern for ostomy patients [66, 70]

Foods that may cause blockages	Gas-producing foods	Odor-producing foods
Raw cabbage	Broccoli	Broccoli
Chinese vegetables	Garlic	Garlic
Corn	Onion	Onion
Raw celery	Eggs	Eggs
Mushrooms	Fish	Fish
Coconut	Cabbage	Cabbage
Apple peel	Brussel sprouts	Brussel sprouts
Tomatoes	Legumes	Asparagus
Popcorn	Cauliflower	Cauliflower
Dried fruits	Carbonated beverages	Baked beans
Nuts		Strong cheese
Grapes		
Oranges		
Pineapple		
Bean sprouts		

surface area for water and electrolytes to be absorbed [70]. A well-balanced diet with adequate fluids and fiber (~30 g/day) is recommended [66, 70, 71]. For constipation, intake of fiber should be encouraged before the use of laxatives [66, 71]. If gas or odor become a concern, patients may be counseled to avoid gas- and odor-producing foods (Table 14.1) [70].

Nutritional Management of Ileostomy Patients

Normal ileostomy output is between 500 and 1000 ml daily [70]. Output may initially be elevated in the post-op period; however, it should decrease to less than 750 ml prior to discharge [66]. A low-fiber diet is often recommended for the first 6–8 weeks after surgery [70]. After 6–8 weeks, patients should gradually transition to a regular well-balanced diet [66, 70, 71]. In general, gas and odor are less of a problem; however, some of the same foods that cause gas and odor for colostomy patients may cause gas and odor for ileostomy patients (Table 14.1) [70]. A reduction in fiber intake may decrease excessive flatus [66]. To prevent the audible sound of air escaping, the stoma patient may be counseled to avoid behaviors that increase air in the intestine such as drinking from straws, chewing gum, drinking carbonated beverages, and skipping meals [70]. The patient should receive education on foods that thicken the output such as bananas, pasta, potatoes, white bread, white rice, pretzels, applesauce, marshmallows, cheese, and creamy peanut butter [66, 70]. Patients may need to experiment with foods because ostomy output can be uncomfortable if it becomes too thick [70]. Patients should be counseled to chew well and avoid foods that may cause blockages (Table 14.1) [66, 70, 71]. Foods high in insoluble fiber should be slowly reintroduced to assess the impact on output [70]. Patients with high output and/or excessive flatus may need to reduce fiber intake to promote

slower transit time and optimize nutrient absorption [66]. To replace fluid and sodium losses, an additional 500–700 ml of fluid and an extra teaspoon of salt per day may be advised [66, 70]. Dehydration is common after ileostomy creation, and may be severe enough to warrant hospital readmission and lead to renal failure [72–74]. Hospital readmission within 30 days of surgery is costly and is receiving attention as a preventable complication increasingly monitored as a quality metric linked to reimbursement [72, 74, 75]. Patients should be counseled to recognize the signs and symptoms of dehydration, including thirst, dizziness, lethargy, headaches, and general malaise [66, 72].

Ostomy Patients with Decreased Appetite and Unintentional Weight Loss

Commercial nutritional supplements may be a useful source of nutrition for ostomy patients who have a decreased appetite after surgery [66]. However, these should be sipped slowly throughout the day due to the hyperosmolar content, considering the potential to increase stoma output [66]. Small, frequent meals and snacks may benefit patients with a decreased appetite to allow increased intake [66]. Dietary fat should not be restricted as it is a valuable source of calories for patients trying to regain weight [66].

Nutritional Management of High Output Stomas

Recently, research on the relationship of high-output stomas (HOS) to electrolyte abnormalities has become an area of interest [76]. The first few days after creation of a new ostomy, output is high, but typically decreases rapidly after intestinal adaptation [66, 70, 76]. However, in some cases this adaptation fails to occur, or is prolonged, putting patients at risk for dehydration, renal dysfunction, electrolyte abnormalities, weight loss, and malnutrition [70, 76]. Potential causes of HOS include acute gastroenteritis, recurrence of IBD, radiation enteritis, intra-abdominal sepsis, partial or intermittent bowel obstruction, *Clostridium difficile* infection, sudden withdrawal of medications, bacterial overgrowth related to diverticula or blind loop fermentation, and short-bowel syndrome (SBS) [70, 77]. HOS is more commonly seen in ileostomy than colostomy patients [70, 76].

Management of HOS consists of identifying the underlying cause and implementing oral and/or intravenous replacement of water, electrolytes, antisecretory and antidiarrheal medication, as well as nutritional and psychological support [70, 76, 77]. Well-planned nutrition interventions can lessen the negative effects of high-output stomas [70]. Nutritional management of HOS includes restriction of oral hypertonic and hypotonic fluids, replacement of depleted fluid and electrolytes, rehydration with glucose–saline solutions, and nutrition support if needed [70].

Protocols for HOS

A prospective study on a cohort of patients who underwent surgery resulting in a stoma found a protocol for detection and management of HOS developed by a multidisciplinary team was effective in addressing potential long-term complications arising from poor nutritional status and chronic electrolyte alteration [76]. A HOS may develop early after surgery (within the first 3 weeks) or late after surgery (after the first 3 weeks), but on average was found to occur approximately 8 days after surgery [76]. This highlights the importance of instructing patients on HOS prior to discharge and follow-up after discharge with a multidisciplinary nutrition team consisting of pharmacists, nutritionists, nurses, and surgeons [76]. Patients admitted to nonsurgical floors may be at risk of receiving advice not supported by the literature; therefore, it would be beneficial to extend protocols to all areas of the hospital [76].

Restriction of Hypertonic and Hypotonic Fluids

High output can be caused or exacerbated by intake of large amounts of oral hypertonic or hypotonic fluids [70]. Intake of hypotonic fluids such as water, sugar-free soda, tea, and coffee causes sodium to shift into the gastrointestinal tract resulting in sodium depletion [70, 77]. Intake of hypertonic fluids such as fruit juice, regular soda, and some commercial oral supplements cause depletion of water and sodium [70]. Patients should be instructed to limit hypotonic and hypertonic fluids to less than 500 ml/day [70, 71, 77]. Restriction of hypotonic and hypertonic fluids has been associated with poor compliance and some patients have been wrongly advised to increase overall fluid intake [77]. In some cases, it may be necessary to advise nothing by mouth (NPO) to mitigate the osmotic effect of oral fluids [70].

Fluid, Electrolyte, and Mineral Repletion

Repletion of fluid and sodium deficit is initially accomplished by administering 2–4 l of normal saline per day intravenously until fully corrected [70]. Magnesium depletion is commonly seen; however, it may be difficult to replete because oral magnesium supplements may increase stoma output and be poorly absorbed [70, 77]. Administering magnesium at night may enhance absorption because intestinal transit is at its slowest [70]. Intravenous repletion may be needed if oral repletion fails [70]. Low potassium levels may be the result of sodium and magnesium depletion and therefore the repletion of sodium and magnesium may be sufficient to correct low potassium levels [70]. Due to increased gastrointestinal losses, zinc deficiency is common and all patients with HOS should receive 220–440 mg of oral zinc sulfate daily [70].

Resumption of Oral Intake

Once repletion of fluid and electrolytes is achieved, resumption of oral intake and discontinuation of intravenous fluids should be attempted [70]. A regular diet moderately high in fat and sodium and small frequent meals should be encouraged [70]. For patients with obstructive symptoms, a low-fiber diet may be advised [70]. It is important to continue restriction of hypotonic and hypertonic fluids [70]. Intake of 1 l of an oral rehydration solution (ORS) sipped throughout the day is recommended to meet residual fluid needs [70]. An ORS is a nearly isotonic glucose–saline solution that contains at least 90 mmol/l of sodium and prevents depletion by inhibiting sodium from being pulled into the intestine which decreases losses [70, 77]. Commercial ORS may be purchased or patients may be provided recipes to make at home [70]. Commercial sports drinks are not recommended because they are too high in sugar and do not contain enough sodium [70]. Oral fluid restriction and intake of additional sodium may be adequate once stoma output decreases to 1000–1500 ml/day [70].

Nutrition Support for Ostomy Patients

When necessary, appropriate nutrition support regimens can improve malnutrition, dehydration, and electrolyte depletion that may occur as a result of HOS [70]. Parenteral or enteral nutrition may be required in patients who have prolonged HOS and are unable to meet nutrient needs through PO (by the mouth) intake alone [70]. Gastric or small-bowel feeding may be initiated in patients with newly formed stomas [70]. It is generally safe to start enteral feedings 1–2 days after stoma creation [70]. Supplemental nocturnal EN may be adequate to meet nutrient needs [70].

Formula Selection for Ostomy Patients

Elemental formulas are not necessary for ostomy patients and may be hyperosmolar and lower in sodium, leading to increased losses of water and sodium [70]. Intact nutrients better promote the adaptation of the small bowel when all or most of its absorptive capacity is lost [70]. Calorically dense formulas may not be well tolerated because they are hyperosmolar [70]. Fiber-containing formulas are not recommended for patients with ileostomies because fiber may draw water and nutrients into the effluent [70]. Fiber-containing formulas may be used to bulk up stools in patients who still have some remaining colon [70]. There is lack of evidence on the use of immune-modulating formulas, though due to hyperosmolar or semielemental content, it can be hypothesized these may not be well tolerated [70]. The ideal formula for stoma patients appears to be a nearly isotonic polymeric formula [70]. Sodium may be added to increase the concentration to 90–100 mL/l to help regulate electrolyte balance [70, 77].

Parenteral Nutrition for Ostomy Patients

PN may be needed if supplemental EN fails to achieve improvement in nutritional status [70]. Management of PN in ostomy patients is similar to standard formulations. However, additional fluid, sodium, magnesium, and zinc may be required [70, 77]. Additional potassium may be added if sodium and magnesium fail to correct low potassium levels [70].

Pediatric Nutrition Concerns in IBD

Twenty-five percent of IBD diagnoses present in childhood, with CD being the most common [78]. Many children have poor nutrition status at presentation which may worsen during the clinical course [78]. Growth failure in pediatric IBD is multifactorial and includes decreased intake, increased metabolic demand, malabsorption, cytokine-induced growth hormone resistance, and corticosteroids [62]. Growth failure is more common in CD (10–56%) than UC (10%) [23, 64]. Undernutrition has been reported in up to 65–75% of patients with CD [60]. Nutritional concerns, linear growth deficiency, and delayed puberty may occur in up to 85% of patients with a childhood diagnosis of CD [23, 60].

In CD, causes of growth deficiencies in height and weight, delayed puberty, and suboptimal bone mass include prolonged diagnostic delay, high initial activity index, and stricturing or penetrating patterns [60]. Recent weight loss is one of the clinical manifestations of CD and treatment has been shown to restore body weight, but not necessarily lean body mass [60].

The primary determinants of nutritional status are food and nutrient intake. Chronic caloric insufficiency is one of the greatest factors of growth deficiency in the pediatric IBD population [64, 79]. Reduced nutrient intake due to disease-related anorexia is believed to be related to tumor necrosis factor alpha (TNF-α) levels in IBD that interact with the hypothalamic appetite pathway [64]. The energy requirement for basal metabolism does not exhibit a compensatory reduction in IBD [64]. Assessment of the adequacy of food and nutrient intake compared to measured or estimated energy and protein needs is critical in the pediatric IBD population [79].

The primary outcome measure of nutrition status in the pediatric population is growth [79]. Growth should be measured at regular intervals including anytime the child presents in a healthcare setting [79]. Growth parameters include length-for-age, weight-for-age, and head circumference-for-age in children <36 months [79]. Standing height-for-age, weight-for-age and body mass index (BMI) are typically collected for children 2–18 years of age [79]. The Centers for Disease Control (CDC) recommend the use of the World Health Organization (WHO) comparative data charts from birth to two years of age and the CDC comparative data charts for 2–20 years of age [79]. In the past, definitions of undernutrition and failure to thrive have included the use of percentiles; it is

now recommended to use *z* score, decline in *z* score, and negative *z* score to identify and document malnutrition/undernutrition [79]. In children, weight is typically affected during acute periods of undernutrition while stunting is a consequence of chronic periods of undernutrition [79]. Severe acute undernutrition, experienced by children ages 6–60 months is defined as a very low weight-for-height (less than −3 standard deviations (SD) [*z* scores] of the median WHO growth standards), by visible severe wasting (mid-upper arm muscle circumference [MUAC] <115 mm) or by presence of nutritional edema [79]. Wasting is defined as a weight-for-age less than −2SD (*z* score) [79]. Chronic undernutrition or stunting is defined by WHO as having a height-for-age or length-for-age that is less than −2SD (*z* score) of the median of the National Center for Health Statistics/WHO international reference [79].

Vitamins, Minerals, and Complementary Nutrition in IBD

Nutrient deficiencies in IBD occur due to multifactorial reasons. This may include blood losses, diarrhea, surgical resections, presence of fistulas, and extent of disease [24]. Routine multivitamin with mineral supplementation is advised to ensure adequate nutrition. Patients with IBD may not appear malnourished, but may harbor multiple vitamin and mineral deficiencies [46]. Clinicians should be aware that nutrient deficiencies may be insidious in IBD.

Vitamin B12

Deficiencies of vitamin B12 may be due to ileal disease and loss of absorptive surface area with anatomical changes. It has been reported up to 20% of CD patients have a B12 deficiency, which increases to up to 48% with terminal ileitis [80]. Vitamin B12 supplementation may be indicated to restore normal levels in those with ileitis or ileal resections greater than 20 cm with loss of ileocecal valve, and yearly B12 levels checked if less than 20 cm [81].

Zinc

Zinc is necessary for wound healing and deficiency affects those with diarrhea, active disease, ostomies, fistulas, and up to 50% of patients with CD [24, 82]. Supplementation with follow-up labs may be advised to ensure repletion and determining when to discontinue.

Iron

Anemia is a common extraintestinal manifestation of IBD. Blood loss and impaired absorption in the duodenum and jejunum may impact iron stores [83]. Ferritin is the best indicator for deficiency, though levels may be normal or increased in response to inflammation [24].

Folate

Folic acid is a cofactor in metabolism of homocysteine and methionine. Folate deficiency may lead to hyperhomocysteinemia which may increase the risk of thromboembolic issues in IBD [80]. Sulfasalazine and Methotrexate may exacerbate folate deficiency as they compete for absorption and render folic acid present in the intestine unavailable. Patients taking either Sulfasalazine or Methotrexate are advised to take 1 mg daily to avoid deficiency.

Vitamin D and Calcium

Vitamin D levels may be impacted by surgical resections, malabsorption, poor sun exposure, and inflammation. The impact of Vitamin D is a highly debated and controversial topic in IBD. Unfortunately, a therapeutic level of 25(OH) Vitamin D is not yet known [84]. A prospective study utilizing the Nurse's health study data found higher levels of predictive 25(OH) vitamin D significantly reduced the risk of CD and UC in women, though larger studies are needed to confirm this study with serum vitamin D levels [85, 86]. Prednisone causes bone loss and reduces circulating calcium in the intestines and bones. Patients are advised to supplement with 1500 mg calcium while taking prednisone [82].

Omega-3 Fatty Acids

Despite much interest in modulating inflammation in other disease states, the evidence is lacking for fish oil in induction or maintenance of remission in IBD [87, 88]. Clinicians may advise patients to include fish in the diet to increase anti-inflammatory fats which may manipulate the microbiome [8, 9].

Probiotics

Probiotics have not yet been shown to benefit CD, but studies have found benefit in pouchitis and in mild to moderate UC [89, 90]. Please refer to the chapter outlining detailed recommendations for both probiotics and prebiotics.

Emulsifiers

There has been recent interest in how food additives alter the microbiome. Carrageenan, xanthan gum, carboxymethyl cellulose (CMC), and maltodextrin act as thickeners and emulsifiers and are widespread in processed foods. These ingredients are considered to be generally recognized as safe (GRAS) by the Food and Drug Administration and found in approximately 60% of processed foods [91]. Recent studies allude to increased inflammatory changes and disruption of mucosal lining in IBD [91, 92]. These findings suggest a balanced diet with consumption of minimally processed foods to avoid excessive exposure and warrants further studies in humans.

Conclusion

Diet and nutritional status impact the overall well-being of patients with IBD. Timely nutrition screening and assessment by early referral to nutrition experts should detect nutrient deficiencies and prevent malnutrition. The goal of nutrition interventions and use of oral diets or nutrition support with close follow-up and monitoring should increase the quality of life in patients with IBD. Although there is much interest in complementary and alternative nutrition, these recommendations are not ready for prime time and further studies are needed.

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Chapter 15
Size Matters – Special Considerations in the Pediatric IBD Patient

Oren Koslowe and Joel R. Rosh

Chapter Highlights

- IBD presenting during childhood is usually more clinically aggressive than adult-onset disease.
- The unique features of pediatric IBD serve as a model for demonstrating that IBD incorporates a family of diseases.
- Treatment goals in pediatric IBD must incorporate restoration of normal growth, development, and psychosocial wellness.
- Care of the pediatric IBD patient is best effected through a multidisciplinary team.
- Increasing levels of multicenter collaboration has led to important findings in the field of pediatric IBD and have created well-characterized inception cohorts that promise to carry forward our understanding of these diseases.

While there are many similarities between pediatric-onset and adult-onset inflammatory bowel disease (IBD), there are critically important differences which will be the focus of this chapter. Along with the recognition that 20–25% of patients with IBD are diagnosed before the age of 18 years, it has become increasingly evident that pediatric IBD is clinically more aggressive. In addition, age-appropriate therapeutic goals warrant an age-directed approach to IBD management. In fact, the distinctions between pediatric- and adult-onset IBD present a prototypical example that rather than having two to three subtypes, IBD more accurately refers to a large

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family of conditions that may share susceptibility genes, but can vary quite significantly in terms of host vulnerability, environmental triggers, natural history, and response to therapy.

Given the somewhat smaller size of the pediatric gastroenterology community relative to that of the adult community, multicenter research and quality improvement efforts have led to the study of the etiologies and outcomes of pediatric IBD. Such collaborations have ushered in an era of unprecedented promise to better understand the pathogenesis and optimized treatment of pediatric IBD. The Crohn's and Colitis Foundation of America (CCFA) has funded the Pediatric Research Organization for Kids with Intestinal Inflammatory Diseases (PRO-KIIDS) Network leading to a prospective, translational study of pediatric Crohn's disease (CD): Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (RISK). The NIH has funded a combined translational and interventional multicenter study of pediatric ulcerative colitis (UC) called Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT). These landmark collaborative efforts have created large, well-characterized inception cohorts that have yielded, and will continue to yield, long-term data which will greatly assist in the understanding of the etiology of IBD and how its therapy can be best personalized.

Presentation and Disease Progression

In considering a comparison between pediatric- and adult-onset IBD, one may first turn to issues related to epidemiology, clinical presentation, and diagnosis. Sauer and Kugathasan analyzed data from a number of studies and found that the median age at diagnosis of pediatric IBD is about 11 years old making growth and development an important therapeutic outcome. A number of studies have looked at the male-to-female ratio in pediatric CD compared to adult CD noting a predilection for males in pediatric CD which is absent in adult CD. While 60–70% of pediatric patients with CD are male, in adults there seems to be a slight predilection for females. In UC, a male-to-female ratio of 1:1 has been noted in studies of both pediatric and adult patients [1, 2].

Additional differences in presentation are related to variations in disease location. Specifically, the colon is involved in pediatric CD much more frequently than in adult disease and leads to colitic symptoms in children with CD more frequently. In a Scottish cohort, isolated ileal disease made up 32% of adult-onset CD (L1 using Montreal classification), and 36% had isolated colonic disease (L2). In children, 75% had at least some colonic involvement with 43% having disease throughout the bowel: ileocolonic and upper gastrointestinal (L3 + L4) [2]. The more aggressive nature of pediatric IBD is likely referable to the greater amount of involved bowel that is present in the pediatric patients.

The disease behavior also seems to differ between the pediatric and adult populations. For instance, the vast majority of pediatric-onset CD has an inflammatory

phenotype at diagnosis. In the same Scottish study, about 5% in the pediatric group had stricturing disease at diagnosis, but about 13% had at follow-up after 4 years [2]. This is indicative of a progressive course and explains why surgery rates for adults are higher initially while, by about 12–15 years after diagnosis, the rates between pediatric- and adult-onset patients are similar [2, 3]. Pigneur et al. noted that the more aggressive course in the pediatric population occurs despite an increased rate of use of immune-modifying agents including anti-TNF therapy. Also notable was the finding that such therapy was used nearly twice as often in the pediatric population than the adult population [3]. The disease progression from inflammatory to stricturing seen in pediatric CD may afford a greater opportunity for early and aggressive intervention. A signal for this can be seen by comparing a Scottish pediatric cohort in the prebiologic era from 1988–2002 to that after 2002 (biologic era). In the earlier cohort, the rate of surgery was noted to be 34% at 5 years, whereas the later cohort had a 5-year surgical rate of 20% [2, 4]. Another study looking at a cohort in Wisconsin from 2000 to 2007 revealed numbers similar to the Scottish study with 17% of CD patients undergoing surgery by 4 years follow-up [5]. While these studies cannot be compared head-to-head, they do contribute to a suspicion that addressing inflammatory disease early on may prevent progression to stricturing disease. Future studies need to be conducted to tease out the specific factors that fully account for this trend toward a decreasing rate in surgical intervention [6, 7].

UC is equally disparate in terms of comparing disease location and course. In the Scottish cohort pancolitis (E3 using Montreal classification) was seen in 82% of pediatric-onset disease at last follow-up compared to 48% of the adult-onset group. Other distinguishing characteristics of pediatric UC include gross rectal sparing at diagnosis in about 5% of patients, and "cecal patches" – islands of inflammation noted in the absence of continuity – seen in about 2% of pediatric UC patients [8]. The surgical rates also speak of the presence of a more aggressive phenotype in pediatrics with about twice as many patients in pediatric-onset UC requiring colectomy within 10 years of diagnosis versus adult-onset (41–20%) [2].

The frequency of surgery in the pediatric population has prompted study of the role for thromboprophylaxis in hospitalized patients which is used routinely in the adult population. The perceived and actual risk of thromboembolic events in children is low, but not insignificant. One study found a rate of about 2% in pediatric IBD patients admitted with colonic disease. The authors offer a risk stratification model and advocate for the potential role of enoxaparin in pediatric patients at high risk for thromboembolic events [9].

There is a subset of IBD patients diagnosed under the age of 5–6 years referred to as early-onset IBD. Those diagnosed under age 2–3 years are referred to as very early-onset IBD (VEO-IBD), and these patients have been noted to have an appreciable rate of identifiable monogenic mutations associated with their intestinal disease [10]. Some of the identified monogenic conditions that may present with intestinal inflammation include common variable immune deficiency (CVID), chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome, and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX). Broadly speaking this group of conditions may cause intestinal disease via defects in the function of the intestinal

barrier, phagocytic activity, or T- and B-lymphocyte selection and activity [11–15]. An in-depth discussion of this particular subgroup of patients is beyond the scope of this chapter, but clinical recognition of IBD in this age group should prompt immunologic and genetic evaluations. Monogenic conditions with bowel inflammation similar to that seen in IBD tend not to respond to traditional therapies, and often have a more severe disease course. An important example of this is the IL-10 receptor mutation that can present with highly destructive perianal disease in infancy and has been successfully treated with bone marrow transplantation [11, 16, 17].

Therapeutic Goals: Growth and Development

One of the most significant and unique issues in pediatric IBD is the potential for the disease to affect statural growth. Slowing of linear growth velocity may be seen in up to 40% of pediatric patients diagnosed with CD, and while less conspicuous, it is also occasionally seen in UC. As such, assessment of growth parameters and careful anthropometric measurements are critical in assessing disease activity and in determining response to therapy over time. Physicians caring for the pediatric IBD patient should also regularly assess pubertal development by incorporating Tanner staging into the physical exam. Growth failure including both poor weight gain/nutritional status and poor linear acceleration result from a multifactorial process [18–20]. Importantly our recognition that many "standard" therapies have been ineffective in reliably restoring adequate linear growth velocity has led to a reappraisal of how to optimize therapy in the pediatric IBD patient and this will be highlighted later in this chapter. The etiology of growth failure has been ascribed to many factors including malnutrition and exposure to glucocorticoids. The inflammatory milieu is now thought to contribute directly to growth failure by affecting the pituitary axis, and perhaps via direct impact on the growth plates of the long bones. However, gaps in our understanding do remain, as the inflammatory process in UC is quite similar to that noted in CD, yet the same degree of linear growth failure is not noted. Recent studies have tended to show improvement in achieving adult height with use of biologic agents, specifically anti-TNF agents; however, persistent growth failure still lingers in a significant minority [18]. There is suspicion that in the presence of active disease a degree of growth hormone resistance ensues and that this population, even in the setting of adequate clinical and biochemical control, may still have active disease [19, 21]. Small-bowel CD seems to be especially associated with decreased linear growth velocity and may warrant more aggressive therapy at outset. As linear growth failure present at diagnosis and as an indicator of ongoing disease activity is recognized, it has become incumbent upon all those caring for pediatric IBD patients to incorporate accurate measures of height and linear growth velocities into the assessment of their patients. To that end, bone-age assessment can be an invaluable tool not only in assessing the impact of the disease at onset but also in monitoring the success, or lack thereof, of therapy especially during the peripubertal years [22].

Therapeutic Considerations

The treatment options for managing inflammatory bowel disease in pediatrics are similar to those available for adults, albeit with fewer agents having specific regulatory approval for pediatric use. As of the writing of this chapter the only medications approved for treatment of IBD in the pediatric population were prednisone and infliximab for UC and CD, adalimumab for CD, and some preparations of mesalamine/sulfasalazine for UC. In looking at the use of immunomodulators in pediatric inflammatory bowel disease, Pigneur noted an increase in use among those diagnosed in the first several years of this century [3], and data from the Pediatric IBD Collaborative Research Group similarly noted that 70% of patients followed from 2002 to 2014 used thiopurines for some time [23]. There is an ongoing reassessment of the value of immunomodulators, specifically the thiopurines, regarding the safety and efficacy in maintaining remission in pediatric CD, and their ability to alter the natural history of this more aggressive disease phenotype. While there is certainly a spectrum of disease severity in pediatrics just as in the adult world, the statistical reality of high inflammatory-disease activity, progression toward fibrostenotic disease with need for surgery, and impact on growth, severely limit the role for 5-aminosalicylates as primary therapy in pediatric CD. The efficacy of nutritional therapy in pediatric IBD has long been recognized and has become a staple of management in Europe as well as in some centers in North America. A recent ECCO/ESPGHAN consensus guideline states that exclusive enteral nutrition (EEN) should be considered as a first-line induction agent [24]. There is an ever-expanding body of literature supporting the efficacy of EEN in inducing remission in CD, and as patients and their families continue to search for alternatives with increased efficacy and decreased toxicity, variants of nutritional therapy as it exists currently are likely to develop either as primary or supplementary treatment options. There are barriers both from patients and healthcare providers preventing more widespread adoption of EEN, but attempts to increase its palatability are in progress. A recent retrospective report from the Children's Hospital of Philadelphia demonstrated the efficacy of their maintenance protocol in which patients were allowed to consume up to 10–20% of calories by way of regular diet with 65% achieving remission [25]. Another study suggested favorable medium-term benefits of EEN induction versus steroid induction in patients subsequently started on early thiopurine therapy [26]. In line with earlier discussion regarding the inflammatory nature of CD at the time of diagnosis in children as well the impact of that inflammatory milieu on growth, data from the above described RISK study indicated that early use of anti-TNF monotherapy (within 3 months of diagnosis) positively affected height z- scores at 1 year follow-up while monotherapy with immunomodulators was no more effective than no early therapy [27]. Despite these evolving medical therapies, surgical intervention to assure growth remains a clinical reality in some cases. This is best utilized in children with persistent growth failure and an isolated area of refractory disease [28].

Cost of Care

It should be mentioned that as the role of biologic therapies in IBD treatment has increased, a substantial portion of the cost of IBD care has moved from surgery and hospitalization to pharmacotherapy. In the ever-changing healthcare landscape, it would be prudent for healthcare professionals to bear in mind the increasing financial burden being placed on the patient. The costs to the system are higher for children than adults which likely reflects the greater disease severity [29]. One study looked at expected yearly out-of-pocket (OOP) costs for patients with IBD and estimated it at about $1600, or nearly double what someone without IBD might be expected to pay [30]. Another study looked specifically at OOP costs for pediatric patients with IBD and found a range, but about 5% pay over $5000 annually [31]. These costs are likely compounded by indirect costs including missed work for the parents and school for the child, and potentially lengthy commutes to get to their IBD center.

Health Maintenance

Anticipatory management, routine health maintenance, and psychosocial wellness are vital in the care of all pediatric patients, especially those with chronic medical conditions. The health-related quality of life (HRQOL) has been used to broadly assess the impact of disease on overall wellness. Not surprisingly, chronic illness in general has been shown to negatively affect HRQOL, but several factors stand out in the pediatric IBD population. Even without IBD, adolescents often deal with issues of acceptance, social isolation, and changes in physical appearance, all while approaching physical and psychological maturation; IBD can, and often does, adversely impact each of those areas and in so doing negatively affects HRQOL [32–34]. While that is often an unfortunate reality of pediatric IBD, there are ways of curbing the negative impact of disease. To start with, good healthcare beginning with physician availability and open communication with education may alleviate unwarranted disease-related concerns and help prevent unnecessary emergency-room visits. As will be discussed regarding transition of care, creating an environment for self-management furthers coping abilities and often helps to enable function despite symptoms. There is often a role for specific psychotherapy which must be individually tailored, but simple measures such as discussing the importance of exercise and proper sleep hygiene may yield significant clinical benefit. Finally, peer support may help with disease acceptance and management. Many centers have active support groups for both families, children and teens, while Camp Oasis, a terrific resource which is sponsored by the CCFA, is an example of how the greater IBD community can help in creating an environment for peer support [32, 35].

Standard guidelines for vaccination schedules should be adhered to, and histories of prior vaccinations should be obtained from the referring primary provider [36]. Many patients with inflammatory bowel disease will eventually meet the criteria for being immunocompromised, and as such attention must be paid to administer

any live-virus vaccines prior to initiation of immunosuppressive agents. Recommendations are to wait at least 3 weeks following the administration of a live-virus vaccine before commencing immunosuppression. While this often creates therapeutic challenges, it is one more reason to consider EEN induction to create a window for vaccine administration [37]. The presence of induced immunosuppression would also warrant receipt of the pneumococcal vaccine. Most children vaccinated before 2010 received the standard pneumococcal conjugate vaccine (PCV7)), but since then an improved vaccine has become standard – the PCV13. It is recommended that those who are immunocompromised and who have only received the PCV7 should receive the PCV13 in addition to the pneumococcal polysaccharide vaccine PPSV23. Checking the status of hepatitis B, varicella, and potentially Epstein-Barr virus when thiopurines are being considered is also reasonable. As the risk of skin cancers, melanomatous and nonmelanomatous lesions, are seen with increased frequency in IBD, especially those on immunosuppressive therapy, it is crucial to educate patients on the risks of sun exposure, and to provide reinforcement of the need for adequate skin coverage and the use of sunblock.

Cancer risk associated with exposure to diagnostic radiation is an equally important topic for pediatric and adult gastroenterologists. Radiation exposure from a typical CT-scan of the abdomen is about 8 mSv; one group looked at the cumulative effective dose (CED) of radiation its patients were exposed to and identified a relatively modest amount, 6%, had a CED of greater than 50 mSv which is considered the dose at which there is reasonable evidence suggesting an increased cancer risk [38]. However, the mean exposure was about 18 mSv, and the authors stressed the absence of data to suggest a truly safe amount of radiation exposure [39]. The cumulative risk of cancer related to diagnostic radiation to age 75 is estimated at 0.6–1.8% [40]; this may reflect a nominal risk for those starting down a path of frequent medical imaging in their 30s, but the risk is certainly magnified in a 10 year-old. The cumulative radiation exposure in children with IBD was looked at by Sauer et al., who found that in those patients for whom 3year follow-up was available, 60% would achieve a CED of greater than 50 mSv by age 35 [41]. Recognizing the particular risk to pediatric patients of decades of potential exposure to radiation, special care must be taken to avoid exposure where possible. The emergency room (ER) is one of the most common places for IBD patients to undergo computed tomography (CT) and there should be communication between the ER and physicians caring for IBD patients to limit the frequency of those studies). Additionally, there should be an attempt to utilize nonionizing radiation, such as magnetic resonance imaging (MRI) and ultrasound where possible [42].

Genetic Considerations

The genetics of IBD are discussed elsewhere in this book and have become quite complex with over 200 loci having been associated with IBD. There have been relatively few GWAS looking specifically at the pediatric population, and while

there are some candidate loci including TNFRSF6B and PSMG1, the search continues to identify pediatric specific genetic markers [13, 43, 44].

Noninvasive means of diagnosing and monitoring IBD are being sought and would have an obvious appeal to the pediatric community as a means of limiting endoscopic procedures which may be quite difficult for children. Unfortunately, while there may be some relatively compelling data in adults supporting a higher sensitivity and specificity for serologic assays when utilized in an appropriate clinical population with a high positive pretest probability of disease, the same has not been true in pediatrics, and diagnostic guidelines have not embraced this strategy [45]. Perhaps part of the challenge in the pediatric population has been the recognition that some serologic patterns seem to vary with age: anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been shown to increase with age through the teenage years, while an antiflagellin antibody, anti-CBir1, has been shown to decrease with age [46]. While results are wanting in terms of supplanting the diagnostic role of endoscopy, there may be potential future utility for serologies in prognosticating disease course and severity [47–50].

Transition of Care

The need for appropriate transition of the young adult-patient from the pediatric to adult care team is important not only for the patient but also for the family and healthcare provider. There are currently both gaps and variability in the transition process, though it is universally accepted as an important step in maintaining appropriate patient care [51, 52]. The patient must be gradually introduced to topics that will ultimately result in greater independence including a complete grasp of their medications, as well as risks associated with certain behaviors such as alcohol and tobacco consumption. The pediatric gastroenterologist should reach out to contact the adult provider to ensure a smooth transfer of information. Ideally the transition would take place within a single institution to facilitate ease of communication and greater familiarity for the patient, but as that is not always feasible, an attempt should be made identify an adult liaison in the community. Helpful checklists for promoting adequate transition are available on websites including www.NASPGHAN.org.

Conclusion

Overall, pediatric-onset IBD has been shown to be more aggressive than adult-onset disease and this likely results from biologic factors including the greater amount of bowel affected in pediatric-onset disease. Specifically, the majority of pediatric patients with UC have pancolonic involvement, and about twice as many progress toward the need for colectomy. Pediatric CD similarly has a different presentation in terms of disease location with the majority of pediatric patients having small- and

large-bowel involvement. Pediatric CD tends to present with more of an inflammatory phenotype compared to a fibrostenotic presentation in adults. The inflammatory picture noted at onset in pediatric CD, seems to lend itself to more aggressive anti-inflammatory therapy that appears to modify disease progression away from fibrosis if addressed early and aggressively. Multicenter collaboration promises to rapidly advance the care of the pediatric IBD patient as pediatric-specific treatment goals that incorporate normalization of growth and development along with psychosocial wellness are optimized.

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Chapter 16
State of the Art and Future Predictions: "By the Way… I'm Pregnant"

Khadija H. Chaudrey and Sunanda V. Kane

New, Good Stuff and Your Predictions

Inflammatory bowel disease (IBD) affects women and men in their childbearing age. Outcomes of pregnancy are driven primarily by disease activity; therefore, remisson is vital at the time of conception and throughout pregnancy. Knowledge of the potential risks of continued medical therapy during pregnancy is extremely important. It is equally important to discuss this information with the patients for informed and shared decision-making. The data that are coming from prospective, population-based registries has been reassuring in terms of medication safety during pregnancy. Outcomes appear to be driven by disease activity, and therefore, it is essential to treat flares actively rather than taking a passive stance with pregnant women. Success rates of in vitro fertilization for those women with surgery have been encouraging, and studies on mode of delivery suggest that C-sections are not mandated and could be detrimental to women with IBD. Ongoing data collection with regard to developmental milestones and long-term outcomes of children born after intrauterine exposure to biologics has been reassuring. Availability of newer anti-integrin agents provides additional therapeutic options for IBD patients but pregnancy safety data have yet to be investigated in clinical practice.

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Introduction

IBD often afflicts individuals in their reproductive and childbearing years. This has implication on patients' sex life, fertility, pregnancy, and nursing. This chapter will encompass issues of sexuality and fertility in male and female patients with IBD. Additionally, management of IBD in pregnancy and lactation will also be reviewed.

Sexuality

Impaired sexuality is not uncommon in IBD patients. The etiology is multifactorial, including symptoms, altered body image, psychosocial factors, and altered anatomy due to surgery. Most common reasons interfering with sexual intimacy are diarrhea, fecal incontinence, abdominal pain, and dyspareunia [1]. Presence of fistulae, especially perianal disease, disfiguring from surgical scarring, and ostomy also negatively impact patients' sex life. Female gender and postoperative states have been identified as risk factors for perception of impaired body image leading to diminished sexuality [2]. Depression is prevalent in these patients, and this has been identified as one of the strongest psychosocial factors for significantly altered and decreased sexual function in IBD patients [3]. Unfortunately, these issues largely go unaddressed during patient visits. Physicians should take an initiative to discuss the issues of body image, sexuality, and depression so that appropriate referrals can be made to additional consultants like a psychologist or psychiatrist.

Fertility

The majority of patients with IBD are in their fertile and reproductive years, considering that 25% of IBD patient population is diagnosed before 20 years of age, and 50% are younger than 32 years of age at the time of diagnosis [4, 5]. Infertility is defined as a disease of the reproductive system causing the failure to achieve a clinical pregnancy after 12 months or more of regular, unprotected sexual intercourse [6]. In general, both male and female patients with IBD have fertility that is comparable to an age-matched general population. Infecundity, on the other hand, is the inability of a female to conceive due to structural or functional inadequacy of the genital system. Large population-based studies have shown that the infertility rate of IBD patients is 5–14% [7–9]. Voluntary childlessness in IBD patients is not uncommon [7, 10]. In a systematic review of fertility in medically treated IBD patients, there was a reduction in fertility in women with Crohn's disease (CD) as compared with controls, reported to be 17% vs. 44%. Similar reduction in fertility was noted in men with CD as compared with controls, reported to be 18% vs. 50% [11]. This was attributed to voluntary childlessness rather than involuntary infertility. Voluntary childlessness is driven by misconceptions about the outcomes of pregnancy in IBD [10].

Although the general IBD patient population has normal fertility, subgroups of patients may be at risk for reduced reproductive capacity due to medications, nutritional deficiency, weight loss, surgery, and underlying adhesions or fistulae that can result in impaired ovulation and tubal function. Pelvic inflammation leading to salpingitis, salpingo-oophoritis, and dyspareunia can cause infertility in patients with active disease [12, 13]. Decreased fertility in men from sulfasalazine is well-established secondary to reversible oligospermia, with reduced sperm motility and abnormal sperm morphology [14, 15]. Proctocolectomy in men can cause impotence or ejaculatory difficulties [16]. Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has been associated with dyspareunia and a reduction in fertility in females due to scarring and formation of adnexal adhesions [17, 18].

Effect of Pregnancy on IBD

The effect of IBD on pregnancy is most strongly determined by the disease state at the time of conception. If conception occurs when IBD is quiescent, the course of IBD is approximately the same as in nonpregnant patient per year, about 30% [19]. UC patients appear to be at higher risk of relapse compared to CD patients; prospective studies suggest that the relapse rate is about 20% in CD patients and 33% in UC patients who conceive during remission. These numbers are better than what had been reported in earlier studies [11]. The exact mechanism behind this difference remains unknown; however, different etiologies have been implicated. Pregnant females with CD quit smoking during pregnancy which may have beneficial effects on the course of pregnancy, or that placental cytokine production in UC patients and the shift from T helper 1 (Th 1) to T helper 2 (Th 2). Interestingly, if remission is achieved during pregnancy, it is likely to persist through the entire course of pregnancy thereafter. If disease is active at conception, then approximately two-thirds of patients will continue to have active disease or worsening disease course during pregnancy [20, 21]. The sequence of events occurring during one pregnancy does not dictate the course in subsequent pregnancies [22]. Of interest, one population-based study followed women for 10 years following pregnancy and reported that the state of pregnancy may be protective against disease activity in the long term. [23, 24] Decreased need of surgical intervention for IBD treatment in multiparous women suggests that multiple pregnancies may be protective against surgery. However, this may just be a reflection of conception by relatively healthier IBD patients who are able to have multiple pregnancies despite the diagnosis of IBD [23].

Effect of IBD on Pregnancy

Pregnant IBD patients with inactive disease at the time of conception and during pregnancy have fetal outcomes comparable to the general population [25]. If the disease is active at the time of conception, then there is risk of fetal loss and preterm

birth [19, 26]. Active disease during pregnancy has been associated with intrauterine growth retardation, preterm birth and low birth weight [27–29]. A population-based Danish study reported that in women with moderate to severely active disease the crude risk of preterm birth was increased with an OR of 3.4 [30]. However, a Northern California-based Kaiser population study, including patients with moderate to severe disease, was not predictive of an adverse outcome [31]. There is no increased risk of congenital abnormalities in the IBD patient population. Studies that report organ-specific congenital abnormalities affecting heart, limbs, or urogenital system, have shown inconsistent statistical variations and no uniform increase has been implicated [32]. Ileal CD and previous bowel resection have been associated with poor outcomes; therefore, it is highly advisable for a patient to conceive when in remission and maintain remission throughout the pregnancy.

Medications During Pregnancy

Medication counseling is of vital importance in IBD patients during preconception period, pregnancy, and lactation. Patients may change or discontinue medication if not properly educated, leading to disease relapse which can have detrimental maternal and fetal outcomes. While previously the US Food and Drug Administration (FDA) classification of drugs was the accepted guide to the safety of medications during pregnancy (Table 16.1), more recently the government has mandated specific discussion of risk and benefit based on available animal and human data. Table 16.2 delineates pregnancy ratings from the historical system.

Table 16.1 US food and drug administration categories for medication use in pregnancy

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in the later trimesters
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

Table 16.2 Pregnancy categories of medications used in IBD patients

Name of drug	Pregnancy category
Methotrexate	X
6-Mercaptopurine Azathioprine	D
Corticosteroids Cyclosporine Tacrolimus Asacol HD Olsalazine	C
Sulfasalazine Mesalamine Balsalazide Infliximab Adalimumab Golimumab Certolizumab pegol Natalizumab Vedolizumab Corticosteroids	B

Aminosalicylates

As a class, this includes sulfasalazine, mesalamine, balsalazide, and all category B drugs. Olsalazine and Asacol HD are category C. Olsalazine has a dearth of pregnancy data and thus rated C; Asacol HD has a FDA warning with regard to its tablet coating which contains dibutyl phthalate, a chemical associated with urogenital malformations in male offspring [33]. In lab studies, amounts given to rodents were 40 times that of therapeutic doses in humans, but because of the lack of controlled safety data in humans, the labeling has been changed. Sulfasalazine has antifolate effects; therefore, daily folate replacement (1 mg twice daily) is recommended in all IBD patients. Sulfonamides displace bilirubin from serum albumin and cause kernicterus; however, this has not been observed with sulfasalazine likely because sulfapyridine has poor bilirubin-displacing ability. As mentioned earlier, sulfasalazine has been clearly associated with reversible infertility in men due to abnormalities in sperm count, motility, and morphology. This effect is not seen with mesalamine use, and semen quality is reported to be normal. Sperms have a lifespan of 120 days, so men considering conception are advised to stop taking sulfasalazine or change over to mesalamine 3 months before attempting conception.

A prospective controlled trial of 165 women exposed to mesalamine compared with matched controls with no exposure showed no teratogenic risk in humans when used in the recommended doses [34]. In addition, a population-based Danish cohort study of mesalamine use in pregnancy did not suggest any increased risk of fetal malformations, even though there was an increased risk of stillbirth and preterm birth in women prescribed 5-ASA drugs during pregnancy, the effects of disease activity versus 5-ASA exposure were indistinguishable [35]. Several other

studies have not found significant association between 5-ASA drugs and adverse pregnancy outcomes [30, 34, 36–39].

Mesalamine use is safe during breastfeeding [40, 41]. Sulfasalazine is excreted in breast milk with sulfapyridine concentrations are as high as ~30–60% of the maternal serum; however, the use of sulfasalazine is considered to be safe while breastfeeding [31, 40, 41].

Antibiotics

The most commonly used antibiotics in the IBD population are ciprofloxacin and metronidazole, which are category C and B respectively. Controlled prospective observational data from 200 fluoroquinolone-exposed human pregnancies demonstrated the rate of major malformations was in the range of 1–5% comparable to controls. Ciprofloxacin was used in 52.5% of these patients, and 68% were treated during the first trimester [42]. In utero exposure to fluoroquinolones has not been associated with clinically significant major musculoskeletal dysfunctions [43, 44]. Metronidazole exposure has been associated with cleft lip with or without cleft palate following first trimester exposure to metronidazole; however, most studies have not shown an increased risk of congenital anomalies or other adverse events including infant cancer following maternal use during pregnancy [45–48]. However, because of the limited evidence of the effectiveness of these agents in treating inflammatory bowel disease and the extended duration of use for the treatment, these drugs should be avoided during pregnancy unless the benefit clearly outweighs the risk. Short-term use for the treatment of pouchitis is reasonable but amoxicillin-clavulanic acid, a category B drug, can be used as an alternative antibiotic during pregnancy for pouchitis.

Metronidazole is excreted into breast milk and thus breastfeeding should be withheld for 12–24 h following a dose of metronidazole [49]. Its use in IBD patients often warrants every 8 h dosing; therefore, a risk-and-benefit assessment should be taken into account and an alternative should be used if possible. Ciprofloxacin is excreted in breast milk; however, its levels in infants are undetectable [50]. Quinolones are therefore low risk to use if necessary. Amoxicillin-clavulanic acid is safe to use during pregnancy.

Corticosteroids

Corticosteroids are category C drugs. Glucocorticoid use during first trimester of pregnancy has been associated with increased risk of oral cleft in neonates [12, 51, 52]. An older meta-analysis reported an odds ratio (OR) for case–control studies examining the risk of oral clefts in any diagnosis requiring steroid use (OR: 3.35; 95% CI: 1.97–5.69). However, for major malformations, the overall risk was low (OR: 1.45; 95% CI: 0.80–2.60) [53]. A prospective controlled study of 311 women

who received glucocorticoids during the first trimester did not show an increased rate of major anomalies, and cases of oral cleft were not noted [54]. Overall, the use of corticosteroids portends only a small risk to the developing fetus when needed to treat moderate-to-severe disease [30]. A small retrospective case series of patients with IBD treated with budesonide during pregnancy did not document congenital malformations or an increase in adverse outcomes [55].

Use of prednisone and prednisolone during breastfeeding is considered safe, while data about budesonide is unclear.

Immunomodulators

Immunomodulators are the most controversial drugs used to treat IBD in pregnant women.

Methotrexate

Methotrexate is a category X drug. It is a teratogen and an abortifacient. Its use is contraindicated women and men who are considering conception. Methotrexate is a folic acid antagonist and its use during 6–8 weeks post conception is associated with methotrexate embryopathy or fetal aminopterin-methotrexate syndrome [51, 52]. Exposure during the period of organogenesis is associated with multiple congenital anomalies as intrauterine growth retardation, decreased ossification of the calvarium, hypoplastic supraorbital ridges, small low-set ears, micrognathia, limb abnormalities, and mental retardation. Exposure in the second and third trimesters may be associated with fetal toxicity and loss. Methotrexate may cause reversible oligospermia in men. No controlled data has been published on congenital anomalies occurring in the offspring of men receiving methotrexate therapy. Methotrexate can persist in human tissue for long periods, so it is suggested that patients wait at least 3–6 months after discontinuation of treatment before attempting conception [12]. Methotrexate is also contraindicated during breastfeeding given high concentrations in breast milk [49].

Azathioprine and 6-Mercaptopurine

6-Mercaptopurine (6MP) and its prodrug azathioprine are category D drugs. Animal studies have demonstrated teratogenicity characterized by increased frequencies of cleft palate, open-eye and skeletal anomalies in mice exposed to azathioprine and cleft palate and skeletal and urogenital anomalies in rats [56]. While transmission of azathioprine and its metabolites from the mother to the fetus has been established, levels have not been associated with any increased risk of congenital abnormalities, preterm

birth, low birth weight, or fetal adverse outcomes [57–61]. The oral bioavailability of azathioprine (47%) and 6-mercaptopurine (16%) is low, and the early fetal liver lacks the enzyme inosinate pyrophosphorylase needed to convert azathioprine to 6-mercaptopurine. Both features may protect the fetus from toxic drug exposure during the crucial period of organogenesis. The largest evidence on safety comes from transplantation studies where rates of congenital anomalies ranged from 0% to 11.8% without recurrent patterns [56]. A large prospective Crohn's and Colitis Pregnancy Registry: Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry of women with IBD exposed to immunomodulators has not found association with the use of immunosuppressants with congenital anomalies, newborn growth and developmental abnormalities, or fetal complications [10]. Similar results have been reported by one of the largest studies for azathioprine use in pregnant IBD patients, Cancers et Surrisque Associé aux Maladies Inflammatoires Intestinales En France (CESAME) [59]. Thiopurine use during pregnancy was not associated with significant differences in overall pregnancy outcomes such as spontaneous abortion, preterm labor, or increased risks of congenital abnormalities. An early study with 6MP suggested that use during pregnancy was actually protective against an adverse outcome, presumably by keeping the mother in remission [58].

A meta-analysis found no link between thiopurine exposure in men at the time of conception with congenital abnormalities despite some conflicting data from previous studies [57, 62–64]. Older studies suggested concern about the possible toxicity with azathioprine and 6MP in the nursing infant so breastfeeding was not recommended [65]. Several newer studies measuring azathioprine levels in breast milk have found trivial or undetectable levels. Successful breastfeeding has been accomplished on azathioprine without any hematologic or clinical immunosuppression [66–68]. Eight nursing women on AZA maintenance therapy had milk and plasma samples measurements at 30 and 60 min and then hourly for the following 5 h after drug administration [69]. Milk levels were noted to be highest at 4 h interval after oral ingestion of drug, but otherwise drug levels are below the detectable threshold. Therefore, it is recommended to wait 4 h after drug intake to breastfed or night-time administration of drug with pumping and dumping of breast milk 4 h later to minimize any newborn exposure [4].

Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus are both Category C drugs. Cyclosporine has been successfully used in steroid refractory ulcerative colitis as well as in the pregnancy patient [70, 71]. Data from transplant patients shows an increased rate of low birth weight babies, higher incidence of maternal diabetes, hypertension and preeclampsia with use of cyclosporine [72]. Cyclosporine use does not appear to impact male fertility [73]. The use of tacrolimus is limited in IBD with reports of perinatal hyperkalemia and prematurity with its use [74]. Compared to cyclosporine, tacrolimus tends to cause less maternal hypertension and hyperlipidemia, but there is a higher incidence of neonatal diabetes [52].

Cyclosporine is excreted into breast milk in significant concentrations and is generally not recommended during breastfeeding [75]. Tacrolimus has low bioavailability following oral absorption that may also decrease the amount of exposure to a nursing infant the manufacturer recommends that nursing be discontinued in general [76–78].

Biologic Therapy

Antitumor necrosis factor inhibitors, including infliximab, adalimumab, certolizumab pegol, and golimumab, are FDA approved to treat moderate to severe ulcerative colitis and CD and all category B therapies. The anti-integrins – natalizumab and vedolizumab – are category B therapies as well.

Infliximab is an IgG1 chimeric monoclonal antibody that is 25% mouse and 75% human with an Fc component. It does not cross the placenta until after week 20 of gestation, at which time organogenesis has already occurred [79]. Placental transfer of infliximab has been detected at week 24 with 80% of the transfer occurring in the third trimester [80, 81]. The median level of infliximab in cord blood has been measured to be 160% that of the mother and can take up to 3–6 months to clear [82]. Infants exposed to intrauterine infliximab therapy should avoid exposure to live vaccinations for at least the first 6 months of life. In the United States, the only live vaccine given during this period is rotavirus; in developing countries, tuberculosis vaccine is commonly administered and should be avoided.

Cumulative evidence from case series and patient registries demonstrate the safety of infliximab during pregnancy [83, 84]. The Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry is a prospective registry of more than 6200 CD enrolled patients with 168 reported pregnancies [85]. Of these, 117 were exposed to infliximab. There was no difference in the rates of miscarriage (10% vs. 6.7%) and neonatal complications (6.9% vs. 10%) between those treated with infliximab vs. those who were not. Retrospective data from the FDA mandated Infliximab Safety Database reported on 96 women (82 CD, one UC, ten rheumatoid arthritis, and three unknown) with direct exposure to infliximab who gave birth to 100 infants [86]. Pregnancy outcomes in these women were comparable to US population of pregnant women and pregnant women with CD not exposed to infliximab.

Adalimumab is also an IgG1 monoclonal antibody that is 100% human with an Fc component. The median level of adalimumab in cord blood has been measured to be 153% of that of the mother [82]. The Organization of Teratology Information Specialists (OTIS) has described outcomes in 38 prospectively enrolled adalimumab-exposed pregnant patients with various diagnoses and a case series of 133 adalimumab-exposed pregnancies [87, 88]. The risk of stillbirth, miscarriage, preterm delivery, and rates of congenital malformation are similar to those reported in the IBD group and general population. Biweekly or weekly dosing can make it challenging to decide when cessation of drug may be ideal.

Certolizumab is a pegylated Fab' fragment of IgG 1 antibody against tumor necrosis factor. The median level of certolizumab measured in cord blood is reported to be 3.9% of that of the mother and less than 2 microgram/ml [82]. It can be safely continued throughout the pregnancy, without a need of cessation in pre- or peripartum.

Golimumab is a human anti-TNFα IgG1 monoclonal antibody approved for refractory moderate to severe ulcerative colitis. The safety profile of golimumab has been similar to other anti-TNF drugs and no significant toxicity has been reported to date. Overall, golimumab is considered safe during pregnancy [51, 89–92].

Men considering conception should continue anti-TNF therapy to control disease activity. Infliximab treatment in males has been noted to decrease sperm motility and morphology [93, 94]. However, the impact of these findings on fertility remains to be examined further. No increase in congenital anomalies of children fathered by men on infliximab has been reported [86].

Insignificant amounts of anti-TNFs have been detected in breast milk, and no significant toxicity has been reported [95]. Infants that have been breastfed while mother was receiving anti-TNF have done well over time without reported toxicity [83, 96].

Though it is currently recommended that anti-TNFs, except certolizumab, be stopped at the onset of the third trimester, women with quiescent IBD who discontinued anti-TNF therapy by week 30 still had detectable anti-TNF levels in cord blood [97–99]. The exact time to withhold anti-TNF prior to delivery is now becoming debatable, especially in high-risk patients where consideration should be given to continue therapy throughout the pregnancy [100]. Cessation of anti-TNF therapy does not lead to an increased risk of disease activity or adverse reactions upon reinitiation after delivery [95]. Current short-term follow-up of children exposed to intrauterine infliximab shows normal development without increased infections, allergic reactions, or decreased response to vaccinations [97]. On the contrary, infants exposed to immunomodulators and biologics combination have been noted to have increase in infections from 9 to 12 months of age [10]. Current recommendations include consideration of disease activity around week 20. If it is clear that treatment is controlling disease and the mother requires continued therapy to control disease activity, then treatment through the remainder of the pregnancy is warranted. If a mother is in remission and treatment is for maintenance, therapy can be held, and if there is a flare, she could be treated with steroids or delivery [80, 101–103].

Natalizumab is a monoclonal antibody of the IgG4 class directed against alpha integrins and carries an FDA category B rating. Vedoluzumab is an IgG1 agent that blocks the $\alpha_4\beta_7$ integrin resulting in gut-selective antiinflammatory activity and is also a category B therapy. Placental transfer of vedolizumab is considered to be similar to all other IgG1 therapeutic antibodies and increases in a linear fashion as pregnancy progresses, with the largest amount anticipated to transfer during the third trimester. There are no controlled studies with vedolizumab in pregnant women; however, analysis of data from the vedolizumab clinical development program provides some early data [104]. Among the 16 vedolizumab exposed partner pregnancies, there were 9 live births, 2 spontaneous abortions, 2 elective terminations, and 3

undocumented outcomes at the last follow-up. Of the 24 vedolizumab treated females, 11 resulted in live births, of which 2 were premature. A congenital anomaly of agenesis of the corpus callosum was reported in the healthy volunteer with an obstetric history of 2 spontaneous abortions and 1 ectopic pregnancy who had received a single dose of vedolizumab 79 days prior to the estimated date of conception. The safety of vedolizumab during breastfeeding remains to be established.

Safety of Diagnostic Evaluation

Radiographic studies should be avoided in pregnant IBD patients to minimize exposure to ionizing radiation unless absolutely necessary and when an alternative is not available. Fetal susceptibility for teratogenicity secondary to ionizing radiation is greatest at exposure between 2 and 20 weeks gestation above an estimated 0.15 Gy threshold [105]. Iodinated contrast exposure has been theoretically implicated in fetal hypothyroidism with exposure; however, more recent studies do not verify this association [106]. Magnetic resonance imaging (MRI) is the best and preferred imaging modality of choice for any pregnant patient. Gadolinium used during MRI is teratogenic in animal studies and should be avoided in the first trimester [107].

Endoscopic evaluation might be clinically warranted in a subset of pregnant IBD patients. If possible, endoscopy should be deferred until the second trimester [108]. Unsedated flexible sigmoidoscopy is the lowest-risk procedure and may be adequate for disease assessment, diagnosis, or tissue acquisition to rule out CMV infection [108]. For pain control, meperidine, a category B drug, is preferred over fentanyl which is category C. Midazolam is category D and should be avoided. Monopolar cautery poses more risk than bipolar cautery, and a grounding pad must be placed away from the uterus.

Mode of Delivery

Obstetric necessity dictates the mode of delivery in IBD patients. A subset of IBD patients that should undergo C-section includes patients with active perianal disease and rectal involvement with CD [109]. C-section can be a consideration for patients with an ileal pouch-anal anastomosis; however, data on pouch function after vaginal delivery is reassuring [110].

Surgery

IBD-related complications such as perforation, intraabdominal abscesses, and obstruction may warrant surgery on pregnant patients. Preterm labor and spontaneous abortion from likely inadvertent uterine manipulation during surgery have been reported; however, complications are rare [12, 70, 111].

Summary

- IBD affects women and men of childbearing age and therefore has implications on fertility, pregnancy, and nursing.
- Patients with quiescent IBD disease have fertility comparable with the general population. However, fertility in patients with IBD may be affected by disease activity, medications, prior surgery, and nutritional status.
- If conception occurs at the time of remission, then patients are likely to remain in remission during pregnancy. On the other hand, up to 70% of patients with active disease at conception are likely to have continued or worsening symptoms during pregnancy.
- The choice of therapy and its continuation during pregnancy and lactation should be based on safety as well as the risk of relapse of the disease if the medications were to be discontinued.
- Data suggest that pregnant females with ulcerative colitis have more disease activity during pregnancy than women with CD.
- Endoscopy should be performed during pregnancy only if medically necessary. MRI is the preferred diagnostic modality in pregnant patients with IBD.
- Patients with perianal disease or rectal involvement with CD should undergo a C-section; otherwise, obstetric necessity dictates the mode of delivery.
- Surgery is associated with premature labor or spontaneous abortion; however, complications are rare.

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Chapter 17
Update on the Surgical Treatment of Inflammatory Bowel Disease

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Key Points

- The rate of surgical intervention for Crohn's enteritis is decreasing.
- There is no anastomotic technique that is clearly superior in preventing surgical recurrence in Crohn's disease.
- Resection margin in Crohn's disease should be to macroscopically normal bowel.
- Crohn's disease is still widely regarded as a contraindication to ileoanal reservoir construction.
- Strictureplasty techniques are important bowel-sparing maneuvers in treating primarily jejuno-ileal Crohn's disease. The role of this technique in large-bowel stricture is not well defined.
- Segmental colectomy is appropriate for anatomically focal Crohn's colitis. Diffuse or multifocal Crohn's colitis in the absence of rectal disease is best approached with subtotal colectomy.
- When feasible, the laparoscopic approach is preferred owing to improved time to recovery and decreased complication rate. The benefit of robotic approach over laparoscopic approach remains to be defined.
- Combined medical and surgical therapy for perianal Crohn's disease can help patients achieve clinical healing and symptomatic control, but disease recurrence is frequent.
- Total proctocolectomy with or without ileal pouch-anal anastomosis is standard of care for ulcerative colitis patients requiring surgery.
- The presence of colon cancer or dysplasia in a patient with ulcerative colitis may impact the choice of surgical technique and increase the need for endoscopic surveillance of the ileoanal pouch.

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- Inflammatory bowel disease patients can thrive on an enhanced recovery protocol, as long as sufficient ancillary support is available to ensure a safe care transition home. Special circumstances including chronic pain and formation of a new ileostomy can put IBD patients at higher risk for readmission.

Introduction

Over the past four decades, patients with Crohn's disease and ulcerative colitis have benefitted from advancements in the medical management of inflammatory bowel disease (IBD), most notably the development of novel biologic therapies [1, 2]. However despite these medical advances, relapse of inflammatory bowel disease remains frequent, and a substantial number of patients still require surgery at some point in their life [3, 4]. Surgical management of ulcerative colitis can be considered curative after total proctocolectomy (TPC). In contrast, surgical treatment of Crohn's disease is palliative and aimed to resect grossly diseased tissue, relieve intestinal obstruction, and address fistulae or septic sequelae of the disease. While these basic surgical tenets have not changed, surgical innovations continue to improve upon perioperative outcomes and, in Crohn's disease, potentially impact disease recurrence. This chapter will review the current surgical approaches to inflammatory bowel disease patients, with specific emphasis on the application of novel techniques.

Surgical Management of Crohn's Enteritis and Crohn's Colitis

Surgery is not a cure for Crohn's disease. In the prebiologic era, Crohn's was described as a "relentless disease" with upward of 90% of patients requiring abdominal surgery within 10 years of their diagnosis, most often for obstruction or other acute complications [5, 6]. Reoperation rate in the prebiologic era due to surgical recurrence was 36–54% by 10 years [7]. Some contemporary centers reported lower incidence of abdominal surgery in the prebiologic era at 40–55%, with significant geographic variability [8, 9]. Several population-based cohorts have attempted to describe the impact of improved medical therapy on rates of intestinal resection. In one cohort out of Cardiff, UK, rates of resection fell dramatically from 1996 to 2003, temporally associated with early thiopurine use [10]. Other studies also support that the rate of surgery was falling in the prebiologic era [11].

The impact of biologic therapy with the introduction of infliximab in the late 1990s is not yet clear; two studies from Ireland and the United States indicate biologic therapy has not impacted rates of initial intestinal resection [12, 13]. A Danish study accruing completely in the postbiologic era report a 29% risk of intestinal resection over 7 years; whether this is due to improved medical therapy with earlier

application of biologic therapy in the disease course ("Top-Down" approach), less aggressive surgical approach, or better diagnostic modalities is ambiguous [14].

Emergent or urgent surgery is required in cases of acute severe Crohn's colitis and enteritis with suspected free perforation, peritonitis, symptomatic fistula, non-resolving abscess or phlegmon, complete small-bowel obstruction, hemorrhage, or in those who fail attempted induction therapy [15]. Elective surgical intervention is warranted in patients with steroid dependency or failed medical therapy, those with symptomatic fibrostenotic disease, dysplastic change, growth retardation, or neoplasia [16]. Intestinal resections with anastomosis, strictureplasty, and perianal exam under anesthesia are the most commonly performed procedures for Crohn's enteritis and colitis.

Intestinal Resection and Anastomosis

The most frequent surgical procedure for Crohn's disease is ileocolectomy or right colectomy, paralleling the most common site of disease at the terminal ileum. These resections comprise around 50% of all initial resections for Crohn's disease. Ileocolic resection entails removal of the terminal ileum and cecum with anastomosis of the remaining ends of the bowel to create the neoterminal ileum. Resection with anastomosis is also a valuable strategy for treatment of limited disease affecting the small intestine and colon.

Division of the thickened mesentery is often the most challenging technical aspect of small-bowel resection for Crohn's disease. Tissue-sealing instruments such as LigaSure® or EnSeal® devices have provided greater ease for this task over the standard clamping and suture ligation of the mesenteric vessels. Both of these devices use the principles of bipolar electrocautery in a manner that is capable of sealing blood vessels of substantial size.

Various anastomotic techniques are available in the surgeon's armamentarium. Anastomoses may be hand-sewn or stapled and may be constructed in an end-to-end, end-to-side, or side-to-side configuration. There is no study that considers all configurations in head-to-head comparison. The most frequently studied configurations are stapled side-to-side functional end-to-end versus sutured end-to-end anastomosis. Early single-institutions studies [17–20] suggested increased rate of complications and surgical recurrence in sutured end-to-end technique. Sutured side-to-side functional end-to-end approach appears similar to the equivalent stapled configuration [21]. Two metaanalysis with slight variation in trial inclusion concluded stapled side-to-side functional end-to-end anastomosis was equivalent or slightly favored in terms of complications, and slightly favored in terms of surgical recurrence, as compared to sutured end-to-end anastomosis [22, 23]. A recent multicenter randomized controlled trial of 139 patients compared sutured end-to-end technique with stapled side-to-side functional end-to-end technique. Leak rate was 7% in each group. There was no difference in symptomatic or endoscopic recurrence [24]. Surgeons have their own anecdotal feelings about anastomotic approach in

Crohn's. Some advocate for the hand-sewn approach to better control for variability in bowel-wall thickness.

In over 70% of Crohn's patients experiencing surgical recurrence, it is just proximal to the site of previous anastomosis [25]. The Kono-S antimesenteric anastomosis, developed in 2003, is a hand-sewn antimesenteric side-to-side functional end-to-end configuration. The closed ends are sutured together, creating a column of tissues to support the diameter and dimensions of the anastomotic lumen and to reduce the tension and torque placed on the anastomosis. This anastomotic technique is based on the principle of recurrence originating at the mesenteric side of the lumen; inflammation and ulceration result in anastomotic deformity requiring surgical revision and is mechanically prevented by the supporting column [26]. In addition, the mesentery is divided close to the bowel lumen to preserve neuronal and vascular arcades.

In one case series with recent update, 96 patients underwent Kono-S anastomosis; at mean follow-up of 22.8 months (3.0–53.9 m), 65% of patients had undergone endoscopic surveillance with an average Rutgeerts score of 0.71, suggesting efficacy in prevention of surgical recurrence in the short term [27, 28]. Another series of 30 patients out of Japan demonstrated similar short-term outcomes [29]. The surgeons involved in these series had their first case instructed by Dr. T. Kono. At this time the Kono-S technique is considered investigational; the efficacy of this technique in lowering the rate of anastomotic recurrences is being further evaluated in an ongoing randomized controlled trial accruing in the United States and Japan.

The extent of surgical resection should be to macroscopically normal bowel in order to preserve bowel length. Frozen section should not be used for intraoperative histologic analysis [30, 31]. A well-conducted randomized controlled trial out of the Cleveland Clinic comparing extended (12 cm) versus limited (2 cm) margin did not demonstrate a difference in recurrence rates, and recurrence did not correlate with microscopic disease in the specimen margin [32].

Ileal Pouch-Anal Anastomosis in Crohn's Disease

Crohn's disease is still widely considered a contraindication to restorative ileal pouch-anal anastomosis (IPAA). Dr. Y. Panis et al. reported on a series of patients with Crohn's disease limited to the colon and without perianal disease that underwent ileal pouch-anal anastomosis. This group reported a 10% rate of pouch excision, which persisted in a long-term follow-up analysis at 10 years [33, 34].

Unfortunately, this low rate of pouch loss has not been seen in other reports. Hyman et al. examined a cohort of 25 patients with preoperative diagnosis of mucosal ulcerative colitis who underwent TPC with IPAA and had histologic evidence of Crohn's disease on final pathologic analysis, defined as transmural inflammation, fissuring ulcers, neuromatous hyperplasia, submucosal edema, or granulomas. There was 28% rate of pouch excision at mean 38-month follow-up. Within this cohort, question of Crohn's was raised preoperatively in nine patients, and of these

only one maintained a functioning pouch [35]. Two contemporary series describe a 45% rate of pouch failure in patients with postoperative or delayed diagnosis of Crohn's disease [36, 37].

Ten-year follow-up at a US center demonstrates ~15% rate of pouch loss in patients with *preoperative* or *incidental* (final pathologic specimen) diagnosis of Crohn's but 50% pouch failure in *delayed* diagnosis of Crohn's disease with ~50% of the cohort experiencing pouchitis and 1/3 developing pouch fistula [38]. Risk factors for delayed diagnosis include younger age of symptom onset, history of mouth ulceration, anal fissure, and three-stage procedure – likely an indicator of disease severity obscuring histologic analysis [39]. Patients with earlier manifestations of Crohn's disease of the pouch within 3.6 years of construction and patients developing fistulizing disease were significantly more likely to suffer pouch failure [40]. In contrast, overall rate of pouch failure in ulcerative colitis is ~5%, with ~1/3 experiencing pouchitis and ~3% fistula rate [41].

In conclusion, a high degree of reservation should be exercised by the surgeon when considering intentional IPAA construction for patients with Crohn's disease. Patients who have isolated colorectal Crohn's disease with no history of perianal disease may be considered for the ileoanal procedure, but these patients must be appropriately counseled and they must be highly motivated for this approach.

Jejuno-Ileal Strictureplasty

Simple intestinal resection with anastomosis is the most common approach for isolated short-segment structuring Crohn's disease. The concept of bowel preservation becomes especially important in patients with extensive multifocal jejuno-ileal disease, long-segment stricture, and in those with new symptomatic structuring disease who have already undergone significant bowel resection in the past and require aggressive measures to preserve as much intestinal length as possible. In order to prevent the nutritional and metabolic consequences of massive small-bowel resection, bowel-preserving surgical techniques such as intestinal strictureplasty have been developed.

The choice of strictureplasty configuration used is dependent on the stricture length and location, and proximity to any nearby sites of disease. Currently, 15 published strictureplasty methods are in use, with Heineke-Mikulicz (H-M) and Finney strictureplasty overwhelmingly utilized due to their simple construction [42]. Originally intended for surgical treatment of duodenal peptic ulcers, H-M strictureplasty is best applied to strictures <5 cm in length. A single longitudinal enterotomy is made over and beyond the area of narrowing with a horizontal closure [42, 43]. Two short strictures in close proximity may be treated with a single H-M strictureplasty. The area of the lumen just proximal and distal to the completed strictureplasty is naturally compromised due to alterations in regional geometry; for this reason sequential completed strictureplasty sites should be no closer than 3 cm apart to avoid flow limiting luminal narrowing of the intervening bowel [44].

For 5–12 cm strictures, Finney strictureplasty is preferred. This technique utilizes a longitudinal antimesenteric incision with folding of the bowel in a U- or hairpin-configuration.

Advanced strictureplasty techniques are considered for longer segment strictures. Dr. F. Michelassi developed a side-to-side isoperistaltic strictureplasty technique in 1992. This technically demanding approach is appropriate for very long areas of structuring disease or to address multiple sequential strictures into one strictureplasty. The bowel is divided at the midpoint of disease. The proximal end is drawn over the distal end in a side-to-side fashion, taking care to align areas of stricture with areas of dilatation. A lengthy hand-sewn side-to-side anastomosis is then performed in two layers. The ends of the bowel are tapered to avoid a blind end. In a multiinstitutional aggregate analysis, overall complication rate at several high-volume centers ranged from 5% to 10% with 22% rate of surgical recurrence at mean 3-year follow-up [42, 43, 45].

Perioperative morbidity with strictureplasty has proven to be low [46]. The most common complication directly attributed to strictureplasty is intraluminal suture-line hemorrhage. Some degree of suture-line hemorrhage occurs in up to 9% of cases with half of these resulting in the need for transfusions in excess of three units. Bleeding severe enough to require reoperation is very uncommon and occurs in less than 1% of cases [47]. Poor healing with suture-line leakage is a more serious, but infrequent complication and occurs in 1–2% of strictureplasty cases. When suture-line dehiscence occurs, reoperation with resection of the strictureplasty and establishment of a temporary ileostomy is often required.

The surgical recurrence rate after strictureplasty is ~30% [48–50]. Given that strictureplasty is bowel conserving, even equivalent recurrence rates to resection could be considered favorable in the long term. In contrast to anastomotic recurrence after resection, recurrences after strictureplasty rarely involve the strictureplasty segment; site-specific reoperation rate is as low as 3% [18]. Strictureplasty may induce disease regression, potentially due to the relief of the intestinal stasis and hence inflammation; the mechanism for this has not yet been elucidated [51]. Much has been said about the risk of leaving diseased tissue in-situ, and the surgeon should be vigilant to biopsy any suspicious sites at the time of strictureplasty. The absolute rate of malignancy in Crohn's small-bowel stricture is <1%, and is largely limited to case reports [52].

Strictureplasty is also well tolerated in select instances of active disease. Recently a modified Michelassi strictureplasty across the ileocecal valve has been employed as the primary treatment for Crohn's terminal ileal disease. Postoperative endoscopic assessment demonstrated remarkable mucosal and bowel-wall healing. Only 1/29 patients went on to require conventional resection at 2 years follow-up [53]. Two patients required a "rescue" procedure to oversew a very early anastomotic leak. While compelling, the technical complexity of this approach probably precludes wide replacement of conventional ileocecal resection.

Strictureplasty is not appropriate for segments of intestine that contain fistulas, abscess, or deep sinuses. Additionally, if the bowel wall is extremely thickened and unyielding, standard strictureplasty techniques are not feasible. With all these

considerations, approximately 15% of patients undergoing surgical treatment for small-bowel Crohn's disease are appropriate candidates for one or more of the strictureplasty techniques.

Endoscopic Balloon Dilation

Endoscopic balloon dilation (EBD) has been employed for the treatment of isolated short-segment strictures, most commonly anastomotic strictures [54]. Technical success in dilating endoscopically accessible strictures is 70–100% with a low complication rate; patients may require repeat sessions to achieve initial clinical benefit. Need for reintervention is ~40% at mean 15 months follow-up, with 28–40% requiring surgery within 3 years [50, 55]. Stricture length of <4 cm is associated with a greater likelihood of technical success [56]. At this time, EBD may be a viable strategy to at least delay surgical intervention, particularly for anastomotic recurrence. The choice of strictureplasty versus EBD is heavily influenced by referral patterns, as colorectal surgeons primarily perform strictureplasty and advanced endoscopic interventionists perform EBD. Multidisciplinary team discussion is encouraged in these complex patients.

Colonic Strictureplasty and the Role of Segmental Colectomy in Crohn's Colitis

Few series report on the strategy of colonic strictureplasty, and nonanastomotic focal colorectal stricture is relatively rare in Crohn's disease. Though operative technique follows the same principles utilized for jejuno-ileal disease, the rationale for bowel preservation is less justified for the colon. In the only small case series on extension of this technique to Crohn's large-bowel stricture, surgical recurrence rate was 36%. This study did include patients with anastomotic stricture and ileocecal stricture [57]. There is no literature to directly support a higher rate of neoplasia in colonic-structuring Crohn's disease, though this is often a concern. Fumery et al. retrospectively assessed 248 Crohn's patients who underwent resection for colon stricture, with a 1.6% rate of dysplasia and 0.8% rate of neoplasia [58]. Overall the strategy of colonic strictureplasty is not often employed, and its place in the therapy of Crohn's colonic stricture is not well defined.

The risk-benefit of subtotal colectomy versus segmental resection in Crohn's colitis with rectal sparing is still under debate. Proponents of segmental colectomy site better functional outcomes to this approach, while those who support subtotal colectomy feel segmental resection carries an unacceptably high risk of surgical recurrence. Several single-institution series do not support the notion that re-resection rate is significantly higher in the segmental colectomy population, and stoma-free survival is also comparable [59–61]. A metaanalysis of six studies

totaling 265 segmental colectomies and 223 subtotal colectomies concluded that while total recurrence is equivalent, surgical recurrence does occur ~4 years *earlier* in patients undergoing segmental colectomy. With longer disease distribution involving two or more segments, subtotal colectomy is favored. Segmental colectomy is still appropriate for clear anatomically defined segments of Crohn's colitis in the absence of dysplasia [62].

Minimally Invasive Approach: Laparoscopic and Robotic Surgery

Difficulty of handling the thick, inflamed mesentery in undernourished and immunosuppressed patients has historically deterred most surgeons from adopting the laparoscopic approach for ileocolic Crohn's disease. However, evidence has been accumulating in support of a minimally invasive approach to this population [63–66], with more experienced surgeons and centers tackling more complex cases [67]. Two randomized controlled trials demonstrated improved postoperative pulmonary function, morbidity, and length of stay in a select population of Crohn's patients [68, 69]. Analysis of the long-term outcomes in these two trial populations demonstrated that laparoscopic ileocolic resection was at least comparable to open surgery, with improved body-image perception, cosmesis, rates of bowel obstruction, and hernia [70, 71] Laparoscopic surgery is associated with significantly lower rates of perioperative morbidity and incisional hernia, with a trend toward lower surgical recurrence rates and fewer postoperative small-bowel obstructions [72]. Four other metaanalyses evaluating laparoscopy to treat Crohn's disease also support these findings, with a significantly shorter length of stay, lower 30-day reoperation rate, and trend toward lower costs [73–76].

Previous studies have demonstrated that ileocolic resection is feasible and safe in the setting of complicated Crohn's disease, including immunosuppressed states, intraabdominal abscess, or fistula [77, 78]. There is not an increase in recurrence in those patients approached laparoscopically, mitigating concern that inability to palpate the small bowel may lead to undiagnosed skin lesions [79]. Prior laparotomy does not impair outcomes of subsequent laparoscopic approach, though there is a higher incidence of intraoperative intestinal injury [80–83]. Factors contributing to an increased likelihood of conversion to an open procedure include high body mass index, known fistula, intraabdominal abscess, smoking, steroid administration, extracecal colonic disease, recurrent episodes, and preoperative malnutrition [84, 85]. Reduction of intraabdominal adhesions following laparoscopic surgery has the potential to reduce the risks of future surgeries. Based on a recent analysis of the Nationwide Inpatient Sample from 2009 to 2011, ~40% of Crohn's ileocolic resections are initiated laparoscopically, with ~20% conversion rate [86].

The American College of Surgeons Oncology Group (ACOSOG) recently published a randomized controlled trial (Z6051 Trial) comparing the effect of laparoscopic-assisted resection versus open resection for stage II or III rectal cancer.

The rate of overall complications did not significantly differ. Because laparoscopic resection had a slightly higher rate of positive circumferential resection margin (CRM) of <1 mm, the trial failed to demonstrate noninferiority of the laparoscopic approach [87]. As CRM is not applicable to benign disease, it would seem the results of this important trial do not inform the IBD surgeon's decision to attempt the laparoscopic approach, except in the setting of IBD-associated rectal cancer.

A novel mode of minimally invasive surgery – single-incision laparoscopic surgery (SILS) – is being utilized at a few centers around the world. Some potential benefits include improved cosmesis and decreased abdominal-wall trauma. These benefits appear to be minimal over the more traditional laparoscopic approaches [88].

Robotic-assisted proctectomy for inflammatory bowel disease is safe and effective compared to the laparoscopic approach in both Crohn's and ulcerative colitis [89]. There is no proven patient benefit to this approach; the surgeon's learning curve is longer and operative costs are higher [90]. Further studies are needed to better define the role and benefit of robotic surgery in inflammatory bowel disease.

Surgical Management of Perianal Crohn's Disease

Perianal involvement of Crohn's disease ranges from mild symptoms to complex fistulizing disease, pelvic sepsis, and so-called "watering-can" perineum. Depending on the method of classification and length of follow-up, perianal complications occur in 10–80% of patients [91]. Surgery plays an important role in diagnosis and treatment of this phenotypically distinct form of Crohn's disease. Exam under anesthesia (EUA) is both diagnostic and therapeutic, with control of sepsis by abscess drainage and delineation of fistula anatomy being dual primary goals. Identified fistulae are controlled with loose draining seton placement to allow continued drainage and to prevent premature skin healing with abscess recurrence. Suspicion of complex collections or multiple fistula tracks should prompt further evaluation with magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) which, in combination with EUA, increases the diagnostic accuracy to nearly 100% [92].

Abscess drainage and seton placement are necessary to control sepsis. Draining setons provide good symptomatic relief and are tolerated very well as a long-term therapy or a bridge to future definitive therapy. Up to 80% of patients will suffer recurrence of abscess and fistula after seton removal [93]. In combination with biologic therapy, ~2/3 of patients will experience complete symptomatic resolution of fistula, and 1/3 of patients will enjoy durable long-term resolution with ongoing maintenance of biologic therapy. Infliximab and adalimumab have very comparable efficacy in this approach [94, 95]. Certolizumab is less efficacious but can still influence fistula closure [96].

After failure of combined draining seton and biologic therapy, additional surgical intervention may be required. Definitive surgical treatments of fistulae are numerous and include fistulotomy, mucosal advancement flap, ligation of the intersphincteric fistula tract (LIFT) procedure, bioprosthetic plug, fibrin glue, and stem

cell injection. The choice of therapy depends on anatomic location, extent of disease, and surgeon preference. Fistulotomy entails laying the fistula open and allowing it to heal by secondary intention. Fistulotomy is reserved for superficial and occasionally simple low intersphincteric fistulas in the absence of proctitis. Fistulotomy, though very efficacious, carries higher rates of incontinence, especially in women. With the involvement of more anal sphincter bulk comes unacceptable incontinence rates and poor healing, and so choosing the appropriate approach involves balancing efficacy and minimizing risk of incontinence [97].

Endorectal advancement flap is aimed at closure of the internal fistula opening by elevating the mucosa, submucosal, and internal sphincter and pulling this distally over the internal opening. There must not be evidence of ongoing proctitis. These flaps are broad-based and should cover the defect without tension. The flap is then sutured in place. Success of this approach is lower than for patients with cryptoglandular fistula, at around 64% with 10% rate of incontinence, and need for reintervention is common [98].

Ligation of the intersphincteric fistula tract (LIFT) involves creating a circumanal incision to enter the intersphincteric space in a patient with an established fistula. The fistula tract is then encircled, ligated, and a portion excised. The success rates of this procedure in non-Crohn's disease patients are reportedly above 75% in experienced hands. Use in fistula related to Crohn's disease, however, has been limited [99, 100].

Other novel therapeutic options include collagen anal fistula plug, fibrin glue, and intralesional stem cell injection. These have shown varying success rates in literature and cost is often high. Stem cell injection is a very new technique based on the unique immunomodulator capabilities of adipose-derived mesenchymal stem cells (ASCs). In a recent phase I/IIa clinical trial, intralesional injection of ASCs resulted in complete fistula closure in 50% of patients [101]. This technique is experimental and still awaiting broad validation. A recent randomized controlled trial of 54 Crohn's patients on stable medical therapy with perianal disease suggested that anal fistula plug was no more effective than seton removal alone, with 30% rate of fistula closure [102]. Fibrin glue also has disappointing efficacy, but given its success rate is greater than 0% and it involves minimal risk, it can be trialed as a first-line approach [101, 103, 104].

All of the above surgical modalities are more effective in terms of symptom control and disease remission with the concomitant use of certain medical therapies. For example, antibiotics such as ciprofloxacin and metronidazole have been shown to lead to symptomatic improvement of fistula drainage; they do not alter the rate of fistula healing [92]. As with draining seton therapy, use of concurrent biologic agents and immune modulators have been shown to greatly improve healing rates and decrease recurrences [105].

Despite the innovations in medical and surgical treatment of perianal fistulizing Crohn's disease, a proportion of patients suffer from severe disease refractory to all of the above treatments. Fecal diversion and ultimately proctectomy are required in these cases due to recurrent sepsis, incontinence, and poor quality of life. Temporary

fecal diversion is associated with ~60% initial clinical response. However, many relapse quickly after attempted reversal, and over 40% of patients undergoing fecal diversion go on to require definitive proctectomy. In a recent metaanalysis, only 17% ever achieve successful restoration of bowel continuity [106, 107]. Though proctectomy is considered a last resort treatment for patients with refractory disease, studies suggest fecal diversion improves quality of life and can allow for patient empowerment in getting used to the idea of a permanent stoma. Fecal diversion may allow the patient to feel more in control of the decision process toward and timing of definitive proctectomy [106, 108].

Surgical Management of Ulcerative Colitis

Approximately 20–30% of patients with ulcerative colitis will go on to require surgical resection in the form of subtotal colectomy or proctocolectomy with or without a restorative procedure [109]. The rate of surgical intervention has not changed in recent years [110, 111]. Emergent indications for surgical therapy include fulminant colitis or toxic megacolon, uncontrolled bleeding, or failure of medical rescue therapy [112]. Elective surgery is necessary for intractable disease with loss of response to best medical maintenance therapy, steroid-dependent patients, patients with neoplasia or high-grade dysplasia, stricture, and select patients with low-grade dysplasia [113]. The following sections will focus on the most commonly performed surgical procedures in the management of ulcerative colitis, namely subtotal colectomy, total proctocolectomy with end ileostomy, and restorative proctocolectomy with ileal pouch-anal anastomosis, as well as innovations in the field.

Subtotal Colectomy

Subtotal colectomy with end ileostomy is a procedure used most commonly in emergency setting of fulminant colitis, toxic megacolon, and hemorrhage [113]. The procedure allows for timely removal of the diseased colon with preservation of the rectal stump, while avoiding rectal dissection in the acute setting and therefore reducing morbidity. Subtotal colectomy is occasionally employed in patients with indeterminate colitis where possibility of Crohn's disease cannot be ruled out; this approach allows thorough histopathologic evaluation of the surgical specimen in order to guide surgical decision-making for or against a restorative procedure after proctectomy. When performing subtotal colectomy, it is acceptable to leave the rectal stump in the pelvis with or without a rectal tube. For cases of severe toxic colitis with a friable rectum, embedding the rectal stump in an extrafascial location with or without creation of mucous fistula may reduce the risk of pelvic sepsis in the case of rectal stump blowout [114].

In select patients, subtotal colectomy with ileorectal anastomosis is a suitable option allowing patients to maintain transanal defecation. Elderly patients, young patients wishing to postpone pelvic surgery to preserve fecundity, and those with colonic dysplasia with rectal sparing may be candidates for this approach. Any degree of proctitis must be under good control. Frequent surveillance for dysplasia/neoplasia and ongoing medical therapy to control proctitis is required; patients unable to regularly follow up should not be offered subtotal colectomy with ileorectal anastomosis. Quality of life is comparable to ileal pouch-anal anastomosis; patients have improved continence and fewer bowel movements but tend to have increased urgency. About 1/3 of patient will require completion proctectomy by 10-year follow-up. Still, preservation of intestinal continuity may be possible with subsequent construction of an ileal pouch-anal anastomosis [115].

Continent Ileostomy (Kock Pouch)

Continent ileostomy, or Kock pouch, is an alternative to conventional end ileostomy. A subfascial reservoir with a nipple valve is constructed that allows for intermittent self-evacuation of enteric contents. The internal reservoir allows the patient to avoid an external appliance, the main benefit to this technique. Though introduced around the time ileal pouch-anal anastomosis was developed as a restorative approach in the 1970s, Kock pouch is now only rarely performed by dedicated surgeons at select centers. Frequent need for reoperation significantly dampens the utility of this approach [116]. Highly informed and motivated patients with contraindication to a restorative procedure such as poor anal sphincter function, those who have failed a restorative procedure, and those intolerant to conventional ileostomy due to peristomal skin conditions may be candidates for continent ileostomy.

The mechanism for continence as well as the source of major complications of this procedure is the nipple valve created by intussuscepting the efferent limb of the stoma. Suturing or stapling the nipple valve in place can reduce slippage and prolapse, but this increases risk for fistula. Although the long-term success rates reach 80%, the rates of reoperation also remain high [116]. In a large study describing the Cleveland Clinic experience with 330 patients undergoing continent ileostomy, 10- and 20-year pouch survivals were 87% and 77%, respectively; however, patients on average required 2.9 surgical revisions during follow-up. Patients who experienced early pouch slippage tended to continue to experience repeat episodes of slippage [117]. Still, patients who retained their Kock pouch were highly satisfied despite frequent need for surgical revision. Continent ileostomy remains a valuable, although rarely used, option for motivated patients with realistic understanding of this revision-plagued technique and willingness to travel to a center familiar with constructing and managing a continent ileostomy.

Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is an attractive option for many patients with ulcerative colitis [41]. This procedure can be accomplished through a one-, two-, or three-stage, or reverse two-stage approach. The two-stage approach with total proctocolectomy and IPAA construction with diverting loop ileostomy as the first step and three-stage approach with subtotal colectomy and end ileostomy as the first step are the most common strategies. Complication rates are similar for both approaches and technique is institution- and surgeon-specific. Patients undergoing a three-stage procedure have been shown to have better nutritional status and lower rates of sepsis at the time of completion proctectomy with IPAA when compared to a two-stage procedure [111].

Initially, the procedure was performed as a true pull-through operation where the rectum was transected at the level of the midrectum, the retained distal rectum was then denuded of its mucosa by an extensive mucosectomy, and the ileal pouch was delivered through the denuded rectal stump and anastomosed to the anal canal. This approach was thought to be necessary to allow appropriate defecatory function. The old pull-through procedure was plagued by infections developing between the ileal pouch and the rectal wall. In the current day, the rectum is transected at the top of the anal canal and the ileal pouch is anastomosed to the anus without being pulled through any remnant of the rectum.

Additional modifications of the procedure include the stapled ileoanal anastomosis. With this modification the anastomosis is created with a stapling device at the top of the anal canal rather than at the dentate line with the older hand-suture technique. This "double-stapled" technique allows for better overall function and in most cases is preferred over the hand-sutured technique. A concern regarding stapled technique is that the procedure leaves behind the anal transition zone (ATZ) and some amount of rectal mucosa that may be at risk for ongoing inflammation and malignant transformation. To date there are few reported cases of adenocarcinoma developing from the ATZ or retained rectal mucosa after double-stapled IPAA in ulcerative colitis patients [118, 119]. The risk for dysplasia in the retained mucosa is associated with a history of cancer or dysplasia in the proctocolectomy specimen. For this reason, most surgeons recommend a complete mucosectomy with hand-sutured ileoanal anastomosis for patients known to have high-grade dysplasia or invasive colorectal cancer. The need for and schedule of surveillance of the ATZ are not standardized; most surgeons recommend anoscopy/pouchoscopy with biopsy every 3–5 years with some advocating for annual surveillance [120, 121].

While many configurations of the ileal reservoir have been described, the J-pouch configuration is by far the most commonly constructed. The S-pouch configuration may be utilized in cases where short mesentery length prohibits reach of a J-pouch to the anus for anastomosis. However, S-pouch is associated with efferent limb outlet obstruction [122]. W-pouch is a larger volume reservoir with initially lower bowel-movement frequency compared to J-pouch. This advantage is only calculable in the short term, and increased technical complexity and long-term risk of "mega-pouch" diminish the utility of this configuration [123, 124].

IPAA in ulcerative colitis is associated with several early and late complications. Fazio et al. reported on the Cleveland Clinic experience of nearly 3000 patients undergoing IPAA for ulcerative colitis. The majority of patients underwent a double-staple technique. Early pelvic sepsis occurred in 6.3% of patients. Late complications included pouch fistula (2.7%), stricture (11.2%), and pouchitis (36%); the rate of pouch failure was 5.1% [41]. Because early pouch complications including sepsis and anastomotic leak are associated with pouch failure, use of diverting loop ileostomy during IPAA healing is justified and utilized in 90% of cases. Pouch fistula and subsequent manifestation of Crohn's disease are also associated with pouch failure. Finally, preoperative *Clostridium difficile* infection has been recently shown to be independently associated with pouch failure [125, 126]. Predictive pouch failure models have been developed to help counsel patients [125].

In order to facilitate the takedown of diverting ileostomy, some surgeons place a bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm®) into the subcutaneous space around the new ileostomy. Seprafilm® has been shown to reduce formation of dense adhesions to the bowel and to aid early stoma closure in rectal cancer patients [127]. Although very promising, this novel technique is not commonly used, pending further study.

Minimally Invasive Approaches to Ulcerative Colitis

As with Crohn's disease, minimally invasive surgery is a desirable approach to patients with nontoxic colitis owing to improved outcomes [128, 129]. Minimally invasive restorative proctocolectomy with IPAA is associated with lower rates of infertility when compared to open approach [130]. In the hands of an experienced surgeon, laparoscopic approach is also an acceptable mode of surgery in emergent colectomy cases in the absence of extreme bowel fragility or prohibitive dilatation [128].

Enhanced Recovery Pathways in Inflammatory Bowel Disease

Enhanced recovery pathways are unifying, multidisciplinary protocols aimed to guide the patient though all phases of care and recovery while minimizing surgical stress and unnecessary interventions. While the details are institution specific, key components common to all colorectal pathways include preoperative patient education, minimally invasive surgery, early feeding on postoperative day 1 or 0, multimodal analgesia minimizing narcotic use, early specific ambulation goals, avoidance of fluid overload, and specific discharge criteria.

Inflammatory bowel disease patients are included in large institutional series reporting on enhanced recovery in colorectal surgery [131]. It is important to note underweight patients and those on long-term steroids are at increased risk for morbidity and readmission; allowance must be made in helping them reach predefined

milestones prior to discharge and ensuring diligent outpatient follow-up [132]. Not infrequently, IBD patients may be on narcotic pain medications preoperatively. Chronic pain increases the risk of uncontrolled postsurgical pain, a known barrier to discharge [133]. New ostomates are also at well-known increased risk for readmission after discharge, with up to 15–20% rate of readmission for dehydration alone. Robust ileostomy pathways have been developed, which have been shown to virtually eliminate readmission for dehydration [134]. Unfortunately, these ileostomy pathways require incredibly vigorous follow-up and patient education, and also assume that local home-care agencies are competent in basic stoma care, which is not always the case.

In conclusion, postsurgical inflammatory bowel disease patients are capable of thriving within enhanced recovery pathways. However, necessary provisions must be made for common special circumstances affecting this patient population that also negatively influence discharge timing and readmission rates, namely malnutrition, chronic pain, steroid use, and ileostomy creation.

Summary

Inflammatory bowel disease surgeons continue to apply techniques that have been developed over the past four decades. Long-term follow-up data at high-volume centers have allowed surgeons to better counsel patients on realistic functional and disease-specific outcomes of these surgical techniques. This has helped better guide the informed consent process. Minimally invasive surgery is now considered standard procedure for colorectal surgeons who find this within their technical expertise. Use of combined advanced medical therapy with biologics and immunomodulators in conjunction with surgical intervention in Crohn's disease positively influences surgical recurrence and underscores the need for a comprehensive multidisciplinary approach to these complex patients.

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Chapter 18
Managing the IBD Patient with Ostomy Complications

Janice C. Colwell

Overview

Patients can face several challenges as they live with an ostomy. Following creation of a stoma, the patient works to acquire basic skills such as changing and emptying the pouching system. Once they master those skills, they should have a pouching system that remains in place with no leakage from the time they place it on until they remove it (average wear time 4 days [1]), which should provide them with the confidence to return to their daily activities. However, the majority of people with an intestinal stoma will develop peristomal or stomal problems during a lifetime of living with a stoma. Peristomal complications can include moisture-associated skin damage, mechanical damage, fungal infection, and peristomal pyoderma gangrenosum, among others. The incidence of peristomal skin complications range from 29% to 63% [2–5]. Many individuals are unaware that they have a skin problem [6–8], and yet it is reported that over 30% of the visits to an outpatient stoma clinic are related to peristomal skin issues [9]. Stomal complications are also a significant problem but the definitions, terminology, and timing of the measurements make it difficult to measure incidence [10]. Several reviews indicate that up to 55% of patients developed a stomal complication which involved changes to both the stoma and the peristomal skin [10, 11]. Stomal complications can include fistulas, prolapse, stenosis, and retraction. Pittman et al. [12] suggest, using annual incidence related to ostomy complications (peristomal and stomal), that up to 84,000 individuals with a new ostomy can be expected to develop an ostomy-related complication annually.

Stoma-related complications in patients with inflammatory bowel disease have been more frequently reported in patients with Crohn's disease than in those with

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ulcerative colitis. In a study by Takahaski et al. [13], the cumulative risk of complications and the need for stomal revisional surgery were significantly higher in patients with Crohn's disease. Stoma-related complications, such as stomal retraction and strictures, may be related to recurrence of inflammatory bowel disease [14].

It is therefore imperative that as part of the routine follow-up of the patient with inflammatory bowel disease and an intestinal stoma, a thorough examination of the stomal and peristomal area be done. The pouching system, including the skin barrier/adhesive and pouch, should be removed to provide access to the stoma and the skin surrounding the stoma. Patients with a stoma should be told to bring a pouch change with them when scheduling their healthcare-provider appointment. Stomal function should be noted by assessing the 24-h volume and consistency of stoma output (by asking how many times the pouch is emptied in 24 h), by noting the presence of pain or discomfort upon effluent passage from the stoma, noting the amount of or lack of stoma protrusion above the skin level, and noting the quality of the stomal tissue. The peristomal skin should be examined for a break in continuity, the presence of persistent redness in the area of adhesive contact, denuded skin, or any other abnormality. Part of the assessment should include questioning the patient about the usual wear time of the pouching system if noted to be significantly less than 4 days as this may indicate a problem with the current pouching system, peristomal skin, or stoma.

The following stomal and peristomal complications that can present in the patient with inflammatory bowel disease will be reviewed: retraction and stenosis, prolapse, stoma fistula, and peristomal pyoderma gangrenosum. A physiologic stoma complication, high stoma output, will also be included.

Stomal Retraction and Stenosis

Stoma retraction is the disappearance of the stomal tissue protrusion in line with or below the skin level [15]. The causes of retraction can be traced to tension on the stoma from several sources: short mesentery, thickened abdominal wall, excessive adhesions or scar formation, increased basal metabolic index (BMI), inadequate stoma length at the time of creation, stoma necrosis, or mucocutaneous separation (Colwell 2005). Retraction is generally seen as an early complication but has been reported with Crohn's recurrence [16]. A stoma that retracts to or below the skin surface can cause pouching system seal failures as the stoma output is discharged at or below the peristomal skin causing denuded skin and undermining the adhesive seal (Fig. 18.1). A convex pouching system along with a belt can be considered for use to help direct the stoma effluent into the pouch. In cases of continued pouch failure with damaged peristomal skin, a local surgical revision of the stoma can be considered.

Stoma stenosis is the impairment of effluent drainage due to narrowing or contracting of the stomal tissue at the skin or fascial level [15]. Stoma stenosis is generally seen late in the recovery process following stoma creation. However, stoma stenosis and retraction can result from Crohn's disease [16]. Patients with retraction

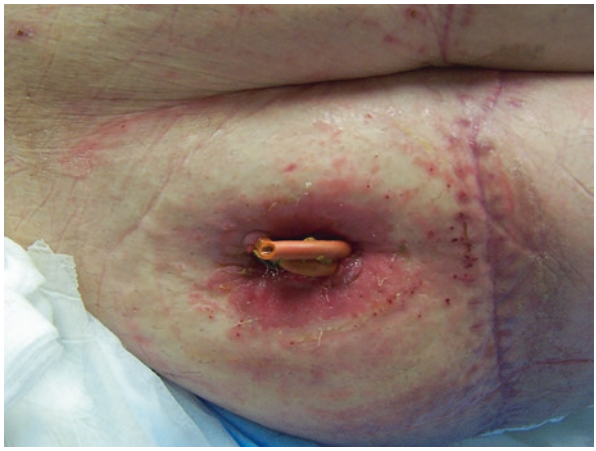

Fig. 18.1 Retracted loop stoma

and/or stenosis report the stoma has "disappeared" below the skin surface, pouching system adhesive failure, pain at the stoma site due to the constriction of the lumen, ribbon-like stool (for the person with a colostomy), intermittent bowel obstructions, and a noisy stoma when stool or gas passes (Fig. 18.2). Assessment of the stoma is done without the pouching system, in sitting, standing, and supine positions, and a digital exam of the stoma to assess lumen size is performed. A contrast study or scope may be indicated to rule out active IBD. Surgery may be indicated for severe stenosis and active inflammatory bowel disease.

Prolapse

Stomal prolapse is the telescoping of the intestine through the stoma [15]. Etiology of a stomal prolapse can include increased abdominal pressure, obesity, enlarged abdominal stoma opening and/or the stoma created outside of the rectus muscle. Prolapse is generally a late complication most commonly seen in loop stomas [2]. Loop ileostomies prolapse have been reported at a rate of ~2% while loop colostomies have higher rates, ranging from 16% to 19% [17]. The presentation of a long segment of bowel is very disturbing to the patient but rarely a surgical emergency (Fig. 18.3). The patient is advised to monitor the color of the stoma mucosa and to report to the emergency department if the stoma tissue becomes dusky or no output is noted in 6–8 h (if an ileostomy). A large opening in the skin barrier of the pouch is recommended to prevent compression of the bowel and manual reduction of the prolapsed bowel can be done if the bowel is not edematous, but it is likely that the prolapse will again occur and will do so until surgically repaired. The dependent prolapsed limb can become edematous and trauma can occur from rubbing through the pouching system onto a belt or snug clothing. Several reports note the use of table sugar to reduce an edematous stoma [18, 19].

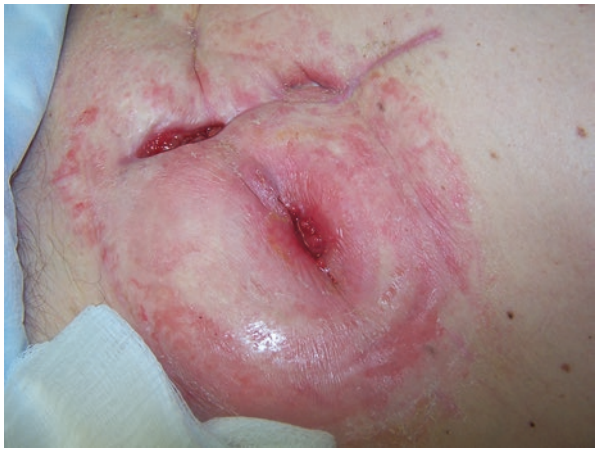

Fig. 18.2 Stenosed stoma

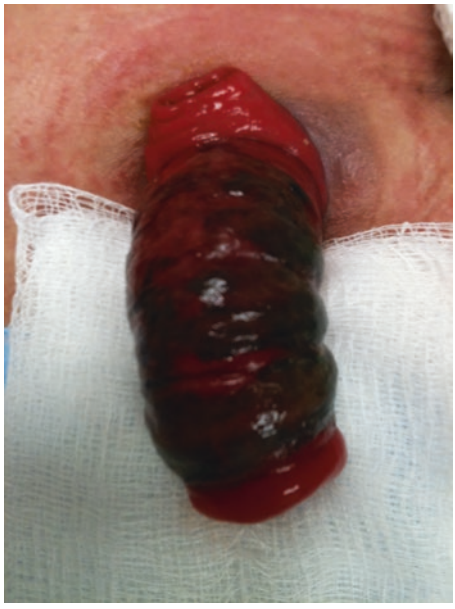

Fig. 18.3 Prolapsed stoma with congestion

Fistula

A stomal fistula is an abnormal opening in the stoma draining effluent from an area other than the stomal lumen (Fig. 18.4). Reporting is poor on this complication as most of the reporting includes enterocutaneous fistula. The patient may present by noting stool draining from an area other than the lumen of the stoma and if the effluent drains near the mucocutaneous junction, the pouch seal may be compromised.

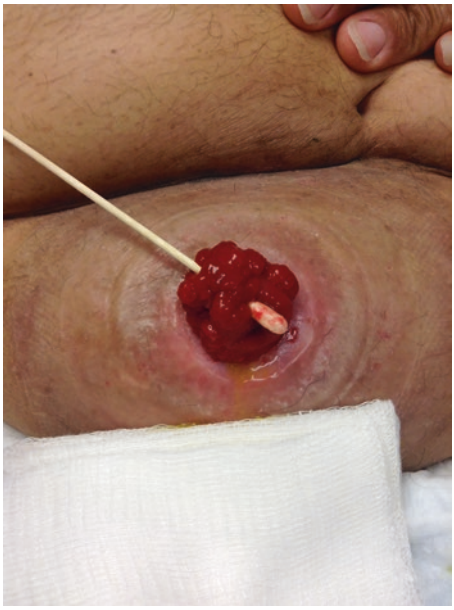

Fig. 18.4 Stomal fistula

Causes of a stomal fistula include suture placed full thickness through the side of the stoma at the time of creation, and more common causes include recurrence of Crohn's disease, poor healing, or mechanical trauma for a pouching system [20]. Most fistulas require reconstruction for repair.

Peristomal Pyoderma Gangrenosum

Peristomal pyoderma gangrenosum (PPG) is an uncommon neutrophilic dermatosis that develops on the peristomal skin. The etiology is unclear and is associated with inflammatory bowel disease [21], and the causative mechanisms are unknown. It is speculated that pathergy, trauma to the skin from pouch application and removal, or fecal contamination may contribute to the development. Wu et al. (2012) suggest that inflammatory bowel disease, abdominal malignancy and neurologic dysfunction have been associated with the development of PPG. In a study by the same authors (Wu et al. 2012), they identified female gender, presence of concurrent autoimmune disorders, and high BMI as risk factors for PPG development. The true incidence is unknown and diagnosis is based upon exclusion of other ulcerations (i.e., pressure from the pouching system, peristomal abscess). Presentation is a rapid onset of pustules that enlarge and open to a full thickness wound with irregular borders, undermining with skin bridges, and purple painful periwound skin with a significant amount of wound drainage (Fig. 18.5). Treatment is concurrently systemic as well as topical wound care. Local treatment should include the use of topical

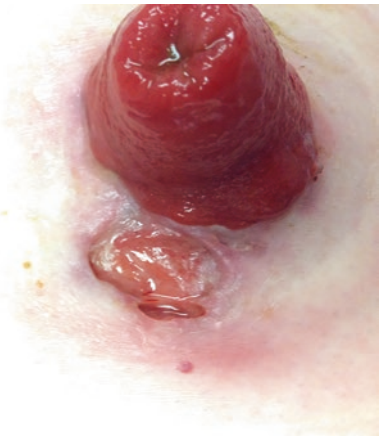

Fig. 18.5 Peristomal pyoderma gangrenosum

steroids, or topical immunosuppressive crèmes such as tacrolimus or pimecrolimus. The challenge in topical management of PPG is the need to maintain a pouch seal over the area and support healing. When initially evaluating PPG, the use of topical lidocaine gel can decrease the discomfort as the area is cleansed and examined. A cream, paste, or ointment can be placed on the ulcers covered with an absorbent dressing such as an alginate, covered by a foam dressing (to absorb the wound drainage) with a pouching system over this avoiding if possible the use of a convex pouching system that can cause further trauma and pain. Systemic treatment can include corticosteroids, cyclosporine, and dapsone, anti-TNF therapy, tacrolimus, and antibiotics if purulent discharge is present [21–23]. Several reports suggest that PPG is associated with systemic IBD [22, 24], and if active disease remains such as in a Hartmann's pouch, surgical excision should be considered. Once the areas involved in the PPG heal, the area forms significant cribriform scarring that can interfere with the pouching system seal.

High-Output Stoma

High-output stoma (HOS) is defined as a range between 1200 and 2000 ml/day. There is an increase in loss of water and sodium that may lead to dehydration and renal impairment. Readmission rates for the treatment of dehydration are high; in a study by Hayden et al. [25], 40.7% of all patients with an ileostomy were readmitted for dehydration. While some of the identified causes of high ostomy output are proximal stomas, other etiologies include short-bowel syndrome, intra-abdominal sepsis, enteritis, medications, and small-bowel obstruction [26]. Two studies noted the time line for dehydration requiring hospital readmission to be between post-op day 2 and 8 [25, 27]. Prevalence has been reported to be 15% in at least two studies [26, 28], but for many clinicians this number may be much higher. After identifying and treating the cause (if determined), a plan of care must be developed with the

patient to monitor stomal and urinary output and electrolyte losses, and nutritional support with dietary guidelines and medications (antidiarrheals, antisecretory medications) must be provided. *Clostridium difficile* infection must be considered as a cause and, if diagnosed, treated before other interventions are planned. Initial management includes restricting oral fluids to 500 ml/24 h with IV rehydration [26, 29] if the dehydration is severe. The patient's stomal and urinary outputs are recorded along with daily weights. Medications used to manage HOS include antimotility agents (loperamide, diphenoxylate) to slow down peristalsis, taken 30 m before each meal and before bed [30]. For patients who are not eating three meals a day (rather are eating up to six small meals in 24 h), a q6h schedule for these medications is advisable [31]. Antisecretory medications reduce gastric acid secretions and thus reduce stomal effluent volume [26, 30]. Nutritional education should include eating slowly, minimal fluid intake with meals, sipping isotonic fluids between meals, low sugar intake, and a low-fat, high-carbohydrate diet ([28, 30]; Rees Parish 2013). The best management of HOS is to identify the at-risk populations and institute a protocol postoperatively, both in the hospital and after discharge. The plan of care for the at-risk patient as well as the patient identified with HOS should include measurement of stomal and urinary outputs both in the hospital and after discharge (sending the patient home with the equipment and a flow sheet for recording), dietary education on fluid and food intake (written information as well as face-to-face education), follow-up appointments with the healthcare provider, contact info if signs and symptoms of dehydration occur and homecare nursing services if appropriate. The presence of HOS can contribute to a breakdown of the skin barrier adhesive component of the pouching system as a highly liquid effluent causes adhesive failure. Frequently a person with HOS needs to change the entire pouching system more often to prevent denuded peristomal skin and pouch adhesive failure. The management of HOS is complex and will require a team approach to organize the nutritional and pharmaceutical therapies along with long-term follow-up to prevent dehydration and renal injury.

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Chapter 19
The New Sheriffs in Town: The Role of APNs and PAs in an IBD Practice

Ashley A. Bochenek

Key Points

- The use of specialty medications has become commonplace in the treatment of inflammatory bowel disease.
- With the incidence of inflammatory bowel diseases on the rise, there is an increased need for providers who specialize in the management of inflammatory bowel disease.
- Advanced practice providers diagnose disease state and disease-related complications, initiate, perform, and interpret diagnostic tests, and develop a therapeutic plan of care for patients.
- Advanced practice providers specialize in various areas of gastroenterology including inflammatory bowel disease, colorectal surgery, ostomy and wound care, nutrition, hepatology, and pediatrics.
- Numerous professional organizations are available to nurse practitioners and physician assistants to help keep them abreast of current therapies in gastroenterology and provide a way to network with other colleagues.
- Specially trained nurse practitioners have proven to perform endoscopy with comparable effectiveness as that of a gastroenterologist.

Introduction

The incidence of inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, is on the rise and now affects a broader patient population than it previously had. Subsequently, there has been a greater need for providers

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who are well versed in treating the diseases. Specialty medications are now commonly prescribed in the treatment of inflammatory bowel disease and require close, frequent monitoring of the patient. As gastroenterologists are becoming increasingly busy seeing new patients for diagnosis and development of a treatment plan, it leaves an increased number of established patients who need routine evaluation and monitoring. Enter the advanced practice provider.

The Role of the Advanced Practice Provider

Advanced practice provider (APP) is a term used interchangeably with physician extender, nonphysician clinician, and midlevel provider. It refers to an advanced practice nurse (APN) or physician assistant (PA). An advanced practice nurse (APN) is a registered nurse who has completed an accredited graduate program as a nurse practitioner (NP), clinical nurse specialist, nurse anesthetist, or nurse midwife.

Nurse practitioners (NPs) have a minimum of a master's degree; however, the American Association of Colleges of Nursing (AACN) has recommended that education for advanced practice nursing be moved to the doctoral level. Most accredited nursing programs have changed the required curriculum to reflect this so that new nurse practitioners will be doctoral prepared. Individual state practice acts govern the rules and regulations under which NPs practice [1]. As of 2016, 20 states and the District of Columbia do not require a practice relationship between NPs and physicians, whereas other states require either a collaborative or a supervising physician [1]. Physician assistants (PAs) have a minimum of a bachelor's degree in any area and subsequently completed a 2-year accredited PA program [1]. State law, facility policy, and physician delegation define the scope of practice of a physician assistant [1]. Physician assistants practice under the supervision of a physician [2]. While NPs and PAs can receive national certification, it is not mandatory in every state [3].

Although the education, clinical experience, and certification vary, both advanced practice nurses and physician assistants function similarly, proving to be great assets to a clinical team. The use of an advanced practice provider is also cost effective as billing under an individual nurse practitioner or physician assistant is reimbursed at 85% of the physician fee schedule [1].

The Role of the Advanced Practice Provider in Gastroenterology

There are many different ways an advanced practice provider can be a valuable team member in the care of the patient with gastrointestinal disease. The Society of Gastroenterology Nurses and Associates (SGNA) defines the role of the APN in gastroenterology to include such tasks as perform advanced patient assessments; diagnose disease and disease-related complications; initiate, perform, and interpret diagnostic tests and endoscopic procedures; develop a therapeutic plan of care; and provide expert consultation and leadership in interprofessional healthcare [4].

Table 19.1 Advanced practice providers in gastroenterology

	Role description	Organizations of interest
Colorectal surgery	Specialize in a variety of anorectal disorders including ileoanal pouch care, functional bowel, surgical correction of perianal abscesses and fistulas, and pelvic floor disorders	CCF, SGNA, WOCN
Hepatology	Manage general hepatology patients as well as patients with hepatitis and primary sclerosing cholangitis. May perform paracenteses and elastography ultrasounds if indicated	ACG, AGA, AASLD, SGNA
Inflammatory bowel disease	Specialize in the care of IBD patients by diagnosing disease state, developing a therapeutic plan of care, and monitoring response to therapy. Provide patient education on routine health maintenance in IBD. May perform endoscopy, varies by institution	ACG, AGA, ASGE, CCF, SGNA
Nutrition	Specialize in patients who require the use of enteral supplements or parenteral nutrition. They can also manage vitamin and mineral supplementation and provide care of central lines and feeding tubes	ACG, AGA, SGNA
Ostomy, stoma, and wound	Specialize in ostomy care by determining site for stoma placement, fitting patients for their appliance, and teaching self-management skills. Can also help manage and treat complications such as peristomal pyoderma	CCF, SGNA, WOCN
Pediatric IBD	Manage the pediatric IBD population by monitoring disease state, response to therapy, as well as growth and nutrition. Able to supervise transitional IBD clinics to help bridge the gap from a pediatric to adult gastroenterologist	CCF, SGNA

Advanced practice providers, trained by specialists within their field, can help patients stay on track with their treatment plan. In medical centers that perform clinical research trials, nurse practitioners and physician assistants can also act as subinvestigators of the clinical trials. They can recruit patients for trials and follow research patients at their scheduled dosing visits to perform history and physicals and monitor progress. Currently there are advanced practice providers in gastroenterology who specialize in managing inflammatory bowel disease, colorectal surgery, ostomy and wound care, nutrition, hepatology, and pediatrics (Table 19.1).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic disease with a patient population that is both young and fertile. The patients are activists and, therefore, are very involved in their own healthcare. Given that the medications used to treat inflammatory bowel disease are immunosuppressive and carry potential risks, there are

understandable concerns about safety. Furthermore, with the treatment paradigm shifting to personalized medicine, there is greater need for patient education and close monitoring of disease state.

Once a plan of care is developed, it is essential that the patient understands the plan and how to make the plan come to fruition. An important role of a nurse practitioner is to provide patient education. Nurse practitioners are often less intimidating than a physician, and therefore patients often feel more comfortable asking them disease- and treatment-related questions. Nurse practitioners as well as physician assistants are well versed in providing education on diagnosis, medications, laboratory tests, procedures, and prognosis.

Inflammatory bowel disease is a chronic disease with many potential, but often preventable, complications. Advanced practice providers can provide counseling on prevention strategies such as vaccinations, bone health, therapy-related testing, cancer prevention, nutritional assessment, and routine health maintenance. The Cornerstones Checklist for IBD Patients was developed with this focus in mind and is an extremely helpful tool to use when caring for your patients.

Vaccinations, which are especially important in our pediatric population, should be addressed at least annually in all IBD patients. Live vaccines (varicella, zoster, MMR) are contraindicated in immunocompromised patients [5]. Patients at risk for these infections should receive the vaccines 1 month prior to starting immunosuppressive therapy. Immunosuppressed patients are encouraged to receive an influenza vaccine annually and a pneumonia vaccine every 5 years. Both females and males between the ages of 9 and 26 should be encouraged to receive the HPV vaccine series to prevent cervical and anal cancers [6].

Unfortunately, most patients with inflammatory bowel disease have been treated with steroids over the course of their disease. Bone density should be assessed in patients with steroid use greater than 3 months and past chronic steroid use of at least 1 year within the past 2 years [6]. Vitamin D level should be assessed at least annually in all IBD patients and more frequently in high-risk patients. Patients with a low dietary intake or who are lactose intolerant are encouraged to take a daily calcium and vitamin D supplement and should have their vitamin D levels assessed routinely. In good practice, a coprescription of a calcium and vitamin D supplement should be given to all patients with each course of oral corticosteroids [6].

Medications currently used in the management of IBD include mesalamines, immunomodulators, corticosteroids, and biologics. Routine use of mesalamines requires monitoring of renal function every 6–12 months to assess for nephrotoxicity. Prior to initiating therapy with azathioprine or 6-mercaptopurine, a thiopurine methyltransferase (TMPT) level will help determine how a patient will metabolize the medication. Before initiating anti-TNF therapy, hepatitis B and tuberculosis infections must be ruled out. If considering natalizumab, exposure to the John Cunningham (JC) virus must be ruled out prior to starting therapy, and routine monitoring for exposure to the virus while on maintenance therapy is mandated every 4–6 months [6]. While on maintenance therapy with either an immunomodulator or a biologic, periodic monitoring of blood count, liver, and renal function is recommended. Corticosteroids should be given only sparingly and are not intended for

long-term maintenance therapy. Consider an ophthalmology exam in patients with long-term exposure to steroids [6].

The concept of personalized medicine uses biomarkers that predict risk for disease and response to treatment to guide patient care [7]. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin have been used to monitor response to therapy. ESR and CRP are nonspecific serum inflammatory markers that are acute phase reactants and may be elevated due to a variety of reasons such as an acute flare or a viral illness. It is also important to note that roughly 20% of people do not make CRP so it will never be elevated when assessed. Fecal calprotectin is a stool test that monitors the level of inflammation in the intestines. However, sensitivity may vary depending on disease location, such as colonic versus small bowel Crohn's disease. If a patient has an elevation in a biomarker during a flare, then it may be useful to check that biomarker prior to initiating therapy and routinely thereafter to monitor response to therapy.

Therapeutic drug monitoring is useful when patients are failing to respond to therapy or if they lost response to their current therapy. For patients taking an immunomodulator, such as 6-mercaptopurine or azathioprine, clinical effectiveness is most compatible with proper dose optimization of the drug. Checking thiopurine metabolites in a patient on therapy will result in 6-thioguanine (6TG) and 6-methylmercaptopurine (6MMP) levels. A therapeutic 6TG (drug level) is between 230 and 400 pmol/8 x 10(8) RBC. In return, the ideal level of 6MMP should be less than 5700 pmol/8 x 10(8) RBC as higher levels have been linked to hepatotoxicity.

Similarly, you can check drug levels in biologics as well, but currently there are only two anti-TNFs, infliximab and adalimumab, that have blood tests available to assess drug and antidrug antibody levels. Patients with suboptimal drug levels and no antibodies present will benefit from a dose escalation of the drug [8]. Patients with suboptimal drug levels and the presence of high antidrug antibodies levels need to switch to another biologic [8]. Another anti-TNF can be used if the patient previously responded to anti-TNF therapy. Patients who have adequate drug levels with no antibodies detected and are failing to respond to therapy may need to switch to another drug class such as antiadhesion therapy or proceed with surgery to remove the diseased portion of the bowel.

Immunocompromised patients are at risk for developing certain cancers. There is a risk of lymphoma associated with some medications used to treat inflammatory bowel disease. This risk must be discussed with the patient prior to starting therapy. Patients with inflammatory bowel disease affecting their colon are at risk of developing colorectal cancer. The risk depends on the extent of the disease, severity of the disease, and duration of the disease. Patients with ulcerative colitis beyond the rectum or Crohn's disease that affects more than a third of the colon should receive annual or biannual colonoscopies with biopsies for surveillance [6]. Annual skin examinations by a dermatologist are recommended for all immunocompromised patients. Female patients who are immunocompromised should receive annual PAP smears [6].

Nutritional assessment is essential in the IBD patients especially those with severe disease and those who have required surgery. Patients with weight loss and

chronic diarrhea are at risk for dehydration and electrolyte imbalances. Crohn's patients with a history of ileal disease or that have had an ileocolonic resection should be checked for vitamin B12 deficiency. A B12 level less than 400 should be supplemented with either oral cyanocobalamin or monthly intramuscular injections. An advanced practice provider can teach injection training *and* bill for the clinic visit. Patients with significant weight loss and malnutrition should have their albumin assessed as well as other vitamins and minerals such as vitamins A, E, and zinc. Iron studies need to be monitored in patients with a previous history of iron deficiency and if they are experiencing hematochezia and fatigue. Some patients with significant disease may even require the use of parenteral nutrition.

Routine Health Maintenance in the IBD Patient

Routine practice of a nurse practitioner emphasizes focus on disease prevention, health promotion, and risk reduction. Patient education is a vital role of the advanced practice nurse. Aside from the aforementioned Cornerstones Checklist for the IBD patient, all advanced practice providers should address health maintenance at every visit. General health maintenance practices important in the patient with IBD include having a primary care doctor, pain management, and smoking cessation.

IBD patients need to have a primary care doctor who oversees their overall care that can manage general health issues, such as monitoring blood pressure and cholesterol and treating routine infections. Communication between the IBD provider and primary care doctor is essential. Patients with IBD should avoid the use of antibiotics except when there is a documented infection. Certain antibiotics such as clindamycin have been associated with *Clostridium difficile* infections and should be avoided if possible [9]. Patients on immunosuppressive therapy should avoid live vaccines but stay current with other routine vaccinations.

Primary care doctors and patients alike need to be reminded that the use of chronic pain medications in inflammatory bowel disease is discouraged. Routine use of narcotics has been associated with opioid-induced constipation, narcotic dependency, and narcotic bowel syndrome. Narcotic bowel syndrome is a term use to describe the effects of chronic narcotic use on the bowel. This is characterized by abdominal pain, bloating, abdominal distention, and occasional vomiting in patients on chronic or escalating doses of opiates [10]. The symptoms of narcotic bowel syndrome are relieved by a slow opiate taper. As recurrence rates are high, narcotics should not be used routinely in patients who have suffered from narcotic bowel syndrome in the past [10]. In all IBD patients, narcotic use should be appropriate (i.e., active perianal disease), infrequent, and monitored very closely (i.e., no refills).

The routine use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with gastritis and even the development of gastric ulcers. Therefore, the use of NSAIDs is discouraged in patients with IBD. Acetaminophen or tramadol is preferred for pain management of IBD-related symptoms or routine aches and pains such as headaches. Given that the use of pain medication is limited, it is important

for patients to know that being on effective IBD maintenance medication is the recommended treatment for their disease, not narcotics.

Smoking has been associated with an increased risk for Crohn's disease. Current as well as past smokers are more likely to develop Crohn's disease than those who have never smoked [11]. Cigarette smoking has also been associated with an increased risk of Crohn's recurrence, incidence of flares, and Crohn's-related complications such as structuring and penetrating disease. In contrast, studies have revealed that smoking is not a risk factor in ulcerative colitis and may even have protective characteristics [11]. All patients with Crohn's disease should be encouraged to stop smoking and directed to a smoking cessation program.

Colorectal Surgery

Colorectal surgery nurse practitioners and physician assistants specialize in a variety of anorectal disorders including ileoanal pouch care, functional bowel, surgical correction of perianal abscesses and fistulas, and pelvic floor disorders [12]. They evaluate patients postoperatively for follow-up regarding wound care, managing drains, and removal of sutures and staples. Advanced practice providers can routinely follow patients in clinic after creation of a J-pouch for issues with fecal incontinence, pouchitis, and the development of Crohn's disease of the ileoanal pouch. These providers typically work very closely with the IBD team to get patients back on effective therapies if indicated.

Ostomy, Stoma, and Wound

Management of the IBD patient with a fecal diversion should include care by a healthcare provider with certification in ostomy and wound care. To become a credentialed Wound, Ostomy, and Continence (WOC) Nurse, applicants must have a bachelor's degree in nursing, graduate from an accredited WOC Nursing Education Program, and then pass the Wound, Ostomy, and Continence Nursing Certification Board (WOCNCB). There is also a nonnursing ostomy certification available to healthcare providers by the Wound Care Education Institute (WCEI). After completing the Ostomy Management Specialist course, applicants need to pass the National Alliance of Wound Care and Ostomy (NAWCO) certification exam.

Certified ostomy nurses are an *essential* team member in the care of the IBD patient. Prior to the surgical creation of a stoma, a certified ostomy nurse chooses the most optimal site for stoma placement. After the creation of the stoma, the ostomy nurse fits the patient for their appliance and teaches self-management skills. It is recommended that all patients with an ostomy make an appointment with the ostomy nurse the same day they see their IBD provider. Ostomy nurse also certified in wound care can help manage and treat complications such as peristomal pyoderma. For more information on ostomy management, please see Jan Colwell's chapter in this book.

Nutrition

Advanced practice providers who specialize in clinical nutrition typically focus on patients who require the use of enteral supplements or parenteral nutrition [12]. However, they can also manage vitamin and mineral supplementation in addition to providing care of central lines and various feeding tubes. Advanced practice providers trained in nutrition can follow patients in clinic for the management of their enteral nutrition and replacement of feeding tubes.

Hepatology

Advanced practice providers who specialize in hepatology manage general hepatology patients as well as patients with hepatitis and primary sclerosing cholangitis (PSC). Once trained, they can perform paracenteses and elastography ultrasounds as needed. PSC is the most common hepatobiliary manifestation of IBD with the prevalence of ulcerative colitis as high as 90% in patients with PSC [13]. Patients with IBD and a concomitant diagnosis of PSC are at increased risk for colorectal cancer as well as cholangiocarcinoma [13]. It is recommended these patients have an annual colonoscopy with biopsies for surveillance and are referred to the liver transplant center.

Pediatrics

Inflammatory bowel disease is a chronic disease of young people with roughly 20% of newly diagnosed patients in the pediatric and adolescent age group [14]. Pediatric IBD is multifactorial and should be treated by a specialist who works in conjunction with a pediatrician in providing continuation of care. Growth failure and failure to thrive are often the preceding factors in the diagnosis of Crohn's disease and ulcerative colitis in the pediatric population. Pertinent issues that affect this population of IBD patients are growth, nutrition, and vaccinations. IBD centers typically offer transitional clinics that help bridge the gap from the pediatric gastroenterologist to the adult gastroenterologist. An advanced practice provider with pediatric and adult expertise, such as a family nurse practitioner (FNP), can help ease the transition for patients and parents alike.

Professional Organizations

There is an abundance of professional societies available to advanced practice nurses as well as physician assistants. There are national and state-governed organizations that promote and advocate for advanced practice providers continuing

Table 19.2 Professional organizations for the advanced practice provider in gastroenterology

	Organization	Website	Description
AASLD	American Association for the Study of Liver Diseases	www.aasld.org	The AASLD is dedicated to finding a cure for liver disease, promoting liver health, and quality patient care
ACG	American College of Gastroenterology	www.gi.org	The ACG aims at advancing gastroenterology and improving patient care by establishing clinical guidelines on gastrointestinal diseases
AGA	American Gastroenterological Association	www.gastro.org	The AGA is an international organization involved in all aspects of the science, practice, and advancement of gastroenterology
ASGE	American Society for Gastrointestinal Endoscopy	www.asge.org	The ASGE has been dedicated to advancing patient care and digestive health by promoting excellence and innovation in gastrointestinal endoscopy
CCF	Crohn's and Colitis Foundation	www.ccfa.org	The CCF is a nonprofit organization dedicated to finding a cure for inflammatory bowel diseases and improving the quality of life of adults and children suffering from these diseases
SGNA	Society of Gastroenterology Nurses and Associates	www.sgna.org	The SGNA is dedicated to advancing the safe and effective practice of gastroenterology and endoscopy nursing through education, research, and promoting the professional development of its members
WOCN	Wound, Ostomy, and Continence Nurses Society	www.wocn.org	The WOCN is an international nursing society with a mission that promotes educational, clinical, and research opportunities that support expert care in ostomy and wound management

education and scope of practice. Outside of the general organizations, there are also organizations geared toward the advanced practice providers who specialize in gastroenterology (Table 19.2).

Crohn's & Colitis Foundation (CCF)

The Crohn's & Colitis Foundation (CCF) is a nonprofit organization dedicated to finding a cure for inflammatory bowel diseases and improving the quality of life of adults and children suffering from these diseases. The CCF funds research in inflammatory bowel disease and provides ongoing patient education. The CCF has more

than 40 local chapters and affiliates nationwide that help bring the CCF's work and mission to local communities.

All healthcare providers who treat patients with IBD should become members of the CCF. It is a great way to network with colleagues and stay abreast of educational programs. The CCF website is a great resource for patients as well with updated information on disease management and medications. The CCF offers more than 300 patient support groups across the country as well as *Camp Oasis*, a summer camp for children suffering from Crohn's disease and ulcerative colitis.

Wound, Ostomy, and Continence Nurses (WOCN) Society

The Wound, Ostomy, and Continence Nurses (WOCN) Society is an international nursing society with a mission that promotes educational, clinical, and research opportunities that support expert care in ostomy and wound management. Nonnurses are also welcome to join the WOCN Society. Benefits of becoming a member include a discount to the annual national conference, access to the bimonthly publication of the *Journal of Wound, Ostomy, and Continence Nursing (JWOCN)*, and access to the forums, a way to interact with other colleagues.

Society of Gastroenterology Nurses and Associates (SGNA)

The Society of Gastroenterology Nurses and Associates (SGNA) is a professional organization of nurses and associates dedicated to advancing the safe and effective practice of gastroenterology and endoscopy nursing through education, research, advocacy, collaboration, and promoting the professional development of its members. Nonnursing memberships are also available to assistive personnel and affiliates involved in or associated with gastroenterology and/or endoscopy nursing practice. The SGNA also provides written standards of clinical practice and role delineation between assistive personnel, nurses, and advanced practice nurses specializing in gastroenterology.

American College of Gastroenterology (ACG)

The American College of Gastroenterology aims at advancing gastroenterology and improving patient care by establishing clinical guidelines on gastrointestinal diseases. Advanced practice providers with a certification as either a nurse practitioner or a physician assistant who work with an ACG Physician Member can also apply to

become ACG members. Some benefits of annual membership include waived fees to the annual scientific meeting, the ACG's *American Journal of Gastroenterology,* and free online CMEs.

American Gastroenterological Association (AGA)

The American Gastroenterological Association (AGA) is an international organization involved in all aspects of the science, practice, and advancement of gastroenterology. The AGA Institute publishes three monthly journals, and the organization's annual meeting, Digestive Disease Week, is the largest international gathering of physicians, researchers, and academics in the fields of gastroenterology, hepatology, endoscopy, and gastrointestinal surgery. For nurse practitioners and physician assistants who become members, the AGA offers a dedicated GI NP/PA listserv and an NP and PA resource center where providers can network with colleagues and stay up to date on educational opportunities.

American Society for Gastrointestinal Endoscopy (ASGE)

The American Society for Gastrointestinal Endoscopy (ASGE) has been dedicated to advancing patient care and digestive health by promoting excellence and innovation in gastrointestinal endoscopy. ASGE promotes the highest standards for endoscopic training and practice, fosters endoscopic research, and is a great resource for endoscopic education. Candidates for the "Associate" ASGE membership include registered nurses, technicians, physician assistants, and nurse practitioners who are employed in the field of endoscopy but do not perform endoscopy. SGNA members receive a discount on associate member dues.

American Association for the Study of Liver Diseases (AASLD)

The American Association for the Study of Liver Diseases (AASLD) is dedicated to finding a cure for liver disease, promoting liver health, and quality patient care. Membership is available to nurse practitioners and physician assistants with benefits including access to the *Hepatology* and *Liver Transplantation* journals and discounted rates to the annual Liver Meeting. The AASLD also offers an NP/PA Clinical Hepatology Fellowship that provides salary and benefit support for certified and licensed nurse practitioners or physician assistants pursuing a full year of training focused on clinical care in hepatology.

The Future: Endoscopy and Special Procedures

In some gastroenterology practices, advanced practice providers are performing procedures such as endoscopy and paracentesis. Occasionally, even specially trained registered nurses are performing flexible sigmoidoscopy. Privileges to perform procedures vary depending on training and certification as well as facility and state regulations.

According to the National Cancer Institute, colorectal cancer is the fourth most common cancer in the United States, with 135, 430 estimated new cases and 50, 260 estimated deaths from colorectal cancer in 2017 [15]. Nonphysician endoscopists have been performing flexible sigmoidoscopy for cancer detection since the 1970s with various studies proving that the efficacy is comparable to that of a physician [16]. In 2001, Medicare expanded coverage to include colonoscopy for colorectal screening.

University of California, Davis, performed a single-center randomized controlled trial comparing the efficacy and safety profile of colonoscopies performed by gastroenterologists and nurse practitioners. Measures included adenoma detection rate, cecal intubation rate, procedure duration rate, sedative and analgesic use, complications, and patient-reported procedural pain scores and overall experience [17]. The nurse practitioner group had a higher adenoma detection rate and higher satisfaction score when compared with the gastroenterologist [17].

Since 2009, gastroenterologists at John Hopkins Hospital have trained nurse practitioners to perform colorectal cancer screening colonoscopies. Their training program follows the ASGE Endoscopy curriculum for physician gastroenterology fellows. These NPs become board certified in Maryland to perform colonoscopies and achieve certification within 1 year of training [17]. In review of the first NP trained in the program, her performance exceeded all benchmarks expected of fully trained gastroenterologists [17].

Some physicians may feel threatened by nonphysician endoscopists. However, training more advanced practice providers to perform colonoscopies can increase the colorectal cancer screening rate in the United States at a reduced cost to taxpayers [11].

Conclusion

Every member of the healthcare team plays a critical role in a patient's road to recovery. Advanced practice providers can help bridge the gap between nurses and physicians to provide a more comprehensive level of care and more informed patient population. They can perform patient assessments; diagnose problems; and order appropriate medications, diagnostic tests, and procedures. Most importantly, they can develop and keep patients on track with a personalized, therapeutic plan of care.

In the future of gastroenterology, nurse practitioners and physician assistants will be performing more procedures such as endoscopy, hopefully to decrease the number of colorectal cancer deaths in the United States. Advanced practice providers are a force to be reckoned with in healthcare, proving to be a very valuable asset to a healthcare team.

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Chapter 20
It's Quality, Not Quantity, That Matters …

Jason K. Hou, Corey Siegel, and Gil Melmed

Introduction

Quality of health care can be difficult to define and can change over time. While there is a tendency to provide "more" care in an attempt to provide "better" care, quantity does not equate with quality. One of the most commonly used definitions of quality of health care comes from the Institute of Medicine, which defined quality as "The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [1]. This definition emphasizes three points: (1) care for the individuals, (2) care for populations, and (3) health outcomes. A more recent definition of quality of health care, often called the "Triple Aim," defines quality as (1) improving the experience of care, (2) improving the health of populations, and (3) reducing per capita costs of health care [2]. The definition of quality of care has evolved over a decade as seen in the emphasis in the Triple Aim on the *experience of care* and the introduction of *cost* when considering quality of care. In this chapter, we will be

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discussing examples and future directions of quality of care as applied to patients with inflammatory bowel disease (IBD).

Defining Gaps in Quality of Care in IBD

The recent emphasis on the quality of health care has arisen with the observation that despite advances in medical research and knowledge, the level of care recommended by established evidence and guideline recommendations has failed to translate into improved outcomes. For example, clinical practice guidelines have existed for many years, yet their recommendations have, in many instances, not been translated into clinical practice. Several professional societies have published evidence-based guidelines and consensus statements to define standards of care in IBD. These include the Crohn's and Colitis Foundation of America (CCFA), American College of Gastroenterology (ACG), and American Gastroenterology Association (AGA) [3–7]. These practice guidelines provide recommendations regarding medication selection, monitoring before and after medication initiation, and screening for IBD-related complications (e.g., colorectal cancer, osteoporosis, infections). Despite these evidence-based guidelines, data indicate consistent gaps and variability in the care provided to patients with IBD [8–11]. Wagnon et al. reported that only 49% of 304 gastroenterologists surveyed followed AGA guidelines on osteoporosis screening in patients with IBD [9]. In a study from the Veterans Affairs healthcare system, the osteoporosis screening rate among at-risk patients with IBD was only 23% [12]. Similarly, in a study in France, only 25% of 46 gastroenterologists surveyed in practice reported appropriate assessment prior to initiation of antitumor necrosis factor (anti-TNF) medications [13]. In a large managed healthcare organization, Velayos et al. observed that surveillance colonoscopy was performed on only 24.6% of eligible patients with IBD [14]. Conversely, in a referral hospital in Canada, 90% of patients with UC had undergone surveillance colonoscopy [15]. To further understand the reasons for these gaps and high degree of variation in care, one study evaluated the attitudes and self-reported IBD practices among gastroenterologists in a large managed care group in Northern California. This study reported that focus on disease activity during clinic visits, belief that screening was the responsibility of another physician, cost, and lack of time and knowledge were barriers to adherence to guidelines [16]. These examples highlight (1) a disconnect between practice guidelines and clinical practice and (2) the suboptimal quality of care across various aspects of IBD management.

Active Interventions to Improve Quality of Care

The failure of guidelines to change clinical practice has been demonstrated not only in IBD, but also across several medical specialties, including diabetes, congestive heart failure, and cirrhosis [17–20]. Passive approaches to disseminating clinical

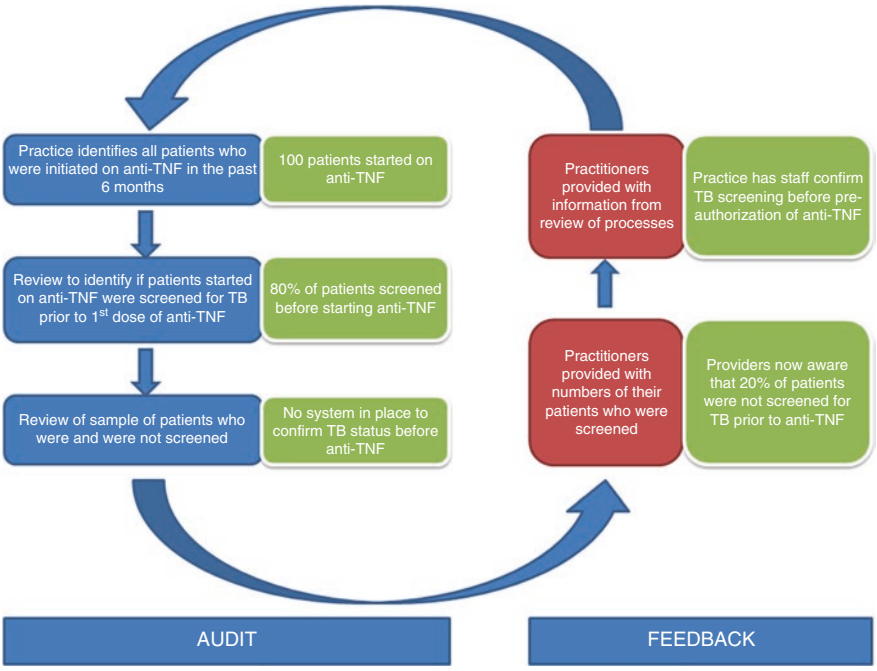

Fig. 20.1 Audit and feedback: screening for tuberculosis (TB) before starting a tumor necrosis factor antagonist (anti-TNF)

guidelines to healthcare providers, such as distribution of guideline documents, do not adequately induce changes in behavior or improve care [21]. Active approaches to changing practice, such as targeted clinical reminders, have been shown to be effective in changing provider behavior [22–24], but the best outcomes are achieved when they are combined with one or more other strategies [25]. One key approach to changing behavior is called "audit and feedback." The primary concepts behind audit and feedback appear simple: provide data on clinical practices to the providers so they can be aware of their practices and make improvements. An example of audit and feedback is provided in Fig. 20.1. Audit and feedback has been found to be one of the most effective interventions to improve quality of care [26–28]. The benefit, as reflected in effect size, of audit-and-feedback interventions can vary and is largest in settings where baseline adherence levels are low [29].

Audit and feedback can be applied to metrics assessing either processes of care or clinical outcomes. Process measures assess "steps" of care, but are not inherently measuring a clinical outcome. They are typically evidence-based practices supported by an association with clinical outcomes. This is in contrast to outcome measures, which directly assess the occurrence of clinical outcomes. For example, the use of steroid-sparing therapy is associated with reductions in steroid-related complications such as bone fracture. Measuring the use of steroid-sparing therapy would be a process measure, while measuring the frequency of bone fractures related to

steroid use would be an outcome measure. Process measures are often chosen to study because of the relative ease of measuring compared to outcome measures; however, they are also only indirect measures which may have less inherent clinical value. Clinical outcomes (such as surgery or death) are inherently more meaningful when discussing with patients and providers; however, they may be relatively infrequent for individual patients, and therefore difficult to measure are compare.

Standardized Quality Metrics in IBD

One of the first attempts to standardize the quality of how IBD care is delivered started in the United Kingdom after an audit in 2006 showed variations in care delivered to IBD patients. Gaps observed included lack of access to dietetic and psychological counselors, and access to specialty care providers [30]. A multidisciplinary panel developed a set of IBD standards defining how care should be delivered to patients with IBD and, importantly, metrics on how the standards would be measured. This set of quality measures in IBD was one of the first to address both structural and process measures with the goal of improving patient-centered care [30].

In Sweden, Rejler et al. developed locally selected quality metrics for IBD based on established quality improvement models, the Donabedian model and the Clinical Value Compass [31]. The focus of selected measures included clinical outcome (anemia, surgery, hospitalization), access to care metrics (wait time), and quality of life (Short Health Scale), demonstrating feasibility of measurement across multiple domains of care [32].

In the United States, IBD quality metrics (Tables 20.1 and 20.2) have been developed through collaboration of multiple professional societies, including the American Gastroenterology Association (AGA) and the Crohn's and Colitis Foundation of America (CCFA). The first adult IBD quality metric program was the IBD Performance Measures as part of the Centers for Medicare & Medicaid Services (CMS) pay for performance (P4P) program [33]. The IBD Performance Measures were meant to provide a standardized means of auditing process measures in IBD care, incentivized financially through CMS bonuses or penalties. Unlike most other CMS performance measures which allow reporting based on billing data alone, the CMS IBD performance measures require manual data collection or participation in a registry, which has limited the implementation and acceptance of their use. These measures were updated in 2015. However, P4P may be phased out by 2019 and will be replaced by incentive payments through alternative payment models and measure reporting through qualified clinical data registries that may rely upon different quality metrics for CMS incentive payments.

The CCFA has developed IBD quality measures using the UCLA/RAND Appropriateness Methodology, intended to reflect expert opinion in the context of the available literature [34]. The CCFA quality measures set differs from the CMS IBD performance measures in that two sets of measures, both process and outcome

Table 20.1 Domains of quality for CMS IBD performance measures and CCFA quality measures

	CMS IBD performance measures	CCFA IBD process measures
Use of corticosteroid-sparing therapy	X	X
Assessment of corticosteroid-related iatrogenic injury bone loss	X	
Assessment of vaccination status	X	X
Testing for latent TB before initiating anti-TNF therapy	X	X
Assessment of hepatitis B virus before initiating anti-TNF therapy	X	X
Tobacco screening and cessation intervention	X	X
Testing for *Clostridium difficile* for flare of IBD with diarrhea		X
Sigmoidoscopy and surgery consultation for severe colitis refractory to IV steroids within 3 days		X
TPMT prior to 6-MP/AZA		X
Proctocolectomy or repeat surveillance for flat dysplasia in ulcerative colitis		X
Surveillance colonoscopy every 1–3 years after 8–10 years of disease		X

Table 20.2 CCFA IBD outcome measures

1. Steroid use
(a) Proportion of patients with steroid-free clinical remission for > 12 months (b) Proportion of patients currently taking prednisone
2. Number of days per month/year lost from school/work attributable to IBD
3. Number of days per year in the hospital attributable to IBD
4. Number of emergency room visits per year for IBD
5. Proportion of patients with malnutrition
6. Proportion of patients with anemia
7. Proportion of patients with normal disease-targeted health-related quality of life
8. Proportion of patients currently taking narcotic analgesics
9. Proportion of patients with nighttime bowel movements or leakage
10. Proportion of patients with incontinence in the last month

measure sets, were developed (Tables 20.1 and 20.2). The CCFA quality measures provide a broad reflection of quality of care, describing "top ten" measures for processes and outcomes that are considered most likely to be associated with improving quality of life for IBD patients. The CCFA quality measures were intended to (1) give guidance to gastroenterology colleagues on where to focus efforts to improve quality and (2) set the stage for an implementation and intervention program using quality improvement methodology.

Implementation of Quality Improvement in IBD

As described earlier in this chapter, publication and distribution of guidelines or quality metrics alone have failed to promote changes in practice. In this section, we will describe several programs that have incorporated audit and feedback among other interventions to promote changes in practice and improve the quality of care in IBD.

Adherence to reporting the CMS IBD performance measures has been very low, ranging from 5.8% to 35.8% [35, 36]. In a study of community-based gastroenterologists with low adherence to reporting CMS IBD performance measures, providers participated in a multistep intervention, which included individual Web-based audit and feedback, two 1-h-long interactive online sessions, and a 20-page monograph. Evaluation of documentation of performance measures was assessed post-training and compared to the individual providers prior to training. Although the overall rates of adherence did not improve, several areas, including the documentation of tobacco cessation and IBD activity, increased from 50% to 80% ($p = 0.001$) and 36% to 40% ($p = 0.27$), respectively [36].

In the United States to date, the most well-developed and successful program of quality improvement in IBD is the ImproveCareNow (ICN) Network [37]. ICN is a collaboration of pediatric gastroenterology centers based on three principles of quality improvement: (1) a multicenter collaboration of pediatric subspecialists, (2) sharing of performance data, and (3) training in quality improvement [37]. Prospective data are aggregated in a central registry to generate weekly audit-and-feedback reports for the participating centers. These reports are reviewed by the sites, and modifications are made to processes to improve outcomes. ICN has observed significant improvement in both process and outcome domains of care, including increases in thiopurine methyltransferase testing prior to thiopurine initiation (from 60% to 80% among CD, and 50% to 73% in UC) and an increase in patients with inactive disease (from 55% to 68% in CD, and 61% to 72% in UC) [38].

In 2013, the CCFA initiated a multicenter IBD quality-of-care project named IBD Qorus. The initiative started with a collaboration of six community and academic adult gastrointestinal (GI) practices and enrolled over 600 patients in the 5-month pilot phase. The collaborative tested processes of patient enrollment, data acquisition, and steps of implementation based of IBD process and outcome metrics. The collaborative has expanded to include over 20 sites in a Learning Health System. IBD Qorus incorporates several key aspects of quality improvement, including audit-and-feedback mechanisms, collaborative sharing of best practices and ideas, development of care pathways, a shared database for outcome data, and a patient portal to engage patients through personalized health status displays and self- entry of patient-centered, patient-reported outcomes.

Challenges in Implementing Quality Improvement in IBD

There are a multitude of challenges in changing clinical practices. Although audit and feedback remains the crux of most quality improvement initiatives, it has several limitations. The first challenge in implementing audit-feedback is the timeliness and validity of data collection. Audit-and-feedback interventions that use individual and local practice data are more likely to produce practice change than regional or aggregate data [32]. However, manual chart auditing is time intensive and impractical to use for sustained audit-and-feedback interventions. The pervasiveness and access to electronic medical records may allow for use of data mining tools, such as natural language processing, to substantially reduce the effort of manual audits [39]. Natural language processing is a technology that utilizes computer-based linguistics and artificial intelligence to identify and extract information from free-text data sources [39]. Natural language processing–based tools have already been developed to describe clinical phenotypes in IBD and indications for colonoscopy; however, they have yet to be tested across different data platforms needed for quality improvement [40, 41].

Assuming that accurate data can be collected, influencing a change in work flow and practice to accommodate the ongoing data collection and collation is another major challenge. Physicians have multiple demands on their time, and quality reporting is an additional burden. Indeed, studies have shown that clinicians see reporting of quality measures as wasteful [42]. However, an audit-and-feedback approach that is (1) integrated into the existing work flow and (2) can improve the ease of performing recommended measures may improve provider acceptance of quality measurement and consequently improve patient outcomes [43, 44]. Several of the current IBD quality improvement initiatives, including ImproveCareNow and IBD Qorus, utilize systemic and multidisciplinary approaches to affect meaningful and durable practice change. Although success and acceptance have been observed with ImproveCareNow in pediatric IBD, translating the success of ImproveCareNow into adult IBD practices adds additional challenges. There are many systematic differences in the delivery of care between pediatric and adult GI patients. For example, pediatric IBD care is clustered primarily in academic centers, whereas adult patients with IBD receive care primarily at community practices. To address this challenge, IBD Qorus relies on engaging patients as the central part of the reporting process to allow sites to customize their focus and approach toward optimizing quality in their practice.

A related challenge for clinicians in accepting and incorporating quality improvement practices is the scarcity of time. Physicians are already faced with limited time for clinical care, and additional processes may inadvertently detract from clinical care. Quality improvement interventions will need to carefully balance the time and resources required for participation and benefit.

Future Directions

The interventions discussed in the chapter touch on each of the aspects of the quality-of-care definition described in the introduction of this chapter. So where will quality of care in IBD be in 5 or 10 years? Diagnostic and therapeutic options for IBD will likely change dramatically in the near future, as will rules and regulations regarding quality-of-care reporting in IBD. Although the metrics by which we define the quality of IBD may change over time, the underlying principles of patient-centered care, consideration of individual patients as well as the population as a whole, and clinically relevant outcomes will remain constant. Quality of care will likely be incorporated into Learning Health Systems – collaborative initiatives that incorporate patient care and integrated electronic medical records, databases that automatically provide audit and feedback to providers, tools to allow for population management keying in on high-risk patients, and the integration of predictive computer modeling based on an individual patient's data [45, 46]. There has been progress in using machine learning to analyze data from electronic health records for predictive modeling to determine an individual patient's risk for complications in chronic disease, such as hypertension and progression to fibrosis in chronic liver disease [47, 48]. One can envision the benefits of an integrated system that seamlessly provides the data required to make informed decision for both patient and providers, such as the likelihood of response to specific therapies, or risks of adverse outcomes, based on an individual patient's data. Much work is still needed to develop these integrated systems, but the work of existing quality improvement networks, such as ImproveCareNow and IBD Qorus, is the initial step to provide high-quality, consistent, patient-centered care for patients with IBD.

Conclusion

Despite advances in the management of IBD, there remain gaps in the quality of care for patients with IBD. Several quality improvement initiatives in IBD have shown promise in bridging the gap in care; however, further studies into integrating processes of quality improvement into routine clinical care are still necessary.

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Chapter 21
The Economics of Inflammatory Bowel Disease

Laura E. Targownik and Charles N. Bernstein

Introductory Points

1. The direct costs of treating persons with inflammatory bowel disease have dramatically increased, owing to both the increasing prevalence of disease and the increasing utilization of biologic therapies.
2. The indirect costs of IBD are also substantial, owing to disability leading to unemployment, underemployment, work absenteeism, and decreased productivity.
3. Treatment of IBD with biologic therapy is of questionable cost-effectiveness, as estimates on the costs versus benefits of therapy vary widely between studies; the likelihood of cost-effectiveness improves if reductions in indirect costs are considered.

Introduction

Crohn's disease and ulcerative colitis, the two main subtypes of inflammatory bowel disease, are chronic, incurable, inflammatory conditions with no well-defined cause and a variable natural history. Recent estimates suggest that the prevalence of IBD in the United States is approximately 440 per 100,000 persons, with an incidence rate of 15–20 per 100,000 per year [1, 2]. Moreover, the incidence rate is rising over time, particularly among the young [3]. Similar epidemiology is seen across economically developed nations located in temperate zones across North America and Europe [4]. Though IBD is less prevalent in nations with less-developed economies [5], the incidence in these areas is rapidly rising, and the reasons behind this increase

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in IBD incidence are speculative [3, 6]. Although IBD can develop at any age, the median age of diagnosis is approximately 35 for CD and 30 for UC [1]. Approximately one quarter of persons will be diagnosed in childhood or adolescence.

As IBD has minimal impact on mortality, a substantial cohort of persons with IBD will be impacted by its symptoms and complications over the course of decades. Over this time, persons with IBD may require ongoing specialist-based medical care, hospitalization for symptom flares, complications, and surgical management, and the long-term use of costly medications. The course of IBD is also heterogeneous between individuals, and thus management strategies must be individualized as well. Given that patients, providers, and third-party payers must be mindful that there are always economic limitations of the totality of care that can be provided, it is important to have an understanding of the costs incurred in the management of persons with IBD, and on how understanding these costs can be used to make decisions in the provision of care that leads to the best possible outcomes at an acceptable cost.

In this chapter, we will provide a brief introduction to the field of health economics, in particular, the basic concepts of economic evaluation, aimed at the lay practitioner, and explain how the analytic tools used in the field can be applied to IBD. Second, we will provide a review of economic analyses which have been performed in IBD. We aim to inform clinicians how these analyses can be used to guide clinical decision making, both in the treatment of individuals and for making global decisions on providing care to the overall population of persons with IBD.

Economics 101

The field of economics is largely concerned with the understanding how persons make decisions in the setting of resource scarcity, meaning that the resources available to individuals for consumption are limited, and that choosing to use a specific resource will provide benefits, though at a cost that will limit our ability to use these resources elsewhere. Health economics is a field of study which applies these principles to how decisions are made by the triad of patients, caregivers, and third-party payers while attempting to improve health. The health-care market is unique from other markets in some significant ways. Among these, most individuals have a limited ability to fully appreciate the benefits and drawbacks of health-care services, often referred to as information asymmetry. As a result, suppliers of health care have the ability to induce demand for health-care services independent of the actual needs of the patient or, conversely, withhold the supply of interventions. Second, most individuals have deferred all or part of the payment for health-care services to private insurers or to governmental agencies which act as health-care providers, insurers, or both. Therefore, patients are often shielded from the true costs of health care, and will consume more services than they would if they were paying on their own. Conversely, the primary goal of patients (maximizing health) is often at odds with those of the payers (minimizing cost). Therefore, many of the decisions

regarding the provision of health-care services are determined by how much the insurer is willing to pay, i.e., how much the insurer values the benefits related to the provision of that service.

Cost of Illness Studies

Disease-specific costing studies (cost of illness studies) are used to determine the value of the health-care resources used by persons with a specific condition over time, or by subgroups of interest within that population. Costs of care are generally divided into *direct costs* and *indirect costs*. Within the framework of IBD, direct costs refer to those which are incurred by the patient and/or the patient's insurer during the course of management of IBD. These include the costs associated with diagnostic testing, including tests to initially diagnose and guide management of IBD; fees and salaries paid to caregivers, including physicians, nurses, and allied health professionals; the structural costs of maintaining facilities such as hospitals and clinics where care is provided; and the costs of pharmaceuticals and medical interventions. *Indirect costs* refer to the impact that having IBD has on a person's ability to maximize their earning potential, and include how having IBD may impact on educational attainment or choice of vocation, how symptoms of IBD can interfere with the ability to obtain and maintain meaningful employment, one's ability to regularly attend to a held job (absenteeism) or on work quality or productivity while attending to a job (presenteeism). Indirect costs also refer to the loss of productivity to society because affected individuals cannot engage fully in their work. Indirect costs also include more intangible domains, such as the effects of IBD on social functioning, emotional state, and overall quality of life. Hence direct and indirect costs affect both the individual and society.

Comparative Economic Analyses

Comparative economic analyses refer to studies that compare the costs and effectiveness of competing treatments or therapeutic strategies with the general goal of maximizing health-related outcomes while minimizing costs. Performing comparative economic analyses requires a methodology for both (a) accurately and objectively measuring all costs and benefits associated with specific management and/or diagnostic strategies and (b) developing a framework for determining the relationships between the aggregated costs and benefits of a given diagnostic or management strategy. The relationship between costs and health outcomes is often expressed as a **cost-effectiveness ratio (CER)**, describing the average cost expended using a particular strategy in order to obtain a desired health outcome or prevent an adverse health outcome. In most instances, comparative economic analyses are performed to compare a new diagnostic or treatment strategy to an existing one, where the new

Table 21.1 Common terms used in comparative economic analyses

Cost-effectiveness	Treating persons with moderate-to-severe Crohn's disease with infliximab costs $18,000 to prevent one IBD-related hospitalization
Incremental cost-effectiveness ratio	Treating persons with moderate-to-severe Crohn's disease with infliximab costs an additional $100,000 to prevent one additional IBD-related hospitalization than would be seen if the same population was treated with azathioprine
Incremental cost-utility ratio	Among persons with moderate-to-severe Crohn's disease, the use of infliximab in place of azathioprine costs an additional $50,000 for each additional QALY gained

strategy is presumably more effective, but also more expensive. The metric used to determine "bang for the buck" is the **incremental cost-effectiveness ratio (ICER)**, which is the additional cost incurred to obtain one more unit of effectiveness (measured either as prevention of an adverse event or improvement in a health outcome) when using the more effective yet more costly strategy in place of the less costly/less effective strategy. In rare instances where a strategy is both less expensive and more effective than its comparator, it is said to be a **dominant** strategy.

In IBD, as in other disease states, the relative value of being in a specific health state is not immediately intuitive. Specifically, if one treatment strategy is shown to cost $25,000 on average to prevent each IBD-related surgery, whereas a competing strategy costs $25,000 on average to bring a symptomatic patient into clinical remission, it is not clearly obvious which situation is the most beneficial. To address this issue, attempts are often made to quantify the relative value of various health states using a common currency, referred to as a **health utility**. When assessing the health utility of health states, perfect health is assigned a score of 1, death is assigned a score of 0, and all other health states are assigned a score based on the perception of that health state on this scale. A list of health-care utilities for specific IBD health states is shown in Table 21.1. These health utilities can then be used in a **cost-utility analysis** to determine the cost per **quality adjusted life year (QALY)** gained, which theoretically allows for direct comparison between strategies with diverse potential outcomes.

Next, we also need to consider the concept of **willingness-to-pay (WTP)**, which takes into account that different payers may be more or less able or willing to spend money in order to optimize health. As an example, a person of limited wealth may be unable to spend $10,000 to gain an additional QALY, whereas this would not be an issue for someone of considerable means. Similarly, an insurance plan with high premiums may have a greater willingness to pay to gain a QALY than a less well-funded plan, and government payers in high-wealth countries will have a greater WTP than in countries with less-developed economies. Therefore the price point at which an intervention or diagnostic strategy becomes cost-effective is not uniform, but varies across health-care systems. In the United States, the acceptable WTP threshold is assumed to be between $50,000 and $100,000 per QALY gained.

Theoretically, it is possible to perform cost-effectiveness analyses by analyzing existing data from individuals with IBD who have been managed using different

diagnostic and therapeutic strategies, enumerating all costs and health-care gains to determine which strategy was most cost-effective. However, these data do not exist for most of the medical decisions we would be considering, and thus, we often rely on the use of economic models, where we attempt to project the costs that would be incurred and the benefits obtained through the care of patients treated under each strategy. These analyses are often limited by the uncertainty surrounding the costs of management strategies, particularly in how these costs may change over time, and also by uncertainty surrounding the likelihood of outcomes under complicated treatment strategies in a heterogeneous population. This is especially germane to IBD, where disease expression and natural history is variable, and there is rapid evolution of new diagnostic tools and drugs. Therefore, most economic models will employ **sensitivity analyses**, where the model is run under a wide range of possible costs and benefits, to determine under which baseline conditions of costs and benefits that a strategy becomes cost-effective.

Direct Costs of IBD

The direct costs involved in caring for the population of persons with IBD has changed dramatically over the past few decades [7], both due to an increasing disease prevalence, but also because of the evolution of medical management, most notable being the introduction of an increasing array of biologic agents [8–11]. The earliest costing study of IBD in the United States was performed by Hay et al. in 1992 [12]. At this time, medical options were essentially limited to corticosteroids, sulfasalazine, and antibiotics, with non-sulfa 5-ASA drugs like mesalamine just entering the marketplace. In this assessment, the direct cost of care expended in the management of Crohn's disease and ulcerative colitis was $1.2Bn and $0.5Bn in total, which worked out to $6561 per person with CD, and $1488 for each person with UC. Inpatient care, including surgical management was responsible for 80% and 47% of costs for CD and UC respectively, whereas medical therapies comprised a mere 10% of expenditures. Kappelmans et al. [7] reassessed the expenditure associated with the care of IBD in 2008, by which time infliximab was in increasingly wide use for persons with CD, and proprietary 5-ASAs were first-line therapy for UC. In this analysis of data from 85 health-care plans, the mean cost of care for CD and UC had risen to $8265 and $5066 respectively, and the share of costs due to medications had risen to 35% and 27% respectively. There is also significant variation between individuals in the costs of care. Kappelmans reports significantly higher costs on average for children and adolescents than for adults, but no differences between men and women. Bernstein et al., in a population-based analysis of Canadians with IBD in 2006 [13], found higher expenditures among persons in the first year following diagnosis, those with recent hospitalizations and surgery, and those using infliximab. Moreover, the mean costs of care rose from $9683 in the year prior to infliximab use to $31,330 in the year following infliximab initiation. The distribution of costs is also very left skewed, with a very small proportion of

persons with IBD being responsible for a very high share of the costs. Feagan et al. [14] reported that 25% of persons with IBD are responsible for 80% of the total direct costs of care. Similarly, Bernstein et al. reported that infliximab users, which despite being only used by 0.7% of the total IBD sample, comprised over half of the drug-related costs [13]. In the most recent assessment by Rocchi et al. [15] in 2012, the estimated annual costs of treatment had risen to nearly $12,000 per patient, with 45% being related to drug use. It can be anticipated that with the more widespread use of biologic agents, and the emergence of novel therapies like ustekinumab and vedolizumab, the cost of medical care for IBD will continue to rise, and it will likely not be offset by reductions in hospitalizations and surgeries.

Outside of North America, a similar shift is apparent in the proportion of costs related to medication use, though the overall costs are much lower. In an analysis of over 2000 Dutch IBD patients, van der Valk et al. [16] reported annual costs of €1476 and €595 for CD and UC respectively, with biologic use making up 64% and 31% of total cost in CD and UC respectively. Even taking current exchange rates into account, the costs of care are substantially lower on a per-patient basis, likely related to structural differences in the health-care systems. To date, there is little information about the direct costs of IBD management for countries with developing economies which have historically had a low prevalence of IBD, such as the countries of Southeast Asia, South America, and Africa. However, the incidence of IBD has been increasing in these regions; this, in combination with increasing industrialization and economic development, will undoubtedly lead to an increase in the demand for IBD-related health care [17].

Indirect Costs

The indirect tangible costs of IBD, being the loss of income and wealth from the patient's perspective, and a loss of productivity from society's perspective, are generally more difficult to estimate than the direct costs related to IBD care. Still, it is important to consider the impact that having IBD has on an individual's ability to earn an income, and on the quality and the quantity of their work output. Symptoms of IBD may be generally disabling, such that they or other consequences of disease activity impair a person from holding any type of employment. This may affect people with overwhelming fatigue, severe abdominal pain, or the consequences of being hospitalized, undergoing an operation, or recovering from surgery [18]. Persons with IBD may also have symptoms that impact on their ability to hold specific jobs [19]. As an example, diarrhea and/or fecal urgency would make it difficult, if not impossible, to hold a job where access to toileting facilities is limited. Furthermore, employers may not necessarily be able or willing to accommodate the medical needs of persons with IBD, including allowing attendance for often frequent physician visits, diagnostic testing, or infusions of biologic agents [20]. Last, parents or guardians of children with IBD may have to miss work in order to provide care when the child is too ill to attend school.

Employment/Workplace Participation

Overall, persons with IBD are less likely to participate in the workforce than otherwise healthy people. In the developed world, the rate of unemployment ranges from 3% to 13% lower in absolute terms among persons with IBD compared to age matched controls [15]. In an analysis of National Health Interview Survey, a representative population-based sample of US residents, nearly one-third of symptomatic persons with IBD were not in the labor force, which was more than twice as likely as otherwise healthy persons [21]. Rates of overall labor force participation were similar between CD and UC.

Persons with IBD also have a higher likelihood of leaving the workplace prematurely and obtaining long-term disability benefits. In the IBSEN cohort of Norwegians with IBD, 18.8% of persons with IBD had received long-term disability within 10 years of diagnosis, a rate nearly two times that of the general population, with the risk being highest among persons with markers of greater disease severity, or having undergone resective surgery [22]. Van der valk et al. [23] reported a higher rate of both full work-related disability and partial disability (having to take a less-intense job) among persons with IBD compared to the general population, with those with CD more affected than UC, though noted the rates were approximately one half of what was seen in a cohort of Dutch patients evaluated in the 1980s. A comparable number of persons with IBD reported long-term disability in a Canadian cohort of persons with IBD followed for over 12 years [24]. Long-term active disease and a lifetime history of major depression were associated with disability, whereas history of IBD-related surgeries or hospitalizations was not. Disability was reported at a higher rate in CD (19%) than in UC (11%) [24].

Absenteeism and Presenteeism

The need to take short-term leave or to miss days of work also occurs more commonly in IBD than in the general population. Gunnarson et al. analyzed the US Medical Expenditure Panel Survey between 1996 and 2006, and found that persons with IBD are more likely to miss work for illness in a given year (72% vs. 55%, $p < 0.001$), and miss an average of 4 additional days of work per year compared to controls [25]. Similar findings have been reported in multiple other studies. Presenteeism, or decreased productivity while still physically showing up to do work, was found in 62% of IBD patients, and 95% of those with active symptoms among a cohort of US persons with IBD [26]. Medical therapies, when effective in controlling symptoms, lead to significant improvements in absenteeism and presenteeism [27].

Education Attainment

There have been relatively few studies assessing how IBD diagnosed in childhood and adolescence affects school performance. Singh et al. linked the Manitoba IBD Dataset to an educational dataset that contained the marks received on standardized testing in mathematics and English taken in 12th grade. This study demonstrated no difference in the test marks between IBD and controls, or in the likelihood of graduating from school in the expected time [28]. Having concurrent anxiety/depression and those coming from a low-socioeconomic class did poorer on standardized tests. Mackner et al. found that children with IBD missed a greater number of school days per year than healthy controls (12.5 vs. 6.9 days, $p < 0.05$); 20% had missed 3 or more weeks of school per year compared to 4% of controls. However, no differences in GPA were seen [29]. Conversely, Ferguson et al. reported that approximately two third of adults with juvenile-onset IBD believed their IBD impacted on their education attainment, which raises the possibility that children with IBD may have changed their educational pathway to mitigate the effects of disease on attainment [30].

Estimation of Indirect Costs

Indirect costs are usually quantified by using the human capital approach, which assumes that productivity losses due to job loss, absenteeism, and presenteeism can be measured as a worker's average annual wage for their age (and potentially other factors, if known, such as sex and occupation group) until retirement. Rocchi et al. estimated costs due to productivity losses of approximately $4200 per Canadian with IBD, for a total cost of just under $1B [15]. In a systematic review of 18 papers enumerating indirect costs of IBD treatment, Kawalec et al. reported annual indirect costs of $8376 in North America and $6433 in Europe, albeit with the caveat that there was a significant amount of heterogeneity between studies in terms of how indirect costs were defined and quantified. Further, treatment of IBD with biologic agents led to significant reductions in the estimates of indirect costs, by increasing workplace attendance and productivity [31].

Comparative Economic Analyses in IBD

While there have been numerous CEAs and CUAs published comparing multiple treatment strategies in IBD, this review will focus on those which have been published in the last 24 months. In general, CEAs have a very short shelf life, as the costs of drugs and medical care can vary substantially over time, and the emergence of new drugs and novel treatment strategies make analyses comparing the older

strategies obsolete. Furthermore, there are few barriers preventing any research group from performing a CEA, which means that the literature becomes flooded with CEAs which have variable quality, lack of comparability, and often poor generalizability to general practice. Moreover, many of these studies are designed and performed by the manufacturers and marketers of the drugs under study, which creates incentives to design studies which are more likely to cast their product in a favorable light. While the International Society for Pharmacoeconomics and Outcomes Research has established quality guidelines for the performance of CEA [32], a critical review by Marchetti et al. in 2014 showed that few of the published studies evaluating cost-effectiveness of biologics in IBD have met these quality measures [33].

In an excellent systematic review, Huoponen et al. reviewed 25 published CEAs and CUAs evaluating the cost-effectiveness and cost utility of biologic agents for CD and UC in a variety of clinical settings [34]. Overall, they found a wide range of ICER per QALY gained with biologic treatment strategies. As an example, the ICER per QALY gained for using infliximab induction for moderate-to-severe UC ranged from dominance (implying that induction biologic therapy provides better outcomes at a lower cost) to €164,626 per QALY gained. In the realm of maintenance therapy for CD, the ICERs ranged from €118,015 to €549,335. Furthermore, sensitivity analyses performed within individual studies led to a wide range of potential ICERs, often ranging from dominance to ICERs in the tens of millions of dollars per QALY gained. Given these wide ranges of possible ICERs, it is difficult to draw any meaningful conclusions about the cost benefits of biologic therapy.

Still, there is a demand for understanding the economic implications of medical therapy in IBD, given that these medications have high upfront costs, yet when effective could potentially have significant impacts on future health-care resource production. From a societal perspective, the use of expensive yet effective medications early in the course of disease may prevent complications and their associated disability, leading to a reduction in the indirect costs of disease by reducing unemployment, underemployment, and absenteeism, which improved productivity. However, given the heterogeneity and lack of precision seen in previously performed comparative analyses, it seems unlikely that economic modeling will provide any definitive answers.

Conclusions

IBD is a common affliction whose management often requires the use of medical therapies that are costly and long-lasting, yet which will have significant direct and indirect medical costs if not optimally treated. Better studies are needed to quantify the true costs of IBD, as well as a balanced enumeration of costs and benefits associated with its treatments. Studies involving economic modeling, when performed, should be commissioned by impartial agents, and performed according to established quality guidelines. Given its increasing incidence and prevalence in both the

developed and developing world, as well as the continued emergence of new therapeutic options and the ongoing drive to shift to lower cost agents, the care of IBD will undoubtedly have a major impact on the budgets of health-care systems throughout the world.

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