Endoscopy in Inflammatory Bowel Disease

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Editors

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Preface

Why did we decide to publish a book on endoscopy in inflammatory bowel disease? The field of IBD has evolved dramatically over the last two decades and particularly treatment options have expanded and become increasingly sophisticated. To keep pace with this development, we have learned that it is important to make the right diagnosis at the right time and with the right tools in order to provide the best solution for these often challenging patients. Symptoms and clinical scores have taken a step back as we realized that both UC and Crohn's disease are often syndromes in which inflammation, dysmotility, bacterial overgrowth, malabsorption and visceral hypersensitivity all contribute to the clinical picture. We have learned that we need to quantify inflammation and structural damage in order not only to establish an objective scaffold for diagnosis but also to monitor disease activity and prognosis. Rightfully so, mucosal healing has become part of the vernacular in clinical practice and a mandatory endpoint in clinical trials. We all knew that gastroenterology is a contact sport but this progress has made us believe that an update in technical and clinical aspects of "visual" technologies was overdue.

Our book will take the reader through a beautiful historic overview of IBD from the "art of medicine" to the age of high-definition, high-resolution imaging and target-specific therapy. Because of their complementary role in diagnosis and management, we included several chapters reviewing traditional, established, and evolving radiological studies and, where possible, we provided a "user's guide" for the non-radiologist. It is only natural that the vast majority of data in the radiology chapters refers to Crohn's disease and its complications. As expected, we dedicated the bulk of this book to endoscopy from basic to advanced diagnosis, scoring systems but also pearls of wisdom accumulated by experienced IBD-ologists over decades of practice. We are also reviewing the role of newer endoscopic techniques such as video capsule and deep enteroscopy in the management of suspected or established Crohn's disease. Several chapters discuss endoscopic disease activity scoring systems while others review the assessment of mucosal healing and postoperative recurrence. There are several sections discussing the role of endoscopy in assessing and managing the patient with surgically altered anatomy including ileal pouches and everything that can go wrong about them. Other chapters discuss endoscopy as a therapeutic tool in patients with gastrointestinal complications such as strictures or massive bleeding. We have specifically addressed the role of endoscopy for neoplasia surveillance with special

emphasis on chromoendoscopy. Finally, there is a dedicated chapter on ERCP and its role in the diagnosis and management of PSC and other biliary complications, although we acknowledge that in this area we are only scratching the rather bumpy surface of the bile ducts.

These features make this volume an excellent resource for trainees, general gastroenterologists, and also for surgeons and experts in IBD who want to savor a nice slice of radiology or sharpen their skill in endoscopy or simply surprise themselves in how far the field of IBD has come and how far we still need to go. At the least, we are hoping to show the readers why we believe that IBD is such an amazing field that fascinates us every single day of our collective professional existence.

The editors draw on their collective decades of endoscopic experience and have solicited authorship from some of the best-known leaders in this field in the world. They have worked painstakingly to develop a user-friendly, easy-on-the-eye textbook that can be accessed both in print and online, while also providing a concise and reliable resource for anywhere between day-to-day and once-in-a-lifetime practice. We recognize that the field of IBD is a rapidly moving target but we think this volume is a pretty good place to start and a large part of it will remain current for many years.

The publishers are to be congratulated for their patience with our sometimes exhaustive attention to detail and quest for perfection and for developing a creative and easy to thumb through volume, which is further enriched by the richly represented images and online video demonstrations.

Seattle, WA, USA — Richard Kozarek, MD
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We would like to thank Diane Lee and Maureen Pierce for their methodical work in keeping us organized and up to task throughout the creation of this book and for keeping everybody else on a tight timeline at the expense of hundreds of friendly or, on a case-by-case basis, sometimes pestering emails.

We are also grateful to our families for their patience in putting up with countless hours and days of absence from the living room while we were glued to our computers working on this volume.

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Part I

Background

1 The Evaluation, Diagnosis, and Treatment of Inflammatory Bowel Diseases over the Past 100 Years: A Brief Review

Frank I. Scott and Gary R. Lichtenstein

Early Descriptions of Inflammatory Bowel Disease

The diagnoses of Crohn's disease (CD) and ulcerative colitis (UC), the two main subtypes of inflammatory bowel disease (IBD), have been well characterized from a phenotypic point of view over the past 100 years. After several decades of refining the terminology used to describe the inflammatory bowel diseases, we have also begun to peel away at the complex pathophysiology of these distinct yet overlapping diseases over the past 20 years, determining what genetic, immunologic, microbiologic, and environmental characteristics that predispose and result in patients developing IBD. With more than 163 single nucleotide polymorphisms implicating the role of various MHC complex proteins, bacteria sensing receptors, autophagy signaling molecules, and cytokine pathways, our understanding of the pathophysiology of these disorders has advanced greatly over recent decades [1]. These advances have led to a myriad of new therapies, including monoclonal antibodies targeting cytokines such as Tumor Necrosis Factor-α(alpha), signals for leukocyte trafficking, and interleukins to add to the classic agents such glucocorticoids and the immunomodulators such as the thiopurines, azathioprine and 6-mercaptopurine, and methotrexate.

With the pace of discovery moving at such a rapid rate, it is often challenging to truly appreciate just how many advances have been made in describing and understanding these often debilitating conditions. While their names were first coined early in the 1900s, descriptions of chronic gastrointestinal upset and diarrhea have been appreciated in the historical record for thousands of years, with noted descriptions by Hippocrates, Aretaeaus of Cappadocia, and Soranus of Rome [2, 3]. Differentiation of chronic diarrheal illnesses from acute infectious pathogens was not possible in these formative years, however. Later descriptions of bloody diarrhea, coined as "bloody flux" by Thomas Sydenham in 1669 and 1670, likely included both chronic and acute forms of diarrhea [4]. The term "ulcerative colitis" was first used in the literature to describe this spectrum of disease in 1859, and "Crohn's disease" was later first described as a separate pathophysiologic entity by Dr. Burril Bernard Crohn, then referred to as terminal ileitis, in 1932 [2, 3].

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In this chapter, we will briefly describe the history for each of these chronic inflammatory gastrointestinal maladies, first with the early clinical descriptions of each disease entity, followed by the examples of the early laboratory, radiographic, and endoscopic evaluations. We will also discuss early leading hypotheses in the pathophysiology of these disorders, as well as the changes these theorems prompted in clinical management over the last century as we have expanded our armamentarium for these diseases.

Early Descriptions of Ulcerative Colitis and Related Complications

Throughout ancient history there have been reports of chronic diarrheal illnesses, often coupled with hematochezia, abdominal pain, and a myriad of additional symptoms [3]. It is difficult in many of these records, however, to discern infectious causes of dysentery and diarrhea from those secondary to one of the inflammatory bowel diseases. Despite these challenges, most historians recognize several well-described cases as likely representing inflammatory bowel disease. One of the first well-documented cases of chronic diarrhea that was thought to have represented ulcerative colitis were reported in the 1700s [3]. The case of Sir William Johnson, a 40-year old male with an 18-year history of bloody diarrhea who later developed several years of intermittent fever, abdominal pain, and jaundice, represents one of the first likely cases of ulcerative colitis, and was likely also afflicted with primary sclerosing cholangitis, as described by Burch and colleagues [5]. It has also been suggested that Bonnie Prince Charles, known as "The Young Pretender," may have also suffered from ulcerative colitis, which was interestingly cured by adopting a milk-free diet [3, 6]. As the concept of performing autopsies became more common throughout the 1800s, pathologic descriptions of colonic specimens in patients with chronic diarrhea became more common as well, and it is thought that many of these descriptions likely represent IBD [3].

The term "ulcerative colitis" first began to appear in the literature in the 1800s. In 1859, a case report by Sir William Wilkes included what is recognized as the first use of the term in a case report of a woman with chronic diarrhea and fever. While the term ulcerative colitis was used to describe this case, it is important to note that on autopsy she was found to have transmural colonic and terminal ileal inflammation [7]. As such, this may have actually represented Crohn's disease, presciently highlighting the diagnostic dilemma that often exists with these disorders even today. With slowly growing awareness, several additional case series of chronic diarrhea, hematochezia, and other symptoms were subsequently published over the remainder of the nineteenth century [2, 3].

Interest in categorizing and describing the colitides increased greatly at the turn of the century, in part due to the 1909 London Symposium on Ulcerative Colitis, held by the Royal Society of Medicine [8]. During this meeting, 317 cases of ulcerative colitis, including the signs, symptoms, possible etiologies, pathologic appearances, potential treatments and surgical procedures, outcomes, and complications were reviewed and debated. These conversations were used to attempt to define the ages of those most afflicted, the symptoms typically experienced, and the impacts of available therapies. This was followed by additional reports from by H. P. Hawkins and Lockhart-Mummery [9, 10]. Numerous additional reports were published throughout the ensuing two decades describing the disease outside of the United Kingdom, findings on barium study, the association of UC with polyposis, and a case series of the disease in children [11–17].

With increased awareness of ulcerative colitis also came multiple reports of its extra-intestinal manifestations. Known complications of the disorder, such as an increased risk of malignancy, erythema nodosum, and hepatic abscesses, possibly representing primary sclerosing cholangitis, were also described in the years after the Royal symposium [18–21]. In the 1930s, further reports of the disorder being associated with thrombotic events, "hepatic insufficiency," and nephrolithiasis also emerged [3, 22–24].

Reports of the course of ulcerative colitis and its effect on pregnancy also emerged soon after the recognition of this disease entity.

While there were some reports earlier, including at the 1909 Royal College symposium, the first publication dedicated to the topic of pregnancy and ulcerative colitis was published in 1931 by Barnes and Hayes, describing the plight of three women who developed ulcerative colitis during their pregnancies [25]. In 1951, a larger cohort of 33 women with ulcerative colitis, with 46 gestations, was described by Abramson and colleagues [26]. Mortality rates for those that developed ulcerative colitis while pregnant were particularly high in this study. A subsequent study did not confirm this increased risk of mortality in a cohort of more than 100 women, though a study by Crohn and colleagues demonstrated that disease activity did appear to be modulated by pregnancy, particularly during the first trimester and immediately after childbirth [27, 28]. Both the Mayo clinic and Truelove and Willoughby later published data consistent with these studies, with an 83 % and 81 % live birth rate, respectively, though the latter study did appreciate lower birth weights, particularly among mothers with active disease [29–31]. Collectively, these findings are consistent with our current understanding of ulcerative colitis and pregnancy, demonstrating an increased risk of pre-term labor, possible risk of increased disease activity for some during pregnancy, and no significant increase in infant or maternal mortality.

The risk of colorectal cancer with ulcerative colitis was also first recognized in the early twentieth century. Crohn and Rosenberg are credited for one of the first case reports of this association in 1925, followed by the first case series of ten patients by Bargen 3 years later [15, 32]. While there were several additional case reports documenting this association, MacDougall and colleagues published one of the first case series attempting to estimate the increased risk of malignancy, describing five cases of malignancy in a cohort of 154 patients with ulcerative colitis [33]. Two additional reports in 1959 and 1964 confirmed this increased risk [34, 35]. Attempts to quantify the actual degree of elevated risk estimated that this risk approximated 60 % in a 1971 study by Devroede and colleagues [36]. While ulcerative colitis is still considered to increase the risk for colorectal cancer, more recent data has suggested that this may be a lesser effect than previously appreciated [37].

Classification, Natural History, and Severity Indices in Ulcerative Colitis

As knowledge of the disease expanded over the initial decades of the twentieth century, so did attempts to generate sub-classifications, both for descriptive purposes and in attempts to define prognosis. Truelove attempted to create subcategories of ulcerative colitis based on symptomatology, defining *chronic intermittent* and *chronic continuous* subtypes of UC [38]. While these official classifications are no longer used today, they do emphasize the degree of variability in the clinical course of these disorders. Other names that began to propagate within the literature also serve this purpose. These descriptors included nonspecific colitis, idiopathic proctocolitis, indeterminate ulcerative colitis, streptococcal colitis, rectocolite hemorrhagique, colitis gravis, azotemic colitis, granular proctitis, mucous colitis, mucosal colitis, and rectocolitis ulcerosa criptogenetica [3]. Over recent years, these terms have been replaced by ulcerative colitis alone, and attempts at classification are now typically limited to description of disease extent, such as proctitis, left-sided colitis, and pancolitis [39]. This classification has been shown to have prognostic implications, with extent clearly being associated with disease progression, probability of colectomy, risk of neoplastic complications, and mortality [40–42].

Consistent with the growing desire to better classify the disease for research purposes and prognostic value, several systems were developed over the latter half of the 1900s to describe disease severity in UC [43]. The first attempt at deriving a risk score for the disease was the Truelove and Witts Severity Index, first published in 1955 in a clinical trial describing the efficacy of steroids in UC [44]. This score was comprised of 6 factors, including number of bowel movements per day, presence of hematochezia,

fever, pulse, serum hemoglobin, and erythrocyte sedimentation rate (ESR). While this scale utilized easily measurable symptoms and laboratory measures, it lacked validation and did not generate a true disease score. This scoring system was employed for two trials evaluating steroid efficacy in ulcerative colitis [44–46].

The next disease classification score for ulcerative colitis to be described was the Powel-Tuck index, which was used to classify treatment response and outcomes in a trial of steroid dosing schemes. As opposed to the scale generated by Truelove and Witts, the Powel-Tuck index generated a severity score using ten risk factors: general health, abdominal pain, bowel frequency, stool consistency, bleeding, anorexia, nausea or vomiting, abdominal tenderness, extraintestinal complications, and fever [47]. An additional variant of this index included sigmoidoscopic appearance, making this the first index to include an assessment of endoscopic severity in ulcerative colitis. Utilization of the Powel Tuck index was limited, however.

In 1988, the Clinical Activity Index (CAI) was first described, used to determine outcomes in a clinical trial comparing mesalamine to sulfasalazine by Rachmilewitz and colleagues [48]. This index was comprised of seven factors, and included number of stools, blood in stools, a global assessment index, assessment of abdominal pain or cramps, fever, extraintestinal manifestations, and laboratory findings. It did not include an endoscopic evaluation, using only these clinical factors. Unlike disease activity scores before it, it was validated in another study of 5-ASA based medications, however [43, 49].

The CAI was followed by the Seo index, also known as the Activity Index, which was one of the first scores in ulcerative colitis developed using advanced statistical methods. Using multivariate logistic regression to assess 18 factors including symptoms, laboratory data, and colonoscopic evaluation in a cohort of 72 patients, the final model included weighted assessments of hematochezia, number of bowel movements, degree of ESR elevation, hemoglobin, and albumen [50]. This score has been used to predict colectomy, and has also been demonstrated to predict response to infliximab in clinical trials [51–53].

There have also been two scores that were developed by modifying previously developed scores. In 1990, Lichtiger and colleagues developed a clinical index based on the original Truelove and Witts score, which would come to be known as the Lichtiger score or Modified Truelove and Witts Severity Index. This score is comprised of number of stools, nocturnal stools, hematochezia, fecal incontinence, abdominal pain/cramping and/or tenderness, general well-being, and utilization of anti-diarrheal agents [54]. This score was developed for a study evaluating the efficacy of cyclosporine in the treatment of severe, refractory ulcerative colitis. It has subsequently been utilized in clinical trials of several recently developed therapies, including infliximab and an anti-adhesion monoclonal antibody, vedolizumab [55, 56]. As with the Lichtiger score, the Simple Clinical Colitis Activity Index was designed using the previously developed Powell Tuck index, with the addition of assessment for urgency, a sigmoidoscopic score, nocturnal symptoms, and a general well-being component. Walmsley and colleagues used these 13 components, in combination with multivariate regression in a population of 57 patients to determine those factors most associated with disease severity. The final model yielded six factors: bowel frequency (day), bowel frequency (night), urgency of defecation, blood in stool, general well-being, and extracolonic manifestations [57].

The two most comprehensive and most utilized clinical assessment tools used today incorporate both clinical indices and endoscopic scores. The UC Disease Activity Index (UCDAI, also known as the Sutherland index) has been employed in numerous clinical trials. Developed in 1987 in a clinical trial of topical mesalamine enemas, this scoring system contains only four components: stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity [58]. The Mayo score, developed in the same year by Schroeder and colleagues for a trial of oral mesalamine, also consists of 4 items: the presence of rectal bleeding, sigmoidoscopic findings, bowel movement frequency, and a physician's global assessment [59] (Table 1.1). In a subsequent analysis, Lewis and Lichtenstein assessed employing only the clinical characteristics of the Mayo score,

Table 1.1 Components of the Mayo score and their associated scores

Components of the Mayo score		
Component	Description	Score
Stool frequency	Normal	0
	1–2 stools/day more than normal	1
	3–4 stools/day more than normal	2
	>4 stools/day more than normal	3
Rectal bleeding	None	0
	Visible blood with stool less than half the time	1
	Visible blood with stool half of the time or more	2
	Passing blood alone	3
Mucosal appearance at endoscopy	Normal or inactive disease	0
	Mild disease (erythema, decreased vascular pattern, mild friability)	1
	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
	Severe disease (spontaneous bleeding, ulceration)	3
Physician rating of disease activity	Normal	0
	Mild	1
	Moderate	2
	Severe	3

The Mayo score is calculated by summing the results from each section of this score system, giving a total from 0 to 12 points

compared both to the full Mayo score and partial Mayo score with endoscopic components, demonstrating that these clinical measures predicted clinical outcomes with equivalent sensitivity and specificity [60].

The most recent endoscopic index is the only index that has been validated. It is called the UCEIS (the ulcerative colitis endoscopic index of severity) [61]. With other endoscopic scoring systems, there was felt to be a high index of variation between readers. Therefore, a new scoring system, which incorporated two phases of development, was created to generate more repeatable measures of severity endoscopically. In the development of this scoring system, there was an initial phase dedicated to determining which factors were most consistent among readers, utilizing descriptors including vascular pattern, edema, friability, bleeding, the presence of mucous, erosions, and ulceration. After assessing these factors among 10 observers and a pool of 24 videos of colonoscopy, they were then further assessed among a pool of 30 investigators assessing 60 videos. Generalized linear modeling was then employed to determine the final components, which included vascular pattern, bleeding, and erosions (Table 1.2).

Table 1.2 Final components of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), as described by Travis and colleagues

Ulcerative colitis endoscopic index of severity		
Component	Description	Score
Vascular pattern	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins	1
	Patchy obliteration of vascular pattern	2
	Complete obliteration of vascular pattern	3
Bleeding	No visible blood	1
	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away	2
	Some free liquid blood in the lumen	3
	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa	4
Erosions and ulcers	Normal mucosa, no visible erosions or ulcers	1
	Erosions: Tiny (≤5 mm) defects in the mucosa, of a white or yellow color with a flat edge	2
	Superficial Ulcers: Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial	3
	Deeper excavated defects in the mucosa, with a slightly raised edge	4

A score is selected for each component and then summed to compute the final score

Modified from Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut 2012 Apr;61(4):535-42 with permission from BMJ Publishing Group Ltd

The Mayo score, UCDAI, and most recently the UCEIS have become the preeminent scoring systems for characterizing disease severity and response to therapy in clinical trials, though none of the systems developed to date have gained widespread use outside of the realm of clinical trials, likely due to lack of validation in this setting and difficulty in administration. Despite their limited clinical utility, these systems have allowed for further assessment of disease severity, have clarified how we describe ulcerative colitis as clinicians, and have greatly impacted our ability to conduct rigorous clinical research.

Early Descriptions of Crohn's Disease and Related Complications

As with ulcerative colitis, there are several descriptions of individuals throughout history that have been considered to possibly have Crohn's disease when reviewed retrospectively. One of the first possible cases may have involved English Royalty: King Alfred the Great, who was the King of Wessex from 871 to 899 [62]. Alfred was known to have suffered from abdominal pain, particularly with eating, throughout his life. King Louis XIII of France was also thought to have Crohn's disease; he was described as having had years of diarrhea, intermittent fevers, and perirectal abscesses [3, 63]. When he passed away at age 42, his autopsy demonstrated fistulae, abscesses, and ulcers involving the small bowel and colon, though there is some debate as to whether this could represent enteric tuberculosis. Another potential pathologic description came from Morgagni, a famed pathologist of the 1700s, where he described a 20-year old male with terminal ileal narrowing, inflammation, and perforation, with mesenteric lymphadenopathy [64].

Several similar case reports were published in the 1800s in England and Ireland. Combe and Saunders published a case of a patient with diarrhea, abdominal pain, and ileal ulceration and shortening in 1813 [65]. Similarly, in 1828, Abercrombie described a 13-year old patient with similar complaints. Fielding and Colles reported on a patient in Dublin in 1830 with diarrhea, as well as profound fistulizing disease of the perineum [66–68]. Fielding published one of the first case series on the subject, summarizing more than 30 patients from the second half to the eighteenth century with symptoms consistent with Crohn's disease [66]. Multiple additional reports were subsequently published preceding the turn of the century, with descriptions including toxic dilation of the bowel, mesenteric lymphadenopathy, liver involvement, and enterovesicular fistulization [3, 62].

As with ulcerative colitis, recognition of Crohn's disease, referred to at the time (and to this day) as "regional enteritis," continued to increase in the early 1900s. With this increasing recognition also came more detailed reports of the underlying pathology of this disorder. Lartigau published a review in 1901 of the literature to date from Europe, as well as a detailed description of an individual with weight loss, abdominal pain, and diarrhea alternating with constipation. On autopsy, he was appreciated to have thickening of the distal small bowel and cecum, with a rigid ileocecal valve. Histologically, Lartigau described multiple lymphoid aggregates without central necrosis; i.e., non-caseating granulomas. This clearly distinguished this case from intestinal tuberculosis [69]. Similar granuloma were also described by Moschowitz and Wilensky in 1923 in a case series of four patients [70]. In 1913, Sir T. Kennedy Dalziel described 13 cases with similar clinical and pathologic findings, also describing inflammatory involvement of the mucosa, submucosa, and muscularis mucosa, consistent with transmural disease that distinguishes Crohn's from ulcerative colitis [3, 62, 71].

In 1932, Burrill Crohn, Leon Ginzburg, and Gordon Oppenheimer published a landmark paper in the *Journal of the American Medical Association* entitled "Regional Ileitis: A Pathologic and Clinical Entity."[72] In this seminal work, the authors described 14 patients with "cicatrizing" inflammation involving the small intestine, and in particular, the terminal ileum. They also highlighted key characteristics of the disorder, such as ulceration, peritoneal irritation, resultant chronic

intestinal obstruction, and penetrating phenomenon, all of which are still considered hallmarks of the disorder today. In the published pathologic description, obtained after surgical resection of the involved ileal segment, acute and chronic inflammation was noted, as was giant cell infiltration. This work was followed by the presentation and publication of a cohort of 52 individuals with similar findings by Oppenheimer and Ginzburg in the same year [73].

The subsequent appearance of the term "Crohn's disease" first occurred in 1933 in a case report by Harris [74], and subsequently the following year in a report by Cushway [75]. The application of this eponym was not universally well-received, however. Several other variants existed initially, including "Saunders-Abercrombie-Crohn's Ileitis," and "Crohn-Dalziel" disease [3, 76, 77]. Contention also may have existed between the authors of the 1932 paper from Mount Sinai, with Dr. Ginzburg submitting a potentially incendiary letter to *Gastroenterology* in 1986 questioning the equivalent contribution of the three authors of this original descriptive paper [78]. Despite this protestation and initial confusion, the name Crohn's disease has become the most widely accepted name for this disorder.

Over the next several decades the clinical entity that was to come to be known as Crohn's disease was further described and categorized as clinicians began to recognize the full extent of the disease process. Inflammatory masses were characterized by Fischer and Lurmann [79]. Brown, Bargen, and Weber described a case of more extensive small bowel involvement in 1934 [80]. Gastric involvement was later described in 1949 at the Lahey clinic by J. R. Ross, and esophageal disease was described the following year by Franklin and Taylor in London [81, 82]. Crohn's colitis was first described in 1952 as "segmental colitis" by Wells, and this was subsequently followed up by a case series of 11 patients who initially presented with small bowel disease but subsequently developed colitis [83, 84]. Isolated Crohn's colitis was further accepted after publications by Brooke, Morson and Lockart, and Cornes and Stecher in 1959 and 1961 [85–87].

Classification and Clinical Indices in Crohn's Disease

With improved diagnostic classification of Crohn's disease came increased understanding of the epidemiology and course of the disease. One pivotal observation appreciated in the mid-twentieth century was that the incidence of Crohn's disease was possibly increasing. Kyle and colleagues postulated this in their work published in 1963, examining possible cases of regional enteritis in Scotland [88]. Similar increases in prevalence were appreciated in Norway in 1966 [89]. While there is reasonable concern for detection bias in these early studies due to increasing awareness of the disorder, there have subsequently been multiple studies confirming both increasing prevalence and incidence over the course of the twentieth century, including a large systematic review by Molodecky and colleagues examining 260 publications from North America, Europe and Asia published from 1920 to 2008, clearly documenting these trends [90].

As with ulcerative colitis, several clinical indices have been developed over the past several decades to better characterize disease severity in Crohn's disease [91]. Many of these instruments were developed in the context of clinical trials. One such instrument was the Crohn's Disease Activity Index (CDAI), which remains a mainstay of disease activity assessment in trials today [92]. This validated scoring system was designed using multivariate logistic regression from a pool of 18 disease-related symptoms. The significant predictors of disease severity were determined to be abdominal pain, general well-being, the frequency of diarrhea, the use of loperamide or diphenoxylate, the presence of extraintestinal or systemic manifestations of disease, the presence of abdominal masses, hematocrit, and weight (Table 1.3). These items are then assigned specific multipliers, yielding a sum from 0 to 600, with <150 being considered in remission, 150–219 having mildly active disease, and 219–450 having moderately active disease. While validated in a separate cohort, there remain some concerns with the inclusion of potentially subjective measures

Table 1.3 The Crohn's Disease Activity Index (CDAI) is calculated over 1 week, using weights for each factor, and then each factor is summed

The Crohn's Disease Activity Index (CDAI)	
Component	Multiplying factor
Number of liquid or soft stools over 7 days	2
Presence of abdominal pain, sum of scores over 7 days from 0 to 3 (none to severe)	5
General wellbeing, sum of scores over 7 days, from 0 to 4 (good to severe)	7
Use of lomotil or opioids for diarrhea	30
Presence of a complication of Crohn's disease[a]	20
Presence of abdominal mass (0 = no, 1 = yes)	10
Deviation from normal hematocrit: Men: 47-Hct Women: 42-Hct	6
Percentage deviation above or below standard weight based on standardized life table used by Metropolitan Life	1

A score <150 is considered consistent with remission

[a]Complications are given 1 point for the presence of each and include

- Arthralgias or arthritis
- Iritis or uveitis
- E. Nodosum, pyoderma gangrenosum, or aphthous stomatitis
- Anal fissure, fistula, or abscess
- Other fistula
- Fever >37.8

such as general well being and severity of abdominal pain in this system. In addition, while useful from a research perspective, the complicated scoring system and requirement for 7-day logs of diarrhea and pain-related symptoms have limited its application in routine patient care; as such, the CDAI has not been applied routinely in clinical practice [91]. Despite these limitations, this system has been used in numerous clinical trials of agents such as mesalamine, budesonide, 6-mercaptopurine, cyclosporine, and infliximab in both induction and maintenance of remission [93–98]. It is important to note that future drug approval may be less dependent on scoring systems such as the CDAI and more dependent on efficacy in patient-reported outcomes [99–101].

A simpler alternative to the CDAI is the Harvey Bradshaw index, which applies point-based scores for general well being, abdominal pain, number of liquid stools per day, the presence of an abdominal mass, and extraintestinal manifestations [102]. This score also has the advantage of eliminating longer recall and not requiring laboratory-based measures. In their original publication on this scoring system, Harvey and Bradshaw demonstrated that this score correlated well with the CDAI in a group of 112 patients. Despite this strong correlation and its relative ease of use, the Harvey Bradshaw index has not gained considerable traction in clinical research, though it was used in a trial assessing the ability of 6-mercaptopurine to induce steroid-free remission in children [103]. Several additional "simplified" scoring systems have been developed, including the Cape Town index and the Organisation Mondiale de Gastronterologie (OMGE), and while these validated scoring systems have been shown to correlate with each other, they also have not gained widespread use [104, 105].

Highlighting the prevalence and severity of fistulizing disease, several scoring systems have been developed specifically to assess response of this complication to specific therapies, as it was felt that this was not adequately captured by the CDAI [91, 106, 107]. The Perianal Disease Activity Index (PDAI) assesses discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration to generate a score from 0 to 20. This tool has also been used in a number of clinical trials involving peri-anal disease. An alternative scale assessing percentage change in fistula drainage has also been developed and utilized in a number of clinical trials, with a cut-off of >50 % decrease in drainage considered to be a clinically meaningful improvement in symptoms [106].

One potential alternative scoring system that focuses on quality of life of individuals with IBD was subsequently developed in 1989 by Guyatt, Mitchell, and colleagues. This questionnaire, known as the IBDQ, removed the physician assessment from the scoring system, further simplifying administration of the device [108]. The IBDQ consists of a 32-item questionnaire that assesses various aspects of social functional status, emotional well-being, systemic symptoms, and bowel-related

symptoms. Both this questionnaire and a shortened version have been validated, and both can be self-administered [109, 110]. Since its development, the IBDQ has become the standard device used to assess quality of life in clinical trials. It was also utilized to develop utilities for various disease states; these estimates have subsequently been used in multiple modeling studies in therapies for inflammatory bowel disease [111].

Scoring systems to assess endoscopic activity in Crohn's disease have also been developed. The first validated instrument of endoscopic activity was the Crohn's Disease Endoscopic Index of Severity (CDEIS), developed by the GETAID group in France in the late 1980s [112, 113]. The CDEIS contains a total of six variables, including number of colonic segments with deep ulceration, superficial ulceration, segmental surfaces containing pseudopolyps, healing ulceration, swelling, erythema, ulceration or stenosis, and the presence of ulcerated and non-ulcerated stenosis in any segment. This scoring system generates a score from 0 to 44, with higher numbers indicating more severe disease involvement. A similar scale has been developed for assessment of the ileocolonic anastomosis in individuals who have required segmental resection; this scoring system is known as the Rutgeerts score, and uses the degree of ulceration and ileitis in the neoterminal ileum to determine a score of 0–4 to predict the likelihood of disease recurrence [114, 115]. As with the aforementioned clinically derived scores, these systems have not routinely been employed in patient care, though the common descriptors used in the scoring system are routinely employed to evaluate disease severity more generally.

Laboratory and Radiographic Evaluation Over the Past Century

Laboratory Abnormalities

Numerous attempts have been made over the years to determine if any laboratory markers of disease activity or severity exist in Crohn's disease and ulcerative colitis. Clinical findings have been considered to be unreliable at times, and endoscopic scores add increased risk and cost to patient assessment for those that have known inflammatory bowel disease. While there have been several candidate laboratory tests over the past century, few of these markers remain in clinical use today. The initial laboratory abnormalities that were appreciated consisted of basic tests performed on initial assessment. Later, as researchers hypothesized what the underlying pathophysiology of the disease was, there was growing need for serologic or fecal tests to assess for allergy, test for markers associated with inflammation such as lysozyme, erythrocyte sedimentation rate (ESR), or C reactive protein (CRP), or attempt to detect specific microbial components.

Imaging

For many decades, the mainstay of imaging in ulcerative colitis and Crohn's disease consisted of barium studies; i.e., barium enema and small bowel follow-through [3]. There were several case reports of the appearance of the colon in inflammatory bowel disease in the first half of the twentieth century, including publications in 1913 by Stierlin and Kienbock and a subsequent report by Kantor in 1927 [3, 116–118]. While several additional case series would be published over the next several decades, it would be several decades before researchers would attempt to correlate these findings with outcome. A longitudinal cohort published by Ricketts, Kirsner, and Palmer in 1948 attempted to ascertain what factors on barium enema predict progression. The researchers noted a low progression rate, however, hampering this analysis [119]. In 1968, de Dombal and colleagues, attempted to discern the prognosis of classic radiographic findings in a larger cohort [120]. In this important work, de Dombal described a cohort of ulcerative colitis patients who had received 340 barium enema studies, describing such classic radiographic findings as decreased colonic length, tone, caliber, and distensibility, reduced haustration, and the presence of ulceration, correlating them to

disease severity and duration, as well as response to conventional therapies. Not unsurprisingly, signs consistent with fibrosis and scarring were associated with increased duration of disease in this study, and decreased colon length was associated with decreased disease activity, likely representing "burnt-out" disease. Ulceration, decreased tone, polyps, and serration all indicated a worse prognosis in the coming year.

Barium-based descriptions of Crohn's disease were published in its seminal description in 1932. Crohn carefully described that the barium enema was frequently negative in these patients, with the exception of ileocecal valve abnormalities, distinguishing it from ulcerative colitis. He also describes changes on "barium meal," or what we refer to as a small bowel follow-through (SBFT), such as distended loops of terminal ileum with delayed motility, puddling of contrast material likely representing ulceration, and stasis, as well as fistula and stricturing changes [72]. In 1934, Kantor published a case series of six cases at Mount Sinai hospital in the *Journal of the American Medical Association*, also describing ileal thickening and ulceration [121].

Barium studies played a key role in the early evaluation and recognition of Crohn's colitis [3]. Bargen and Weber described a series of 23 patients with migratory regional colitis, which is now felt to be consistent with Crohn's disease [122]. Marshak appreciated colonic changes in individuals with regional enteritis as well in 1951, and presented these findings at the American Gastroenterological Association annual conference in 1955, describing the difference between these imaging studies and those seen with ulcerative colitis [3]. In 1959, he published a significant work describing 8,000 individuals with regional enteritis and 4,000 with granulomatous colitis, sparking a significant increase in research into distinguishing the latter from ulcerative colitis [123].

Over the remainder of the twentieth century, barium enema and small bowel studies remained the mainstay of radiographic evaluation of these diseases. While standard CT scans were useful in assessing penetrating lesions and abscesses, they often lacked sufficient sensitivity to discern fine mucosal abnormalities. Sensitivity and specificity of the upper GI series could be augmented with the placement of a nasojejunal tube and enteroclysis, though this was time consuming and particularly uncomfortable [124]. Initial description of the technique of enteroclysis is credited to Dr. Hans Herlinger of the University of Pennsylvania. Recent technologies have augmented our radiographic armamentarium, however. CT enteroclysis (CTE) (originally described by Dr. Dean Maglinte of Indiana University) has demonstrated promise, particularly in Crohn's disease. Using both IV contrast and a larger volume negative oral contrast medium coupled with thin cut imaging, CTE has demonstrated improved sensitivity in comparison to small bowel barium studies in several small series in detecting subtle mucosal changes, while adding the ability to detect classic CT findings such as mesenteric fat stranding, mucosal enhancement, abscesses, and fistulae [124]. Wold and colleagues demonstrated improved diagnostic sensitivity in a cohort of 20 patients with CTE compared to SBFT, correctly identifying 10/13 CD cases in a cohort of 20 patients, compared to 8 of 13 by SBFT [125]. In 1997, Vassilios Raptopolous, from Beth Israel Hospital in Boston, MA, was credited with the first description of CT enterography. Raptopolous and colleagues described 22 individuals with CD, comparing CTE to SBFT, and noted that 4 additional findings were appreciated in the CTE group compared to SBFT, while Mazzeo and colleagues demonstrated an 86 % sensitivity and 100 % positive predictive value for findings with CTE in a series of 33 patients [126, 127]. However, with this improved diagnostic accuracy comes potential increased risk due to radiation exposure as well.

Another new technology, magnetic resonance enterography (MRE), aims to eliminate this risk, using oral contrast and IV gadolinium, and several studies to date have demonstrated superiority of this technique over small bowel imaging as well [128–130]. Further research is needed to determine if MRE and CTE are equivalent, however, and one must also account for differential in costs and the age of the individual when determining which procedure is ideal as well. Collectively, however, these techniques offer

new means of assessing the severity of disease for the clinician, using less invasive means than previously available.

Early Endoscopic Descriptions in IBD

Colonoscopy is a key component in the modern evaluation of patients with inflammatory bowel disease. However, for much of the twentieth century, this technology was profoundly limited both in its technology and applicability.

The majority of colonic mucosal examinations early in the history of IBD were performed at the time of autopsy. Technology in the first half of the twentieth century likely contributed to this lack of exploration. Early rigid sigmoidoscopy consisted of a simple tube, with the operator utilizing a headlamp for better visualization, and the addition of a distal light to the rigid scope did not occur until 1903 [131, 132]. These devices were soon used in the evaluation of ulcerative colitis, despite their limitations. The first endoscopic descriptions in inflammatory bowel disease involved rigid sigmoidoscopy in patients with ulcerative colitis. The first of these reports was described by John Percy Lockhart-Mummery at the same seminal meeting where many physicians used to describe the first large case series of ulcerative colitis in 1909 in the London [9]. In this seminal report, Mummery described rigid sigmoidoscopy as a potentially safe procedure if performed with minimal insufflation. In addition, he provided some of the first endoscopic descriptions of the UC, describing various degrees of ulceration "extending over a large area, the mucous membrane being excoriated and red"[9].

There were few case reports devoted to sigmoidoscopic diagnosis of Crohn's disease early after its initial description, likely given the extent and location of the disease along with the previously described delay in recognizing colon-specific forms of the disease. In fact, Crohn himself stated in his seminal paper in 1932 that an abnormal sigmoidoscopy was not consistent with regional enteritis, and that "the diagnosis is purely roentgenographic, the clinical differentiation being impossible" [72]. With growing recognition of Crohn's colitis, collated descriptions of the endoscopic appearance began to appear. Selzer and McCarthy published two cases in 1958 where regional enteritis was diagnosed via sigmoidoscopy [133]. In one case, sigmoidoscopy to 8 inches demonstrated a polypoid ulcerating, bleeding mass, partially obstructing the lumen and inflammatory in nature on repeat biopsy. Fistulae were subsequently discovered radiographically. In a second case, multiple pedunculated bleeding polyps were appreciated at 5 inches, which were again determined to be inflammatory. An ileosigmoid fistula was appreciated on barium enema. Lockhart-Mummery and Morson further documented sigmoidoscopic findings in patients with Crohn's in a cases series of Crohn's of the large intestine published in 1960. The authors carefully documented the location of disease in these 25 patients, and described normal sigmoidoscopic appearances in those with normal rectums and sigmoid colons. However, for several patients, they were able to describe strictures ("reddened, narrow, and rigid") with active ulceration, and granularity and friability, as well as edema, and purulent discharge [134].

With the advent of "colonfiberoscopy," or the flexible fiberoptic colonoscope, and the publication of several studies describing its application came further endoscopic characterization of Crohn's disease and ulcerative colitis [135, 136]. A large series of 255 patients using these new techniques was published by Teague, Salmon, and Read in 1973 in *Gut*, in which 55 were referred for having inflammatory bowel disease [137]. The authors noted that this new technology allowed for greater characterization of both diseases, with mucosal findings not always coinciding with what was appreciated on barium study.

As the endoscopic evaluation of disease has progressed from a technical standpoint, the role of colonoscopy has grown in IBD. As previously discussed, numerous means of grading severity of disease endoscopically have been developed, looking for such key characteristics as degree of friability via application of swab or touching the mucosa, ulceration, loss of haustral folds, erythema, and granularity [43, 91].

Colorectal cancer screening is now a key component of inflammatory bowel disease care as well [138]. Lastly, surveying for mucosal healing and response to therapies is progressively being incorporated into trial design and clinical care in both ulcerative colitis and Crohn's disease [139].

Pathophysiology and Therapy in IBD: Predominant Hypotheses of the twentieth Century

As the clinical knowledge of inflammatory bowel disease's enteric and extraintestinal manifestations expanded, so did attempts to better characterize the pathophysiology of these diseases over the last century. There were numerous hypotheses that were postulated in the early through mid-1900s regarding the possible etiology of this disorder. Here, we will discuss several of the preeminent theories in the early twentieth century.

One of the predominant hypotheses early in the history of IBD was that the condition was caused, at least in part, by an underlying infectious organism [3, 140]. Multiple possible infectious agents were considered, from oral bacterial infectious agents to mycobacterial species, though no specific organism has been successfully cultured and proven to comply with Koch's postulate to date. Oral bacterial agents were one of the first postulated infections thought to be involved in IBD, triggered by observing an association with dental extractions, abscesses, and the development of ulcerative colitis in several patients [3]. Bargen subsequently published a study in 1924 where he was able to induce bloody diarrhea in rabbits with bacterial fecal cultures from patients with IBD [141]. Cook and Rosenow induced colitis in another animal model via injection of rabbits with fluid derived from oral abscesses as well [142]. Numerous other bacteria were implicated in the etiology of ulcerative colitis: *Pseudomonas* species, *Clostridium* species, *E. coli*, *Bacillus*, *Proteus*, fungal histoplasmosis, and viral species have all been evaluated over the ensuing decades [3, 140]. While microbial culture techniques have advanced over the past several decades, no causative organism has been isolated that could routinely induce chronic enteritis and colitis in models and was discovered in individuals with the disease.

Some infectious agents have been implicated in worsening the clinical picture of ulcerative colitis, however, including *Clostridium difficile* and viral infections such as cytomegalovirus. More recently, attention has turned to the composition of the bacterial flora of the gut, or microbiome, and the role of dysbiosis in IBD [143]. This remains an active area of research as we attempt to discern the interactions between the colonic microenvironment and the host immune system [144, 145].

Another leading theorem that has gained growing supportive evidence over the years is that of the role of the immune dysfunction in the pathophysiology of ulcerative colitis. The hypothesis of various immune mechanisms playing a significant role in the pathophysiology of ulcerative colitis first began to formalize in the 1920s, 1930s, and 1940s [146]. Numerous potential food allergies have been implicated over the years, including food-derived and plant-based allergens. Initial research focused on hypersensitivity reactions within the colon [3, 147, 148]. This hypothesis was felt to be supported by the presence of mucosa edema and hyperemia, as well as elevated histamine levels in the mucosa and stool in a series of 17 patients with ulcerative colitis [149] . Binder and colleagues also appreciated that patients with ulcerative colitis were more likely to have other diseases postulated to be allergic in etiology at the time, including asthma, urticarial illnesses, and rhinitis [150].

It was soon appreciated, however, that inflammatory bowel disease may represent a more robust immune dysfunction than an allergic response to an environmental antigen for most patients. In the 1940s, it was appreciated that ulcerative colitis was associated with other diseases with presumed autoimmune etiologies, such as autoimmune thyroiditis, systemic lupus erythematosis, and autoimmune hemolytic anemias [151–153]. Several research groups demonstrated that specific antigens in the diet stimulated the immune system, with formation of antibodies likely secondary to increased intestinal permeability, and

that avoidance of these agents improved the course of disease for some [154–156]. Kirsner and Goldgraber were two of the first researchers to appreciate the relationship of antigen exposure and the development of experimental colitis in an animal model looking at immune complex deposition using egg proteins [157]. These complexes were directly associated with areas of the colon involved with colitis. These findings were later reproduced by Callahan, Goldman, and Vial, and become a key component of experimental animal models of colitis [3, 158]. In 1960, Kirsner and Bregman described hemagglutinating and precipitating anti-colon antibodies in patients with ulcerative colitis, and these antibodies were later confirmed by several other research groups as well [3, 159, 160]. Similar immune complexes in human ulcerative colitis were later appreciated in 1978 by two additional research groups, and IgG molecules directed against basement membrane with subsequent complement activation and dense neutrophilic infiltrate in a cohort of over 60 patients with active disease were also appreciated [161, 162]. It was recognized early on, however, that these antibodies did not appear to be directly involved in the pathophysiology of the disease, and were instead considered to represent a marker of active disease and colonic inflammation.

Antibodies that were directed against bacterial components, including an antigen present in E. Coli O14 and certain species of *Enterobacter* were also determined to interact with proteins present in human colonic epithelium [163]. Similar antibodies were later appreciated in some family members of patients with ulcerative colitis as well [164]. It is important to note, however, that several other research groups appreciated differing results, with some antigens for specific bacterial species generating an autoantibody response to colonic epithelium while others did not [165, 166].

There was also a growing body of literature describing cellular dysfunction in hosts with IBD as well. In 1972, the Shorter hypothesis was conceived, which postulated that for some individuals, likely those with an innate predisposition, non-specific bacterial antigens generated a hypersensitivity state by crossing the mucosa of the GI tract during infancy before non-permeability was established, thereby eliciting a non-specific T cell response, with subsequent mucosal damage due to a robust inflammatory response [167]. Brandtzaeg later demonstrated that some individuals possessed an increased concentration of plasma cells, possibly explaining the increased immunoglobulins previously appreciated [3, 168]. Several early studies in the 1960s and 1970s appreciated variable levels of lymphocyte activity in patients with ulcerative colitis and Crohn's disease, with some research groups appreciating normal activity to specific antigens and mitogens, while others demonstrated reduced global lymphocyte reactivity [169, 170]. In 1967, Bendixen and colleagues appreciated that cell mediated immunity was altered in patients with ulcerative colitis but normal in patients with Crohn's disease [171]. It was subsequently suggested that reduced lymphocytic activity may actually be attributed to nutritional status as opposed to active inflammatory bowel disease [169].

Research has continued to unravel the functions of specific immune cell types and how they interact in inflammatory bowel disease over the past 30 years. Early initial research focused on the activity of NK cells and cytotoxic T-lymphocytes in Crohn's disease and ulcerative colitis [3, 172–175]. Researches in 1979 and 1980 appreciated a marked increase in B-cell function, with increased immunoglobulin secretion, with different subtypes in CD and UC [176, 177]. Significant research has also delved into the role of the cell-mediated immune system, assessing how T-cell function, and in particular Th1 and Th2 cell regulation may contribute to an intrinsic defect in immune tolerance of the host microbiome [178, 179]. This work continues, however, as researchers continue to attempt to clarify this inherently complex system. Based on work conducted by Fuss and colleagues in 1996, it was initially thought that due to differences in cytokine secretion by CD4+ Th cells in the lamina propria of patients with Crohn's disease compared to those with ulcerative colitis, that Crohn's was primarily driven by an aberrant Th1 response and ulcerative colitis was driven by Th2 cells [180]. It has recently come to light, however,

that both of these subtypes are likely involved in both diseases, and it is dysfunction of a regulatory subtype of T cell, Th17 cells, that is intrinsic to inflammatory bowel disease [181].

As medical science continued to unravel the complex interactions that comprise the immune system, further attention has been paid to particular cytokines and chemokines in the pathophysiology of inflammatory bowel disease. Cytokines are small molecules used by many types of cells to communicate with other cells, both nearby and via the vascular and lymphatic systems. When these molecules bind to their specific receptors on target cells, they can induce a wide range of cellular responses dependent on the signal and the receiving cell, ranging from marked activation and proliferation to senescence and apoptosis.

Researchers subsequently began to identify some specific cytokines as pro-inflammatory and others as immunomodulatory. It was recognized in the early 1990s that the cytokine-based milieu in patients with active ulcerative colitis and Crohn's disease differed from normal individuals; the evidence of the pivotal role of cytokines in this process was later confirmed via the creation of knock-out murine models for cytokines thought to be involved in regulation of inflammation [182]. This led to further attempts to generate antibodies directed against inflammatory cytokines that could control inflammation in experimental mouse models [183]. Several studies attempted to target cytokines such as IL-10 and IL-11, but while efficacious in murine models, these agents did not yield significant benefit to patients [184, 185]. This pioneering work did lead to the development of anti-TNF agents, however, which have become one of the mainstays of therapy in inflammatory bowel disease. As we continue to understand how these cellular signaling proteins interact with cells, this will potentially continue to lead to further drug discovery and therapeutic options.

The explosion of genetic research in the past 20 years has also markedly impacted the understanding of the pathophysiology of ulcerative colitis. Case reports first described familial clusters of inflammatory bowel disease as early as the London 1909 Symposium, though this was not largely explored until several decades later [10, 146]. As several large case series by Kirsner and Palmer, Paulson, and Houghton and Naish, among others, began to appear in the 1950s, it became clear that there was an increased risk for family members of those with ulcerative colitis [3, 186–188] Similar observations were being made in Crohn's disease at this time as well, with Crohn and Yarnis identifying 12 instances of multiple family members with regional enteritis [189]. In 1958, Schlesinger and Platt appreciated an increased risk among those with Ashkenazi Jewish heritage [190]. As this link became more defined, reports of disease subtype concordance were also published, with strong concordance among family members with Crohn's disease and moderate concordance with ulcerative colitis, particularly in monozygotic twins [3]. Despite this mounting evidence, it was clear early on that inheritance patterns of inflammatory bowel disease were certainly non-Mendelian, hampering discovery of candidate genes that conveyed a strong enough risk for detection given the limited techniques available at the time. It would not be until 1996 when a true candidate gene, NOD2/CARD15 would be discovered on chromosome 16 by Hugot and colleagues [191, 192]. The function of this particular gene, which is involved in regulating the immune response to bacterial cell wall components within enteric crypts, has provided significant insight into the pathophysiology of inflammatory bowel disease, and Crohn's disease in particular. This gene remains the strongest genetic risk factor for inflammatory bowel disease, though recent advances in genetic mapping and genome-wide association studies have subsequently yielded more than160 potential gene candidates in both ulcerative colitis and Crohn's disease in pathways ranging from cytokine systems and MHC complex formation to intracellular signaling and apoptosis. The difficult task of determining the function and confirming the attributed risk due to each of these loci still remains [193]. However, this growing body of research has highlighted key pathways for targeting new therapies.

Therapeutic Approaches in Inflammatory Bowel Disease

Surgical therapies comprised the initial predominant therapeutic options in both ulcerative colitis and Crohn's disease. Early surgical approaches were quite different than the more uniform recommendations of colectomy for ulcerative colitis in the early 1900s, with varied approaches including appendicostomy, cecostomy, and colostomy [3, 194, 195]. There were some early proponents of ileostomy, however, including Strauss and colleagues, who advocated for this option in 1923 [196] . However, adequate surgical technique for the routine development of an ileostomy hampered the surgery until further improvement by Brooke and Turnbull in the 1950s [197–199]. At the same time, two separate surgeons, Cattell and Miller, described multi-stage surgical approaches of: (1) ileostomy, subtotal colectomy, and abdominoperineal resection, or (2) ileostomy and proctocolectomy, respectively [3]. Subsequent pouch-based procedures would later be developed by Kock, Ravitch and Parks [200–202].

Initial surgical evaluation for Crohn's disease often consisted of open surgical exploration for concern of abdominal mass or perforated appendicitis [62]. The futility of surgical intervention was readily recognized early in the history of Crohn's disease due to its high risk of recurrence [3]. For the first several decades after recognition of this disorder, surgical approaches typically involved either ileostomy or surgical resection of diseased segments with subsequent re-anastomosis. The latter typically lead to recurrence and further resection.

Steroids

With the discovery of ACTH and development of glucocorticoids in the 1950s, it was not long before these agents were considered in inflammatory bowel disease. Gray and colleagues, as well as Kirsner, Palmer, and Klotz published two case series demonstrating the benefit of ACTH in Crohn's disease and ulcerative colitis [203, 204]. Truelove and Witts published the first randomized controlled trial of cortisone in ulcerative colitis in 1955, assessing the outcome of 210 patients, with 109 receiving cortisone [44]: 68.8 % improved or were in remission in the cortisone group, compared to 40.6 % in the control group. The steroid group also had better response in their first episode of colitis and fewer relapses. Later, in 1979, Summers and colleagues demonstrated that prednisone was capable of inducing remission in Crohn's disease in a large randomized controlled trial [205].

Not all groups were able to produce results as promising as these early studies however. Kirsner and Sparberg demonstrated considerably more variability in a cohort of 54 patients with Crohn's disease [206]. There was also growing concern about their long-term efficacy in maintaining remission as well—a finding that has been demonstrated in large cohort studies in the modern era [207]. This lack of efficacy in maintenance therapy, as well as the litany of side effects associated with long-term exposure to steroids, prompted research into newer agents.

Aminosalicylates

5-ASAs were first synthesized 1942 [208]. Initially utilized to improve symptoms in patients with rheumatoid arthritis (RA), sulfasalazine (SASP) was incidentally noted to improve bowel-related symptoms in a subset of patients with colitis as well, prompting further research. In 1962, Baron and colleagues performed a clinical trial in a cohort of 60 patients with active ulcerative colitis, with 20 receiving sulfasalazine, 20 receiving placebo, and 20 receiving a third 5-ASA-like compound [209]: 16 of 20 patients had significant clinical improvement in the sulfasalazine arm, compared to 7 of 20 in the placebo arm. The ability of sulfasalazine to maintain remission was later demonstrated by Misiewicz and colleagues in 1965 [210]. Summers and colleagues also demonstrated efficacy in Crohn's disease as well. [205] However, there were potential limitations,

most significantly related to side effects, such as fever, headache, and agranulocytosis.

With the subsequent determination that the active component of the drug against ulcerative colitis was the 5-ASA moiety, while the sulfa component was responsible for the majority of symptoms, the quest to develop multiple new moieties began [211]. Multiple similar compounds have been developed, exploiting the 5-ASA molecule to create similar compounds such as mesalamine and balsalazide, in the 1980s and beyond [93, 212, 213]. These agents have continued to demonstrate benefit in ulcerative colitis, but recent systematic review has called into question their usefulness in Crohn's disease [214–216].

Immunomodulators

As hypotheses concerning the role of immune dysfunction in inflammatory bowel disease gained mounting evidence, a theory that was only supported by the advent and efficacy of corticosteroid therapy, research into therapeutic options that further modulated the immune system expanded. One of the first classes of medications to be considered in both ulcerative colitis and Crohn's disease was the thiopurine analogues, 6-mercaptopurine and azathioprine, as these had both demonstrated some efficacy in other diseases that were thought to be immune-mediated [217]. Early data consisted of case reports of the use of this class of medications. Bean published a report on the use of 6-mercaptopurine in a patient with ulcerative colitis in 1962 [218]. Kirsner commented on the use of 6-mercaptopurine in a patient with ulcerative colitis in a review on the role of the immune system in inflammatory bowel disease in 1965 [217]. One year later, another report by Bowen, Kirsner, and colleagues on 10 patients treated with the thiopurine azathioprine was published, with 8 out of 10 patients demonstrating a clinical response determined to be "favorable" by the authors [219]. Of importance this study was also the first to recognize the therapeutic index of this agent, with toxicity appreciated in those receiving 6 mg/kg but not those receiving doses in the 2–3 mg/kg range. Similar reports soon followed in Crohn's disease, with Brooke and colleagues demonstrating the efficacy of azathioprine in six patients in 1969 in the journal *Lancet* [220].

Controlled trials of the use of azathioprine and 6-mercaptopurine in both ulcerative colitis and Crohn's disease were published soon after in the 1970s. Jewell and Truelove published the final results of their clinical trial of azathioprine in ulcerative colitis in 1974 [221]. They interestingly did not appreciate benefit for those with their first bout of ulcerative colitis requiring steroids, but did note some benefit in maintenance therapy in those with chronic disease. In 1971, Rhodes and colleagues published the first controlled trial of azathioprine, and this was soon followed by several other clinical trials of both this drug and 6-mercaptopurine [222–224]. The benefit of both of these medications in the maintenance of response and remission has persisted in multiple trials in both ulcerative colitis and Crohn's disease [225, 226].

Methotrexate has also demonstrated benefit in Crohn's disease. This agent has been one of the cornerstone therapies in rheumatology for the management of rheumatoid arthritis. Kozarek and colleagues demonstrated potential benefit with this agent in a pilot study of 21 patients with ulcerative colitis and Crohn's, demonstrating significant clinical response to the medication in both groups, and mucosal healing in those with Crohn's disease [227]. Feagan and colleagues demonstrated significant benefit in two subsequent randomized controlled trials at both 25 mg and 15 mg, given intramuscularly [228, 229]. Controlled trials assessing the utility of this agent in ulcerative colitis are ongoing, however.

Cyclosporine is an intravenous immunomodulator that was also studied in several uncontrolled and controlled trials in both ulcerative colitis and Crohn's disease for salvage therapy. Several case series and a randomized controlled trial have demonstrated the benefit of this therapy in ulcerative colitis [54, 230, 231]. Unfortunately these agents have not demonstrated similar benefit in

Crohn's disease [97]. Furthermore, the mode of administration and the long-term toxicity of this agent have prevented the widespread utilization of cyclosporine.

Biologic Therapy

As research progressed beyond a rudimentary understanding that IBD represents an increased inflammatory response to understanding the underlying mechanisms by which this inflammation occurs, research began to target specific intercellular signaling molecules. As previously discussed, the first cytokine target to demonstrate significant clinical efficacy was Tumor Necrosis Factor-α. The first agent to demonstrate benefit was cA2, a monoclonal antibody with both a murine and human component (this agent would later become known as infliximab). In a pivotal case series published in *Gastroenterology*, van Dullemen and colleagues demonstrated a series of ten patients in which eight patients responded to cA2 therapy [232]. Several subsequent landmark clinical trials such as ACCENT 1 and 2, and ACT 1 and ACT 2 were published in both Crohn's disease and ulcerative colitis demonstrating infliximab's efficacy in inducing and maintaining remission, as well as treating fistulizing disease [98, 106, 233, 234].

Several additional anti-TNFs have subsequently been approved by the US Food and Drug Administration (FDA) over the past decade. Following the success of infliximab, a second, fully humanized agent with a self-administration system called adalimumab was developed. This agent has demonstrated efficacy in inducing and maintaining remission, as well as in the therapy of fistulizing disease [235–238]. A pegylated formulation designed to have a longer half-life, called certolizumab pegol, has also been approved for use in Crohn's disease [239–243]. A fourth agent has recently been approved for ulcerative colitis as well, also using a pen-based delivery system, called golimumab [244, 245].

There has also been significant progress in developing agents that inhibit leukocyte trafficking, thereby inhibiting pro-inflammatory cells from reaching areas of active disease. The first of these agents to be FDA-approved, natalizumab, is an antibody directed against the α4 integrin, which mediates the transfer of lymphocytes from the blood stream to the brain and GI tract. It was initially studied in multiple sclerosis, but was soon approved in Crohn's disease as well, with two separate clinical trials demonstrating efficacy in inducing and maintaining remission [246–248]. However, it was soon realized that inhibition of leukocyte trafficking in the brain also promoted the development of progressive multifocal leukoencephalopathy (PML), a devastating neurologic complication caused by the John Cunningham (JC) virus [249, 250]. Because of this risk, the drug was temporarily removed from the market, but since has been reinstated with required adherence to a strict monitoring program. Furthermore, screening for the antibody against JC virus, which is ubiquitous, and considering therapy if this test is negative, has been postulated to improve quality of life in patients with Crohn's disease [251]. Several new agents are currently being investigated that target gut-specific leukocyte trafficking, downstream intracellular signals related to cytokine production and proliferation, and specific cytokines such as IL-23 [252–255].

Conclusion

Remarkable progress has been made in the field of inflammatory bowel disease in the past 100 years. From the initial clinical definition of both ulcerative colitis and Crohn's disease, we have developed new tools and techniques for classifying and surveying disease severity. With further research and understanding of the underlying pathophysiology, we have over the past 20 years just begun to disassemble the complex immunologic underpinnings of these diseases, allowing for new therapeutics to be developed at a breathtaking pace. As physicians we can only hope the next 100 years of IBD-related care yield as significant a gain in knowledge as the former.

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Part II

Current Noninvasive Imaging Studies

Ultrasound

2

Nadia Pallotta and Enrico S. Corazziari

Introduction

The inflammatory bowel diseases (IBD) include primarily Crohn's disease (CD) and ulcerative colitis (UC). In the diagnostic work-up of patients with IBD, the early and accurate assessment of site, extension, activity and severity of intestinal lesions as well as of possible complications—at the time of diagnosis and throughout the course of the disease—is mandatory in order to plan the appropriate treatment and for prognostic implications. The diagnosis of IBD relies on a combination of clinical symptoms and endoscopic, histological, radiological, and/or biochemical investigations [1]. UC involves the mucosa continuously from the rectum proximally, and colonoscopy with biopsy is the reference standard for assessment of disease extent, activity, and severity. Unlike UC, CD may affect any part of the gastrointestinal (GI) tract and causes, typically, transmural inflammation that in turn determines a profound alteration of the multilayered structure of the intestinal wall due, to some extent, to an increased presence of collagen in the muscular layer (Fig. 2.1). Whereas in the suspicion of IBD, ileo-colonoscopy with biopsies from the terminal ileum and from each colonic segment, is a well-established and currently performed diagnostic step in the assessment of lower GI tract, the assessment of small bowel (SB) has been for many years a challenge for clinicians due to its anatomy, location and inaccessibility to routine endoscopy. Although in CD any part of the gastrointestinal tract may be affected, involvement of the ileum is the most prevalent and the disease is limited to the small bowel in about 40 % of the patients [2, 3]. Moreover patients with ileal disease are more likely to develop intestinal complications such as strictures and fistulas [4, 5]. Therefore, assessment of the small bowel is mandatory in the evaluation of patients with suspected CD in differentiating CD from other enteropathies as well as in the follow-up of patients with proven CD. Fluoroscopic barium studies—i.e., SB follow-through (SBFT) and SB enteroclysis (SBE)—have been for many years the cornerstone for the diagnosis of CD of the small bowel [6–8]. Recently evidence-based guidelines available through the American College of Radiology (ACR) recommend CTE as a first-line test for adult patients with suspected Crohn's disease and CTE is considered acceptable also in the pediatric population [9]. SBFT is usually considered suboptimal even if less expensive and more avail-

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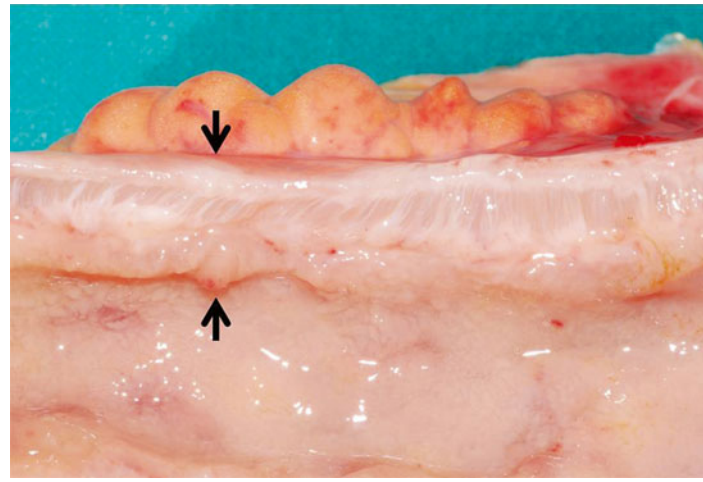


Fig. 2.1 Surgical section of small bowel from a patient with Crohn's disease. The wall (*arrows*) is significantly thickened especially at the level of *muscularis propria. By courtesy of Prof. Chiara Montesani and Anna Maria Pronio, University of Rome "Sapienza", Italy*

able. However, due to the radiation exposure and the infrequency of small bowel pathology, radiology, either CTE or SBFT, is not recommended as a screening investigation without significant clinical suspicion of intestinal disease. Notably, radiology should be avoided in CD patients who require repetitive follow-up assessments in the setting of a chronic disease that often progresses with complications. As such, it has been shown that CD patients, including children, receive a mean of 8.1 mSv of diagnostic radiation *per* year of follow-up and in those with complications cumulative effective dose (CED) is even higher, reaching up to 75 mSv [10–13].

Therefore, recent interest has focused on implementing radiation-free, cross-sectional techniques, primarily ultrasound (US) and magnetic resonance (MRI). US and MRI, like CTE, and unlike traditional barium studies and endoscopy, assess the entire intestinal wall, can evaluate mucosal as well as transmural alterations, and allow a complete and accurate staging of the bowel, abdomen and perineum with the unique advantage to assess mural and extramural disease.

In this chapter we will target the applications and limitations of bowel US in IBD, focusing on the usefulness of bowel US in the early detection and follow-up of Crohn's disease, affecting mostly the small bowel. Endoscopy continues to be the reference standard to evaluate the upper and lower GI tract.

Bowel Ultrasound in Ulcerative Colitis and Crohn's Disease

Due to noninvasiveness, low cost, radiation-free and widespread availability, transabdominal ultrasound (TUS) is a very useful modality for IBD imaging [14–16], while disadvantages include operator dependency and difficulty to thoroughly visualize the entire GI tract, since the lumen is virtual and it may contain gas, a condition that hinders sonographic reflection [16, 17]. Over the past few years, technological development, including high frequency transducers (typically 7–12 MHz), harmonic imaging combined with the use of oral (small intestine contrast ultrasonography, SICUS) [18–20], and intravenous contrast agents (CE-US), have improved performance of ultrasound in the assessment of the gastrointestinal tract [21, 22].

The detection of bowel diseases relies on the assessment of intestinal wall and lumen, on the detection of enlarged mesenteric nodes, and/or of fluid in the peritoneal cavity.

At ultrasound the normal bowel wall is characterized by the presence of five concentric layers alternately hyperechoic and hypoechoic (Fig. 2.2). *Normal stratification* of the bowel wall is defined by the presence of the five layers, while *loss of stratification* is defined by the lack of one or more layers [16]. The normal bowel wall

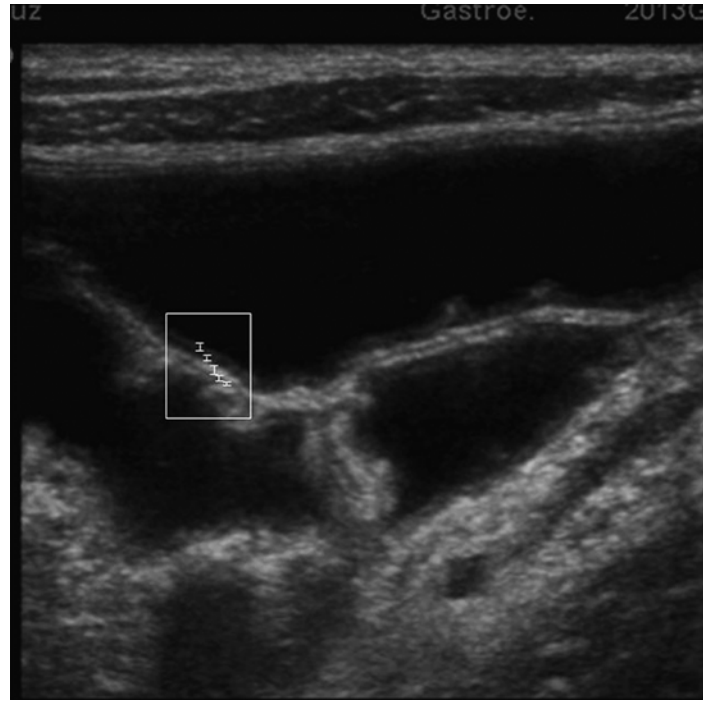


Fig. 2.2 Small Intestinal Contrast Ultrasonography (SICUS) image of two adjacent jejunal loops after oral administration of the anechoic contrast solution. The five layers of the wall are recognizable (*white lines*) starting luminally: (1) a thin echogenic layer, (2) hypoechoic layer, (3) hyperechoic layer, (4) hypoechoic layer, and (5) a hyperechoic layer

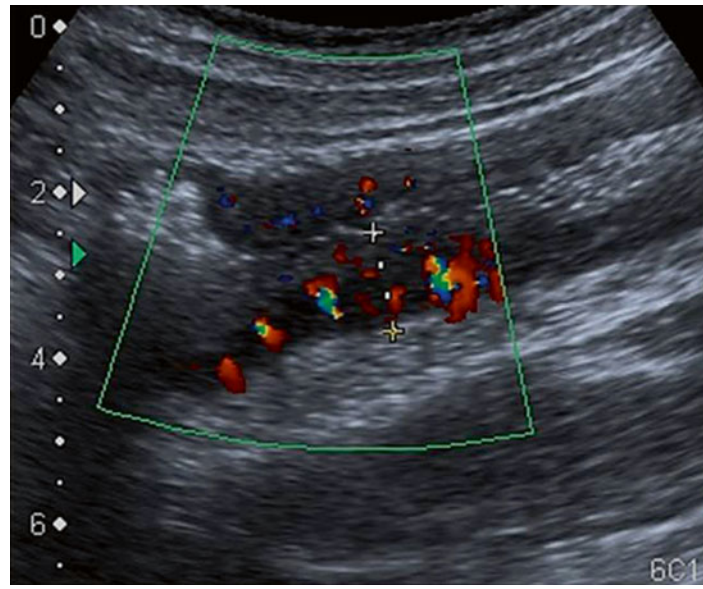


Fig. 2.3 Color Doppler examination of the descending colon in active CD. Mural thickening, loss of stratification of the bowel wall, and increased vascularity on color Doppler denoting inflammatory hyperemia. *By courtesy of Fortunata Civitelli, MD Department of Pediatrics, Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome*

thickness has been reported to be <3–4 mm and <1.5–3 mm in the terminal ileum, and ≤5 mm and <2 mm in the colon, in adults and in children, respectively. The assessment of bowel vascularisation by color Doppler provides additional information, particularly on disease activity (Fig. 2.3). The vascularity of bowel wall can be assessed according to the intensity of color signals or by the analysis of Doppler curves from vessels within the bowel wall [23].

Crohn's Disease

Bowel TUS has become the first-line imaging procedure in the diagnostic work-up of patients with suspected Crohn's disease [1, 24] and in the follow-up of patients with known CD. In CD the intestinal wall is often macroscopically greatly thickened (Fig. 2.1). In addition, the transmural inflammation progresses deeply into the serosa and outside, potentially producing fissures and fistulae (Fig. 2.4), which may reach adjacent loops, organs, and skin or end blindly in the mesentery or resulting, at times, in intra-abdominal or retroperitoneal abscesses. The mesentery surrounding diseased loops is often thickened and fatty (Fig. 2.1 and Fig. 2.2) and may contain enlarged lymph nodes (Fig. 2.5). The diagnosis of CD with ultrasound relies on the assessment

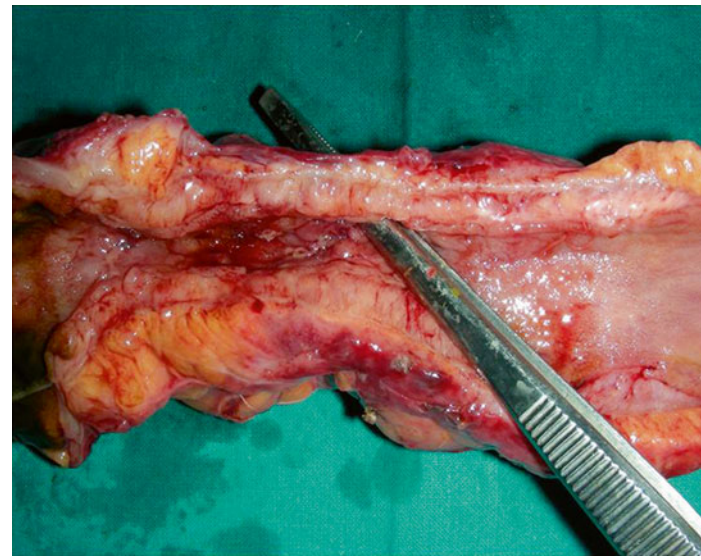


Fig. 2.4 Surgical section of small bowel from a patient with Crohn's disease. The lumen is narrowed and the forceps show a fistula arising from the lumen through the thickened wall. *By courtesy of Prof. Chiara Montesani and Anna Maria Pronio, University of Rome "Sapienza", Italy*

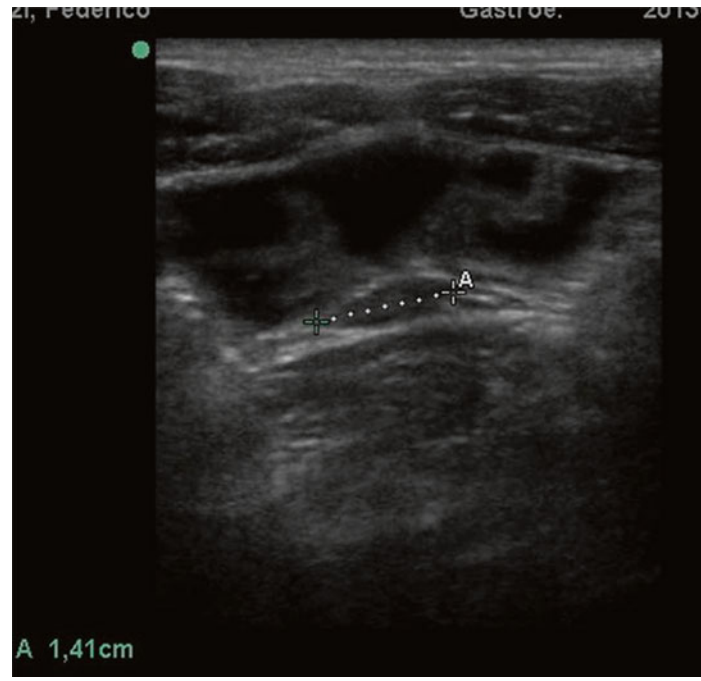


Fig. 2.5 SICUS. Thickened hyperechoic mesentery with enlarged mesenteric node (A). The intestinal lumen is distending by anechoic contrast

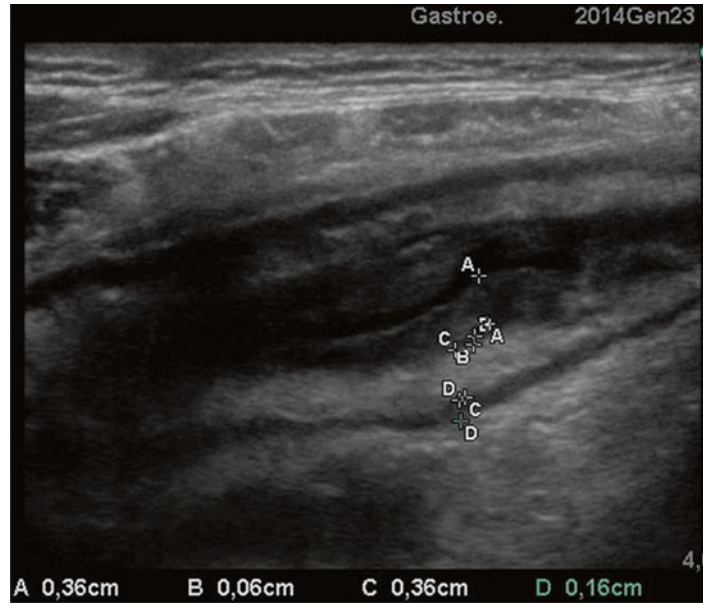


Fig. 2.6 CD of small bowel at SICUS: thickened small bowel wall characterized by a stratified echopattern with thickening of mucosa (A-A) and submucosa (C-C)

of those pathological features that may be essentially differentiated in *mural* and *extramural* features [16]. At ultrasound the *pathological mural alterations* appear as: (1) increased thickness of intestinal wall (Fig. 2.6), (2) variation of transmural echopattern (Fig. 2.7a), (3) interruption or loss of echo-stratification (Fig. 2.7b), (4) presence of variable enlargement of the different five layers, (5) increased Color-Doppler signal (Fig. 2.3), and (6) loss or reduction of peristalsis in the small bowel and of *haustra coli* in the colon. In *early CD* the wall stratification is usually preserved, the submucosa is thickened and appears as a hyperechoic band (Fig. 2.6), while in severe disease the stratification may disappear (Fig. 2.7a, b). In *longstanding disease* fibrosis results in thickened bowel wall, which is hypoechoic with loss of normal stratification; moreover fibrofatty proliferation of the mesentery tends to isolate pathologically stiff loops. At ultrasound the pathological *extra-mural changes* are assessed by the presence of: (1) fatty hypertrophy of the surrounding mesentery (Fig. 2.8), (2) enlarged lymph nodes (Fig. 2.5), (3) abscesses (Fig. 2.9), (4) fistulas (Fig. 2.10).

Bowel Ultrasound in the Early Assessment of Patients with the Suspicion of Crohn's Disease

Abnormal *bowel wall thickness* (BWT) is the most important TUS sign of CD and in unselected groups of patients, based on BWT values, sensitivities of 75–94 % with specificities of 67–100 % have been reported [15, 25, 26]. The wide variability of sensitivity and specificity values across studies reflects differences in the study design, size, and characteristics of the study samples and in the different reference standard value as threshold for a positive diagnosis. These methodological issues were evaluated in a meta-analysis [27] that, starting from 44 full-text studies, recognized only 7 prospective and appropriately designed studies (5 case control and 2 cohort studies). The results of this analysis showed that when more than 3 mm cut-off level was applied for abnormality in wall thickness, the sensitivity and specificity of TUS in the diagnosis of CD were 88 % and 93 %, while when a cut-off level of more than 4 mm was used, sensitivity was 75 % and specificity 97 %. The role of US to

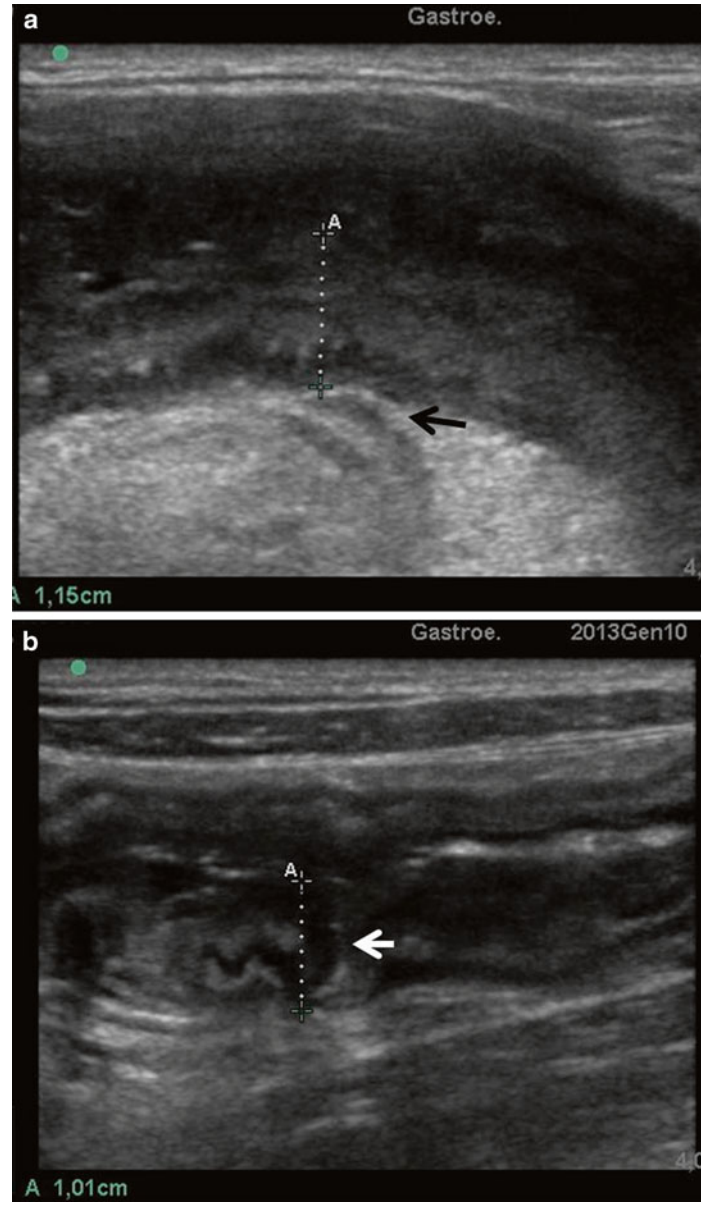


Fig. 2.7 CD of small bowel at SICUS. (**a**) The wall is thickened with loss of multilayered stratification with a hypoechoic peri-intestinal lesion (arrow) arising from the thickened intestinal wall through a wrapping mesentery. (**b**) The wall is thickened (A) with loss of multilayered stratification with a hypoechoic lesion (*arrow*) penetrating the thickened intestinal wall

assess CD has been most extensively investigated for small bowel CD and the highest reported level of diagnostic sensitivity of TUS was achieved in investigations performed in populations mainly affected by known CD located in the terminal ileum [24]. This study, however, lacks a control group and was carried out by qualified investigators with specific expertise in tertiary referral centers. Several studies evaluated the accuracy of TUS in localizing Crohn's disease lesions and most of them agreed in reporting the highest sensitivity (approximately 90 %) of TUS in detecting CD located in the terminal ileum and the lowest accuracy for those located in the upper small bowel and in the rectum [17, 28]. Few studies have evaluated the diagnostic accuracy of TUS as a screening technique for yet undiagnosed small bowel pathology [17], and most report unsatisfactory sensitivity (74–85 %). The main limit of bowel TUS is its inability to visualize the

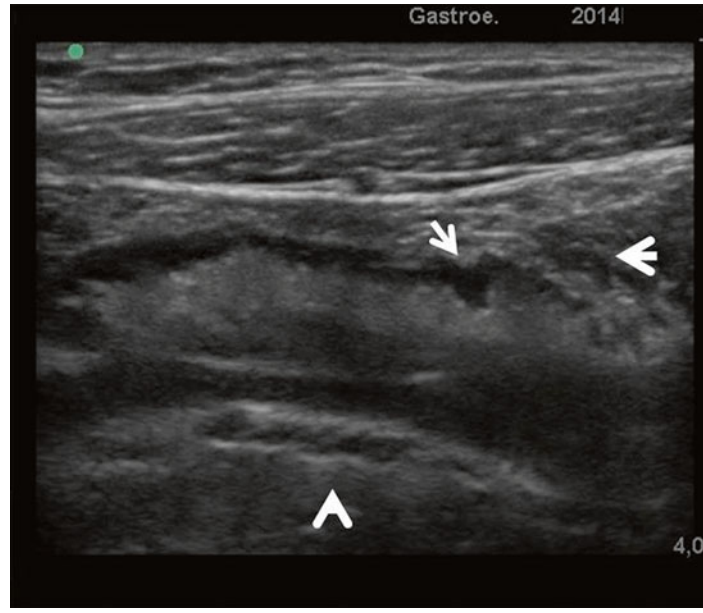


Fig. 2.8 SICUS appearance of mesenteric fat hypertrophy (*arrowhead*), and of entero-mesenteric fistula (*arrows*)

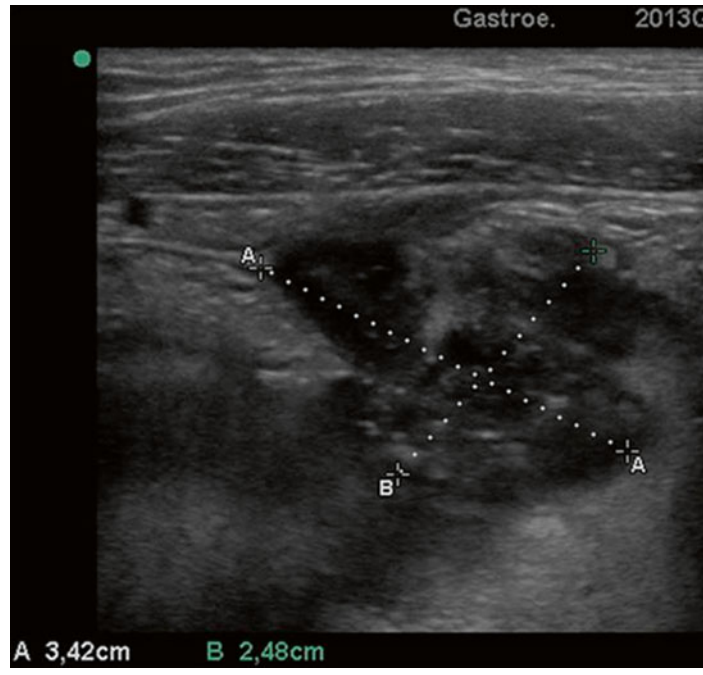


Fig. 2.9 Transverse US section (3.5 MHz probe) at level of the lower abdominal right quadrant. A round-shaped hypoechoic image of 3.4 cm (see calipers) is shown

entire gut that has a virtual lumen and may contain gas making the intestinal wall barely visible. However, the difficulty in visualizing bowel wall is overcome by distending the intestinal lumen with anechoic fluid. After the ingestion of small amounts (250–375 mL) of polyethylene glycol 3,350–4,000 (macrogol) solution [17, 18], the entire small bowel from the duodenal-jejunal angle to ileocecal valve can be visualized with the Small Intestine Contrast US (SICUS). SICUS undertaken in healthy controls in vivo and independent of the volume of oral contrast used,

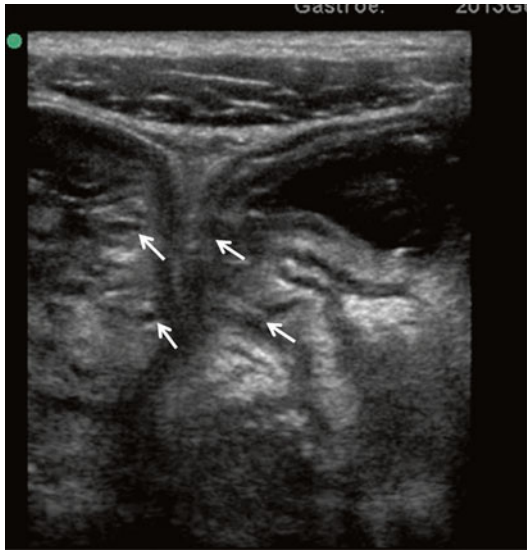


Fig. 2.10 Entero-enteric fistula appearance at SICUS as hypoechoic ducts between the intestinal loops (*arrows*). Note the anechoic contrast distending the lumen and the mesenteric fat hypertrophy

Table 2.1 SICUS: Normal values of wall thickness and lumen diameter of small bowel in healthy controls assessed in two consecutive evaluations

	Wall thickness (mm)		Lumen diameter (mm)	
Location	1st	2nd	1st	2nd
Jejunum	1.7 ± 0.4 1–2	1.2 ± 0.4 1–2	18.4 ± 2.3 15–21	16.8 ± 2.2 15–21
Ileum	1.9 ± 0.3 1.3–2	1.2 ± 0.4 1–2	18.4 ± 1.8 16–20	17.8 ± 2.8 13.7–20
Terminal ileum	1.9 ± 0.3 1.3–2	1.7 ± 0.6 1–2.3	17.2 ± 2.2 14–20	15.7 ± 2.8 11.3–19

Table 2.2 Sensitivity and specificity of TUS and SICUS in detecting small bowel lesions in undiagnosed patients

	Patients	TUS		SICUS	
	n (%)	TP	FN	TP	FN
IBS	36 (39.6)	–	0	–	0
Crohn's disease	16 (17.6)	11	5	16	0
Ulcerative colitis	7 (7.7)	–	0	–	0
Malignant tumors	6 (6.6)	3	3	6	0
Celiac disease	5 (5.5)	2	3	4	1
Undefined colitis	4 (4 %)	–	0	–	0
Polyps	4 (4 %)	0	4	3	1
Others	13 (14.3 %)	4	0	4	0
Total	91 (100 %)	20	15	33	2

TP true positive, *FN* false negative, *IBS* Irritable Bowel Syndrome

Table 2.3 Sensitivity and specificity of TUS and SICUS in detecting small bowel lesions in patients with known CD

	Patients	TUS		SICUS	
Lesion	n (%)	TP	FN	TP	FN
Terminal ileum	18 (32.7)	14	4	17	1
Ileum-jejunum	23 (41.8)	20	3	23	0
Ileo-colonic	14 (25.5)	14	0	14	0
Total	55 (100)	48	7	54	1

TP true positive, *FN* false negative

Table 2.4 Agreement between TUS and SICUS and surgery and SBFT in the detection of the small bowel CD lesion site

	Patients	TUS	SICUS
	N	k	k
Surgery			
Proximal lesions (≥1)	8	0.54	0.93
Distal lesions (≥1)	39	0.68	0.93
SBFT			
Proximal lesions (≥1)	12	0.31	0.83
Distal lesions (≥1)	45	0.61	0.93

allowed objective normative values of wall thickness (≤ 3 mm) and lumen diameter (≤25 mm) to be defined (Table 2.1, Video 2.1) [19]. These normative values provide useful measurements to discriminate normal from abnormal findings. Based on these normal cut-off values, it has been shown that SICUS is comparable to radiology and superior to standard TUS in detecting intestinal lesions both in patients with undiagnosed small bowel diseases and in those with known CD (Tables 2.2 and 2.3) [17, 20]. Sensitivity of TUS and SICUS were 57 % and 100 % and 87.3 % and 98 %, in the undiagnosed and in known CD patients, respectively. In addition, it has been shown that SICUS is more accurate than TUS in detecting both proximal and distal small bowel CD lesions compared to radiology [17] and surgery [29] (Table 2.4, Video 2.2). These results have subsequently been confirmed by other authors in several studies [30–32].

Notably SICUS enables initial assessment of wall alteration limited to the mucosa and submucosa in CD (Fig. 2.11). The latter is associated with slight thickening of the intestinal wall, which may be missed in absence of the lumen distension by oral contrast (Video 2.3).

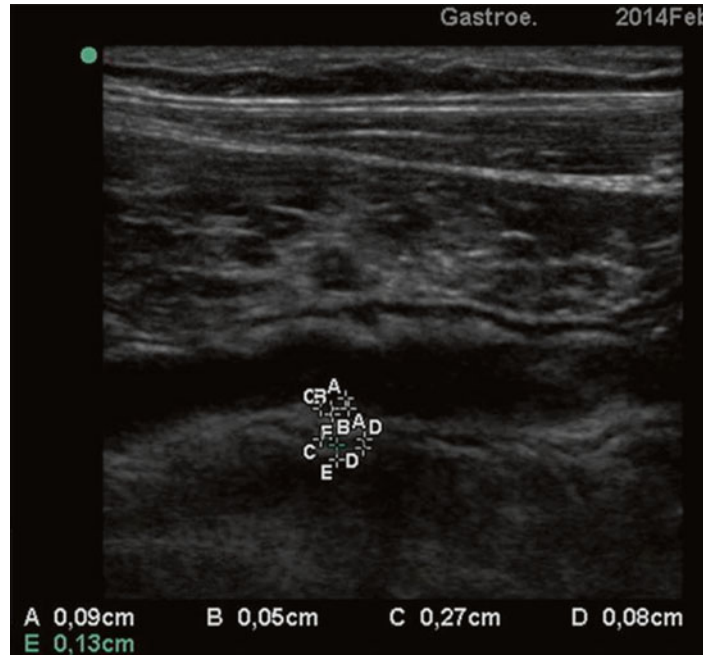


Fig. 2.11 SICUS: the thickness of intestinal wall appears slightly increased with a multilayered structure and mucosa enlargement (A-A)

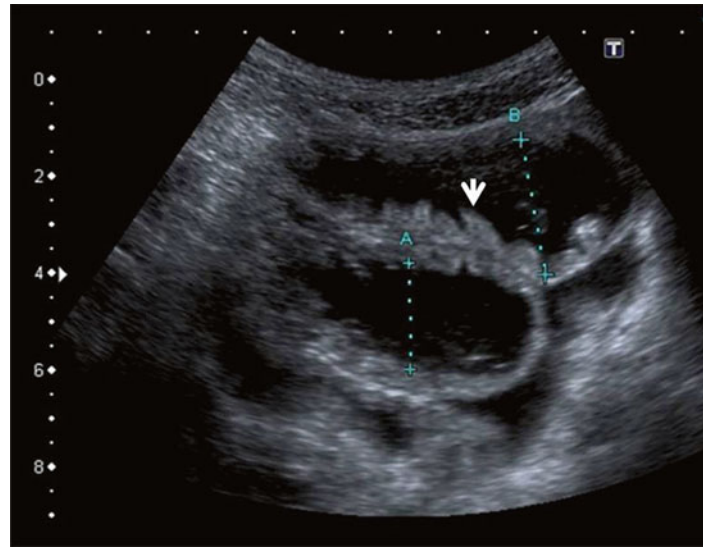


Fig. 2.12 SICUS: The longitudinal scan demonstrates anechoic contrast filled lumen; intestinal folds are seen as tiny intraluminal echogenic indentations of the intestinal wall (*arrow*)

Furthermore, SICUS allows identification and assessment of the characteristic distribution of intestinal folds (Fig. 2.12) and recognition of endoluminal structures such as polyps from the intestinal wall (Fig. 2.13, Video 2.4).

It has been recently shown that SICUS is a safe, accurate, radiation-free alternative for the assessment of small bowel disease also in pediatric patient population [28]. The reported ability of SICUS to accurately identify the presence of small bowel disease compared to small bowel follow-through (SBFT) and ileocolonoscopy in a pediatric cohort of patients is even higher than in adults with a sensitivity and specificity of 96 % and 100 %, respectively (Table 2.5). In addition, as in adults, this study confirmed that SICUS is as

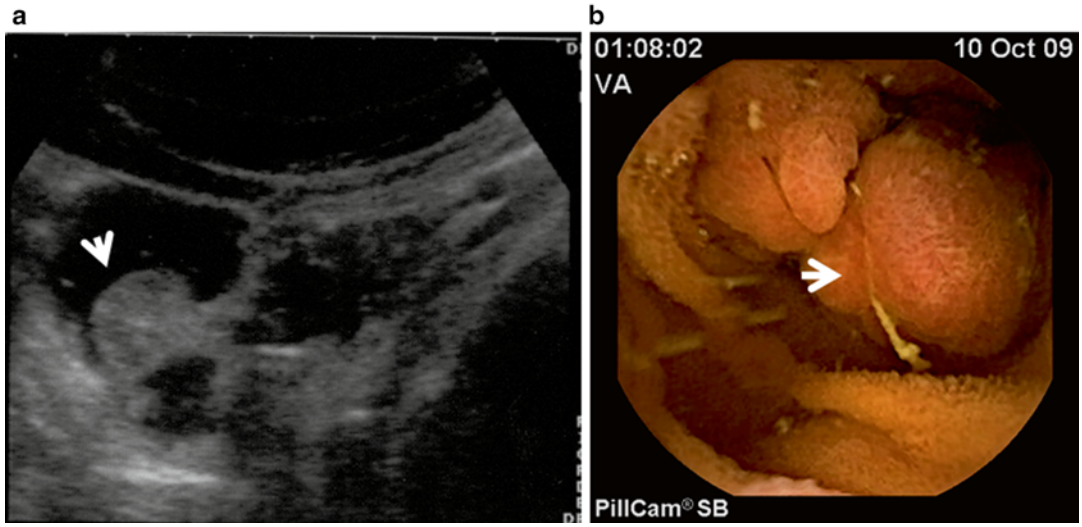


Fig. 2.13 Polyp of the small bowel. *Panel A*: SICUS: a fixed round echogenic structure (*arrow*) is visible within the contrast-filled ileal lumen. *Panel B*: Wireless capsule endoscopy: a corresponding endoscopic image. *By Courtesy of Erminia Romeo, MD and Luigi Dall'Oglio, MD Ospedale Pediatrico Bambino Gesù Rome, Italy*

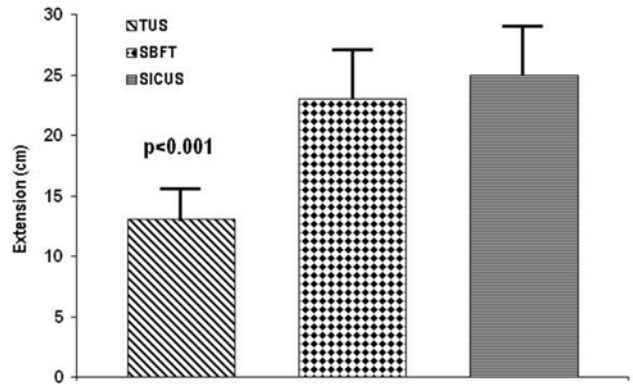
Table 2.5 Sensitivity, specificity, PPV, NPV and statistical agreement of SICUS and TUS with SBFT in detecting presence and site of small bowel CD lesions in pediatric patients

Modality	Site	SE % (95 % CI)	SP % (95 % CI)	PPV % (95 % CI)	NPV % (95 % CI)	k	p
TUS	Proximal	50 (23–76)	100 (87–100)	100 (60–100)	79 (62–91)	0.40	ns
	Distal	83 (64–94)	100 (68–100)	100 (83–100)	69 (45–91)	0.68	0.05
SICUS	Proximal	93 (66–100)	100 (87–100)	100 (75–100)	96 (81–100)	0.93	<0.05
	Distal	97 (81–100)	100 (68–100)	100 (85–100)	92 (60–100)	0.94	<0.001

Proximal SB: jejunum and proximal ileum; distal SB: distal and terminal ileum; *SE* sensitivity; *SP* specificity, *NPV* negative predictive value, *PPV* positive predictive value, *k* kappa-statistics

accurate as SBFT in detecting both proximal and distal small bowel lesions, whereas agreement with SBFT was markedly lower for TUS without oral contrast, mainly for the proximal sites lesions (Table 2.5). Although feasibility and reliability of this technique in pediatric clinical practice ought to be confirmed in further studies, the diagnostic accuracy of SICUS, with a considerable negative predictive value and such high level of agreement with radiology, suggests that a normal SICUS at the initial diagnostic workup in a child with suspected CD could avoid radiation exposure and invasive and/or more expensive investigations.

It should be pointed out that compared to standard TUS, SICUS is a time-consuming technique, the duration of the examination being on average 45 min. Although SICUS may appear to be a more expensive technique than traditional TUS, the lack of radiation actually makes it a cost-effective alternative to the less available and more expensive MRI. When considering colonic CD, US is more accurate in the assessment of intestinal wall pathology located in the sigmoid/descending colon, followed by the cecum/ascending, and transverse colon, while accuracy for rectal disease is poor [33]. A systematic review of



Bonferroni Multiple Comparative test	Mean difference	p	95% CI
TUS vs SBFT	-13.64	<.0001	-17.67; -9.60
SICUS vs SBFT	-1.50	.6	-5.53 ; 2.53
TUS vs SICUS	-12.14	<.001	-16.17 ;-8.10

Fig. 2.14 One-way ANOVA with Bonferroni post-test for comparative evaluation of the extent of small bowel lesions at transabdominal ultrasonography (TUS), SICUS, and small bowel follow-through (SBFT)

6 studies investigating US for assessment of ileocolonic CD found sensitivities ranging from 63 to 100 % and specificities from 77 to 100 % [27]. The accuracy of standard ultrasound compared to endoscopy in the assessment of presence and severity of CD located in the colon improves markedly with hydrocolonic sonography [34], but these findings have not been reproduced.

The effectiveness of intravenous contrast agents in the detection of Crohn's disease remains, despite some positive findings, largely uninvestigated [21].

Assessment of Extension of Lesions of Crohn's Disease

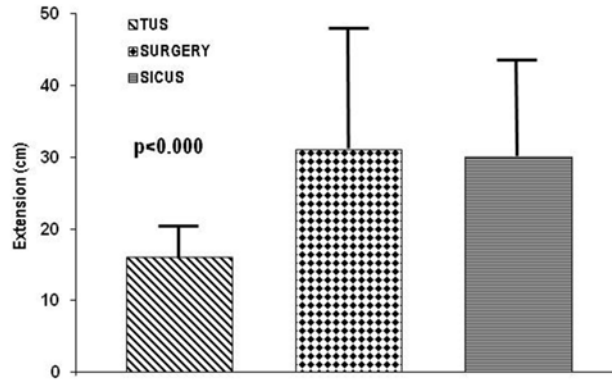
To date few studies have assessed the accuracy of ultrasound to assess extension of CD intestinal involvement and reports have been equivocal regarding the correlation of TUS with radiology and intraoperative findings [33, 35–37]. Two studies [33, 35] performed in the same group of patients reported a significant correlation (r = 0.51) between TUS and small bowel enema in the assessment of CD lesion extension. However, this finding was not confirmed by a study that, while not contradicting such correlation, showed that when an appropriate test of comparative analysis is employed, (i.e., ANOVA), the accuracy of TUS in the assessment of extension of small bowel lesions is lower than that observed at SICUS and confirmed by SBFT or surgery [17, 29].

The use of oral contrast improves ultrasound accuracy in assessing extension of small bowel CD lesions in both adults and children independent of the site of lesions (Figs. 2.14 and 2.15).

These findings are of clinical relevance in patients with suspected CD, as well as in those with a previously established diagnosis, to help address follow-up and appropriate management of a progressive disease.

Assessment of Crohn's Disease Activity

Assessment of inflammatory activity is a central component of the management of Crohn's disease patients. Measurement of disease activity has traditionally involved a combination of clinical, biochemical (ESR, CRP, α1-antitrypsin, fecal calprotectin), imaging, and endoscopic methods; although no ideal reference standard



Student's t test	Mean difference	p	95% CI
TUS vs Surgery	-13	<.0000	-16.99; -9.27
SICUS vs Surgery	0.255	0.829	-2.11 ; 2.625

Fig. 2.15 Extension of small bowel CD lesions at TUS, SICUS and surgery. The difference between paired measurements of CD lesion length at SICUS and at TUS and surgery against their mean and statistical difference is also reported

currently exists [38]. Clinical scoring systems such as the CDAI have been shown to have low correlation with mucosal inflammation, poor inter-observer reproducibility and, more relevantly, may not detect asymptomatic inflammation [39]. Laboratory parameters are not specific and endoscopy, including double balloon enteroscopy, is invasive and limited to mucosal assessment. Computed tomography (CT) involves the use of ionizing radiation whereas magnetic resonance (MR) imaging is expensive and time consuming. Several studies evaluated the relationship between CD activity assessed as CDAI and/or with biochemical parameters, and TUS features of the bowel wall with equivocal results [40–42]. Previous studies have shown significant but weak correlation between the degree of bowel wall thickening and its extent and clinical (CDAI) and biochemical parameters (ESR, CRP) [40]. As such, an ultrasound index of intestinal inflammatory activity has been developed based on the wall thickness and stratification of the diseased gut demonstrating a strong correlation with the endoscopic and radiological score but a weak correlation with clinical (CDAI) and biological indices of inflammation [41].

The introduction of second-generation ultrasound contrast agents in combination with low mechanical index harmonic ultrasound allows accurate imaging and analysis of bowel wall microvascularity that takes part in the pathogenesis of CD inflammation [43]. Several studies have examined both qualitative and quantitative measures of bowel wall enhancement obtained from CEUS as a means of assessing inflammatory activity in Crohn's disease with inconsistent results [44–49]. Some studies have demonstrated a significant relationship between measurements obtained from CEUS and clinical or endoscopic indices of disease activity [44, 45] while others have failed to confirm similar results [46, 47], suggesting that mural microvascularity may be variably increased in active disease. Experimental data have previously shown that regional blood flow is, in fact, reduced in Crohn's disease and associated to microvascular ischaemia [49].

In conclusion ultrasound appears to be of limited value in assessing CD activity.

Assessment of the Abdominal Complications of Crohn's Disease

Contrast radiology, CT, MRI and TUS have been widely and variably utilized for the diagnosis of Crohn's disease complications such as strictures, fistulas and abscesses that often develop during the lifelong course of CD [29]. Historically, contrast

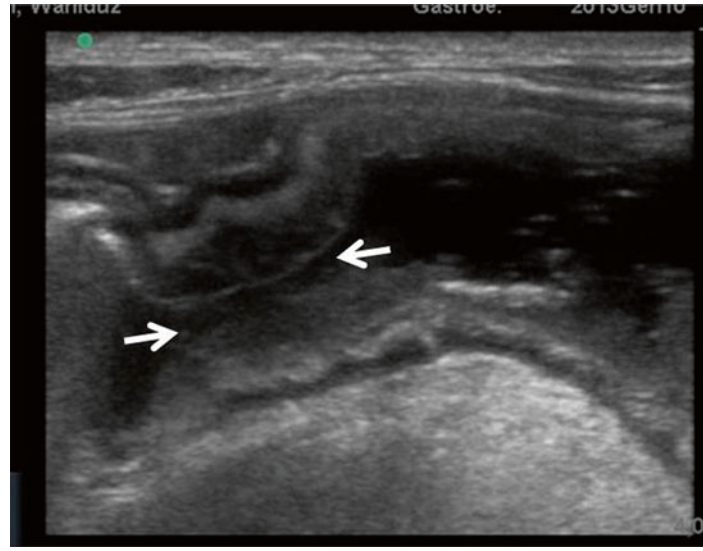


Fig. 2.16 SICUS. Crohn's disease of the distal ileum. Short segment of luminal narrowing (*arrows*) in absence of pre-stenotic dilatation. The presence of oral contrast allows the accurate measurement of luminal diameter and the extension of stricture and of a dynamic assessment of the stenotic bowel loop

radiology was the only diagnostic tool to detect small bowel strictures, but it has been shown to be inaccurate in the detection of fistulas and abscesses and is not indicated in patients with symptoms of obstruction. CT is useful for the detection of shallow abscesses [50] but its diagnostic accuracy for CD strictures and fistulas is low when compared with surgical findings [50, 51]. In any case, radiation-free methods are preferable in CD patients who require repetitive follow-up assessments. MRI is valuable to detect abscesses, but is limited in the identification of low-grade strictures [52] and to discriminate them from muscular bowel wall contractions; finally, its accuracy in the detection of fistulas is not yet fully established [37]. Standard transabdominal ultrasound (TUS) has proved to be valuable in detecting small bowel CD strictures and abscesses whereas its sensitivity in detecting entero-enteric fistulas is still debated [15, 50]. Surgery remains an important component of treatment of CD and an accurate preoperative assessment of CD lesions and associated complications is required to plan the surgical approach and intervention [53], more so if a laparoscopic approach is chosen. US being non-invasive, inexpensive, repeatable and accurate is the ideal method to be employed in the follow-up of CD patients for timely and early detection of disease progression.

CD Strictures

The clinical course of Crohn's disease is characterized by the occurrence of intestinal strictures in 21 % of patients with ileal CD and in 8 % of those with ileocolic disease and often requires surgery. A cohort study showed that 22 % of patients with stricturing CD underwent surgery during a 5-year follow-up interval [54]. Although previous small series have suggested a high diagnostic accuracy of contrast radiology for the detection of strictures, a large study by Otterson et al. [55] found that, in comparison to operative findings, small bowel follow-through incorrectly predicted the number of strictures in 30 % of patients. Bowel stricture can be demonstrated by ultrasound as thickened bowel wall associated with a narrowed lumen and increased diameter of the proximal loop greater than 3 cm [15]. Using this definition, TUS correctly detects the presence of at least one stricture in 70–79 % of unselected CD patients and in more than 90 % of those undergoing surgery for severe obstructive symptoms with 7 % false-positive diagnoses [35, 56, 57]. The use of an oral contrast agent (Fig. 2.16 and Fig. 2.17) leads to a significantly greater accuracy of ultrasound in detecting the presence and number of CD strictures (Table 2.6). A recent study that compared surgery to SICUS noted that the latter has a high diagnostic accuracy to detect: (1) the presence of more than two

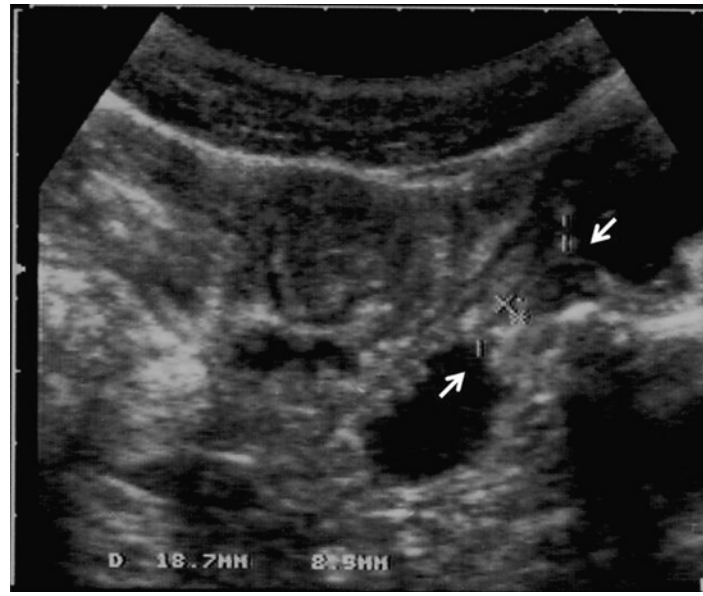


Fig. 2.17 SICUS. Crohn's disease of the jejunum. Short segment of luminal narrowing (*arrows*) in absence of pre-stenotic dilatation. The presence of oral contrast allows the accurate measurement of luminal diameter and the extension of stricture. The presence of intestinal folds allows to localize the site of stricture

Table 2.6 Comparative results of surgical and SICUS evaluation by k-statistics in the assessment of CD complications

		SICUS			
Surgery	N	N	Sens (95 % CI)	Spec (95 % CI)	k
Patients with strictures	40	39	97.5 % (87–100)	100 % (68–100)	0.93
• Stricture alone	17	16	94 % (74–99)	100 % (67–100)	0.945
• Stricture and fistulas	16	16	100 % (80–100)	100 % (60–100)	1
• Strictures, fistula & abscess	7	7	100 % (61–100)	100 % (44–100)	1
Patients with fistulas	28	27	96 % (82–99)	90.5 % (71–97)	0.88
• Entero-enteric	12	11	100 % (76–100)	82 % (61–93)	0.77
• Entero-mesenteric	9	9	100 % (67–100)	100 % (87–100)	1
• Entero-colic	13	7	54 % (29–77)	100 % (85–100)	0.61
Patients with abscesses	10	10	100 % (72–100)	95 % (83–98.6)	0.89
Patients with MFH	27	26	96 % (82–99)	91 % (72–97.5)	0.88
No SB CD complications	4	3	98 % (88–100)	75 % (30–95)	0.75

strictures, (2) stenoses located in the proximal small bowel, and (3) extension of strictures, independent from the presence of pre-stenotic dilatation and of obstructive symptoms. The presence of the pre-stenotic dilatation has been regarded at imaging techniques as the hallmark of fibrotic strictures [55]; in contrast, in one study a pre-stenotic dilatation was present at surgery and pathology in only one-third of the patients [29].

Further characterization of the stricture is made possible by considering US features of the intestinal wall. It has been proposed that the loss of stratification is associated with a low degree of fibrosis and a preponderance of inflammation, while the presence of stratification, in turn, correlates with fibrotic tissue apposition. Fibrosis may also lead to decreasing echogenicity of the submucosa and increasing echogenicity of the muscular layer [58]. Finally it has been suggested that contrast-enhanced Doppler US may assess CD inflammatory activity within strictures by evaluating the intramural blood flow

that is increased in inflammatory strictures and reduced in fibrotic ones [59, 60]. A comparable accuracy was shown by CEUS and Doppler US, although the correlation with CDAI was higher for CEUS than for US [61].

Fistulas

Fistulas, which frequently complicate the course of Crohn's disease, are the result of transmural extension of the inflammation and may end blindly in the surrounding mesentery or connect intestinal loops or adjacent organs. According to the site and the organs involved, fistulas are defined as internal, often asymptomatic and unrecognized (enteroenteric, enteromesenteric), external (enterocutaneous, enterovesical, enterovaginal) and perineal—the latter giving rise to symptoms are usually clinically obvious and more easily detected. A cross-sectional study of CD patients evaluated with CT enterography revealed a fistula prevalence of 17 %, of which about half were entero-enteric [62]. At ultrasound, fistulas appear as hypoechoic, duct-shaped peri-intestinal lesions, (Fig. 2.8 and Fig. 2.10) with a cross-sectional lumen diameter less than 2 cm and sometimes displaying echoic spots. The accuracy of TUS in the assessment of intra-abdominal fistulas varies according to the reference standard. So far there is no reliable technique for the diagnosis of this complication and the reference standard for the detection of fistulas in CD is inspection during surgery [63]. Two studies have previously compared surgical findings with the diagnostic performance of TUS [50, 57] and one [50] reported contrast radiology and CT in the detection of internal fistulas reporting a sensitivity of 87 % and 71 %, and specificity of 90 % and 95.8 %, respectively. More recently, the diagnostic accuracy of standard US and SICUS in the assessment of intra-abdominal fistulas has been compared to surgery and pathological findings [29]. This study confirms an excellent specificity (100 %) of standard TUS, but in contrast to previous reports, demonstrated that SICUS has a better sensitivity (96 % versus 55.5 %) than TUS in the detection and characterization of internal, entero-enteric and entero-mesenteric fistulas with a comparable specificity (90.5 %). In the Maconi et al. study [50] the sensitivity of TUS in the detection of internal fistulas was enhanced up to 97 % by combining it with contrast radiology and CT. Similar diagnostic accuracy has been obtained in our experience with the use of SICUS alone (Table 2.6). It is likely that the oral contrast distending the intestinal lumen allows better visualization with characterization of fistulas. Intravenous contrast-enhanced US and power-Doppler may be used as diagnostic tool in the suspicion of a fistula by detecting increased intramural blood flow in the fistula wall [64].

Finally, a previous report suggests that US may supersede X-ray fistulography in the characterization of external fistulas after the injection of hydrogen peroxide and povidone iodine into the fistula [65].

Intra-abdominal Abscesses

The prevalence of intra-abdominal abscesses in CD patients is about 4 % and usually occurs as a complication of fistulizing disease [62]. Intra-abdominal abscesses are equally detected by MRI, CT and TUS. Even if the diagnostic yield is lower for small, deep, interloop, mesenteric abscesses [50], TUS is considered a first-level procedure in the suspicion of intra-abdominal abscesses. At ultrasound an abscess appears as a hypo-anechoic round shaped lesion with a cross-sectional diameter more than 2 cm, sometimes with internal echoes due the presence of debris or air (Fig. 2.9). Four studies [50, 51, 57, 66] have compared preoperative findings at TUS and CT, and one with SICUS [29] with operative findings in detecting the presence of abscesses. All five studies showed high diagnostic accuracy of US with a mean sensitivity and specificity of 91.5 % and 93 %, respectively, although SICUS appears to be more sensitive than standard US [29].

Mesenteric Fat Hypertrophy

Presence and location of mesenteric fat hypertrophy (MFH) (Fig. 2.8 and Fig. 2.10) may influence the surgical approach [67] and its preoperative assessment may be important. Recently it has been shown in a cohort of CD patients undergoing surgery for disease complications that MFH was detected in 55 % of patients at

surgery [29]. To date, the presence of mesenteric fat hypertrophy has received little attention in the follow-up of CD patients. MFH has been found at US in about 50 % of CD patients and has been correlated with clinical activity of CD, internal fistulas and increased bowel thickness [68]. The diagnostic accuracy of SICUS for MFH is high with a sensitivity of 96 % and specificity of 91 % (Table 2.6). Notably in this cohort of patients MFH was associated with fistulas but not with strictures, confirming previous surgery findings that MFH is associated with a transmural inflammation [67].

It should be emphasized that the high prevalence of intestinal complications reported in the aforementioned studies is not representative of the CD population at large and may falsely elevate the reported sensitivity of US and SICUS in detecting CD complications. Nevertheless, the use of a luminal contrast agent markedly increases the diagnostic efficacy of TUS in detecting CD complications and SICUS may be appropriate as a noninvasive technique in the follow-up of CD patients to promptly diagnose complications, and plan surgical intervention.

Postoperative Follow-up and Prediction of Crohn's Disease Recurrence

In patients submitted to surgery for ileo-colonic Crohn's disease, recurrence of CD intestinal lesions at the level of ileo-colonic anastomosis and neoterminal ileum is extremely frequent. Indeed, it is now firmly established that surgery, even though apparently radical and despite initial clinical remission, does not offer a definitive cure. A seminal, prospective endoscopic cohort study demonstrated that the postoperative clinical course of Crohn's disease can be predicted by the severity of endoscopic lesions during the first year after resection [69]. Patients with diffuse recurrent lesions in the neoterminal ileum within 1 year of resection present symptoms earlier and are more prone to have complications than patients with no or very mild lesions who more likely have an uneventful postoperative clinical course. However, even mild recurrent CD lesions such as aphthae have the tendency to progress, often in absence of symptoms, into more severe involvement such as ulcerations and strictures [70]. Based on these observations, and considering that patients are often asymptomatic despite the presence of recurrent CD lesions, it has been proposed that patients with CD have endoscopic evaluation of the neoterminal ileum 6–12 months after surgery to guide therapeutic management [71]. In absence of symptoms, however, patients are not keen to undergo colonoscopy. Because of its invasiveness and need of intestinal preparation, ileocolonoscopy greatly affects patients' compliance. Indeed, in a large survey it has been shown that colonoscopy failed in 25 % because of patients' intolerance and in 35 % for inadequate preparation [72]. A noninvasive method that visualizes the entire small bowel, such as MRI or US performed after the ingestion of oral contrast, is likely to improve patient's compliance to undergo follow-up and can be planned early after surgery and the procedure time adjusted at will. Previous studies have assessed transmural lesions after curative ileal resection in CD patients at the level of neo-terminal ileum with MR and standard TUS [73, 74]. Both MR and TUS did not provide sufficient resolution to differentiate initial lesions in patients with endoscopic scores 1 and 2. Thereafter, two ultrasound studies [75, 76] done after the ingestion of an oral contrast, reported that wall thickness >4 mm at the level of neoterminal ileum had a high sensitivity in detecting severe endoscopic CD recurrence (i.e., score 3 and score 4) as opposed to a low sensitivity in detecting mild lesions (score 1 and score 2). More recently it has been shown [77] that compared to the Rutgeerts score at ileocolonoscopy, the combined evaluation at SICUS of wall thickness at level of the ileocolonic anastomosis (Fig. 2.18), and of the extension of transmural lesions of neoterminal (Fig. 2.19) ileum better discriminate mild (score 1 and score 2) or no recurrence (score 0) from severe (score 3 and score 4) endoscopic recurrence (Table 2.7).

The ROC curve analysis shows that the two combined variables represent an almost perfect tool in discriminating patients with score 0 from

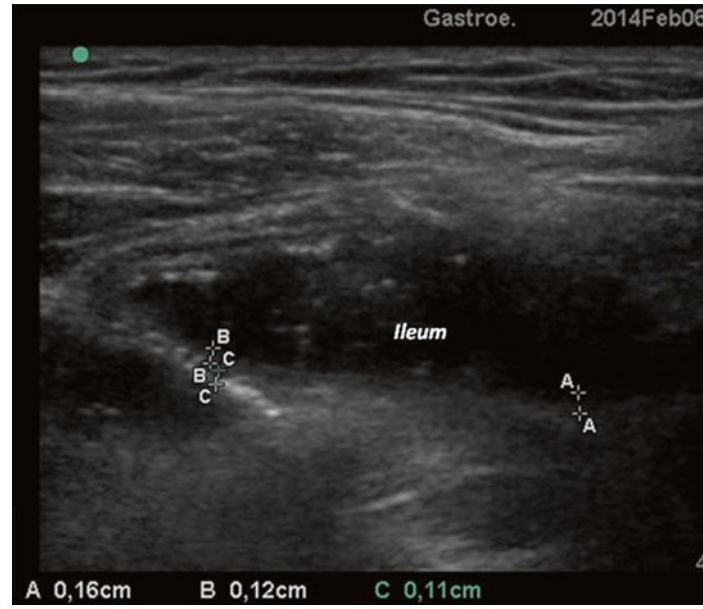


Fig. 2.18 SICUS assessment of ileo-colonic anastomosis in CD patient without recurrence. Calipers indicate thickness of ileal (up) and colonic (down) limbs (2.8 mm). Neoterminal ileum is shown

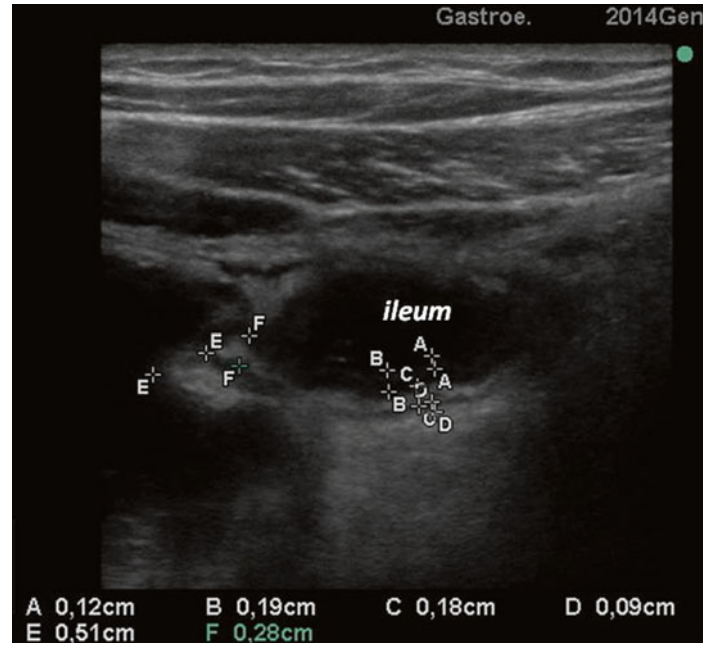


Fig. 2.19 SICUS assessment of ileo-colonic anastomosis in CD patient with recurrence. CD transmural involvement of ileo-colonic anastomosis (thickness 7.9 mm E-F) and neoterminal ileum (A-A, extending for 4 cm)

those with score 1–4 and a good tool in discriminating patients with score 0 from those with score 1. In addition, aside from an endoscopic scoring system, this study finds an association between the US grading of transmural lesions at the level of ileo-colonic anastomosis (ICA) and disease extension along the neoterminal ileum (Fig. 2.20). Notably in patients with a Rutgeerts score of 1, lesions are confined to anastomosis in half of patients at SICUS whereas in most patients (93 %) substantial transmural involvement occurs even in the presence of few aphthae and without gross mucosal ulceration at endoscopy. In the Rutgeerts et al. study, patients with no (score 0)

Table 2.7 Estimated adjusted odds ratios (AOR) with 95 % confidence intervals (95 % CI) from two logistic models of having Rutgeerts score 0 versus 1–4 (section A), and 0 versus 1 (section B) on the basis of ICA wall thickness value and extension of increased (>3 mm) neoterminal ileal wall thickness

	AOR	95 % CI	p value
Score 0 vs. 1–4 (section A)			
ICA wall thickness (for 1 mm increase)	1.96	1.22–3.15	0.01
Extension of increased (>3 mm) neoterminal ileal wall thickness (for 1 cm increase)	1.18	1.08–1.30	<0.01
Score 0 vs. 1 (section B)			
ICA wall thickness (for 1 mm increase)	1.81	1.12–2.93	0.02
Extension of increased (>3 mm) neoterminal ileal wall thickness (for 1 cm increase)	1.15	1.06–1.24	<0.01

or very mild (score 1) and those with severe (score 3 and score 4) lesions at endoscopy were grouped together as they had, respectively, nearly asymptomatic or aggressive disease 1 year after surgery. Patients with intermediate severity of lesions (score 2) had no clear clinical prognosis and they progressed with either mild or aggressive disease. By assessing transmural lesions at the level of the ileocolonic anastomosis as well as the proximal extension in the neoterminal ileum, SICUS has the potential to grade the severity of transmural involvement of recurrent CD lesions in patients who have undergone ileal resection. Given the potential for SICUS to define early extension of transmural lesions, it may be relevant to assess its use in future prospective studies as it is potentially important to define how the degree of transmural involvement may affect the postoperative clinical course.

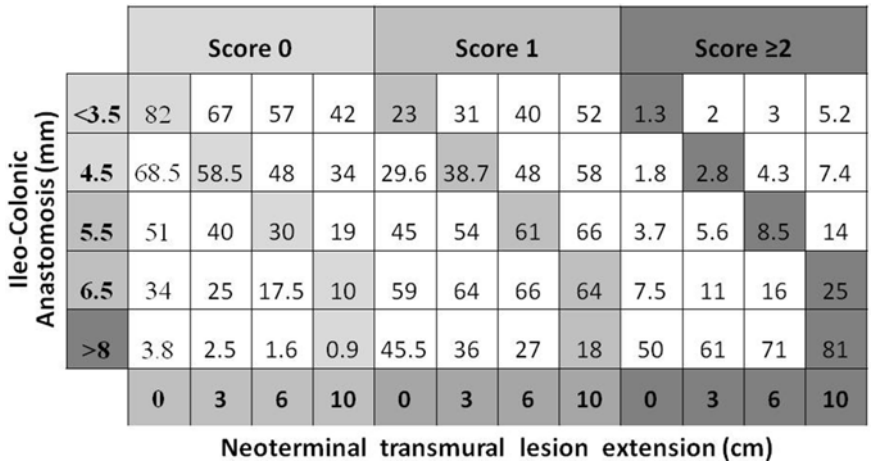


Fig. 2.20 Predicted probabilities of having a score of 0 (*pale gray*), 1 (*gray*), and ≥2 (*dark gray*) from a polychotomous ordinal logistic model with ICA wall thickness and extension of neoterminal intramural lesions as covariates. In absence of transmural lesion (extension 0) of the neoterminal ileum, the predicted probability of having a score of 0 is 82 % when ICA wall thickness is ≤3.5 mm and progressively decreases to 3.8 % for ICA wall thickness ≥8 mm. The probability of having a score of 0 progressively decreases from 67 to 42 % for transmural lesions of the neo-terminal ileum increasing from 3 cm to 10 cm. In absence of transmural lesion (extension 0) of the neoterminal ileum, the predicted probability of having a score of 1, progressively increases from 2 to 45.5 % for wall thickness of ICA increasing from 3.5 mm to 8 mm. In absence of transmural lesion (extension 0) of the neoterminal ileum, the probability of having a score of 1 with ICA wall thickness >8 mm is low (45.5 %). When the extension of transmural lesions at the level of neo-terminal ileum increases from 3 to 10 cm, the probability of having a score of 1 progressively increases from 23 to 52 %. In absence of transmural lesion (extension 0) of the neoterminal ileum, the predicted probability of having a score of ≥2 is <1.3 % (a) when ICA wall thickness is ≤3.5 mm and progressively increases to 50 % for ICA wall thickness >8 mm. With ICA wall thickness ≥8 mm and with transmural lesions of the neo-terminal ileum increasing from 3 cm to 10 cm, the probability of having a score of ≥2 progressively increases from 50 to >81 %

Ulcerative Colitis

Since the inflammation in UC affects exclusively the recto-colic mucosa, colonoscopy with biopsy is the gold standard for the assessment of disease extent, activity, and severity, thus bowel US has a limited usefulness in the diagnosis and in the follow-up of patients with UC, except for severe disease or in presence of severe comorbidity. A few studies have assessed the diagnostic accuracy of TUS in diagnosing ulcerative colitis in small numbers of patients with sensitivities ranging from 48 to 100 % and specificities from 82 to 90 % [78] (Fig. 2.21 and Fig. 2.22). Current evidence indicates that in UC diagnostic accuracy of TUS is also related to disease site, as sensitivity is high for sigmoid/descending colonic disease (reaching 97 %) [79] but low for rectal disease [22]. The utility of US for assessing activity of colitis has been assessed in small series of patients showing that the mean colonic wall thickness was higher in moderately or severely inflamed bowel compared to normal segments [23, 80, 81].

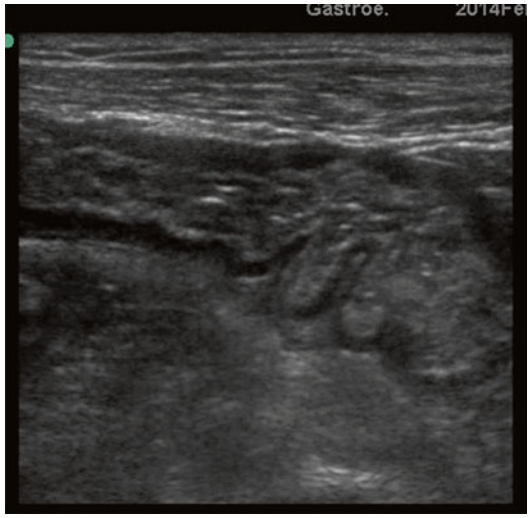


Fig. 2.21 TUS, normal appearance of intestinal wall at the level of sigmoid colon

Recently Civitelli et al. [82] in a prospective and blind study compared colonoscopy with US in assessing the extent and activity of disease in 60 consecutive pediatric UC patients. The results of the study showed high agreement (90 % concordance) with endoscopy in the assessment of disease extent, with a sensitivity ranging between 75 % at the level of right colon to 96 %

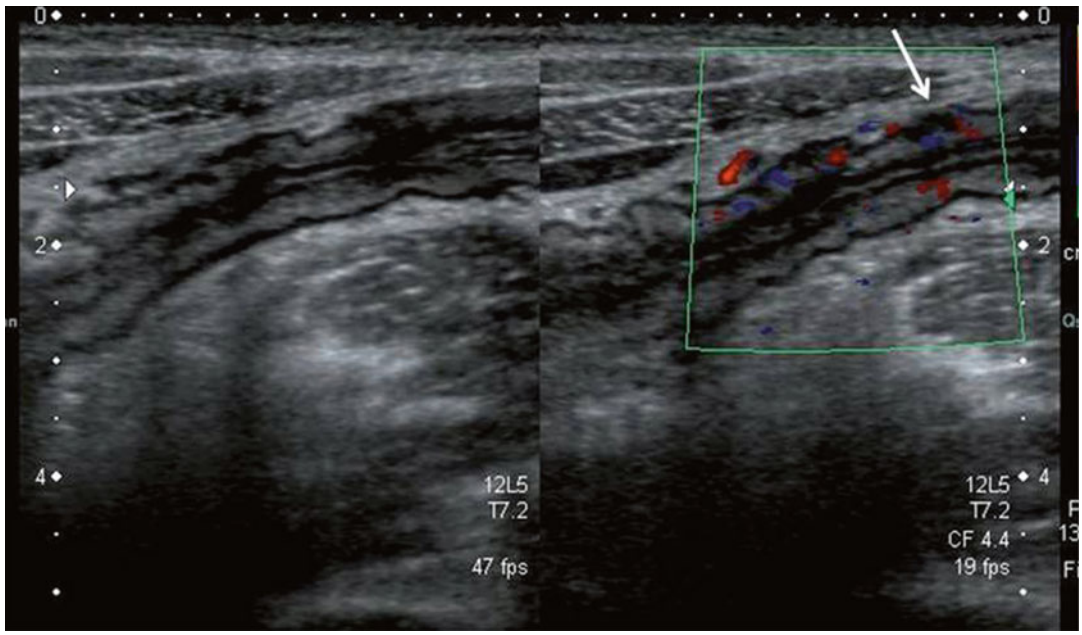


Fig. 2.22 TUS. Ulcerative colitis. Longitudinal scan of descending colon. The wall thickness is increased (>3 mm), with normal multilayered echo-pattern

at the level of left colon as well as a specificity of 100 % for all colonic sites. In addition, a US score ranging from 0 to 4 was assessed based on increased BWT ($p<0.0008$), vascularity ($p<0.002$), loss of haustra ($p=0.031$) and loss of BW stratification ($p=0.021$). At multiple regression analysis endoscopic severity demonstrated a strong correlation showed ($p<0.0001$) with the US score as well as Ulcerative Colitis Activity Index (PUCAI) and Mayo endoscopic subscore (MS).

Conclusion

Due to noninvasiveness, low cost, absence of radiation, and widespread availability, ultrasound has been widely used to assess those aspects of the GI tract that are not easily accessible to endoscopic investigations and, in particular, the mural and extramural GI pathology of the small bowel. The greatest advancement in ultrasonographic assessment of the GI tract has been made with Small Intestinal Contrast Ultrasonography (SICUS), which is superior to the standard transabdominal US. It has a high sensitivity, and nearly perfect specificity to diagnose Crohn's disease lesions of the small bowel, identifying the site and extension of the inflammatory lesions as well as complications such as strictures, fistulas, and abscesses. Moreover, SICUS has been shown to predict—similar to endoscopy—the severity of postoperative inflammatory recurrence after ileocolonic curative resection for terminal ileocolon Crohn's disease, making its noninvasive nature an attractive alternative for postoperative follow-up.

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3 Fluoroscopic Techniques for the Interrogation of IBD Patients

Stephen W. Trenkner and Joel G. Fletcher

Historical Perspective and Introduction

Burrill Crohn and colleagues described regional enteritis in 1932 [1]. Over Dr. Crohn's career, he worked closely with renowned gastrointestinal radiologist Dr. Richard Marshak, who performed and developed many fluoroscopic techniques, and who described many of the morphologic features of Crohn's disease and its progression from mild mucosal inflammation to stricture and penetration over time. At the end of his career, Dr. Marshak published an annual oration summarizing ten principles of Crohn's disease, many of which form the basis for classic understanding of the disease today [2]. Amongst the early fluoroscopic observations that Marshak and Crohn made were that Crohn's disease can involve any segment of the intestinal tract and that recurrence after surgical resection occurs in the majority of patients, almost always at the anastomosis, most frequently on the small intestinal side [2]. Additionally, they observed that Crohn's inflammation tends to recur at the same sites within the bowel and rarely spreads proximally or distally in the absence of surgery.

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Because patient symptoms in IBD do not relate to inflammatory biologic activity or anatomic structural deformity [3], objective markers of intestinal inflammation are required for accurate and comprehensive IBD assessment. Endoscopy, fluoroscopic and cross-sectional imaging all provide anatomic, objective information that can be correlated with serologic markers and patient symptoms. Understanding the complementary nature of modern radiologic and endoscopic observations are critically important in the age of biologic therapies that can alter or delay progressive destruction of the gastrointestinal tract [4], but which also carry some risk.

While fluoroscopy was the mainstay of anatomic imaging for decades, the last 20 years have seen the adoption of CT and MR enterography to image the small bowel, pelvic MRI to image perianal fistulizing disease, and capsule endoscopy and balloon-assisted enteroscopy to image the mucosal surface of the small bowel, in addition to other new endoscopic techniques. In the current era of multimodality small bowel imaging, fluoroscopy retains a role in addressing some of the weaknesses and challenges of existing cross-sectional and endoscopic techniques, and offers an imaging alternative in patients who cannot undergo cross-sectional imaging.

Herein, we review different fluoroscopic imaging alternatives to assess for mucosal inflammation, penetrating and obstructive disease, comparing them to cross-sectional techniques, and highlighting relative strengths and weaknesses.

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Assessment of Mucosal Inflammation

Multiple fluoroscopic techniques such as the small bowel follow through (SBFT), peroral pneumocolon, fluoroscopic enteroclysis, double contrast upper GI and barium enema can be used to assess the mucosa and intestinal lumen for early or advanced Crohn's disease. While the sensitivity of fluoroscopic methods for mild disease is substantially less than optical techniques, the fluoroscopic examination provides a means to assess bowel segments that are endoscopically inaccessible as well as provide a succinct overview of Crohn's disease involvement. In many instances, the critical clinical question is not if mild disease is present, but if aggressive therapy has altered advanced inflammatory changes within the gut. In addition, real-time assessment with enteric contrast and air insufflation at fluoroscopy (e.g., peroral pneumocolon) permits distinction between spasm and stricture. Finally, because of declining fluoroscopic volumes at many institutions, radiologist experience with fluoroscopy is as important to comprehensive assessment as formal training in CT and MR enterography [5].

Imaging Findings

Fluoroscopic findings in small bowel Crohn's disease are generally classified as active inflammatory subtype, fibrostenotic subtype, fistulizing/perforating subtype, and reparative/regenerative subtype [6]. Inflammatory findings can be divided into those that occur in early and mild Crohn's disease, and those that occur in advanced inflammation [7]. In any single inflammatory lesion, a spectrum of findings may be present (Fig. 3.1). Fluoroscopic findings of early active inflammation include lymphoid hyperplasia, slight thickening

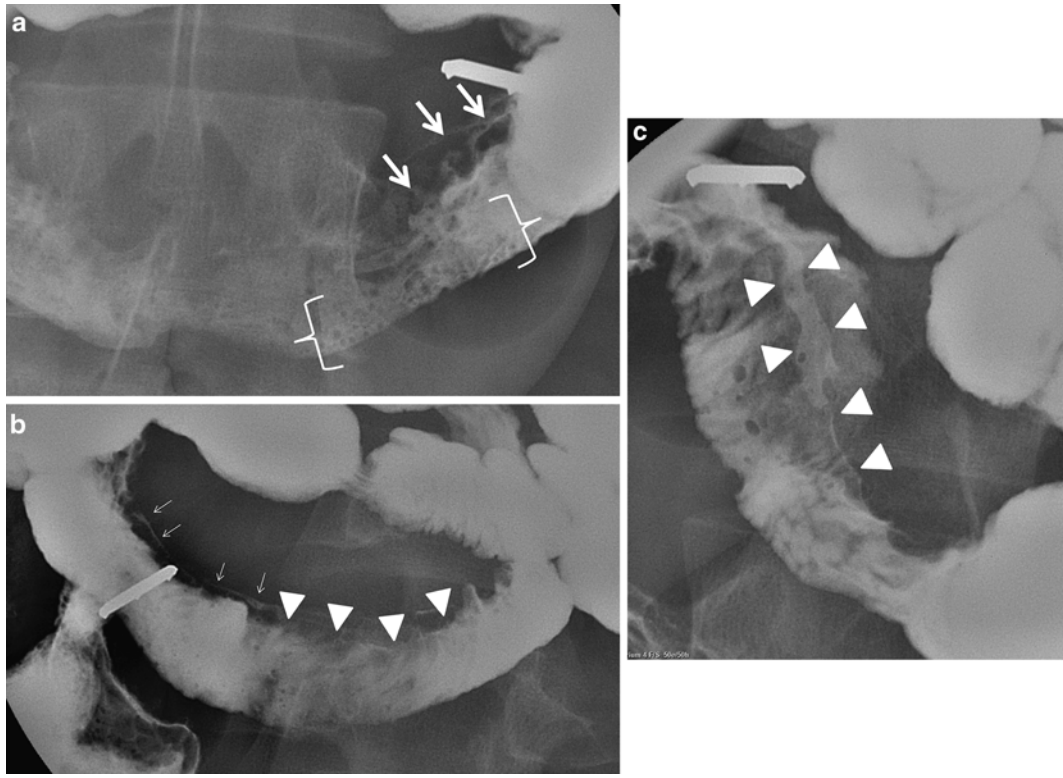

Fig. 3.1 A 17-year-old male on Adalimumab and steroids with persistent abdominal pain. Images show serial spot films from a SBFT demonstrating (**a**) lymphoid hyperplasia (*in brackets*), (**a**) aphthous ulcerations along the mesenteric border (*arrows*), (**b** and **c**) mesenteric border linear ulcer (*arrowheads*), and (**b**) a long intramural sinus tract (*small arrows*). (**c**) The mesenteric border ulcer is viewed in profile and enface. In most small bowel lesions with mucosal inflammation, multiple radiographic findings will be present

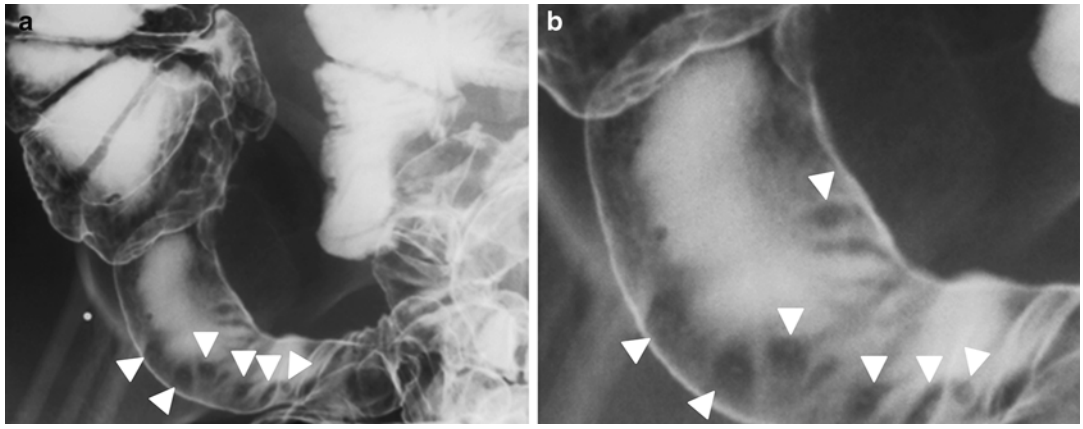

Fig. 3.2 (**a, b**) Peroral pneumocolon demonstrating double contrast appearance of aphthous erosions (*arrowheads*) in the terminal ilium

of the small bowel folds, and aphthous ulcerations [8, 9]. Lymphoid hyperplasia appears as numerous 3-mm lucencies over a segment of bowel (Fig. 3.1). Aphthous ulcerations appear as rounded lucencies approximately 5–10 mm or less in size with a central barium collection, and are almost always seen with normal intervening mucosa (Figs. 3.1 and 3.2) [10]. Aphthous ulcerations are thought to occur in mucosal lymphoid tissue [10]. The lucent halo corresponds to a mound of edema around the central erosion, in which barium collects. Thickening of folds also occurs due to localized lymphedema, granuloma formation, and fibrosis [2].

Aphthous ulcerations are best seen using double contrast technique or with careful palpation [11]. As ulcerations progress and become deeper, longitudinal and transverse ulcers coalesce and combine with edema and traction to form the classic cobblestone pattern (Fig. 3.3) [2]. Transmural ulcerations can progress to form "rose thorn" ulcers, which project perpendicularly beyond the lumen.

One of the early morphologic patterns recognized by Marshak, Herlinger, and others is the asymmetric inflammation of Crohn's, which is generally most pronounced along the mesenteric border of the small bowel. Inflammation and edema along the mesenteric border leads to straightening of the mesenteric border, with ulcerations occurring in this region. Ulcerations can progress and coalesce until the classic mesenteric border linear ulcer of Crohn's disease is seen. This is a pathognomonic finding (Figs. 3.1 and 3.3) [9]. In profile, the linear ulcer often has a shaggy appearance due to mucosal erosion with a nearby line of radiolucency representing edema surrounding the ulcer (Fig. 3.1). As the disease progresses, sacculations occur along the antimesenteric border of the bowel lumen, where there is a relative absence of inflammation and fibrosis (Fig. 3.4). Straightening of the mesenteric border can also be due to fibrofatty proliferation, which also occurs along the mesenteric side and is seen as creeping fat at surgery. At fluoroscopy, fibrofatty proliferation displaces normal bowel loops away from involved loops and crowds the uninvolved loops into different areas of the abdominopelvic cavity. In the rectum, fibrofatty proliferation displaces other bowel loops superiorly in the pelvis.

Spasm of mildly inflamed small bowel is a known early sign of Crohn's disease. One of the strengths of fluoroscopy is the ability to visualize luminal narrowing in real time to discriminate between true narrowing and spasm. Fluoroscopy can be used to accurately measure stricture length without resorting to post processing methods or crude estimation across multiple slices, and to map nearby strictures preoperatively for potential surgical resection or strictureplasty (Fig. 3.4). While CT and MR enterography are highly accurate for the detection of strictures and fistulae [12],

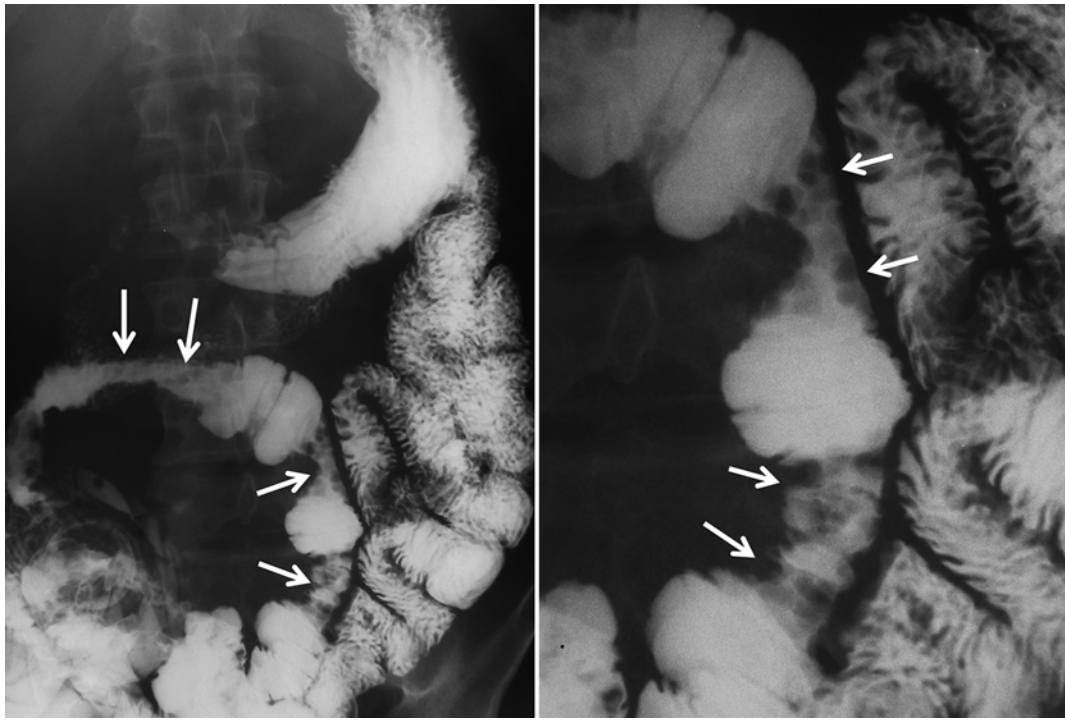

Fig. 3.3 Small bowel follow-through from 42-year-old man with multiple segments of ileum involved by Crohn's-related inflammation, demonstrating confluent linear and transverse ulcers showing a cobblestone pattern (*arrows*). Cobblestone pattern arises from a combination of linear and transverse ulcers, edema, and sometimes fibrosis

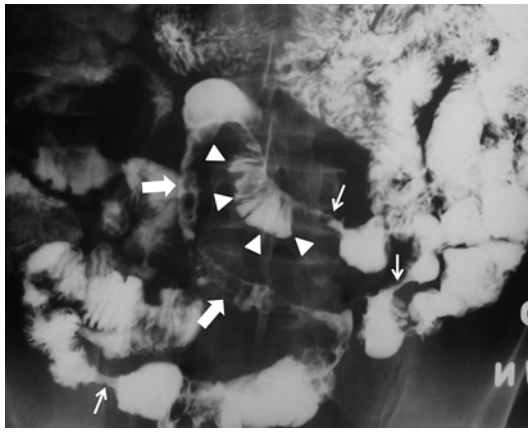

Fig. 3.4 Small bowel follow-through demonstrating the string sign (*small arrows*), antimesenteric border sacculation (*arrowheads*), and long segmental involvement with cobblestoning (*large arrows*)

clear delineation of multiple strictures is sometimes problematic as areas of spasm or collapse can be misinterpreted [13].

Small Bowel Follow Through

SBFT is performed by having the patient ingest multiple cups of thin liquid barium and fluoroscopically evaluating the contrast column from the duodenal bulb to the terminal ileum. Frequent palpation under fluoroscopy should be performed to efface the small bowel loops to visualize aphthous ulcers and other radiographic features, in addition to assessing peristalsis and fixation of small bowel loops. Occasional overhead images provide a global view of diseased loops and their location. While large volumes of barium are generally used to speed the examination and unmask strictures and obstructing lesions, smaller volumes can also be used in patients unwilling to ingest the large volumes necessary for CT and MR enterography.

Several studies of patients with known or suspected Crohn's disease who underwent cross-sectional enterography and SBFT by experienced

fluoroscopists have been performed. They demonstrate slight but significantly decreased sensitivity and unchanged specificity for SBFT compared to CT enterography for detecting active mural inflammation [14–17]. When intubation of the terminal ileum can be successfully accomplished at colonoscopy, there is little improvement in cost effectiveness when performing additional SBFT; however, incremental effectiveness is substantial when terminal ileal intubation cannot be performed [18].

SBFT has several relative strengths compared to CT and MR enterography, which should be exploited in the appropriate clinical contexts. Real-time examination permits the best and easiest distinction between spasm, collapse and stricture. During CT enterography, usually only one acquisition of the bowel is performed to minimize radiation dose. Observation over time is permitted at fluoroscopy. Additionally, inexperienced radiologists not infrequently overlook jejunal inflammation at CT enterography (manifested by asymmetric wall thickening and hyperenhancement) or confuse it with the normal feathery appearance of the valvulae conniventes or jejunal collapse, which is observed in approximately one-third of routine CT enterography cases. Advanced jejunal inflammation can be entirely occult at routine abdominopelvic CT, when bowel loops are not distended. At fluoroscopy, advanced inflammatory changes cannot be confused with the jejunal fold pattern of the valvulae conniventes, as the bowel loops are markedly distorted by cobblestoning, linear ulcers with sacculation, and stricture formation (Fig. 3.5). While fluoroscopy can take longer when smaller volumes of barium are ingested, fluoroscopists can examine the patient over multiple time-points (sometimes several hours), so patients that are unwilling to consume large volumes of enteric contrast can be imaged. As such, fluoroscopy provides the best overview for complex postoperative anatomy, stricture mapping, as well as providing the easiest method for estimating small bowel length [19] (Fig. 3.6). As such, side-to-side anastomoses are sometimes mistaken at cross-sectional enterography for dilated segments proximal to a stricture, and such postoperative changes are easily determined at fluoroscopy.

Peroral pneumocolon is performed after a SBFT by insufflating air into the colon (Fig. 3.2). Air refluxes into the terminal or neo-terminal ileum to provide exquisite double contrast images of the ileal mucosa (Fig. 3.7). This double contrast technique is extremely useful as the distention allows excellent evaluation of anastomotic and ileal strictures (Fig. 3.8).

There are no prospective studies that we are aware of comparing cross-sectional imaging techniques to the SBFT with peroral pneumocolon for the detection of active inflammation. The strengths of this exam are that by achieving maximum distension spasm can be differentiated from strictures, and that double contrast visualization of the terminal ileal mucosa is achieved. Apthous ulcers can be detected. These findings can be particularly useful after ileocolic anastomosis, where there is generally some nonspecific inflammation at endoscopy and hyperenhancement at cross-sectional enterography (Fig. 3.9). Peroral pneumocolon is probably the best method to assess for mucosal inflammation at fluoroscopy in the presence of an ileocolic anastomosis, as air is easily refluxed into the distal small bowel.

There are several weaknesses of the SBFT, which should be considered. As mentioned, there is a sensitivity penalty in not performing cross-sectional enterography [14, 16], but in the presence of low probability of disease, the SBFT can add substantial confidence to ileocolonoscopy in making the correct diagnosis [18]. Mild jejunal disease can still be challenging, but moderate and advanced inflammation can be reliably detected. Unlike cross-sectional enterography, the mesentery, colon, anus, and appendix are not imaged, so the SBFT alone cannot reliably stage the full extent of Crohn's involvement along the GI tract. Additionally, to detect penetrating disease by SBFT, barium must fill sinus tracts or fistulae. In contradistinction, fistulae and sinus tracts at cross-sectional enterography often do not contain enteric contrast but are easily recognized as enhancing, extraenteric tracts that stand out from

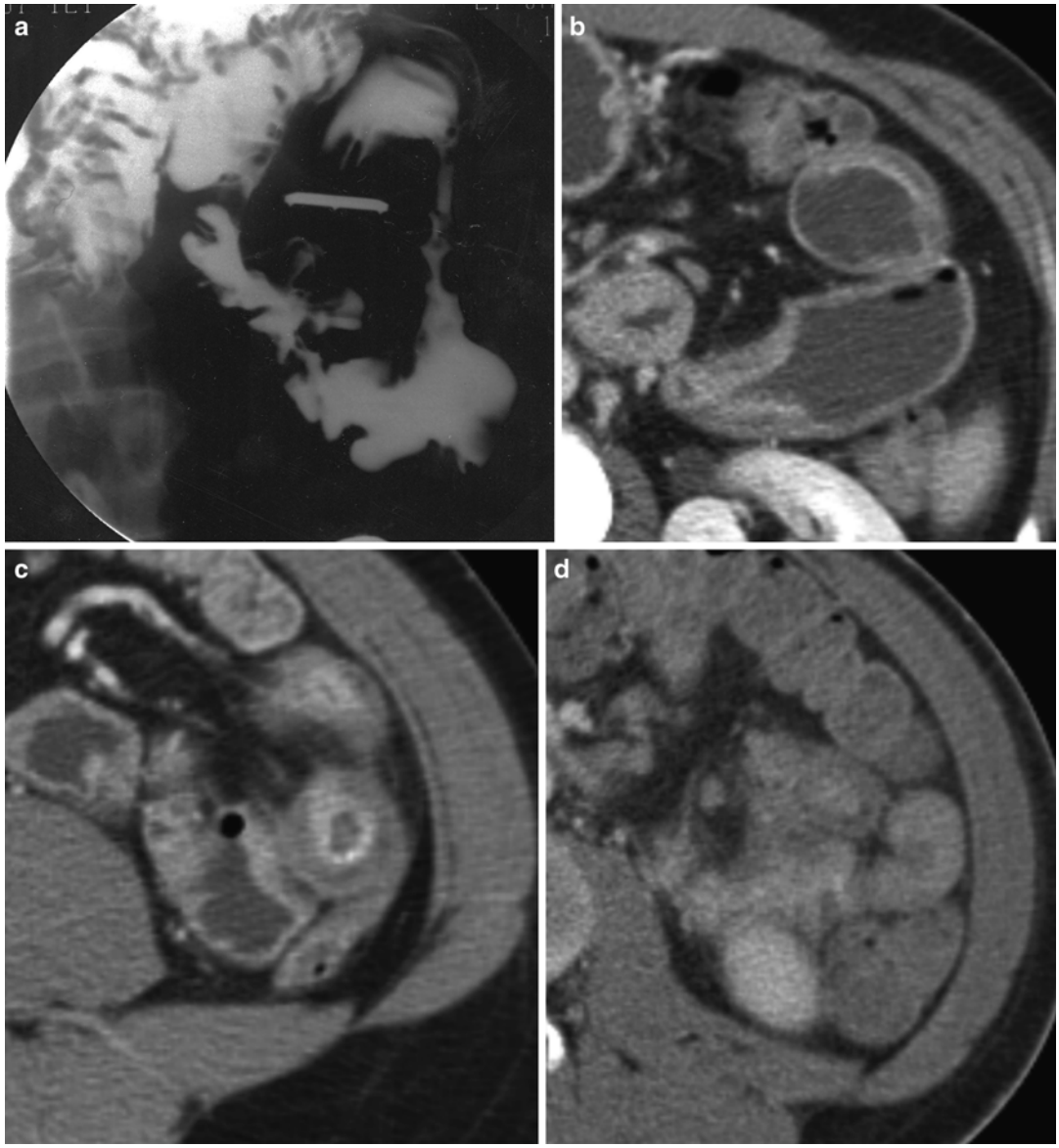

Fig. 3.5 Jejunal Crohn's disease as demonstrated by (**a**) small bowel fluoroscopy, and (**b** and **c**) CT enterography. Findings such as asymmetric narrowing and string sign are easy to identify at small bowel follow-through, with recognition of analogous cross-sectional findings required at CT enterography; e.g., (**b** and **c**) asymmetric wall thickening and hyperenhancement, and target sign, but entirely occult at (**d**) routine abdominal CT

the surrounding mesenteric fat and which cause tethering of involved small bowel loops [15, 17, 20]. The SBFT can be performed in patients with a small bowel obstruction but is rarely needed and is often unfruitful owing to the time required for examination.

Retrograde Small Bowel Examinations

Retrograde examinations provide excellent visualization of the distal small bowel, and, in the setting of an end ileostomy or ileal pouch - anal

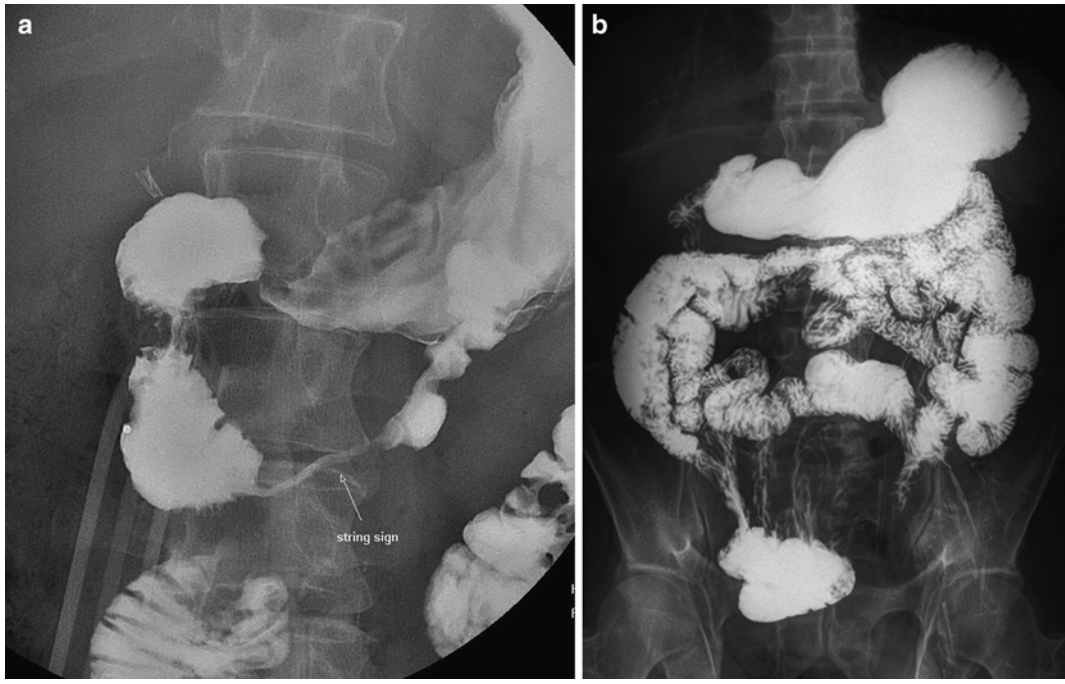

Fig. 3.6 Single contrast upper GI demonstrating a long segment duodenal stricture (the string sign). Small bowel follow through represents an ideal way to measure (**a**) the length of strictures and (**b**) bowel length (in a patient with prior colectomy)

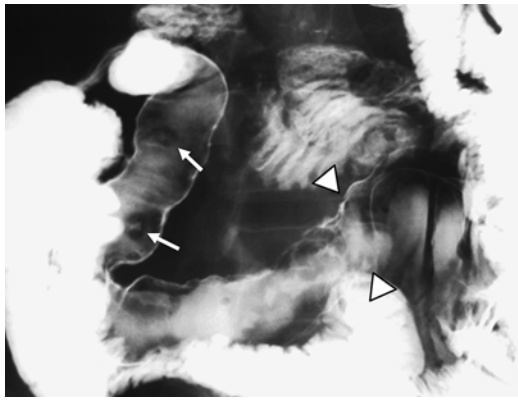

Fig. 3.7 Images from a peroral pneumocolon clearly show aphthous erosions (*arrows*) in a distended terminal ileum, in addition to a widely patent ileocolic anastomosis (*arrowheads*)

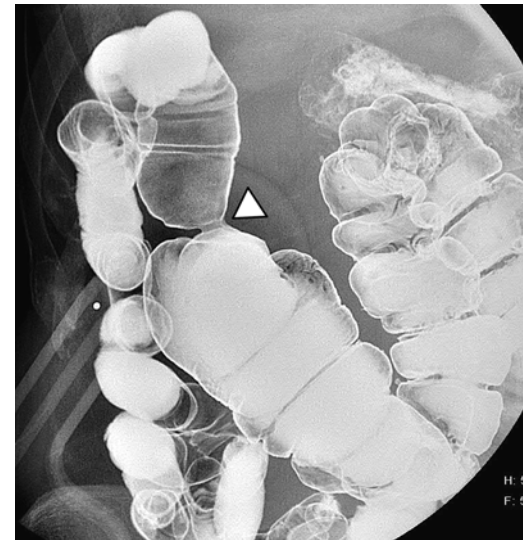

Fig. 3.8 Peroral pneumocolon in another patient with prior right hemicolectomy and end-to-end ileotransverse colostomy demonstrates a stricture at the ileocolic anastomosis (*arrowhead*), but normal mucosa in the terminal ileum

anastomosis, address weaknesses inherent with cross-sectional enterography. In patients with an end ileostomy, a red ball, cone, or Foley catheter balloon is held outside of the stoma with the end

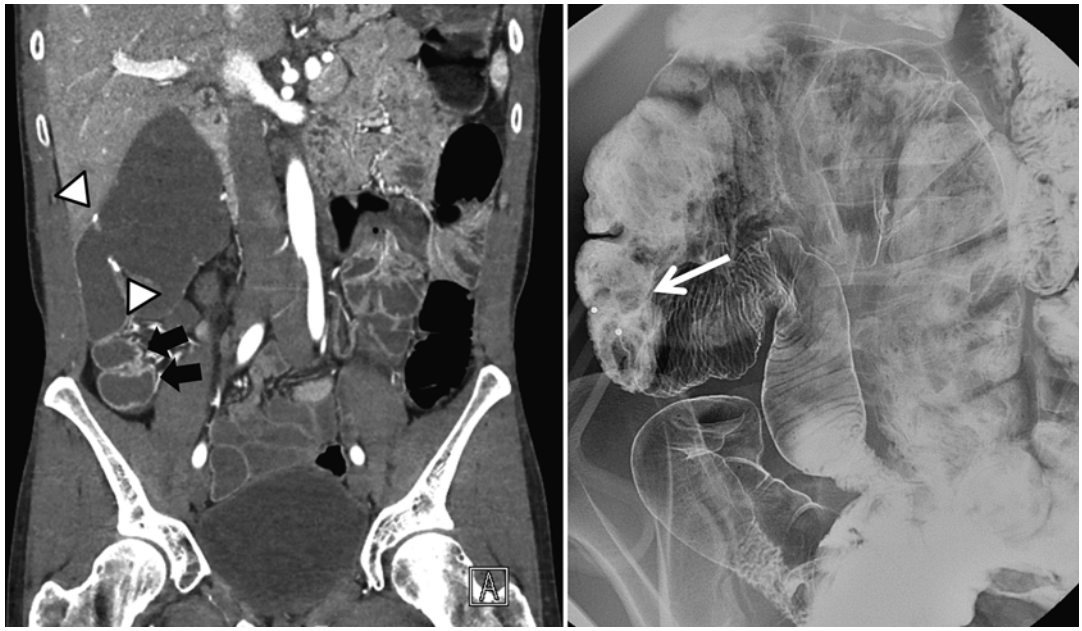

Fig. 3.9 *Left panel*: Crohn's patient with prior right hemicolectomy and ileoascending anastomosis (*arrowheads*) at CT enterography, with questionable mural hyperenhancement in the neoterminal ileum (*black arrows*). *Right panel*: Peroral pneumocolon nicely demonstrates the anastomosis (*white arrow*), and normal appearing ileal mucosa. Patient treatment remained unchanged as a result of peroral pneumocolon

of the catheter in the distal ileum. These exams are generally performed after the stoma adhesive is removed so there is a good seal between the Foley balloon and the stoma. Retrograde exams after IPAA are usually performed using a pediatric enema tip. It is extremely important not to use a large enema tip with a retention balloon, as such an enema tip can disrupt the anal anastomosis. Air can be insufflated by cutting the plastic tube through which enteric contrast is delivered and attaching a bulb with a one-way valve to the enema tubing.

We have encountered cases where a distal ileal obstruction is falsely interpreted on CT enterography in patients with IPAA. This confusion is fairly common and is due to the dilated appearance of the distal bowel loops, which can be functional. With retrograde examination, the bowel caliber is easily assessed, in addition to the frequency of peristalsis, making the diagnosis of functional dilation of the distal ileum very easy in this clinical setting (Fig. 3.10 and Fig. 3.11). Another advantage of retrograde studies is they can be performed very quickly without any drinking required on the part of the patient. Finally, in the perioperative setting, tiny leaks at the ileoanal anastomosis or from the blind end of the j-pouch create stranding in the fat adjacent to the ileal pouch or phlegmonous change at CT, but retrograde exams clearly depict the leak due to the increased intraluminal pressure, which is applied (Fig. 3.12).

Relative weaknesses of retrograde examinations of the small bowel are that they cannot comprehensively evaluate the ileoanal pouch for inflammation, and some fistulizing complications as the peri-pouch tissues may not be seen. Obviously, these techniques image only the distal bowel near the anus or ostomy.

Single and double contrast enteroclysis are performed after nasojejunal intubation. Barium is instilled via the nasojejunal tube so that the small bowel is visualized as a continuous column of barium. Due to the rate of instillation, the small bowel lumen becomes distended. Single contrast enteroclysis is one of the best radiologic tests for

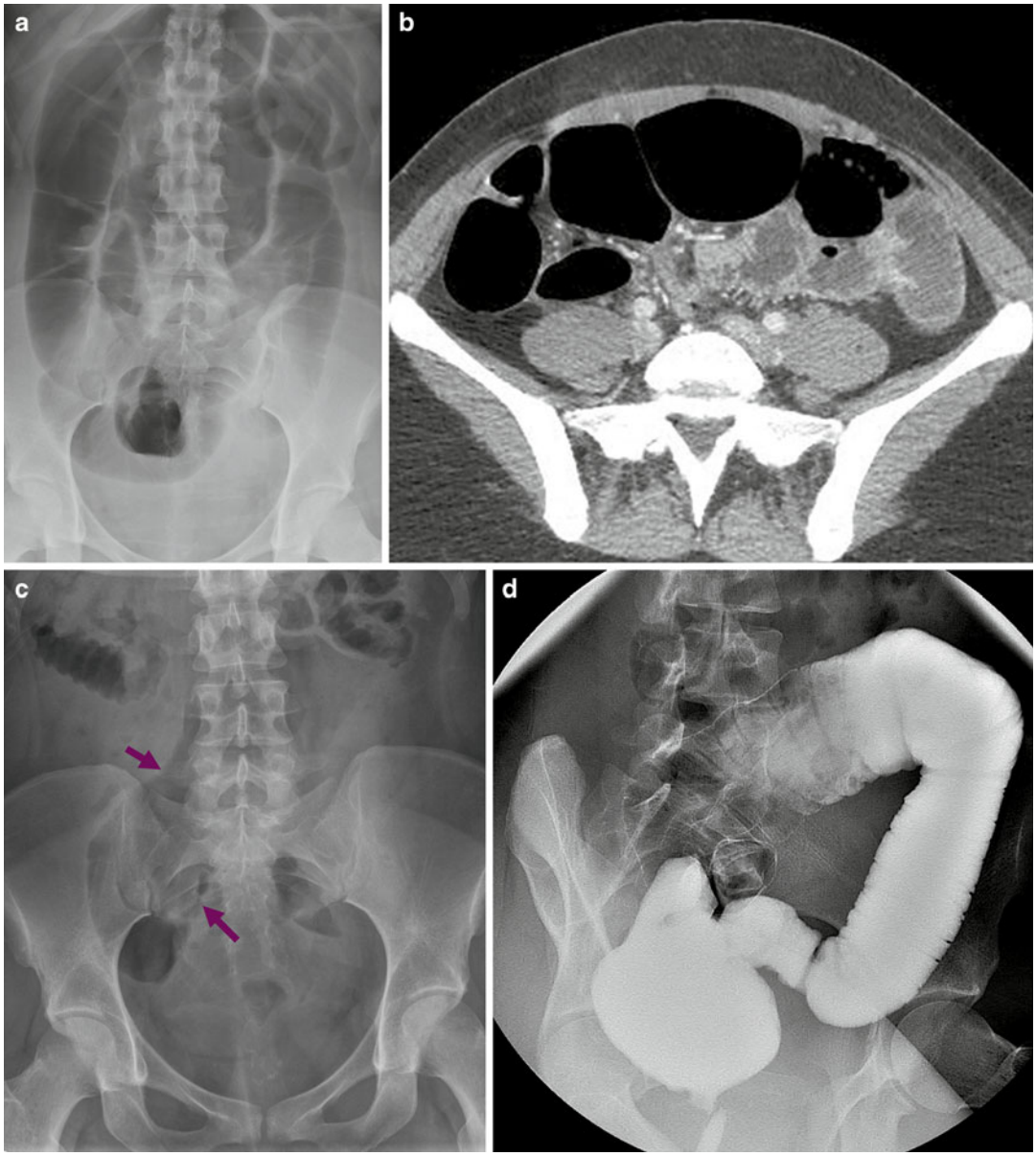

Fig. 3.10 A 24-year-old woman with prior proctocolectomy for ulcerative colitis as well as prior operation for small bowel obstruction that was not confirmed at surgery. (**a**) Plain film demonstrates multiple dilated small loops in the mid abdomen, with (**b**) CT enterography demonstrating similar findings. CT enterography was misinterpreted as small bowel obstruction. (**c**) At scout film prior to retrograde study, there is a dilated ileal loop in the mid abdomen. (**d**) Retrograde study demonstrates normal appearing ileal pouch, and functional dilation of the distal ileum without any obstruction and normal appearing mucosa

partial small bowel obstruction, but double contrast technique better visualizes the small bowel mucosa. Double contrast enteroclysis can be performed using barium and air (conscious sedation is often employed), or barium and methylcellulose [21, 22]. Air double contrast enteroclysis is probably the best method to visualize the subtle findings of early Crohn's disease [22], but there is limited data comparing this technique to endoscopic reference standards in Crohn's patients [23].

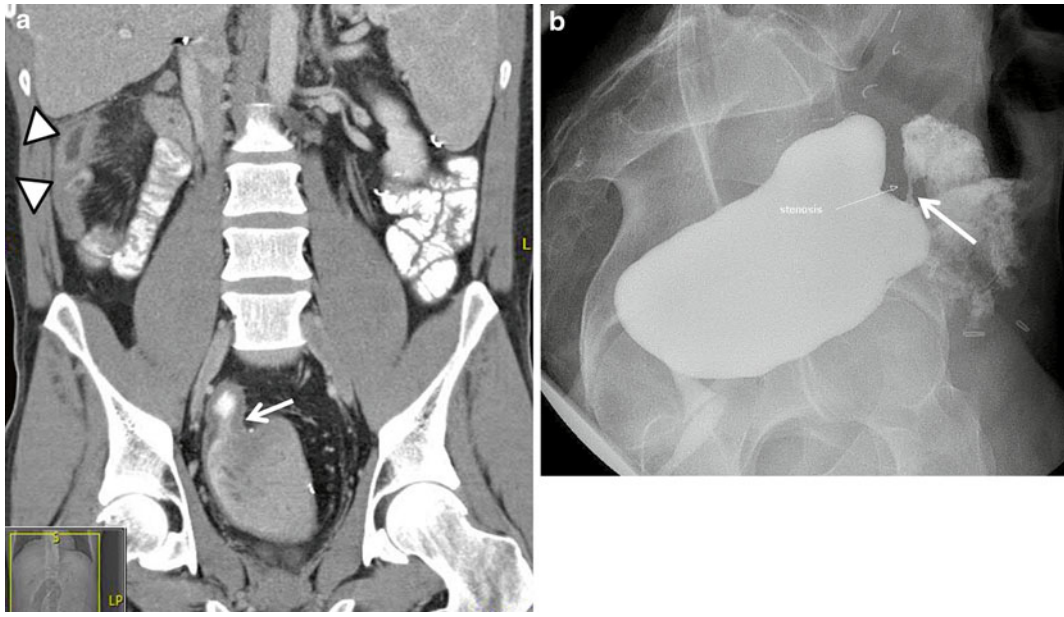

Fig. 3.11 (**a**) CT enterography after proctocolectomy and ileal pouch anal anastomosis demonstrates active recurrent Crohn's disease in the ileum (*arrowheads*), but cannot assess for obstruction just proximal to the j-pouch, where there is wall thickening (*arrow*). (**b**) Retrograde single contrast enema easily demonstrates the distal ileal stricture (*arrow*)

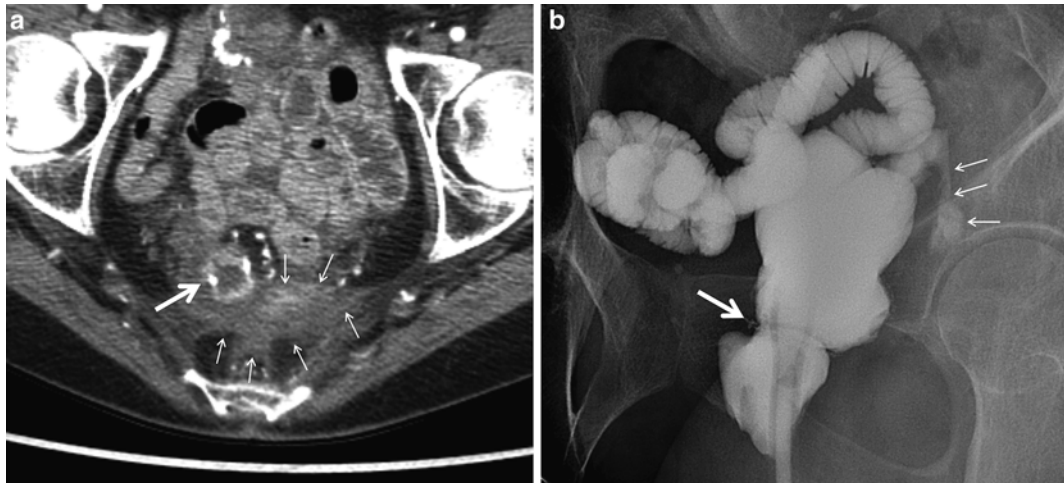

Fig. 3.12 CT enterography performed 6 months after total colectomy and ileal pouch anal anastomosis. (**a**) Shows an axial image at the top of the pouch (*arrow*), with peri-pouch stranding, fluid and enhancement (*small arrows*), with unclear etiology for these findings. (**b**) Retrograde enema using iodinated contrast demonstrates a normal pouch-anal anastomosis, with a leak from the blind end of the pouch (*small arrows*). The large arrow shows normal appearance to ileo-anal anastomosis

With air double contrast enteroclysis, conscious sedation is required, and localization can be a problem due to superimposition of bowel loops. Fluoroscopic enteroclysis is generally performed only by experienced GI radiologists, and due to the length of the exam and patient discomfort, special arrangements often need to be made unless an institution performs many of these

studies. Many institutions do not offer fluoroscopic enteroclysis, while others only perform single contrast enteroclysis for potential low-grade bowel obstruction.

Barium enema can be performed with single or double contrast technique and begins with placement of a rectal tube. In single contrast barium enema, barium is refluxed from the rectum to the proximal colon and hopefully into the ileum. With double contrast barium enema, a higher density barium is employed and instilled through approximately half the colon, after which air or carbon dioxide is added using a one-way ball valve, to coat the mucosa and distend the colonic segments, providing a double contrast view. Because the barium enema is insensitive compared to endoscopy for mucosal inflammation, its routine use to detect inflammation in IBD patients is discouraged when endoscopic techniques are available. Barium enema is useful to examine the proximal colon and to demonstrate the length of a stricture when portions of the colon are inaccessible endoscopically. However, it is important to understand that cancers, particularly in ulcerative colitis, can appear identical to benign strictures at barium enema. Moreover, unlike ileocolonoscopy with biopsies, barium enema cannot screen for dysplasia or findings of chronic inflammation. Single contrast barium enema can be performed with either barium or water-soluble contrast. Its use after surgery to assess for the integrity of anastomoses with water-soluble contrast is routinely used at many institutions prior to ileostomy takedown.

Double contrast upper GI examination is performed by ingesting an effervescent agent followed by high density barium. Double contrast examination is useful in the setting of Crohn's disease when endoscopy cannot be performed or when a stricture cannot be traversed with the endoscope (Fig. 3.6a).

Assessment of Penetrating Disease

Unlike the assessment of mucosal and mural inflammation, cross-sectional imaging options (CT enterography, MR enterography, and MR pelvis) each have unique strengths and weaknesses that need to be adapted for patients with penetrating disease, and fluoroscopic techniques can be useful in particular clinical scenarios. Often two modalities are needed in specific presentations. In the presence of a large enterocutaneous fistula, the fistula may decompress the small bowel loops that connect to the fistula, so they are poorly visualized at cross-sectional imaging. At fluoroscopic investigation with a fistulogram (discussed below), sterile water-soluble contrast is injected under pressure using a syringe so that contrast fills the bowel loop to which it connects. Additionally with chronic inflammation, fistulae are sometimes not seen at cross-sectional imaging, particularly in the pelvis, as the traditional hyperenhancement that signals their presence is often not present. This is particularly true of rectovaginal fistulae, which can be chronic with little inflammation, and which are notoriously difficult to image with all imaging techniques.

SBFT can provide a surgical road map for some fistulae, as there is near 100 % specificity when a fistula is found (Figs. 3.1 and 3.13). However, as mentioned, enteric fistulae and abscesses often do not fill with contrast, so SBFT underestimates these findings as it is a low pressure technique compared with a fistulogram. A fistulogram is performed by cannulating a fistula or cavity with a catheter and injecting sterile water-soluble contrast under pressure. Because of the increased pressure, it is generally excellent for delineating enterocutaneous fistulae, but often does not visualize disease activity in the adjacent small bowel loop. Additionally, it requires that the skin site of the fistula has anatomy favorable to cannulation.

Assessment of Obstructive Disease

The unique ability of fluoroscopy to perform retrograde examinations should be exploited in the busy IBD practice, particularly in patients with low grade or distal obstructions, absent ileocecal valve, or patients with suspected motility disorders. Underlying obstruction is defined by persis-

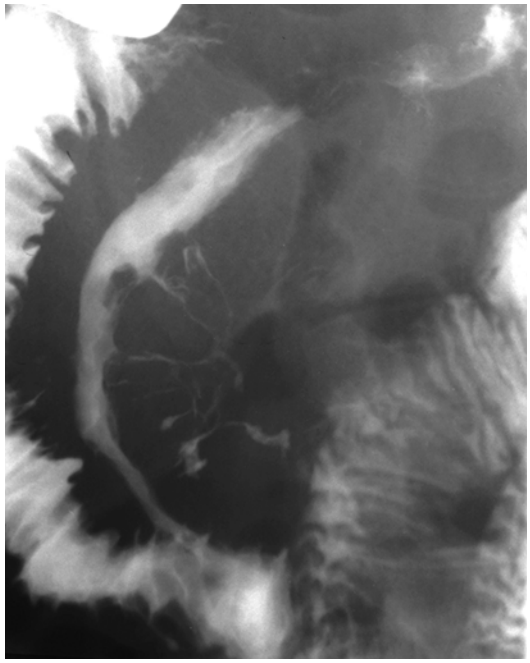

Fig. 3.13 Spot image from small bowel follow-through demonstrates a long segment of jejunal Crohn's disease with cobblestoning and small intermural sinus tracts extending to a small mesenteric abscess of asterisk-shaped fistula complex. Fistula complexes with spoke-wheeled sinus tracts extending to actively inflamed loops are often seen in penetrating Crohn's disease

tent segmental dilation of small bowel proximal to a narrowed segment. As Crohn's progresses over time, strictures arise in areas of severe active and chronic inflammation, with most strictures having both inflammatory and fibrotic components [24]. Due to mucosal destruction associated with the underlying inflammatory component, it is not possible to delineate inflammatory-predominant from fibrotic-predominant strictures fluoroscopically (but this remains a challenge using cross-sectional imaging as well). Long-standing chronic inflammation of the mesenteric border often leads to shortening of the mesenteric border and sacculation along the anti-mesenteric border (Fig. 3.4). The "string sign" refers to a markedly narrowed lumen—usually due to a combination of fibrosis with inflammation—and refers to the appearance of a circumferentially narrowed lumen with proximal areas of dilation (Figs. 3.4 and 3.6).

Peroral pneumocolon and other retrograde examinations are among the best tests to make the distinction between spasm and stricture (Fig. 3.14). Additionally, retrograde fluoroscopic examination permits visualization of small bowel peristalsis in patients with suspected motility

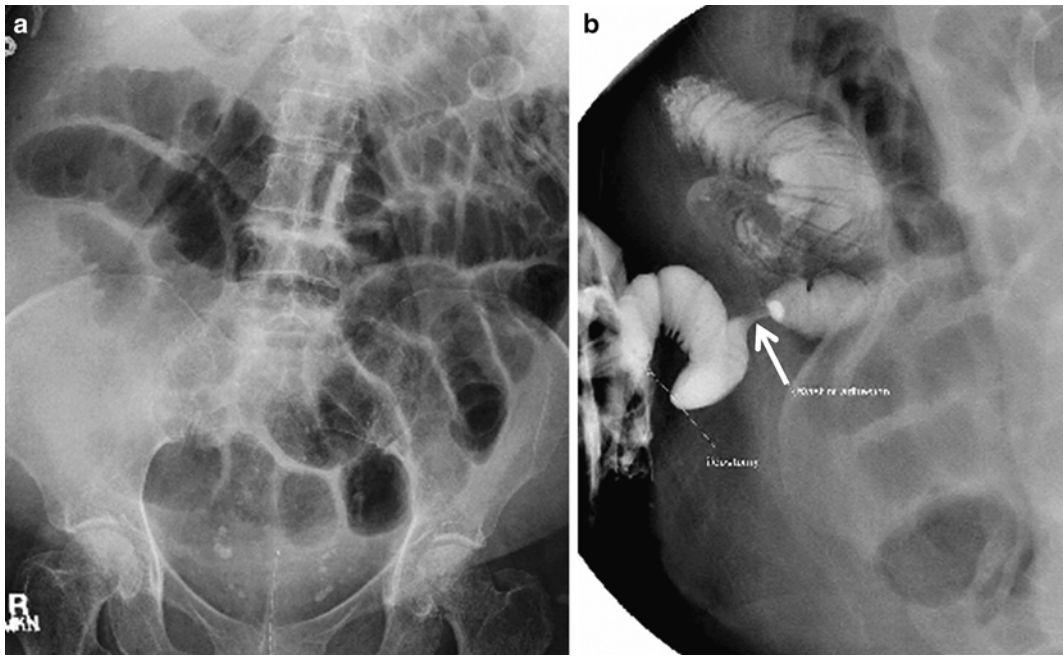

Fig. 3.14 (**a**) Plain film taken in a 72-year-old female with total colectomy and end ileostomy. (**b**) Retrograde evaluation through the stoma demonstrates a stricture in the neo- terminal ileum as it traverses the abdominal wall (*arrow*)

disorder. In addition to SBFT and retrograde exams, barium proctography may be beneficial in IBD patients with suspected pelvic floor dysfunction as a cause of abdominal pain. SBFT can often visualize strictures in patients without obstructive symptoms, as is seen with cross-sectional enterography. Many Crohn's patients with small bowel strictures are asymptomatic [14].

Conclusion

Fluoroscopy initially delineated many of the morphologic patterns of Crohn's inflammation we now see using optical and cross-sectional imaging techniques, and provided key insights for understanding the natural progression of Crohn's disease. In current multimodality, interdisciplinary IBD practice, there remain important roles for fluoroscopy, often in a complementary role in assessing bowel that cannot be visualized using endoscopy, in regions where cross-sectional enterography is questionable or indeterminate, and in specific clinical scenarios where there are known weaknesses of cross-sectional enterography (especially in post-surgical patients after ileocecectomy or ileal pouch anal anastomosis).

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CT Enterography in Crohn's Disease

4

David H. Bruining

Introduction

Computed tomography (CT) enterography has become a vital tool in the noninvasive assessment of inflammatory bowel disease (IBD). This has largely been driven by the need for objective Crohn's disease evaluations, noting its predilection for small bowel involvement. CT enterography (CTE) utilizes a large volume of neutral oral contrast along with enteric phase intravenous contrast to perform both intestinal and extra-intestinal interrogations. It has a high sensitivity and specificity for active luminal inflammation, and it can detect stricturing and penetrating complications. Robust data now demonstrates that CTE alters physician management plans. Emerging procedural modifications will likely keep CTE as an integral part of future Crohn's disease diagnostic and management algorithms.

Justification of Use

The implementation of CTE into clinical practice has arisen out of a diagnostic void that persisted despite laboratory testing and endoscopic examinations in IBD patients. Crohn's disease can occur anywhere in the gastrointestinal tract from mouth to anus, often with small bowel involvement. Recent data has suggested that up to 54 % of Crohn's disease patients may have active small bowel disease despite a normal endoscopic ileum. [1] This may occur due to either proximal or intramural disease with mucosal sparing. Second, symptoms such as diarrhea or abdominal pain correlate poorly with active IBD. Lastly, Crohn's disease patients may develop occult strictures and internal penetrating disease, a potential source of great morbidity. Approximately 20 % of Crohn's disease patients undergoing CTE at tertiary care centers have internal penetrating disease (abscess, phlegmon, or fistula), a new finding in 58 % [2] (Fig. 4.1). Similarly, 19 % have extra-intestinal IBD manifestations. The need to address these issues has made CTE an extremely valuable modality. It is an objective tool to transmurally assess the entire small bowel, locate penetrating disease, document strictures, and identify extra-intestinal disease manifestations. These features explain why CTE has been shown to alter management plans and physician perception for the benefit of corticosteroids in nearly 50 % of patients.[3, 4]

Technique

CTE is the culmination of targeted modifications designed to enhance intestinal mural assessments. This includes the use of large volume (approximately 1,350–1,500 ml) of neutral oral

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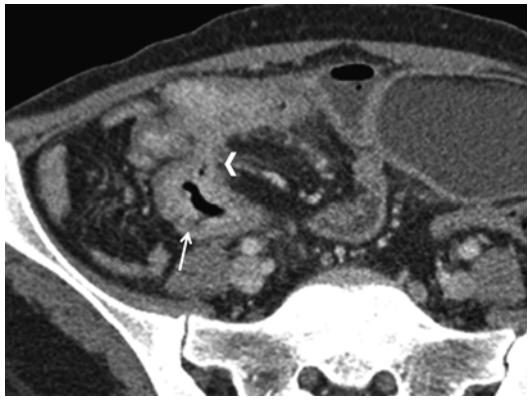

Fig. 4.1 CT enterography performed in a patient with multifocal Crohn's ileitis. Images reveal a penetrating ulcer (*arrow*) and a complex enteroenteric fistula (*arrow head*)

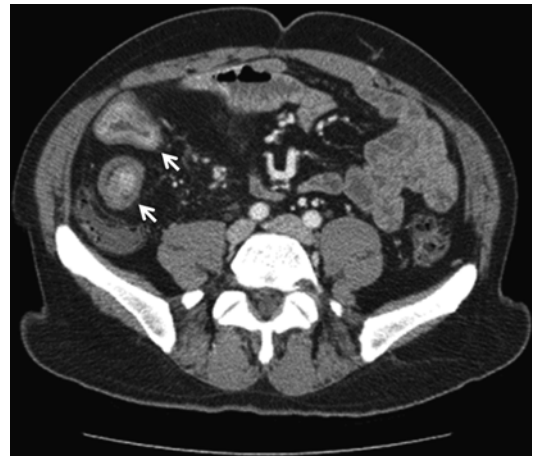

Fig. 4.2 Crohn's disease patient with active ileocolonic Crohn's disease. CTE demonstrates intestinal regions with mural hyperenhancement and thickening (*arrows*)

contrast to distend the small intestine.[5] This maneuver is of great benefit for analyzing wall thickness, enhancement, and stricture detection. Various oral products have been utilized including water, mannitol, low contrast barium solution (Volumen), or polyethylene glycol.[6] Iodinated intravenous contrast is provided with image acquisition typically in the enteric phase (45–50 s after contrast injection) when peak small bowel enhancement occurs.[7] High resolution images are constructed in multiple planes with a slice thickness of ≤ 3 mm. Unlike magnetic resonance enterography (MRE), antispasmodic agents are not required for high quality CTE imaging. Exams should extend through the perineum to detect perianal disease. This process for CTE imaging maximizes the detection of enhancing small bowel lesions, inflammation, penetrating disease, and strictures. CTE has become preferred over CT enteroclysis due to similar diagnostic accuracy (80 % and 88 % respectively), but greater patient tolerance with CTE.[8]

Performance Characteristics

Various CTE parameters have been evaluated for their ability to detect active small bowel inflammation. Candidate variables have included mural hyperenhancement, bowel wall stratification, wall thickening, increased mesenteric fat density (fatty proliferation), and dilated vase recta (comb sign) (Fig. 4.2). Using ileoscopy as the gold standard, mural hyperenhancement and increased wall thickness appear to be sensitive features for active intestinal inflammation.[9, 10] While not all studies have demonstrated a correction between elevated serum C-reactive protein (CRP) levels and abnormal small bowel imaging (small bowel follow-through or CTE) [11], a large retrospective study (n = 143) has reported a relationship between elevated CRP concentrations and increased mesenteric fat density.[12] While this remains an area of debate and active research, the ideal predictive model for active small bowel inflammation may include both mural hyperenhancement and dilated vasa recta, having a receiver operating characteristic (ROC) curve with an area under the curve (AUC) of 0.75. This model was not improved with the addition of any additional clinical or laboratory variables.[13]

CTE has been widely assessed in comparison to other small bowel imaging modalities. A prospective 4-way comparison trial was performed utilizing ileoscopy, CTE, capsule endoscopy (CE), and small bowel follow-through in 41 patients with established or suspected Crohn's disease.[14] CTE and CE had similar sensitivity for detecting active small bowel inflammation (82 % and 83 % respectively), but CTE had a

significantly higher specificity (89 % versus 53 %). MRE appears to have a similar performance profile (sensitivity and specificity), but CTE demonstrates higher image quality and greater interobserver agreement.[15] Additional advantages of CTE over MRE include its lower cost, wider availability, and shorter image acquisition time. Limited prospective data is available comparing CTE to small bowel ultrasound,[16] and it is unclear whether ultrasound will be able to accurately and consistently detect strictures and penetrating disease as is noted with CTE.

Indications/Applications

The indications for CTE continue to expand in IBD cases. In patients with suspected Crohn's disease, it can be used to further establish the diagnosis, assess luminal extent, and determine severity of disease. It can also be used to help determine direction (antegrade versus retrograde) when balloon-assisted endoscopy (BAE) is needed for histologic confirmation of the diagnosis. For individuals with established Crohn's disease, CTE can provide an objective measure of response to treatment[17], detect penetrating complications and strictures, and note extraintestinal disease manifestations. These applications have earned CTE a prominent role in IBD diagnostic and management algorithms.

Future Innovations

Additional modifications and new applications are on the horizon for CTE. A key concept remains ionizing radiation dose reduction. This focus is driven by the desire to minimize potential patient risks, acknowledging that the data behind this risk assumption is limited.[18, 19] It is an area of great debate that will likely become less of an issue as low-dose CTE becomes standard practice.[20]

Technologic advances may also allow CTE images to assess bone health. Contrast enhanced CT examinations can be used to calculate not only bone mineral density (BMD) scores, but also bone strength.[21] This is a comprehensive bone analysis that can be done without additional radiation exposure. CTE bone assessments could eliminate the need for dual-energy X-ray absorptiometry (DEXA) scans in patients undergoing CT exams, and greatly increase osteoporosis screening in IBD patients.

Conclusion

CT enterography has emerged as a vital component to Crohn's disease assessments. It allows clinicians to objectively evaluate previously inaccessible regions of the small intestine, and detect penetrating complications, strictures, and extraintestinal disease manifestations. These findings alter physician management plans. New applications and techniques will likely keep CTE utilization at the forefront of IBD interrogations.

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Magnetic Resonance Enterography

5

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Introduction

In patients with inflammatory bowel disease (IBD) several tools can be used for imaging and diagnosis, including ileocolonoscopy, capsule endoscopy, ultrasound, small bowel follow-through examination, computed tomography (CT) and magnetic resonance (MR) enteroclysis and enterography.

MR has become one of the radiological methods of choice in the assessment of disease activity, severity and extension in patients with inflammatory bowel disease, complementary to endoscopy and biopsy.

The ability to evaluate the bowel wall changes, location, extent and the possibility to detect extramural complications such as fistulae and abscesses is an essential advantage of MR.

MR has a very high soft tissue contrast, the capability for multi-planar imaging, and of increasing importance is the lack of ionizing radiation, given the predominant involvement of young patients.

The assessment of disease activity, severity and extension is important to determine the therapeutic strategy (patients are initially treated with medical therapy with surgery being considered in the context of lack of/poor response and/or complications), and also has prognostic implications.

Imaging Techniques and Performance Characteristics

The small bowel follow-through (SBFT) and enteroclysis used to be the radiological imaging method of choice for evaluating the small bowel in IBD, as more than 70 % of patients have involvement of the small intestine [1]. Since the increasing development of cross-sectional imaging techniques in the last decades, CT and MR have replaced barium series.

Magnetic Resonance Enterography (MRE) has the advantage of being a non-ionizing radiation imaging method compared to SBFT, CT enterography (CTE) and enteroclysis.

Compared to the SBFT, MRE and CTE are both superior in visualizing and localizing extraintestinal manifestations of IBD and in improving delineation of bowel segments. MR and CT are also less operator dependent and less time consuming.

In many radiology departments the SBFT has become a rarely utilized technique in the radiological management of patients with IBD.

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A lot of studies have been done comparing CTE and MRE and there are still controversies and individual/geographic preference with regards to preferred technique [2, 3]. Both modalities have advantages and disadvantages but have comparable sensitivities in IBD diagnosis. CT has a higher spatial resolution, less motion artifacts and shorter examination times, resulting in better image quality. Also, CT has lower cost and is more readily available.

The major advantage of MR is the absence of ionizing radiation and in addition significantly better contrast resolution. The continuing advances in MRE techniques provide better distinction between acute and chronic disease with new techniques such as diffusion-weighted imaging [4, 5] and the promising magnetization transfer imaging [6–9]. MR offers evaluation of bowel wall motility and inflammatory strictures, by using dynamic imaging [10–13].

CT is preferred in an acute setting—for example, in cases of pain, fever, high CRP, peritonitis—and is more accurate in detecting free air in the peritoneal cavity. Both CT and MR can be used for the initial diagnosis, but MR is the modality of choice for follow-up of patients with known IBD who are asymptomatic or have non-acute symptoms suspicious of recurrence. MR is the best imaging modality in the assessment of perianal disease [14], a common finding in patients with Crohn's disease (CD).

Compared to CTE and MRE, endoscopy has the advantage of direct visualization of the bowel lumen and mucosa and most of all the ability to simultaneously biopsy bowel wall abnormalities and achieve a conclusive diagnosis. On the other hand, CTE and MRE do not require patient preparation nor sedation, provide evaluation of the entire bowel and bowel wall, and have the ability to detect and evaluate extraluminal disease.

Video capsule endoscopy (VCE) [15] has proven to be superior compared to all available radiological imaging techniques in the assessment of mucosal abnormalities in non-stricturing CD, particularly in patients where other endoscopic and radiological examinations are negative. Given that capsule retention is the main disadvantage of this technique, MRE can be performed prior to capsule endoscopy. Also, the specificity of lesions detected only on VCE for a conclusive diagnosis of CD is not established.

Multiple studies have been performed comparing several diagnostic techniques in the diagnosis of CD, including MRE and bowel sonography (BS), but only one recent prospective study of 249 patients [16] has directly compared the diagnostic accuracy of BS and MRE, using endoscopy as the gold standard. The results confirmed a comparable high diagnostic accuracy of more than 90 % for the diagnosis of CD both in BS and MRE. Bowel sonography was less accurate in determining the length of the inflamed bowel segment if the involvement exceeded a length of 40 cm to 50 cm. BS was less sensitive if the proximal small bowel segments were involved (duodenum and jejunum) and also less accurate compared to MRE in the assessment of fistula, especially in the deep pelvic region, and of other penetrating disease complications. Both techniques do not utilize ionizing radiation. Compared to MRE, BS is more operator dependent, has lower cost, is less time consuming, and is better tolerated by the patient. Therefore BS could be used as a primary screening tool in the management of CD by pre-selecting patients needing additional work-up by MRE for optimal assessment of disease extension and evaluation.

MR Enteroclysis and MR Enterography

Technical Aspects, Preparation and Protocol

For safety and preventing accidents in the MR environment it is necessary to screen patients for pacemakers and other devices that can alter or lose functionality. Metallic implants, surgical clips, prosthesis or other foreign material [17] that can move or cause artefacts may result in a decrease in image quality and interpretation. The most important contraindications for MRE are the inability to ingest oral contrast media, need for anesthesia, severe anxiety and claustrophobia.

For small bowel imaging, patients are asked to fast 4 h before the examination to minimize fecal matter in the bowel during the study.

Luminal distension is essential for correct evaluation. Collapsed bowel loops can wrongly suggest the presence of pathology or can obscure lesions. To prevent false bowel wall assessment, a large volume (1–2 L) of oral contrast should be ingested by the patient before starting the examination. In our institution we commence oral contrast ingestion 45–60 min before starting the MRE; however, this may vary according to institutional practice or protocols as there are no general guidelines for the timing of administration of oral contrast and imaging.

Three categories of oral contrast agents—negative, positive and biphasic agents—can be used [18, 19]. Negative contrast agents make use of superparamagnetic iron oxide agents, the two main forms being magnetite and maghemite, which have low signal on T1- and T2-weighted images. Positive contrast, such as diluted gadolinium (1 mmol/L), milk with high fat content and some fruit juices containing manganese (e.g., grapefruit or pineapple juice) can have high signal on T1- and T2-weighted images. Biphasic contrast agents, with variable signal intensities, are preferable. After intravenous contrast administration, the low T1 signal of the enteric contrast allows better assessment of the contrast-enhanced bowel wall. The high T2 signal allows good evaluation of the thickness of the bowel wall and bowel folds.

Several studies have compared different biphasic agents, including water, methylcellulose, mannitol (2 %), sorbitol solution (2,5 %), locust bean gum (0,2 %) [20], VoLumen (EZ-E-M, Westbury, NY) and polyethylene glycol.

Theoretically water meets the criteria for a perfect biphasic MR contrast agent, and it offers good delineation of the bowel wall. However, its rapid physiological absorption makes it impossible to achieve desirable luminal distension and consequently necessitates use of additives [21].

Biphasic agents are generally well tolerated and can in some cases cause mild diarrhea and cramping.

Colonic distension can be improved by simultaneous administration of a rectal water enema, which allows better assessment of colonic wall disease.

Luminal distension can also be achieved by MR enteroclysis that requires placement of a nasojejunal tube. Fluoroscopy is used to follow and confirm the position of the tube distal to the ligament of Treitz. Administration of 1–2 L of oral contrast can be done manually or by using an infusion pump. Bowel filling and distension can be followed by using fast and fluid sensitive coronal images, so-called true FISP sequences [19].

Both techniques have advantages and disadvantages. MRE can be performed without using ionizing radiation, having overall better patient acceptance, lower cost and is less time consuming. With MR enteroclysis better distension of the proximal small bowel is achieved [22], and is the preferred technique for patients having pathology in that region, and has a better diagnostic performance for detection of mucosal lesions. Both techniques perform similarly for depiction of stenosis, fistulas and abscesses. MR enteroclysis is preferred over MRE in case of low-grade small bowel obstruction and when the patient is unable to drink the enteric contrast.

Patients can be examined in prone or supine position. Prone position reduces motion artifacts from bowel peristalsis and respiration and allows better separation of the small bowel loops. Prone position improves luminal distension but does not result in a better lesion detection nor characterization [23].

On the other hand supine position is a lot more comfortable for the patient. It improves patient compliance given that most of the patients with CD are slim and may suffer from discomfort in the abdominal wall due to prior surgery or other abdominal wall complications.

An anti-spasmodic is given to the patient before the contrast-enhanced MR sequences, in most centers a dose of 0.5 mg to 1 mg of glucagon (Glucagen; Novo Nordisk, Begsvaerd, Denmark) or 20 mg to 40 mg of hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Ingelheim, Germany; not licensed for use in this application in North America) is given intravenously to reduce bowel motility. Intravenous administration is preferred over intramuscular

injection given the faster onset of action on bowel motility. It should be given slowly to prevent nausea or vomiting. The dose can be given in 1 shot or split in 2—half a dose at the beginning of the examination and the other half before the dynamic contrast enhanced sequences. In case of supplementary colonic filling, half a dose can be given when starting the colonic filling to reduce colonic spasm.

Contraindications for glucagon are diabetes, pregnancy, insulinoma and pheochromocytoma [3]; the most common contraindications for Buscopan are diabetes, pregnancy, prostate hypertrophy and glaucoma.

MRE examinations are performed with administration of intravenous gadolinium contrast, except for patients with contraindications, such as risk for nephrogenic systemic fibrosis in patients having severe renal insufficiency [24] and allergy to gadolinium. Based on the guidelines of the European Society of Uroradiology Contrast Medium Safety Committee (ESUR CMSC), the intermediate and lowest risk gadolinium contrast media may be given to pregnant women; the high-risk gadolinium-based contrast agents are contraindicated [25]. Gadolinium is given in a standard dose of 0.1 mmol/kg at an injection rate of 2 mL/s.

The MRE is performed by using one or two phased array body coils to cover the complete abdomen. The main three types of sequences overall used in a standard MR enterography are (1) half-Fourier acquisition single-shot turbo spin echo (HASTE), also called single-shot fast spin echo (SSFSE); (2) balanced refocused gradient echo (SSFP), also known as fast imaging with steady-state precession (true FISP), fast imaging using steady-state acquisition (FIESTA) or balanced fast field echo (FFE); and (3) pre- and post-contrast fat-saturated three-dimensional (3D) T1-weighted ultrafast GRE. All sequences are usually acquired in the coronal and axial plane. There is no general consensus on post-contrast imaging resulting in differences in number and timing of post-contrast imaging sequences. At our institution, post contrast T1 sequences are taken at 45, 90 and 135 s (Table 5.1.

Table 5.1 MR imaging protocol

Sequence type	Orientation	Number of slices	Slice thickness (mm)	Slice gap (mm)	Field of view (mm)	TR (ms)	TE (ms)	Fat saturation	Matrix	Flip angle (°)
Single-shot TSE-T2 (HASTE, SSFSE, SSTSE)	Coronal	26	5	0	380×308	1,550	91	No	512×307	150
	Axial	50	5	0	380×308	1,550	69	No	512×307	150
Balanced GRE (TrueFISP, FIESTA, Balanced FFE)	Coronal	28	3 and 5	0.3–0	400×400	4.52–4.6	2.26–2.3	No	320×240–320×250	80
	Axial	50	5	0	400×275	4.6	2.3	No	320×250	80
Cine scans	Coronal	1	10		380×380	4.16	2.08	No	256×205	70
T1-3D GRE (VIBE, LAVA, THRIVE)	Coronal	48	3	0	400×400	3.98	1.85	Yes	384×269	10
T1-3D GRE (VIBE, LAVA, THRIVE)	Axial	64	3.5	0	400×300	3.66	1.65	Yes	256×166	10
DWI	Axial	31	5	0	380×380	6,600	69	Yes	192×154	90

Parameters were established with the Aera 1.5 Tesla system (Siemens, Erlangen, Germany)
TSE turbo spin echo, *GRE* gradient echo, *DWI* diffusion weighted imaging

MR Characteristic Small Bowel Findings in Crohn's Disease

Bowel Wall Abnormalities

Wall Thickening

Thickening of the bowel wall (Fig. 5.1) occurs due to edema and infiltration with inflammatory cells in active inflammation or due to deposition of collagen in fibrostenosing disease, and is one of the most important imaging abnormalities in CD [3, 9, 18, 26]. Normal bowel wall thickness (in optimal distended bowel) ranges from 1 to 3 mm and in case of CD inflammation has values ranging from 5 to 10 mm. The bowel wall thickening may be asymmetric due to the preferential inflammatory involvement of the mesenteric side of the bowel wall. The post-contrast T1-images and the HASTE sequences allow better assessment of bowel wall thickness compared to the true FISP images. The black boundary artefact seen on the true FISP images can confound evaluation of wall thickness whereas the HASTE sequences are relatively insensitive to this artifact.

Bowel Wall Edema

Increased signal intensity [3, 9, 18] of the thickened bowel wall on the HASTE sequences can suggest bowel wall edema and indicate active inflammation, whereas low to moderate T2 signal intensity may suggest underlying fibrosis. However, the absence of high signal intensity in the thickened wall does not exclude active disease. High T2 bowel wall signal intensity can also be present in case of intramural fat deposition, found in chronic inflammation, and can be differentiated from edema by using fat-saturated T2 sequences (Fig. 5.2).

Fold Abnormalities

Good bowel distension and absence of flow artefacts are crucial to assess fold abnormalities, to avoid false-positive and false-negative results. In case of suspected fold abnormalities and insufficient bowel distension more MR sequences can be acquired after additional ingestion of oral contrast material. True FISP images are superior for evaluating some fold abnormalities given the minor flow artifacts. The latter are also reduced by anti-spasmodic agents, given that they reduce fluid flow in the bowel lumen.

Alterations in fold patterns are more evident along the mesenteric border, characteristic of the disease and can manifest in different ways. The three main patterns of fold abnormalities are diffuse fold thickening, ulceration of folds, or in more severe disease cobblestoning [11, 20].

Early areas of mucosal ulceration (Fig. 5.3) present as small foci of hyper-intensity surrounded by a rim of edema, deeper ulcerations present as lines of high signal intensity in the thickened bowel wall on the T2 images, paralleling the lumen or protruding transversely into the wall. Cobblestone appearance is the result of a combination of longitudinal and circumferential ulcers and fissures separating islands of mucosa.

Better assessment of mucosal ulcerations can be obtained by using high resolution MR imaging compared to standard MRE [27], although it remains inferior compared to endoscopy.

Strictures

These are segments of persistent narrowing of the bowel lumen (Figs. 5.4 and 5.5) with or without bowel wall thickening. They are considered to be functionally significant if there is an upstream bowel dilatation of more than 3 cm and defined as nonfunctional if the bowel lumen is narrowed more than 10 % compared to neighboring bowel loops in the absence of bowel dilatation [20]. Differentiating active from chronic strictures has important therapeutic implications and remains a diagnostic challenge on MRE.

Non-fibrotic strictures tend to have wall thickening with high signal intensity on the T2 sequences, suggesting the presence of bowel wall edema, whereas fibrotic strictures have lower signal intensity in the bowel wall on T1- and T2-weighted images.

Bowel Wall Enhancement

Bowel wall enhancement is increased compared to the surrounding normal bowel loops and correlates with bowel inflammation and disease activity [11, 20]. The evaluation of the different

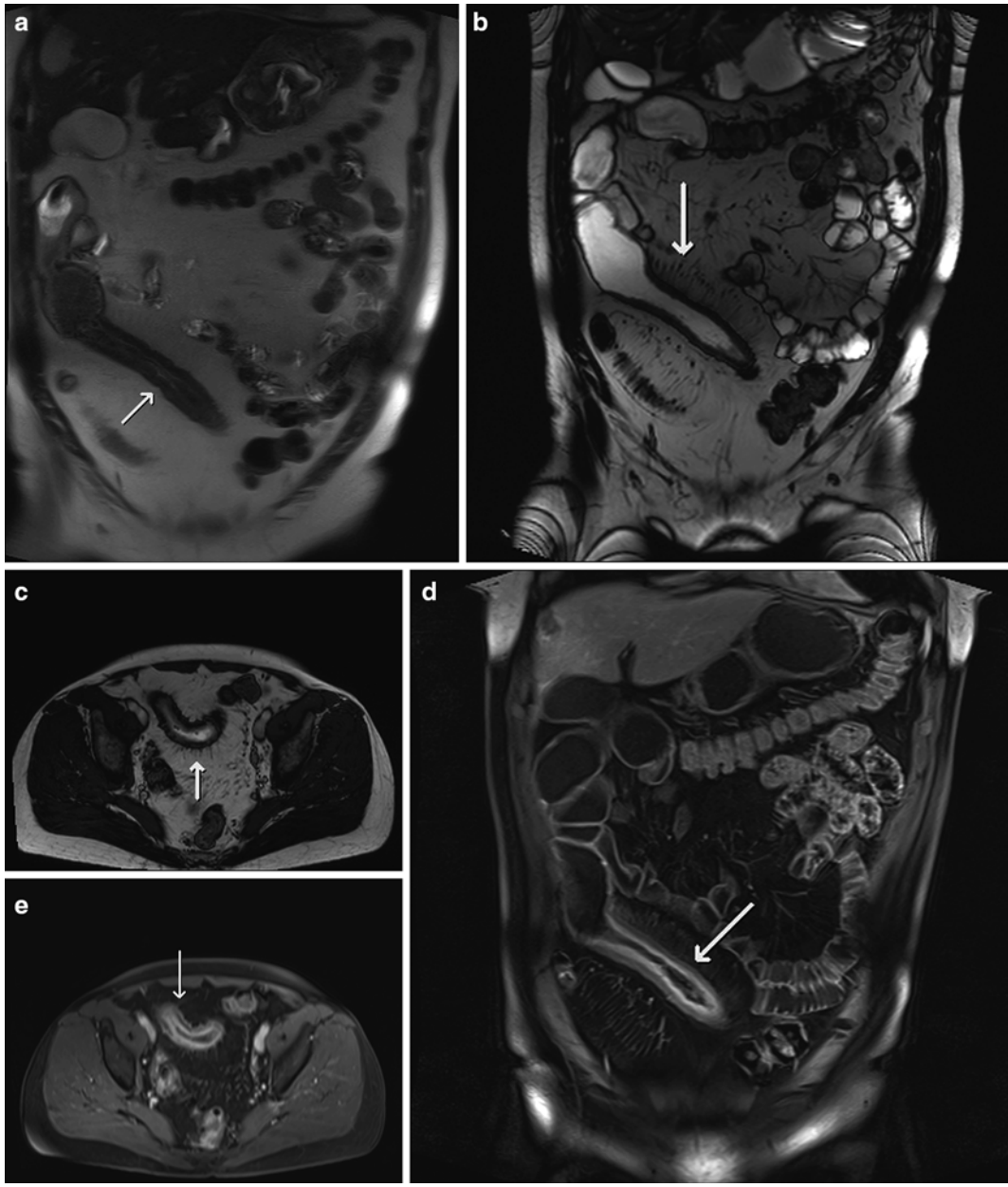

Fig. 5.1 (**a**) Acute-on-chronic CD in the distal ileum in a 58-year-old patient with circumferential wall thickening (arrow) on the coronal HASTE image. (**b**) Coronal and (**c**) axial true FISP images show dilated peri-ileal blood vessels or comb sign (arrows). The presence of layered enhancement pattern of the bowel wall (arrows) on (**d**) the coronal and (**e**) axial fat-suppressed 3D T1 GRE images

patterns of bowel wall enhancement can be useful in determining the level of disease activity.

Three-layered pattern of contrast enhancement (Fig. 5.6), also called mural stratification, consists of strong enhancement of the mucosa, relatively poor enhancing submucosa, and strong enhancement of the serosa; this type of enhancement, in combination with bowel wall edema, is found in active inflammation. Strong mucosal enhancement is one of the most sensitive indicators of active CD.

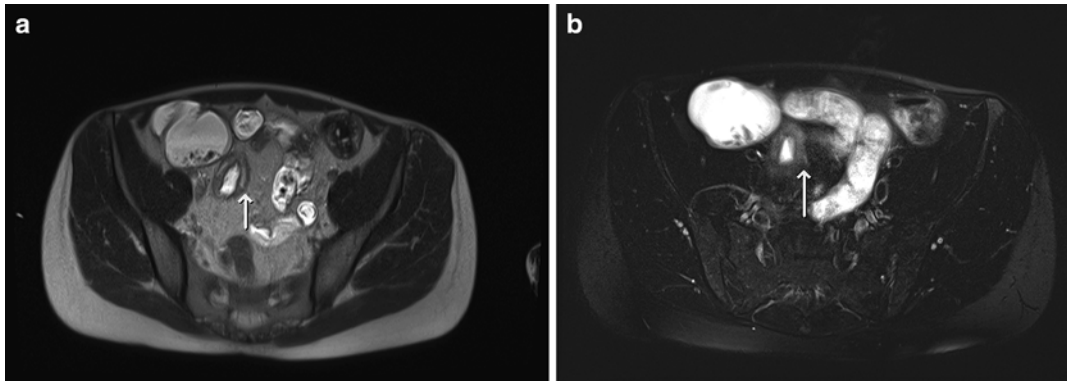

Fig. 5.2 A 31-year-old patient with acute-on-chronic CD in the distal ileum. (**a**) Axial HASTE and (**b**) axial T2-weighted fat-suppressed TSE images show bowel wall thickening with high T2 signal consistent with edema (arrows) and acute inflammation

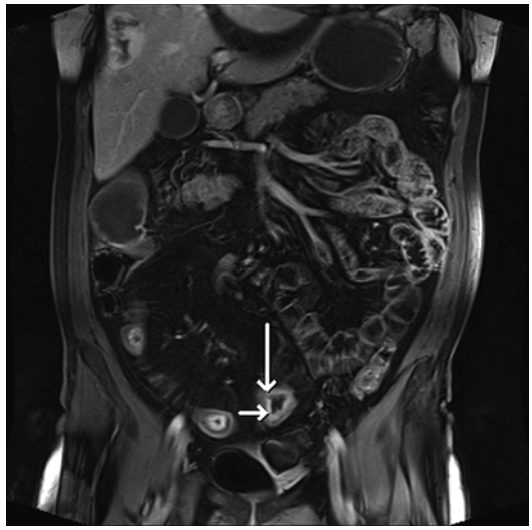

Fig. 5.3 Acute inflammation of the distal ileum with mucosal ulcerations (arrows) on the coronal fat-suppressed 3D T1 GRE image in a 58-year-old patient with CD

Diffuse and intense homogenous contrast enhancement suggests transmural inflammation, but remains nonspecific given the fact that it can be found in active and chronic disease.

Minimal and heterogeneous bowel wall enhancement is rather seen in segments where fibrosis predominates.

Pseudodiverticulum and Pseudosacculation

Pseudodiverticulum and pseudosacculation are the result of the asymmetric and preferential

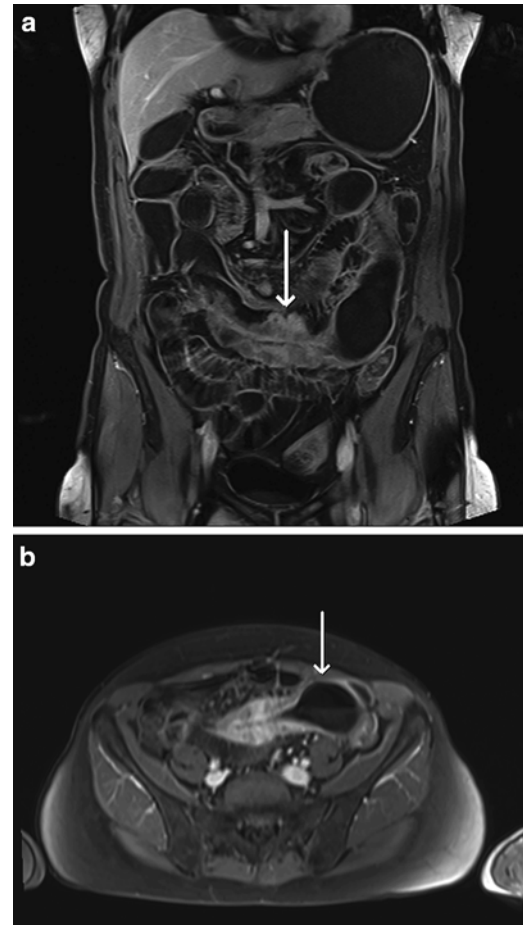

Fig. 5.4 A 58-year-old patient with long-standing CD and right colectomy. (**a**) Coronal and (**b**) axial fat-suppressed 3D T1 GRE images show severe wall thickening and stenosis (*arrow image* **a**) with secondary obstruction (*arrow image* **b**)

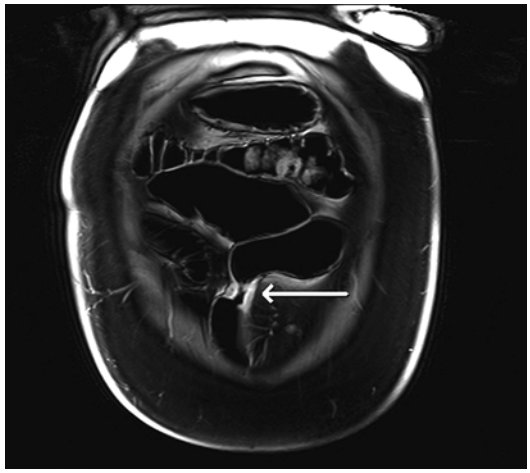

Fig. 5.5 The presence of a short inflammatory segment or skip area (*arrow*) on the ileum with secondary obstruction on a coronal fat-suppressed 3D T1 GRE image

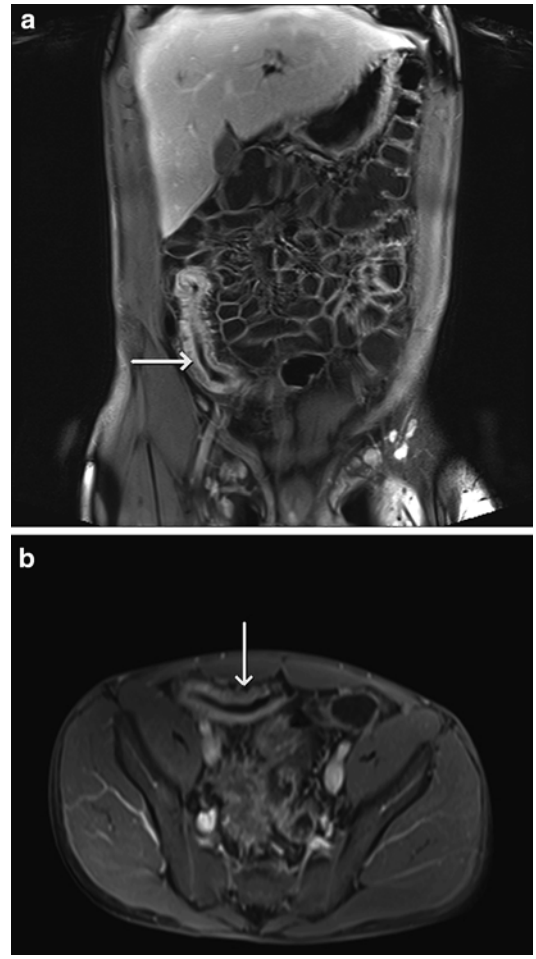

Fig. 5.6 (**a**) Coronal and (**b**) axial fat-suppressed 3D T1 GRE images in a 20-year-old male with wall thickening and strong mucosal enhancement (arrows) of the distal ileum, indicating acute CD

inflammation of the mesenteric side of the bowel wall and relative sparing of the opposite bowel wall. Fibrosis in the diseased mesenteric wall results in shorting of this side of the bowel wall and dilatation of the opposite wall, leading apparent sacculation or formation of a diverticulum [18]. In contrast to diverticular disease in the colon, CD involves all layers of the bowel wall, and focal dilations are called pseudodiverticula or pseudosacculations (Fig. 5.7). As this is seen in the chronic setting of CD, other concomitant signs of chronicity are usually present.

Extraintestinal Findings

Engorgement of the Vasa Recta

Engorgement of the vasa recta is the result of increased blood flow through the vasa recta to the inflamed bowel segments. If these vessels have a perpendicular course to the long axis of the diseased segments it is called the comb sign (Fig. 5.8). Fine lines of low signal intensity on the true FISP images and high signal lines on the post-contrast T1 images are seen.

The comb sign is seen in the setting of active inflammation [3, 18].

Fat Stranding

Inflammation of the mesenteric fat or mesenteric edema surrounding the inflamed bowel segments, together with the comb sign, bowel wall edema and strong enhancement of the bowel wall, strongly suggest active disease [3].

Fibrofatty Proliferation

Fibrofatty proliferation is usually seen in patients having a history of longstanding CD and can be a useful diagnostic discriminator as it is rarely seen with other differential diagnosis.

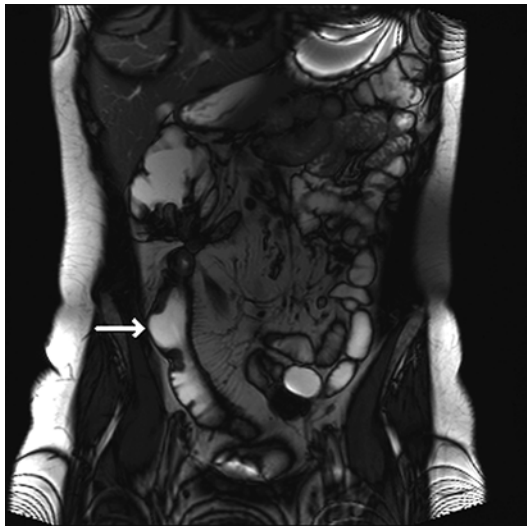

Fig. 5.7 A 34-year-old patient with CD. Pseudosacculation (arrow) of the antimesenteric wall within the inflamed distal ileum on the coronal true FISP image

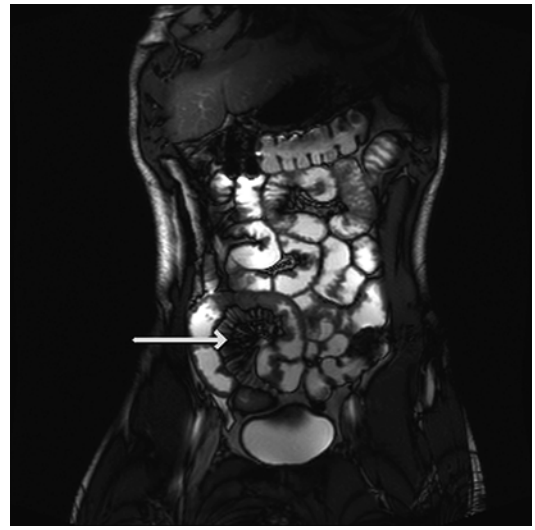

Fig. 5.8 Coronal true FISP image of a 20-year-old patient with CD, showing moderate to severe comb sign (*arrow*)

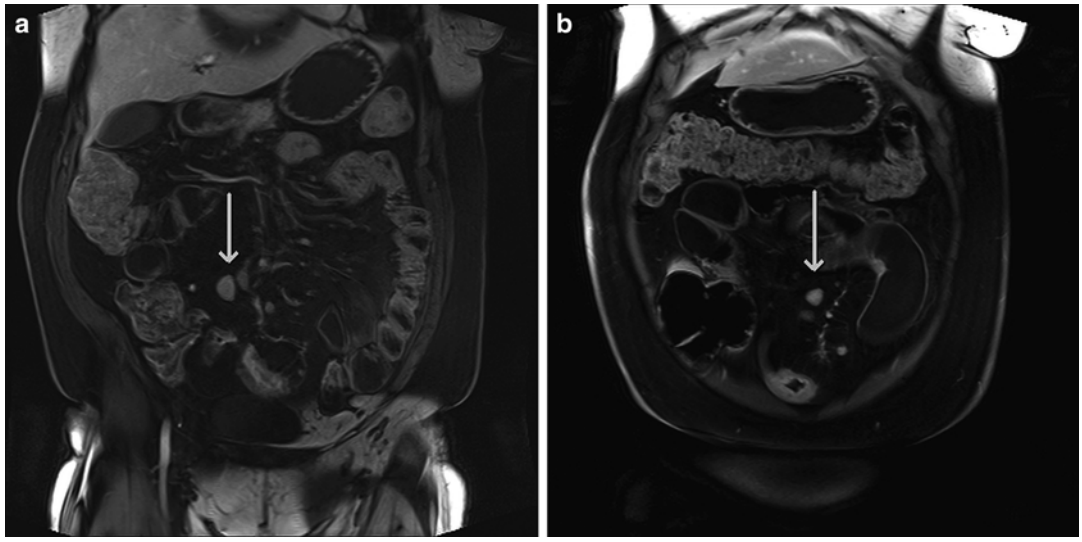

Fig. 5.9 A 52-year-old patient with CD. (**a**, **b**) Coronal fat-suppressed 3D T1 GRE images showing mesenteric lymph nodes (*arrows*) adjacent to the inflamed bowel segments

Hypertrophy of fat surrounding diseased bowel loops, can be symmetric or asymmetric [18], in the latter preferentially involving the mesenteric border of the bowel, and can produce mass effect on the surrounding bowel loops or organs.

Lymph Nodes

Enlarged mesenteric lymph nodes (Fig. 5.9) are often seen in patients with active and inactive CD and they are frequently, but not always located in the area of the diseased bowel loops, often around the ileocolic vessels, given the preferred side

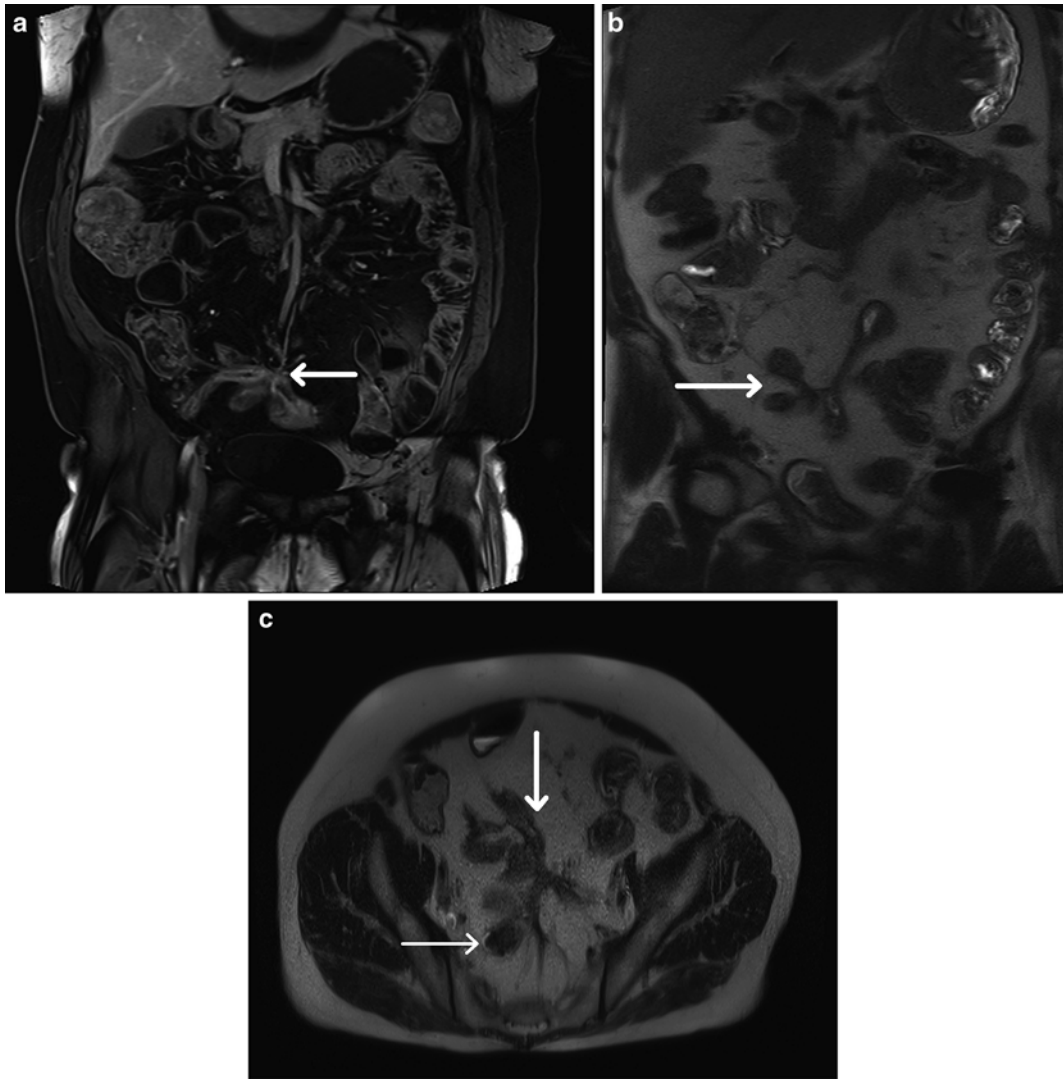

Fig. 5.10 A 52-year-old patient with penetrating CD. (**a**) Coronal fat-suppressed 3D T1 GRE, (**b**) coronal HASTE, and (**c**) axial HASTE show bowel wall thickening of the distal ileum with associated luminal narrowing (*arrow image* **a**). Fistula involving distal ileum segments (*thick arrow image* **c**) and the sigmoid (*thin and thick arrow image* **c**), with secondary tethering of the surrounding bowel loops (**b** and **c**)

of the disease. A study [28] showed that the mesenteric lymph nodes in CD present with a different degree of homogenous contrast enhancement, depending on the disease subtypes and therefore quantification of enhancement ratios could be useful for disease subtype classification.

If multiple enlarged mesenteric lymph nodes are present, lymphoproliferative disease should be excluded, given the additional risk as a consequence of CD treatment.

Fistulas and Sinuses

When a transmural ulcer communicates with an adjacent epithelial surface, it becomes a fistula [9, 18]. Most fistulas (Figs. 5.10 and 5.11) arise between small bowel loops (entero-enteric fistula) or between a small bowel loop and a colon segment (entero-colic fistula), but can also communicate with other organs, such as bladder, skin or even local muscles. The fistulas are usually seen as high signal tracts on the T2 images, with variable

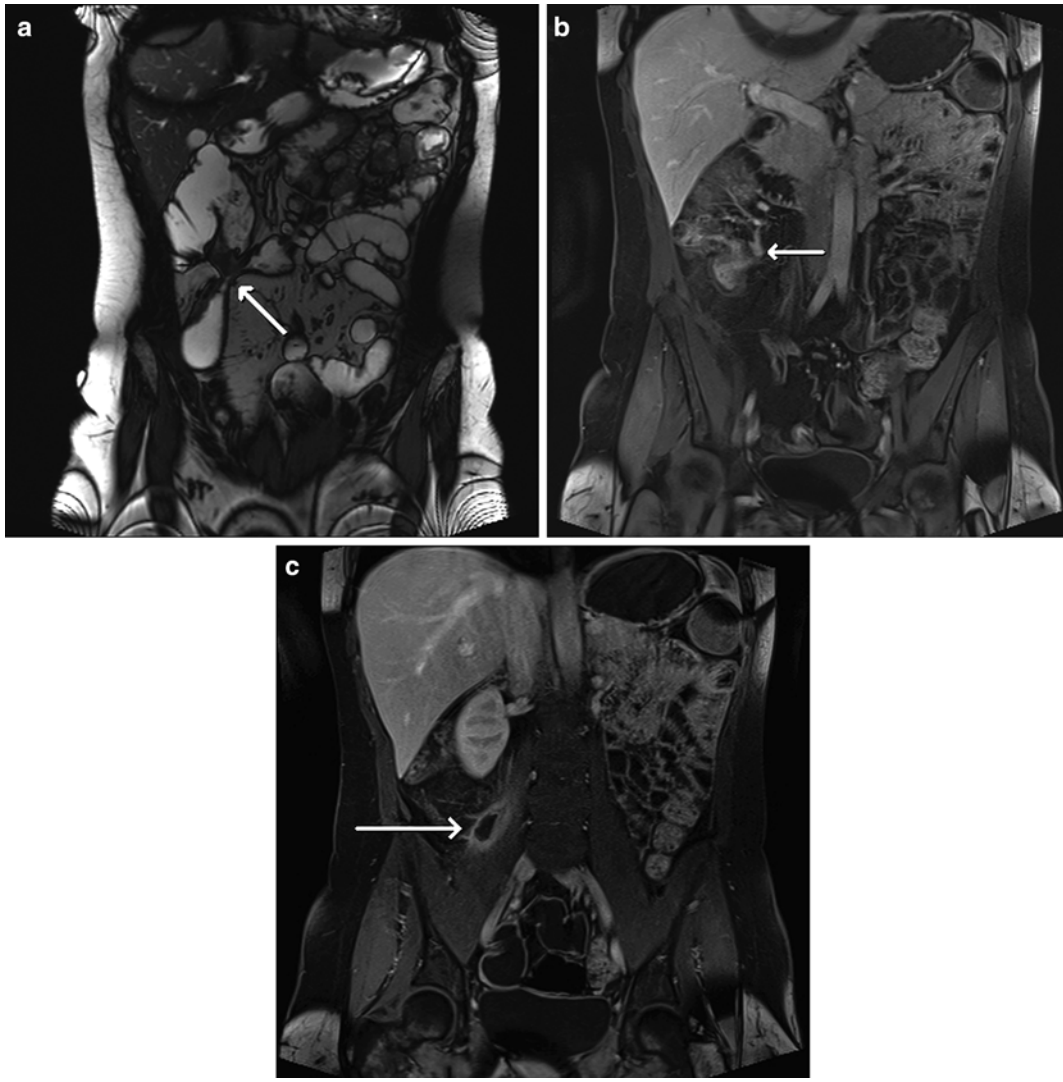

Fig. 5.11 Fistula and abscess in a 34-year-old patient with CD. (**a**) Coronal true FISP and (**b**) coronal fat-suppressed 3D T1 GRE images show the presence of fistula (*arrows*) involving the distal ileum, caecum, ascending and transverse colon, with tethering of the surrounding bowel loops. (**c**) The presence of an abscess (*arrow*) in the right psoas muscle on the coronal fat-suppressed 3D T1 GRE image

degrees of enhancement after administration of intravenous contrast material. These fistula tracts may vary from single to complex, sometimes having stellate appearance with multiple tracts radiating from a central point to adjacent bowel, other organs or even local muscles, such as the psoas muscle. Fistulas can easily be depicted on MR, with the exception of enterocutaneous fistulas. The latter are harder to visualize because of their superficial location and the compression in the often prone positioning of the patient makes it more difficult to assess these enterocutaneous tracts. If there is clinical suspicion of cutaneous fistula, supine positioning of the patient is preferred and additional sequences in the sagittal plane can be taken to better assess the location and extent of the fistula. In some cases MR images provide insufficient assessment and

additional conventional radiology techniques are necessary, such as fistulography.

If a transmural ulceration does not communicate with another epithelial surface, it is a blind-ending tract and called a sinus. These sinuses have the same MR characteristics as fistulas.

Abscess

An abscess (Fig. 5.11) is an encapsulated fluid collection with peripheral contrast enhancement [18]. They can contain air and their content is often heterogeneous due to the presence of solid material and gas. Abcesses are easily depicted on MR, having high signal on T2 and low signal on T1. On the other hand, small amounts of air in a collection might be difficult to visualize. The detection of an abscess is important, because it is a relative contra-indication to the use of anti-TNF-alpha drugs. In some cases these abscesses can first be treated with imaging-guided drainage before starting medical therapy.

Free fluid in the peritoneal cavity can be seen in CD patients, but is not specific.

Other Findings

Extra enteric related findings or complications can be seen on the MR images in this patient population: most commonly seen are cholelithiasis, nephrolithiasis, primary sclerosing cholangitis, thromboembolism and sacroiliitis.

Standard MR Sequences and Techniques

Both HASTE and true FISP-sequences are standard fluid-sensitive sequences. HASTE images allow better assessment of bowel wall and mesenteric edema and better detection of free abdominal fluid. The true FISP sequence, being a superfast sequence with absent motion and flow artifacts, provides brighter images that allow an anatomical overview of the position of the bowel loops, offers the possibility to depict bowel angulations suggesting the presence of underlying inflammatory or postoperative adhesions, and can sometimes suggest the presence of sinus tracts or fistulas. The true FISP sequence gives a good visualization of the wall, the folds and the lumen of the bowel, the latter being the result of the aforementioned absence of flow artifacts. The chemical shift artifact, being an MR artifact on the true FISP images (due to differences between resonant frequencies between fat and water) allows depiction of submucosal fat in the bowel wall [19] and improves visualization of lymph nodes and vascular structures. Despite the fact that several artifacts confer an advantage to the true FISP sequences, image quality and interpretation decreases in case of presence of metallic prosthesis, surgical clips and intraluminal air, causing susceptibility artefacts.

In case of abdominal wall involvement, additional sagittal true FISP images can be taken to better evaluate the presence and extent of fistula, or patients having a stoma.

T2-sequences with fat saturation are used in some institutions, with additional lowering of the field of view and using multiplanar reconstructions. These sequences tend to improve detection of bowel wall edema, visualization of mucosal ulcerations, and evaluation of transmural and mesenteric changes, but their use is not standardized.

Compared to the T2-sequences, the contrast-enhanced T1 images are superior in the overall assessment of disease activity, severity and extent [11, 27, 29, 30]. These contrast-enhanced images are highly sensitive for diagnosing patients with active disease and enhancement is associated with clinical activity. The factors that influence bowel wall enhancement are very complex [31]. In patients with chronic CD, an increased permeability of the blood vessel wall results in an increased bowel wall enhancement. Combining features of bowel wall enhancement and increased bowel wall signal intensity on the (fat-saturated) fluid sensitive images, helps us in differentiating active (increased signal intensity indicating the presence of edema) from chronic disease (absence of high signal intensity in case of fibrosis).

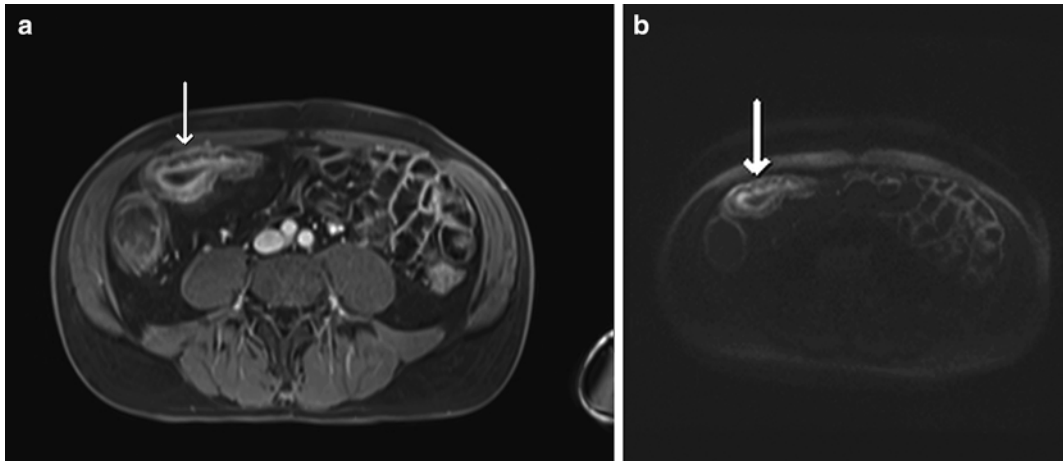

Fig. 5.12 A 57-year-old patient with CD. (**a**) Axial fat-suppressed 3D T1 GRE image shows acute-on-chronic inflammation with layered enhancement pattern (*arrow*). (**b**) High signal in the bowel wall on the diffusion-weighted image with b-value of 1,200s/mm^2 consistent with restricted diffusion (*arrow*) indicating acute inflammation

New MR Sequences and Techniques

Diffusion-Weighted Imaging

Diffusion-weighted imaging (DWI) is based on the difference in mobility of water molecules between different tissues to obtain image contrast (Fig. 5.12).

In a lot of radiology departments DWI is a standard imaging sequence in the MRE protocol. A lot of studies have investigated the use of DWI in the assessment of inflammatory bowel disease and it has been demonstrated that inflamed bowel segments show restricted diffusion (hyperintensity on high-b-value DWI and reduced apparent diffusion coefficient). By calculating the apparent diffusion coefficient (ADC), DWI can even provide quantitative assessment of the degree of inflammation. A prospective study shows [5] that DWI-MR imaging in inflammatory colon disease (CD and ulcerative colitis) is a reliable tool for detecting colonic inflammation (with more accuracy in ulcerative colitis) even without bowel preparation or the use of intravenous contrast, and therefore could be a good alternative for patients who are unable to ingest oral contrast or for patients having contraindications to the administration of IV contrast.

Cine Sequences

In inflammatory bowel disease it is known that diseased segments may have motility changes, specifically reduced motility, or areas of paralysis. These motility disorders of the bowel segments can be evaluated using repeated fast true-FISP sequences in a single plane within one breath-hold. These so called *cine sequences* can provide qualitative and quantitative assessment of bowel movements. A recent study [10] showed that CD was associated with motility abnormalities and that a larger number of CD-specific findings, such as wall thickening, stenosis, layering of the bowel wall, ulcerations, comb sign and abscesses, were detected at cine MRE compared to static MRE—meaning that more patients with CD can be detected by using cine MR imaging instead of static MRE.

In a retrospective study of 43 patients [13], MR-detectable motility alterations of the terminal ileum were correlated with histopathological findings, both in active and chronic CD, by using a set of coronal 2D true FISP pulse sequences covering the entire abdomen from anterior to posterior over 17 s in one breath hold. A software-quantified motility index was derived from the terminal ileum and compared

with histopathological results from biopsies of the terminal ileum. The results of this study show that there is significant correlation between motility alterations of the terminal ileum both in active and in chronic CD, but that motility changes do not allow differentiation of active and chronic disease.

Magnetization Transfer Imaging and T2 Relaxometry

Differentiating bowel stenosis caused by active inflammation due to bowel wall edema or chronic fibrosis due to scarring remains one of the biggest challenges in the management of CD patients. It is important to distinguish acute from chronic inflammation. Acute inflammation is managed medically, whereas for severe fibrotic strictures or stenosis surgery is indicated.

Magnetization transfer (MT) imaging is based on the magnetization interaction between bulk water protons and macromolecular protons. It demonstrates the transfer of energy from protons in free water molecules to those associated with large molecules such as collagen. The MT effect increases with the number of macromolecules and is therefore higher in fibrotic tissues. The results of a recent prospective study [6], where 31 patients with CD were examined, were very promising and demonstrated that the magnetization transfer ratio (MTR) (quantitative measure of the interaction between the low and high-mobility proton pools) was higher in chronic-fibrotic strictures compared to normal bowel wall and that the MTR in acute inflammatory stenosis is equivalent or slightly lower than in unaffected bowel segments. Similar findings were demonstrated in an animal study in 2011 [32], where the investigators found an increase in the MTR in PG-PS (peptidoglycan-polysaccharide)-induced fibrotic segments of bowel wall in rats compared to a control group. The study also showed a positive correlation between the MTR, the grade of fibrosis, and the amount of type I collagen.

In a recent study [33] mice were exposed to repeated cycles of DSS (dextran sodium sulphate) to induce bowel wall fibrosis and connective tissue changes, as occurring in CD. In vivo MRI T2 relaxometry was performed and was able to differentiate between acute and chronic phases of bowel wall inflammation and fibrosis. In a more recent abstract [34] from the same group, they tried to assess the value of T2 relaxometry in patients with CD, comparing the rectums of a group of healthy people and a group of patients with CD. Findings were consistent to those in their prior animal study.

Therefore MT and MRI T2 relaxometry could be promising tools to assess fibrosis in CD.

MRI Scoring Systems of Disease Activity and Severity

Several studies have shown that MRI is able to detect acute inflammation, evaluate disease severity and detect extraenteric complications in patients with CD, and some of them have suggested MRI disease activity scores. The use of scoring systems simplifies the quantitative analysis of inflammation for comparison between patients or in the evaluation of the patient's response to their therapy. Several studies have been focusing on the diagnostic accuracy of various signs for the detection of active inflammation. Other studies have focused not only on the detection but also on the severity of acute inflammation.

In 2008, an MRI score was created [35] using ileocolonoscopy with biopsy as a gold standard. Several MR findings—such as wall thickness, mural contrast enhancement, layered wall enhancement, mucosal abnormalities, luminal stenosis, mesenteric involvement and pathologic lymph nodes—were evaluated and their results were divided into three main categories: no disease activity, mild activity, and moderate to severe disease activity. The authors tried to create a scoring system as a tool for standardized overall interpretation of the MR findings in the small bowel. Utilizing this activity score, the authors achieved a sensitivity of 0.93 and a sensitivity of 0.87 to predict lesions at ileocolonoscopy.

In 2009, a prospective study compared MR findings with abnormalities on endoscopy in 50

patients with clinically active and inactive CD [36]. The results provide evidence that some MR findings—such as bowel wall thickening, bowel wall edema, increased signal intensity of the bowel wall on T2-weigthed images and relative contrast enhancement—closely parallel the severity of endoscopic lesions (Crohn's Disease Endoscopic Index of Severity). The authors also found that ulcers, enlarged lymph nodes and pseudopolyps were more likely to be present in bowel segments with more severe endoscopic abnormalities. Based on these MR findings, the investigators proposed a simplified score, called the Magnetic Resonance Index of Activity (MaRIA) (1.56 × wall thickness in millimeters + 0.02 × relative contrast enhancement + 5 × edema + 10 × ulceration), for quantitative assessment of the disease in each involved bowel segment [36]. This index had a high correlation with the endoscopic findings in the corresponding bowel segment. A global MaRIA score calculated by adding individual segmental scores also had significant correlation with the total endoscopic severity score. The MR index had a sensitivity of 0.81 and a specificity of 0.89 for the detection of endoscopic disease activity, and a sensitivity of 0.95 and specificity of 0.91 for the detection of ulcerative lesions. Both the simplified and global MaRIA scores also correlated strongly with the C-reactive protein (CRP) concentration and the Harvey-Bradshaw index (HBI) [36].

The same investigators [37] later validated the MaRIA score in another study of 48 patients using the same MR protocol and again using endoscopy as the reference standard. The segmental and global MaRIA scores correlated strongly with the Crohn's Disease Endoscopic Index of Severity (CDEIS), CRP concentration and HBI. They proposed the use of MaRIA as the reference index for measuring CD activity by MRI: a cutoff point of 7 or more for defining the presence of active disease and a cutoff point of 11 or more for the assessment of the presence of severe disease (ulcerative lesions) in a segment-by-segment analysis.

An alternative MR activity score, (CDA score) [38], using histopathology in surgical resection specimens as a reference standard was recently proposed. Several mural and extramural MR findings of the involved bowel segments were evaluated, and bowel wall thickness, T2 signal intensity of the bowel wall, mural enhancement and perimural T2 signal intensity correlated strongly with the histopathologic activity. Based on the fact that bowel wall thickness and mural T2 signal intensity best predicted active inflammation, the following model was derived:

$$\begin{aligned}&\text{acute inflammation score (AIS)}\\&= 1.79 + 1.34\,\text{mural thickness}\\&\quad + 0.94\,\text{mural T2 score}\end{aligned}$$

The model achieved a sensitivity of 0.81 and a specificity of 0.70 for predicting acute inflammation.

All of these studies have used endoscopy and/or histopathology and surgery as reference standards. Endoscopy has, compared to cross-sectional imaging, several disadvantages, such as the lack of visualization of the entire bowel wall and the extramural changes. In addition to the invasive nature there is also limited accessibility and visualization of the small bowel. Comparing MRI with these different techniques may be one of the reasons for the difference in accuracy in evaluating disease activity [39]. A meta-analysis reviewing the accuracy of MRI in Crohn's disease showed that MRI tends to overcall disease severity, particularly in patients having mild disease and those in remission. On the other hand, high accuracy has been found for diagnosing patients with severe disease [39].

Impact of MR in Clinical Practice

Accurate evaluation of biologic activity is crucial to the management of CD. In clinical practice a combination of clinical symptom scores, laboratory markers, and endoscopic disease activity is used to evaluate patients. In general, patients with findings suggesting active inflammation require medical therapy. Reducing the inflammatory activity by suppressing the immune system is the main goal of these medical therapies. Medication side effects, including an increased

risk of infections and malignancy, create an impetus for their use in patients with objective evidence of active disease. Findings suggestive for fibrostenotic disease can be an indicator for surgery, although a histopathologic overlap between inflammation and fibrosis has been suggested by several authors [9].

MRE is accurate in assessing disease activity and severity, and can contribute to a change in medical and surgical management [1]. In a group of 120 patients [1], based on physical examination and MRE findings, 31 % had no changes in their medical management, 53 % had alterations in their medical treatment, and 16 % underwent an operation for complicated CD or in patients refractory to medical therapy. In all surgical patients, the intraoperative findings were consistent with the MRE diagnosis [1]. In a study of 51 patients [40] investigated for small bowel CD, MRE had a positive impact on therapeutic management in 61 % of the patients. In a single referral center study [41], MRE findings led to escalation of medical therapy in 55 % of patients and surgery in 32.5 %. The review of surgical resection specimens correlated with MRE findings of disease activity and fibrosis in 92 % of cases.

Although differentiating inflammation and fibrosis is limited in current imaging protocols, recent studies using the previously mentioned new MRI techniques provide promising results that require confirmation in larger studies.

MRE appears to have an important role in disease monitoring under therapy. Absence of clinical symptoms as well as mucosal healing on endoscopy does not exclude active disease. Studies comparing endoscopic findings and cross-sectional imaging in CD confirm that despite the presence of normal mucosa on endoscopy there are still patients having mural and mesenteric disease or having disease in small bowel segments that are inaccessible by endoscopy [42, 43].

The effect of corticosteroid therapy on disease activity was evaluated by MRE in a small study including 8 patients with Crohn's disease [44] undergoing MRE on a low-field MRI (1,0 T) before and after treatment. The MRE parameters that showed a significant improvement with treatment were bowel wall signal intensity on T2, contrast enhancement, and bowel wall thickness. The effect of infliximab on transmural lesions in the ileum has been evaluated by MR enteroclysis in a multi-center prospective study [45]. The 15 patients included in this study had an MRE prior to the first infliximab infusion and a second and third MRE at weeks 2 and 26. A new MRE score of severity in ileal CD (MICD) was developed to assess CD severity and complications, by combining indicators of transmural inflammation, extramural disease and intestinal obstruction. The results of this study showed that the MICD index, ranging from 0 to 14 (maximum 8 points for active inflammation and maximum 6 points for complications), correlated with the CDAI but not with CRP. The authors also concluded that normalization of MRE findings is rare after infliximab therapy. In a retrospective study of 50 patients [46] with CD, the effect of anti-TNF therapy (infliximab or adalimumab) was assessed using serial MRE examinations and a CDA-based score [38]. The inflammatory activity and the length of the diseased bowel segments as well as the degree of inflammation in stenotic lesions with prestenotic dilatation improved in the anti-TNF responders. In a prospective multicenter study of 48 patients [47] with active disease and ulcers, the effect of 12 weeks of corticosteroid or anti-TNF therapy was evaluated on mucosal healing, defined as the disappearance of ulcers in endoscopy examination. The MaRIA score and the Crohn's Disease Endoscopic Index of Severity were used for quantitative assessment of disease activity. The study showed a high degree of correlation between mucosal healing on endoscopy and the resolution of the transmural and extramural inflammatory changes on MRE, evaluating both ileum and colon.

Given the promising results of these studies, we can suggest that integrating an MRI activity score in the management of CD patients may be helpful in the assessment of therapeutic efficacy. With this objective in mind, a unique, simple and reliable MRI scoring system needs to be validated in prospective studies and with consensus from radiologists.

We have already mentioned that in the last decade the treatment goals in CD have changed and are evolving. In the majority of these patients the disease is progressive and leads to irreversible bowel damage, there is an increasing interest in treating beyond the control of clinical symptoms and inflammatory markers. The ultimate goal for a lifelong disease presenting mainly in young adults is the preservation of intestinal function and the prevention of disability. Therefore, therapeutic management is currently focused on reaching complete or deep remission as soon as possible, in order to improve long-term outcome.

To pursue this therapeutic objective, the Lémann bowel damage score for Crohn's disease has been proposed [48, 49]. This is centered on measuring cumulative structural bowel damage, rather than disease activity. This score measures bowel damage, using a 3-point score system for strictures and penetrating lesions visualized by endoscopy, ultrasound, CT or MRE, and history of surgery or other mechanical interventionals. This score may facilitate the stratification of patients with CD based on their risk of bowel damage progression and allow the comparison of the effect of various therapies on the resolution of structural damage in these patients.

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Part III

Endoscopic Diagnosis/DDX CUC/CD

Role of Endoscopy in Diagnosis of Crohn's Disease and Chronic Ulcerative Colitis

6

Stephen M. Vindigni, Anand Singla, and Scott D. Lee

Introduction

The diagnosis of inflammatory bowel disease (IBD) often requires a combination of clinical, endoscopic and pathological studies. Of currently available diagnostic clinical studies, endoscopy with biopsy—defined for this chapter as colonoscopy with intubation and evaluation of the terminal ileum (ileoscopy) and esophagogastroduodenoscopy (EGD)—is the most essential study in the diagnosis of IBD. Endoscopy during the initial diagnosis of IBD can differentiate other etiologies that have a similar clinical presentation. Endoscopy is the most accurate study to assess extent and severity of disease, and differentiate ulcerative colitis (UC) and Crohn's disease (CD).

This chapter will review the appropriate utilization of endoscopy in the initial diagnosis of IBD and its role in differentiating UC from CD. Additional chapters within this text will discuss other applications and modalities of endoscopy in greater detail.

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Esophagastroduodenoscopy

While an EGD can play a significant role in the initial diagnosis of suspected IBD, our current understanding of the clinical significance of the findings on an EGD have not been well defined nor have they been systematically evaluated. There is a small percentage of patients that require an EGD in order to make the initial diagnosis of IBD and in some patients an EGD can provide clinically significant supplemental information. Apart from these examples where EGD is necessary or helpful, most patients do not require EGD during the initial workup of suspected IBD.

Ulcerative Colitis

By definition, patients with UC have disease confined to the colon and should not have involvement of the upper gastrointestinal (UGI) tract. Therefore, routine utilization of EGD in patients with suspected UC is limited. However, performing routine EGD in patients being evaluated for suspected UC has been proposed in the pediatric literature to differentiate between UC and CD. In pediatric patients, because general anesthesia rather than conscious sedation is routinely used

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during all endoscopic procedures, consideration is given to performing all potentially necessary procedures during a single session. This practice avoids potential additional general anesthetic for the patients but also results in many pediatric patients with suspected UC and no UGI symptoms having an EGD performed during their initial evaluation. In this group of patients with no UGI symptoms undergoing an EGD, there have been numerous case reports describing upper gastrointestinal findings in patients carrying the initial diagnosis of UC. These findings include diffuse duodenitis, diffuse gastritis, gastroduodenitis, and even diffuse enteritis [1–4]. Furthermore, there is a report of duodenitis on EGD in a symptomatic patient with established UC following colectomy [5]. Kundhal reported upper GI findings in 39 children with suspected IBD colitis and normal small bowel radiographs [6]. Nonspecific chronic inflammation in the stomach was found in roughly equal proportions (75–92 %) of CD and UC, although focal antral gastritis was much more common in CD (52 %) compared to UC (8 %). Five (14 %) of patients had a diagnosis change from UC or indeterminate colitis to CD based on EGD findings of granulomatous gastritis [6]. There is limited long-term data regarding the endoscopic UGI findings in confirmed UC patients and therefore, the clinical significance and outcomes of these findings is unknown.

Routine EGD during the initial diagnosis of suspected UC is generally not critical and not recommended to be performed during the initial evaluation of adult UC. However, an EGD may provide clinically significant information in UC patients with UGI symptoms and if performed can assist in differentiating UC from CD, which may have an impact on treatment choices. Based on the findings in the pediatric literature, we recommend consideration of EGD with random biopsies of the stomach and duodenum and targeted biopsies of any endoscopic abnormalities during the initial evaluation of suspected UC if: the patient has any current or past UGI symptoms, the patient requires general anesthesia for colonoscopy, or if there are any clinical abnormalities (e.g., B12 deficiency) [7, 8]. We also recommend an EGD be performed in patients where the initial colonoscopy results in difficulty differentiating UC from Crohn's colitis (i.e., indeterminate colitis). An EGD will not delay making the diagnosis of UC; however, a significant number of patients with UC will have UGI findings.

Crohn's Disease

The prevalence of CD involving the UGI tract, defined as involvement of the esophagus, stomach and or duodenum has not been systematically evaluated [9]. Available studies in adult CD patients are very limited and therefore the true prevalence is not well characterized in adults. The Montreal classification for CD acknowledges and recognizes potential involvement of the UGI tract with the designation of L4 for isolated UGI involvement, which can be independent or serve as a modifier for L1–L3 (ileal, colonic, and ileocolonic disease, respectively) [10].

Compared to adults, EGD is more routinely performed in pediatric patients with suspected CD for the same rationale described regarding the use of EGD in suspected pediatric UC patients. With the more uniform employment of EGD in pediatric CD patients, the prevalence of UGI involvement in pediatric CD has been better characterized. The pediatric literature suggests that the incidence of macroscopic UGI tract involvement in patients with CD can be as high as 30 % [11]. The prevalence of microscopic involvement of the UGI tract can be as high as 60 % [12–14]. In patients with UGI involvement, the disease is often concomitantly manifested elsewhere in the GI tract (e.g., terminal ileum, colon, rectum, or perianal area) [9]. Isolated upper GI tract disease in the absence of lower GI tract involvement is rare, with a reported prevalence of 0.7 % [15, 16].

The role of EGD in the evaluation of CD is not as clearly defined as the role of colonoscopy. Currently, routine EGD is not recommended in all patients suspected of having CD by society guidelines; however, there is evidence in the pediatric population to suggest that performance of an upper endoscopy at the time of diagnostic evaluation of a child with colonic IBD may help differentiate CD from ulcerative

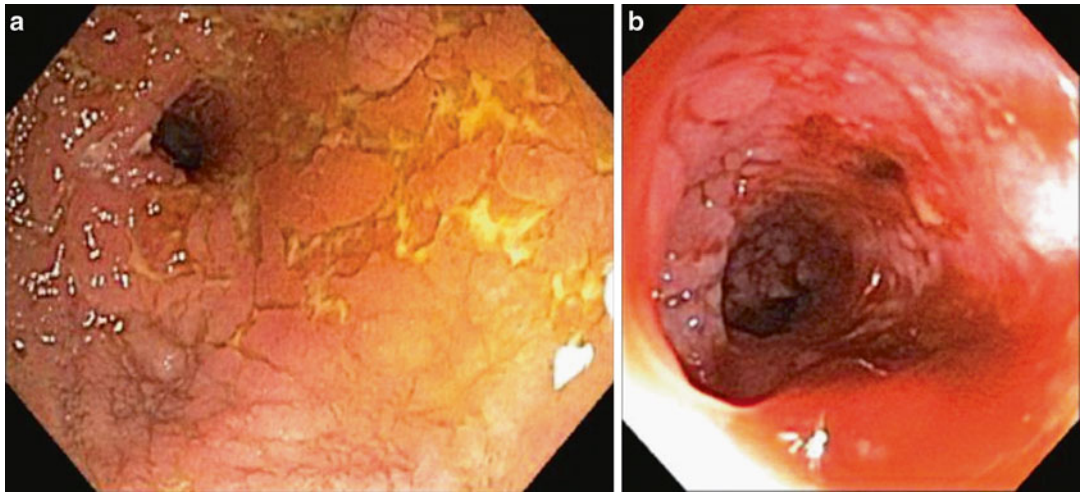

Fig. 6.1 (**a**, **b**) Duodenal stricture

colitis [7, 9]. Gastric antral biopsies may have pathognomonic changes of CD and can establish a definitive diagnosis of CD patients with indeterminate colitis [6]. As the majority of pediatric colonoscopy requires general anesthesia and with the relatively high incidence of UGI involvement in the pediatric literature, routine EGD is generally recommended at the time of colonoscopy for the pediatric population as part of the initial evaluation of suspected IBD [8]. If an EGD has not yet been performed and the diagnosis of CD is definitively made with ileocolonoscopy, it may be difficult to justify performing an EGD routinely in the absence of UGI symptoms, unless it would change the choice of therapy [17].

Common endoscopic findings in CD include erosions, ulcerations, erythema, edema, and thickened mucosal folds in the UGI tract [9, 18]. The endoscopic appearance is not specific for IBD and there are no pathognomonic endoscopic findings of CD. The presence of focal inflammation of the esophagus is more consistent with CD than ulcerative colitis, though the endoscopic appearance cannot be necessarily distinguished from chronic inflammation secondary to reflux [19]. The finding of esophageal aphthous ulcerations is more specific for CD but the endoscopic appearance still does not distinguish CD as the definitive etiology [20].

The presence of chronic gastric inflammation, particularly in the antrum, has been reported commonly in both CD and ulcerative colitis and therefore this finding may not distinguish CD from UC [19]. Duodenal inflammation and duodenal aphthous ulcerations can be commonly found in CD, but the endoscopic appearance is still not pathognomonic for CD [19]. Because *Helicobacter pylori* (HP) infections are common and can result in endoscopic inflammatory changes similar to those found in CD, it is important to check for infection on biopsy and treat accordingly [14]. For those patients with suspected CD that have endoscopic UGI inflammatory lesions with HP found on biopsies, we would recommend appropriate therapy and repeat EGD to evaluate for persistent lesions in the absence of HP. The presence of strictures in the esophagus, pylorus or duodenum (Fig. 6.1a, b) are uncommon, but can be caused by CD. The finding of a stricture is consistent with long-standing chronic inflammation from CD with the development of fibro-stenosis [20, 21]. As with colonic strictures, it is recommended that directed biopsies of the stricture be obtained to rule out other etiologies such as tumors.

Our current understanding of UGI CD has not been systematically evaluated with regards to the true incidence, prevalence, response to therapy or the natural history. The incidence of patients

requiring surgical intervention with UGI CD, is also not well defined, likely because surgery of the UGI tract carries significant morbidity relative to surgery on other parts of the GI tract. Nonetheless, it is important to ascertain if patients have UGI involvement to ensure that these patients have adequate control of disease to try and prevent complications and the need for surgical intervention.

Small Bowel Evaluation

The evaluation of the small bowel is discussed in more detail in Chaps. 2, 3, 4, and 5.

Capsule endoscopy (CE) may be beneficial in that the small bowel can be non-invasively visualized with relatively low risk; however, the procedure lacks the ability for biopsy or intervention. In cases when colonoscopy, EGD and small bowel follow-through have been negative, CE findings can be diagnostic. Additionally, CE can assist with evaluating the extent of disease, response to therapy, and detecting recurrence. CE is discussed in more detail in Chap. 7.

Double-balloon enteroscopy (DBE) has a limited role since the development of capsule endoscopy. This modality is discussed in more detail in Chap. 8.

Colonoscopy with Ileoscopy

Colonoscopy with ileoscopy is essential in the initial evaluation of suspected IBD in the vast majority of patients. In addition to assessing the severity of disease, endoscopy is also essential to differentiating IBD from other conditions, which may present with similar clinical signs and symptoms. The most common other etiologies include colitis secondary to infectious, ischemic, medication and radiation. Since up to one-third of patients with bloody diarrhea and suspected IBD are found to have an infectious cause, this differentiation is essential [22]. Infectious etiologies tend to present with a yellow or pus-like exudate layered on the mucosal surface; and this endoscopic finding is considered a less common finding in CD or UC [23]. The color of the colonic mucosa has been described as a means to differentiate infection from IBD as infections can produce an intense red-maroon color to the mucosa; IBD patients tend to have a deeper red color, however, this is very subjective and we do not recommend that color be used as routine or primary means for differentiating IBD from infectious etiologies [23]. Non-steroidal anti-inflammatory drugs (NSAIDs) and sodium phosphate-based bowel preparation have been reported causing changes in the mucosal appearance that can mimic the appearance of IBD; therefore, these agents should be avoided when possible prior to colonoscopy for the evaluation of suspected IBD [9, 24]. There are no pathognomonic findings of CD on colonoscopy, thus the diagnosis requires thorough history taking, physical examination, serum and stool studies, and biopsy with pathological review is essential.

When IBD is suspected, colonoscopy with ileoscopy should be performed as part of the initial evaluation. An exception to this is in patients with a severe, acute presentation of IBD. Patients with bowel perforation, hemorrhage or toxic megacolon should be immediately considered for surgical intervention and colonoscopy is in general contraindicated [23].

During the initial colonoscopic exam, taking biopsies is essential. Biopsies should target endoscopic abnormalities, but biopsies of normal tissue in the absence of endoscopic lesions should also be taken and include the ileum, colon and rectum. Sampling of normal tissue is particularly important in the identification of skip lesions. An index colonoscopy at the time of diagnosis with documentation of rectal and ileal involvement, distribution of inflammation and severity of disease is critical as future medical therapy will likely produce changes in mucosal presentation (i.e., patchiness) and may hinder the differentiation of UC versus CD.

When performing colonoscopy, the endoscopic appearance of IBD-associated mucosa has limited specificity in differentiating UC from CD. This is particularly true since the endoscopic presentation is variable depending on disease severity and duration. Despite this, inflammation

Table 6.1 Common findings in IBD patients using EGD, capsule endoscopy, and colonoscopy

	Procedure			
	EGD	CE	Colonoscopy with ileoscopy	Pathology
UC	Normal appearing esophagus, stomach and duodenum	Normal appearing small bowel	Rectal involvement with continuous, proximally advancing inflammation with clear demarcation of normal and abnormal mucosa Mucosal edema and granularity Congestion of vasculature with easy friability and bleeding Pseudopolyps, although not specific May see backwash ileitis for several centimeters	Crypt architecture distortion, sometimes with abscess Decrease in goblet cells Rarely mucin granulomas Basal plasmacytosis Paneth cell metaplasia
CD	Duodenitis with edema, erythema, thickened duodenal folds Erosions Nodular lesions Friability with bleeding Duodenal stricture Similar findings in stomach including pyloric stricture	Mucosal breaks, although not specific	Inflammation limited to rectum, left colon, right colon, or diffusely through the colon. May also extend to ileum Often patchy or segmental involvement with skip lesions Discrete and/or serpiginous ulcers Cobblestoning +/– aphthous ulcers +/– rectal sparing +/– perianal involvement +/– fistulas	Crypt architecture distortion, sometimes with abscess Non-caseating granulomas Patchy distribution

visualized on endoscopy should be characterized regarding both extent of involvement and severity. Involvement of the colonic mucosa may be endoscopically limited to the rectum (i.e., proctitis), left colon (distal to the splenic flexure), extending to the right colon, or diffusely through the colon (i.e., pancolitis) in both UC and CD. Since it may help support a CD diagnosis, it is important to closely evaluate the anal and peri-anal area.

Crohn's Disease

While the endoscopic appearance of the colon in CD can be identical to UC there are several findings that have been more commonly associated with CD. The endoscopic findings including patchy or segmental colitis, rectal sparing, and involvement of the terminal ileum. Anal or perianal areas are also suggestive of CD rather than UC [9] (see Table 6.1).

Another endoscopic finding more typical of CD patients with mild disease is small aphthous ulcers, which are related to submucosal lymphoid follicle expansion; these punched-out ulcers

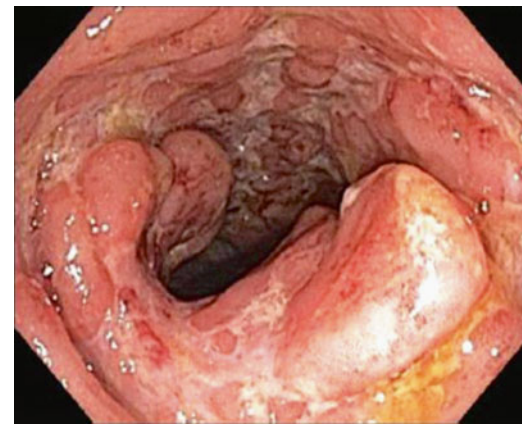

Fig. 6.2 Linear ulceration in Crohn's disease

can coalesce to form a larger ulcer with a star appearance, referred to as stellate ulcers [22]. With increased severity of CD, the submucosa becomes more edematous, which creates a cobblestoned appearance; this suggests a chronic process. In very severe cases, patients may have larger ulcers that are linear (bear claw) (Fig. 6.2) or deep and serpiginous in shape [25]. Both the findings of aphthous ulcers or deep linear or serpiginous ulcers have been more commonly

associated with CD. Of note, the colonoscopic findings used to describe UC can all be present in patients with Crohn's colitis and this can be indistinguishable from typical UC. These findings are described in the following section regarding the colonoscopic appearance of UC.

Ulcerative Colitis

What helps distinguish CD from UC is that in the latter, inflammation starts in the rectum with proximal extension in a continuous, circumferential manner without skip patterns. Involvement can end at any location or extend to the entire colon, but the entirety of segment that is involved should have uniform involvement regardless of the extent of disease. By definition, the rectum in a patient with suspected UC should be involved. If there is no microscopic and/or macroscopic evidence of UC on rectal biopsies, UC is ruled out.

Endoscopically, patients with newly developed UC present with a loss of mucosal vascularity. As the disease advances in duration and severity, the appearance progresses to mucosal edema, hyperemia from increased surface blood flow and vasculature congestion with easy friability (Fig. 6.3) and bleeding; the severity of endoscopic inflammation is generally worse in the rectum unless rectally instilled medications have been used. There are often clear boundaries between inflamed and normal mucosa [26]. Persistent edema creates an irregular granular appearance ("wet sandpaper") [23]. With more severe disease, discrete ulcerations develop and often bleed spontaneously, but unlike in CD, these ulcers are also surrounded by inflamed mucosa and there should be no skip lesions [22, 27, 28] (Fig. 6.4).

As the disease becomes more chronic, the mucosa begins to atrophy resulting in narrowing of the lumen and a loss of haustral folds [27] (Fig. 6.5). This results from changes in the muscle layer in the setting of chronic inflammation.

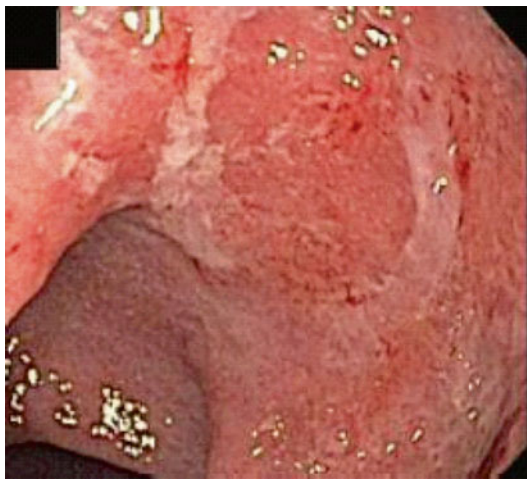

Fig. 6.3 Mild UC with friability

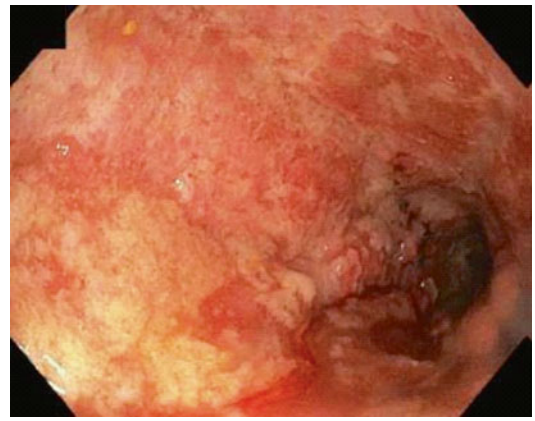

Fig. 6.4 Severe UC

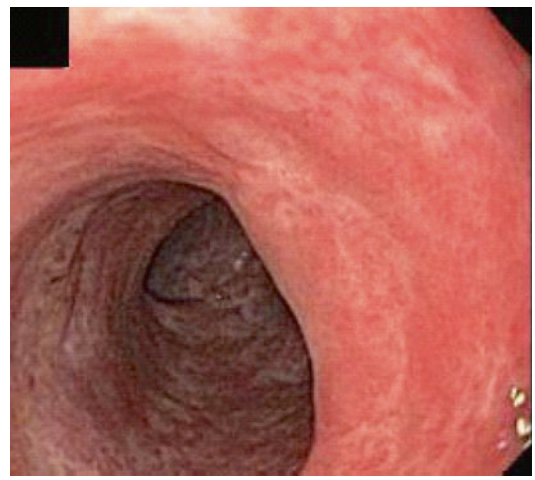

Fig. 6.5 Loss of mucosal vascularity and loss of haustral folds

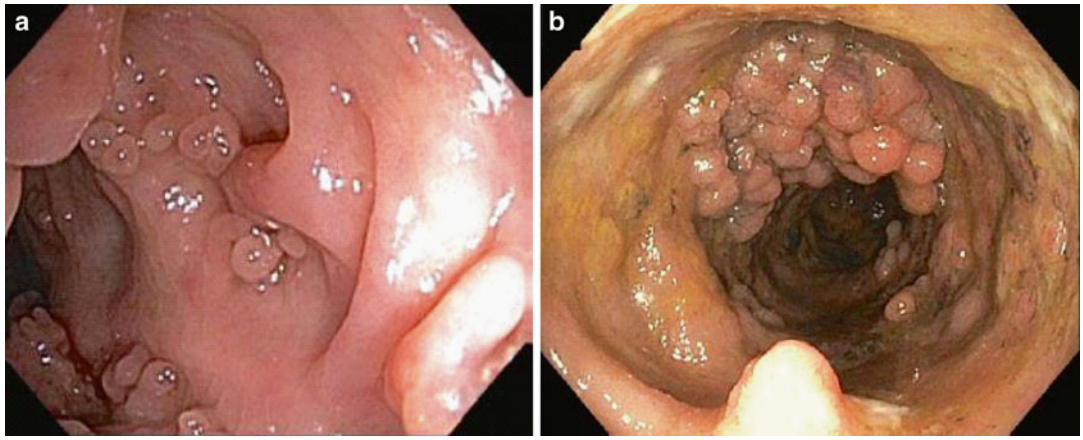

Fig. 6.6 (**a**, **b**) Pseudopolyps

As ulcers heal and are replaced with scar tissue, residual mucosa protrudes in a nodular fashion forming pseudopolyps (Fig. 6.6a, b). The finding of pseudopolyps is not exclusive to UC, but this finding is less common with other etiologies [26]. Although there is no known malignant potential of pseudopolyps, biopsies should be taken as it is not possible to distinguish pseudopolyps from other polyps on their endoscopic appearance. In particular, targeted biopsies should be obtained when a pseudopolyp is isolated, greater than 1 cm and/or when there is a hemorrhagic surface to rule out dysplasia [26].

One exception regarding rectal sparing in UC patients has been described in patients with UC and primary sclerosing cholangitis [22]. However, this again is not a pathognomonic finding and the entirety of the patient's disease should be taken into account to distinguish between UC and CD.

Significance of Ileoscopy

In all cases of suspected IBD, intubation of the terminal ileum (TI) with biopsies should be attempted and with the exception of a stricture, should be achievable in the vast majority of patients. With any new IBD diagnosis, it is important to establish the extent and distribution of disease. Involvement of the ileum generally suggests CD (a finding that may result in a change from a prior UC diagnosis). As histology is more

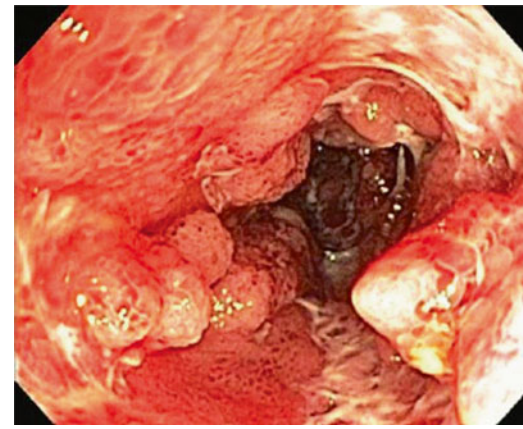

Fig. 6.7 Severe ileitis

sensitive than endoscopy to detect CD, biopsies regardless of the endoscopic appearance of the TI are essential. Ileal involvement (Fig. 6.7) does not simply result in a CD diagnosis, however, since there is a subgroup of patients that have suspected "backwash ileitis," estimated at about 10 % of patients with pancolonic UC [24, 26]. This is generally described as a patchy, non-ulcerative inflammation of the terminal ileum. CD ileitis is favored if discrete ulcers and/or strictures are present; "backwash ileitis" would not produce ileal stenosis, cobblestoning (Fig. 6.8a, b), or any ileocecal valve abnormalities [8, 24]. While TI involvement in IBD is not considered pathognomonic of CD (Fig. 6.9), the finding of "backwash ileitis" has not been extensively evaluated with

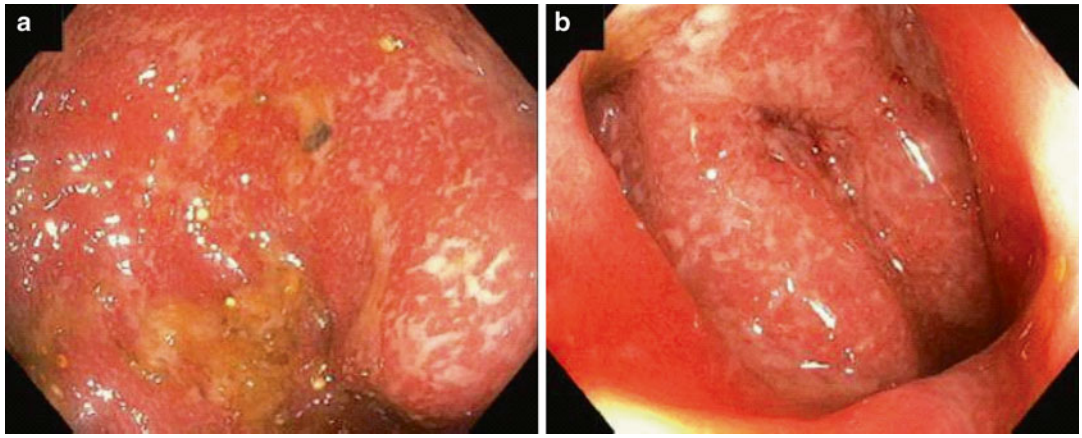

Fig. 6.8 (**a**, **b**) Mild UC (cobblestoning)

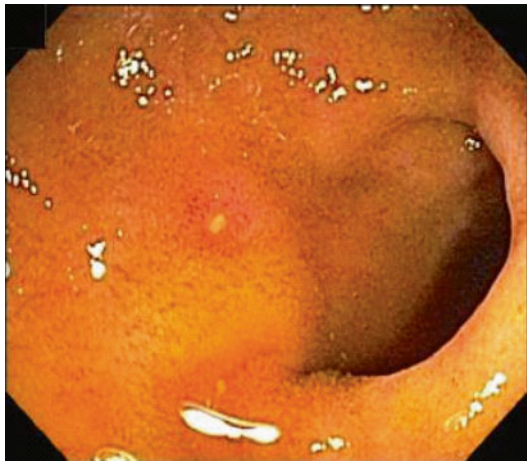

Fig. 6.9 Aphthous ulceration of terminal ileum

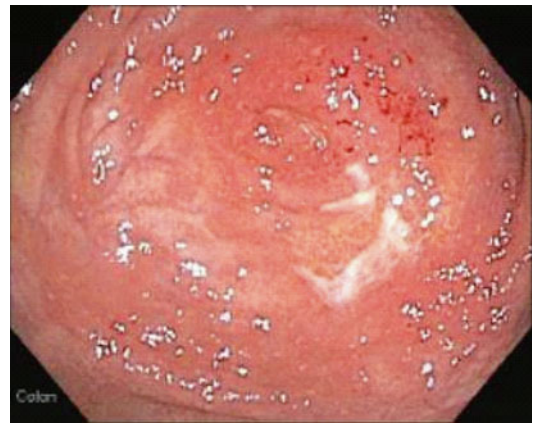

Fig. 6.10 Peri-appendiceal inflammation in UC

regard to the long-term significance and what, if any, effect it may have on the outcome in treatment of IBD patients. We consider the findings that characterize "backwash ileitis" as non-specific and suggest this finding be interpreted with caution, especially if making therapeutic decisions based on this finding.

Occasionally, UC patients who do not have pan-colitis, will have inflammation of the appendiceal orifice (Fig. 6.10). Despite the segmental nature and lack of contiguous colonic involvement of peri-appendiceal inflammation in patients without pan-colitis, this endoscopic finding has been described as a feature more consistent with UC rather than CD [24]. The etiology and significance of this cecal patch is unknown. As the long-term significance has not been well defined, as with "backwash ileitis," we recommend caution in making any therapeutic decisions.

As discussed in more detail in Chap. 16, colonoscopy is also the primary method of colorectal cancer surveillance, which is of greater importance in IBD patients.

Flexible Sigmoidoscopy

Full colonoscopy with ileoscopy is recommended for a new IBD diagnosis. However, in patients presenting with fulminant colitis or toxic mega-colon, colonoscopy may be relatively contraindicated and a flexible sigmoidoscopy may be a slightly less invasive option to obtain endoscopic evaluation

and biopsies. Sigmoidoscopy in these limited scenarios can be used to confirm the diagnosis of IBD and rule out other etiologies that could present with a similar clinical presentation, including infectious etiologies such as cytomegalovirus (CMV) that require biopsy to make the diagnosis.

Beyond routine sigmoidoscopy, there is potential benefit of endoscopic ultrasonography (EUS). In IBD patients, the most common use of EUS is in the evaluation of perianal disease. EUS has also been used to evaluate the presence of fistulas, abscesses and lymphadenopathy [9]. While not first line, EUS also may play a role in the differentiation of UC versus CD. Since CD characteristically has transmural involvement, EUS may help to assess the depth of mucosal involvement [9, 29]. As the results of performing EUS for this modality have been variable, this is not currently recommended as a routine part of the initial evaluation of suspected IBD.

Scoring Systems

There are multiple scoring systems to assess the severity and progression of IBD [26] (see Tables 6.2, 6.3, and 6.4).

For CD, the Endoscopic Index of Severity (EIS) evaluates ulceration and inflammation and is considered the gold standard for CD, although it is challenged by multiple variables, a wide-ranging scoring system and may be more difficult to use in everyday clinical practice. The Simple Endoscopic Score (SES) similarly looks at endoscopic variables (i.e., ulceration, inflammation, narrowing). A third scoring system is the Rutgeerts score, which is the gold standard for postoperative disease recurrence, but has no role in assessing remission from medications.

For UC, there are many more endoscopic scoring systems, although none have been validated. The easiest to use is the Mayo endoscopic subscore, which evaluates erythema,

Table 6.2 Most common endoscopic scoring systems

Simple endoscopic score for Crohn's disease				
Variable	Score			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0. 1–0.5 cm)	Large ulcers (0.5–2 cm)	Very large ulcers (>2 cm)
Ulcerated surface	None	<10 %	10–30 %	>30 %
Affected surface	Unaffected segment	<50 %	50–75 %	>75 %
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Simple endoscopic score for Crohn's disease
Total score = sum of 4 variables for 5 bowel segments (rectum, left colon, transverse colon, right colon, ileum)

Table 6.3 Crohn's disease endoscopic index of severity (CDEIS)

Crohn's disease endoscopic index of severity (CDEIS)					
	Rectum	Sigmoid and left colon	Transverse colon	Right colon	Ileum
Deep ulcerations = 12 if present in the segment; 0 if absent					
Superficial ulceration = 6 if present in segment; 0 if absent					
Surface involved by the disease measured in centimeters					
Ulcerated surface measured in centimeters					

Total score is divided by number of location explored. Three points added if ulcerated stenosis present and an additional three points are added if non-ulcerated stenosis is present. CDEIS score ranges from 0–44

Table 6.4 Complete Mayo score

Complete Mayo score	
Endoscopic findings:	
0	Normal or inactive disease
1	Mild disease (Erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked Erythema, lack of vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment:	
0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease
Stool frequency sub-score:	
Rectal bleeding sub-score:	
Total	

vascularity, friability, bleeding, erosions and ulceration; it uses a four-point scale. The Baron score and modified Baron score is similar. Other endoscopic scoring systems include the Truelove and Witts or Powell-Tuck sigmoidoscopic assessment, the Rachmilewitz endoscopic index, and the Sutherland mucosal appearance assessment [26].

Currently, endoscopic scoring systems are primarily research tools. While the endoscopic appearance has been shown to be a clinical predictor of outcomes in patients with IBD, due to the lack of widespread use, a standardized scoring system and the complexity of some of the scoring systems, the endoscopic scoring systems are not utilized widely in clinical practice. Until further studies are performed that validate the endoscopic scoring systems as having a role in the management of IBD patients, it is unlikely that using an endoscopic scoring system in clinical practice is of significant utility.

Conclusion

Currently, there is no single pathognomonic test available to diagnose IBD. Colonoscopy with ileoscopy and biopsy is the best test for making the initial diagnosis of IBD and should be performed on all patients with suspected IBD. In UC, colonoscopy with ileoscopy alone is adequate to assess the entire extent and severity of disease based on the distribution of UC. In CD, colonoscopy with ileoscopy is necessary, but in up to 30 % of CD patients, upper GI involvement implies that colonoscopy and ileoscopy alone will not be sufficient to evaluate the entire extent and severity. However, even among those with UGI involvement, only in the minority will UGI endoscopy have an impact on the patients' treatment.

In summary, colonoscopy with ileoscopy should be performed in all patients with suspected IBD. Performing an EGD for suspected IBD is not currently recommended for all patients, but it can play an important diagnostic role in a significant number of patients with suspected IBD. Despite advances in diagnostic testing for IBD, endoscopic visualization with biopsy is still the gold standard in the initial evaluation of suspected IBD and clinicians seeing these patients should understand the critical role that endoscopy plays in the diagnostic workup and treatment of potential IBD patients.

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Capsule Endoscopy in the Evaluation of Inflammatory Bowel Disease

7

Erika S. Boroff and Jonathan A. Leighton

Introduction

Inflammatory bowel disease (IBD) encompasses two major disease entities, namely ulcerative colitis (UC) and Crohn's disease (CD). Whereas UC is associated with diffuse and continuous inflammation confined to the colon, the inflammation associated with CD is trans-mural, and may occur anywhere within the gastrointestinal tract. Presenting symptoms are often nonspecific, including abdominal pain, diarrhea, bleeding, and weight loss. There is often a prolonged interval between symptom onset and diagnosis, especially with CD. Diagnosis can be challenging, as there is no single test that confirms the presence of IBD, and as a result, a prolonged interval between symptom onset and diagnosis is not uncommon. To diagnose CD or UC, the clinician must rely on a combination of endoscopic, radiographic, histologic and serologic testing [1, 2].

Traditional ileocolonoscopy has been the cornerstone of diagnosis and surveillance of IBD, allowing for the direct visualization of the intestinal mucosa and the identification of the distribution and patterns of inflammation that can distinguish between UC and CD [3]. However, in the case of CD, if inflammation is confined to the small intestine and/or more proximal in location, ileoscopy may not make the diagnosis. Therefore, in patients where small bowel inflammation is suspected but not diagnosed with ileocolonoscopy, further evaluation of the small bowel is deemed essential to make a proper diagnosis.

Historically, endoscopy of the small intestine has been limited to the proximal jejunum visualized during push enteroscopy, and to the terminal ileum during ileocolonoscopy. In the past decade, however, the advent of the capsule endoscope has rendered complete endoscopic visualization of the entire small bowel possible. Capsule endoscopy (CE) has become a significant tool in the diagnosis and continued evaluation of patients with suspected and established CD and may be useful in UC as well.

Capsule Endoscopy

The video capsule endoscope is an ingestible and disposable video camera that captures and transmits high quality images of the mucosa of the small intestine. In 85–90 % of patients, the entire length of the small bowel is traversed and photographed [4]. There are currently five small bowel capsule endoscopes available for clinical

Electronic supplementary material: Supplementary material is available in the online version of this chapter at 10.1007/978-3-319-11077-6_7. Videos can also be accessed at http://www.springerimages.com/videos/978-3-319-11076-9.

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Table 7.1 Comparison of capsule endoscopes: small bowel, colon and patency capsule

Capsule endoscope	Manufacturer	Dimensions	Field of view	Image capture	Battery life	Data transmission
PillCam SB	Given Imaging, Yoqneam, Israel	11×26 mm	156°	2-6 fps	12 h	Radiofrequency
Endocapsule MAJ-1469	Olympus Medical Systems Corporation, Tokyo, Japan	11×26 mm	145°	2 fps	8 h	Radiofrequency
OMOM	Jinshan Science and Technology Co., Chongqing, China	13×27.9 mm	140°	2 fps	8 h	Radiofrequency
MiroCam	IntroMedic Co., Ltd., Seoul, Korea	10.8×24.5 mm	170°	3 fps	12 h	Electrical field propagation
CapsoCam SV1	Capsovision, Saratoga, USA	11×31 mm	360°	20 fps×2 h then 12 fps	15 h	Capsule retrieved then USB download
PillCam Patency Capsule	Given Imaging, Yoqneam, Israel	11×26 mm	n/a	n/a	n/a	n/a
PillCam Colon	Given Imaging, Yoqneam, Israel	11×32 mm	172°	6 fpm in stomach 4–35 fps in SB	10 h	n/a

Fps frames per second, *fpm* frames per minute, *USB* Universal Serial Bus

use and research (Table 7.1, Fig. 7.1). Each system contains: a light-emitting diode (LED) light source, a lens, a camera derived from a complementary metal oxide semiconductor (CMOS) or a charge-coupled device (CCS), a battery, and a wireless transmitter [5–7]. The capsule is typically ingested following an 8- to 12-h fast and some form of bowel preparation. Patients are allowed to drink clear liquids 2 h following capsule ingestion, as the capsule usually clears the stomach within 30 min. For patients with gastroparesis, the capsule can be placed endoscopically in the duodenum. The patient wears an external recorder with a self-contained antenna to receive images captured by the internal camera. During the 8–12 h of active battery life, the capsule is transported distally through the gastrointestinal tract via peristalsis while images are recorded. The images are reformatted into a video file that can be downloaded and reviewed on a standard computer using specialized software [5, 6]. The advantages of the CE procedure over more invasive endoscopy techniques include the ability to visualize the majority of the small bowel mucosa with minimal patient discomfort and the avoidance of general anesthesia. In addition, physicians require less training to deploy the video capsule, even when manually inserted into the small bowel in patients with variant anatomy, than that necessitated by advanced endoscopic techniques. The disadvantages of the CE procedure are the inability to clear the intestinal mucosa of debris or reposition the capsule, and the inability to obtain tissue for histology. CE relies on intestinal motility and a patent small bowel lumen. Delayed gastric emptying, and slow small-bowel transit can lead to exhaustion of the battery life before the capsule reaches the cecum. In some studies, this was 20 % of capsules deployed [8]. Known small bowel strictures are a relative contraindication to deployment of a video capsule.

Preparation

Adequate inspection of the small bowel mucosa depends on a quality bowel preparation, as the capsule does not have the ability to clear debris from the lumen. Currently, there is no standard bowel preparation, nor is there an established scoring system to compare the quality of the

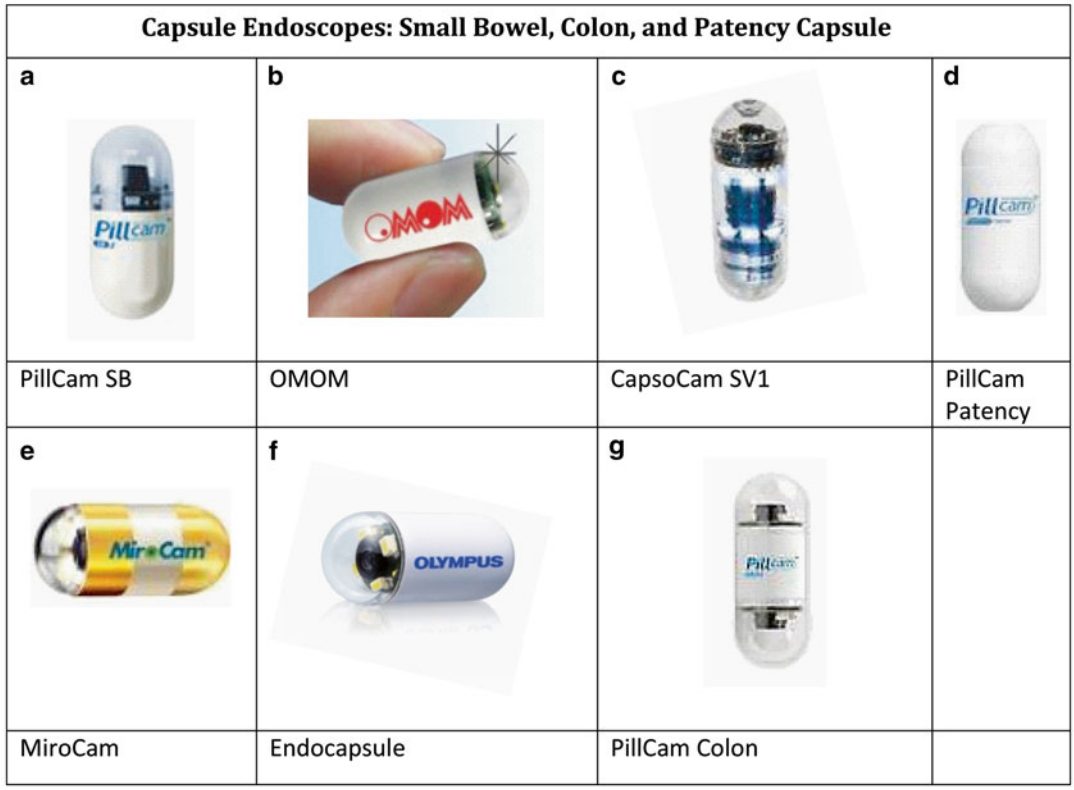

Fig. 7.1 Images of capsule endoscopes: small bowel, colon, and patency capsule

small bowel preparation. A combination of a clear liquid diet and fasting, the use of osmotic laxatives and medications to stimulate peristalsis, have all been used to prepare the small bowel mucosa for CE. One meta-analysis of eight studies demonstrated superior mucosal visualization when the bowel was prepared with sodium phosphate (Na-P), polyethylene glycol (PEG) or erythromycin prior to the capsule compared with clear liquid diet alone [9]. A second meta-analysis of 12 studies demonstrated improved diagnostic yield of CE when patients were treated with an osmotic laxative prior to CE compared with those patients who received a clear liquid diet alone (odd ratio [OR] 1.81; 95 % confidence interval [CI], 1.25–2.63; $p=0.002$) [10]. A third meta-analysis of eight randomized controlled trials confirmed an improved diagnostic yield for CE when PEG-based bowel preparations were used prior to capsule deployment (OR 3.11; 95 % CI = 1.96–4.94; p <0.0001)[11]. Interestingly, sub-group analysis did not demonstrate a benefit of Na-P preparations compared to fasting alone (OR 1.32; 95 % CI = 0.59–2.96; p < 0.0001). The volume of the bowel preparation required has also been evaluated. A prospective randomized study compared 2 and 4 l of PEG solution in 201 patients undergoing CE for gastrointestinal bleeding, abdominal pain or suspected CD. The 2-l preparation demonstrated equal efficacy to the 4-l preparation in terms of mucosal visualization, capsule completion rate and identification of small bowel pathology, suggesting the 2-l preparation was adequate for CE. [12] There is no standard method to report the quality of the small bowel preparation in capsule endoscopy. A score has been proposed using the proportion of mucosa visualized on images, and a quantification of the degree of obscuration of the mucosa by bubbles, debris or bile. [13] The inter-observer agreement of this method was excellent in one study (k = 0.8), although the system has yet to be

validated prospectively. To date, there is no consensus regarding the standard method to prepare the small bowel for CE, although expert consensus favors the use of some type of preparation.

CE in Suspected Crohn's Disease

Crohn's disease is a chronic inflammatory disorder that may affect any segment of the intestinal tract. Up to 90 % of patients will have involvement of the terminal ileum and colon at diagnosis or in follow-up, and ileocolonoscopy is adequate to make the diagnosis [14–16]. However, in a subset of patients, mural inflammation is confined to the proximal small intestine, out of the reach of the standard colonoscope. [4, 14, 17] To adequately evaluate for the presence of CD in this subgroup of patients, a more thorough assessment of the small bowel is required. Traditionally, small bowel follow-through (SBFT), occasionally augmented by push enteroscopy or ileoscopy has been utilized to evaluate for small intestinal disease. Unfortunately, SBFT has limited ability to detect mild mucosal inflammation found early in the course of CD, and in particular, for disease confined to the proximal small bowel [4, 18, 19]. Push enteroscopy and ileoscopy are limited in their scope, leaving the majority of the small bowel mucosa out of reach. This difficulty in evaluating the small bowel adequately likely explains in part the historical delay in the diagnosis of CD between 1 and 7 years from symptom onset [20, 21].

The advent of capsule technology has facilitated the evaluation of suspected small bowel CD, allowing for more thorough assessment of small bowel mucosa along the entirety of its length, including the segments previously inaccessible via push enteroscopy and ileoscopy (Fig. 7.2, Videos 7.1, 7.2, 7.3, and 7.4). The technology appears to have additional diagnostic yield of up to 70 % for CD isolated to the small bowel following a negative ileocolonoscopy [4, 18, 22]. In a study of 80 patients with suspected CD completing CE, SBFT and ileocolonoscopy, CE demonstrated superiority to SBFT in the detection of inflammatory lesions, with the combination of CE and ileocolonoscopy identifying 97 % of all inflammatory lesions, and SBFT and ileocolonoscopy detecting only 57 %. Of the patients diagnosed with CD, 55 % were diagnosed based on CE findings alone. [4] Ileocolonoscopy demonstrated similar diagnostic yield to CE for the identification of lesions in the terminal ileum and cecum. Whereas ileocolonoscopy detected most of the cecal inflammatory lesions, CE identified the majority of lesions confined to the terminal ileum, suggesting these two modalities are complementary in the evaluation of suspected CD, although the study recognized that ileocolonoscopy should be the first test in the evaluation of suspected CD (Fig. 7.3).

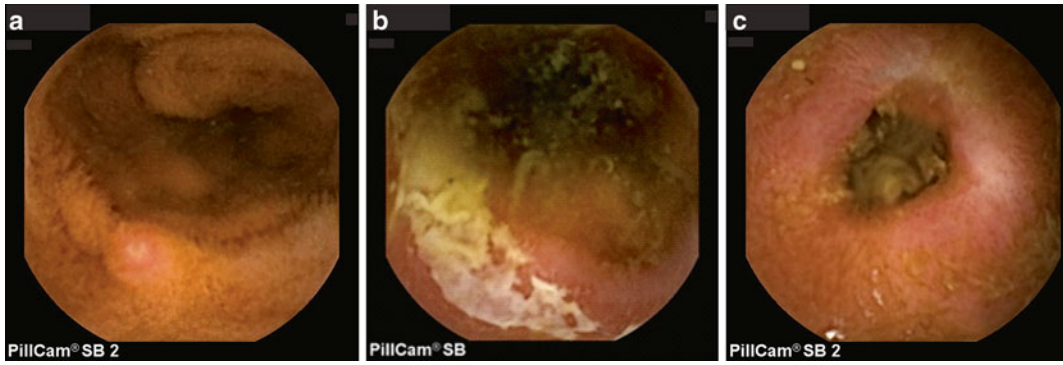

Fig. 7.2 Small bowel capsule endoscopy findings in inflammatory bowel disease. (**a**) aphthous ulcer; (**b**) ulcer with exudate; (**c**) small bowel stricture

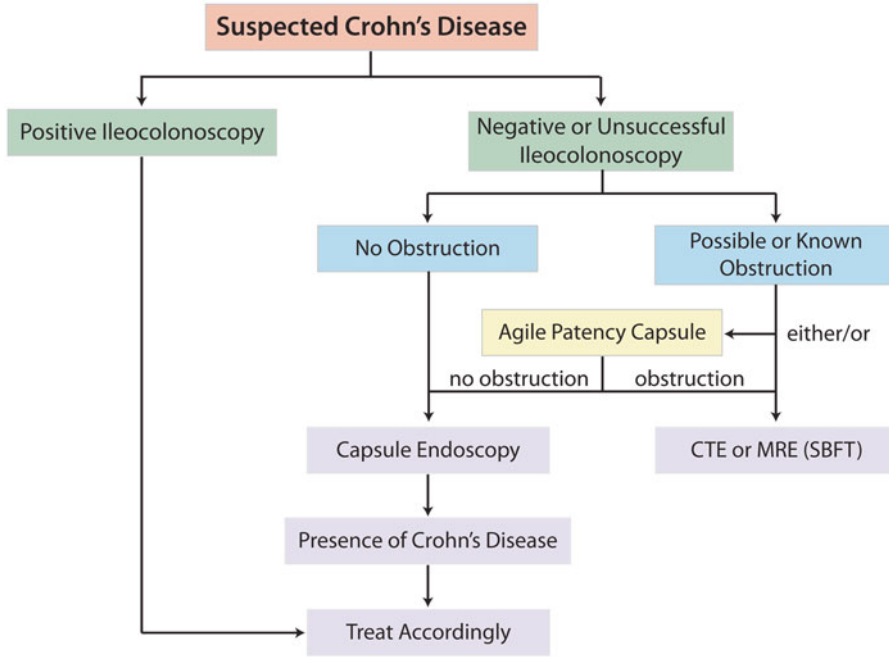

Fig. 7.3 Capsule endoscopy in the evaluation of suspected Crohn's disease. *CTE* computed tomography enterography, *MRE* magnetic resonance enterography, *SBFT* small bowel follow-through. Adapted from Mergerner K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, et al. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Endoscopy 2007; 39(10):895–909

Commensurate with the development of the video capsule endoscope has been the advancement in techniques of cross-sectional imaging, namely CT enterography (CTE) and MR enterography (MRE). Both modalities have demonstrated improved sensitivity for the detection of small bowel pathology, leading to multiple proposed algorithms in the evaluation of IBD. CTE and MRE have the advantage over CE of providing information regarding transmural inflammation, and the ability to detect the presence of extraluminal disease such as lymphadenopathy, abscesses or fistulae [17]. CE may be superior, however, in detecting superficial mucosal ulcerations found early in the course of CD. Another limitation to the use of CTE and MRE is the need for large volumes of oral contrast for adequate visualization of the small bowel, which may be difficult for patients with diminished oral intake or partial small bowel obstruction. In addition, small bowel wall thickening may be overestimated if the intestinal lumen is not adequately distended with oral contrast during the study. CTE is more widely available than MRE and is less expensive; however, CTE requires a considerable radiation exposure, which becomes a particular issue in younger patients who may require repeated examinations. MRE may have the advantage over CTE in the ability to differentiate in some instances between fixed fibrostenotic lesions and potentially reversible inflammatory strictures [23, 24]. The diagnostic yield of CE, CTE and MRE was compared in a meta-analysis of 12 trials involving 428 patients with suspected CD [22]. CE demonstrated incremental yield over that of SBFT (32 %, $p<0.001$, 95 % CI 16–48 %), ileocolonoscopy (22 %, $p=0.009$, 95 % CI 5–39 %) and CTE (47 %, $0<0.001$, 95 % CI 31–63 %). In this study, CE did not demonstrate clear superiority to MRE, although the number of patients in this subgroup were small ($n=31$). A subsequent study of 93

patients with suspected or newly diagnosed CD evaluated this issue further [25]. Patients underwent ileocolonoscopy, CTE or MRE, followed by CE if no evidence of stenosis was identified on the preceding endoscopic and radiographic studies. The sensitivity and specificity for the diagnosis of CD of the terminal ileum were 100 % and 91 % for CE, compared with 81 % and 86 % for MRE, and 76 % and 85 % for CTE. Of note, 25 % of patients were excluded from CE due to stricturing disease, suggesting that preceding small bowel radiography or use of a patency capsule in some instances may be warranted to reduce the risk of capsule retention.

One detractor from the yield of CE in IBD patients is the potential lack of specificity of some of the mucosal abnormalities identified, due to a lack of histology confirmation, and lack of diagnostic criteria to define CD by video capsule. Mucosal erosions and ulcerations may be associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and have been identified in asymptomatic individuals in the absence of IBD [26–28]. To improve the positive predictive value of CE findings in suspected CD, a thorough history including recent ingestion of NSAIDs should be taken. Other conditions associated with small bowel ulceration include celiac disease, infections, ischemia, autoimmune enteropathy, and lymphoproliferative disorders. Regarding diagnostic criteria to establish a diagnosis of CD on CE, Mow et al. proposed the criterion of three or more ulcerations, identified in the absence of NSAID use for CD diagnosis. Ulcers were further defined as "white lesions within a crater," with surrounding erythema, to be distinguished from erosions that were "white lesions with surrounding erythema" in the absence of mucosal depression [29]. The development of a validated scoring system of mucosal changes to diagnose small bowel CD may improve the specificity of CE in future study.

Capsule Endoscopy Scoring Systems

Two endoscopic scoring systems describing the severity of CD have been validated in ileocolonoscopy but not in CE. These include the Crohn's Disease Endoscopic Index of Severity (CDEIS) [30], which grades both ulcerations and stenosis, and the Simple Endoscopic Index of Severity (SES-CD)[31], which grades both ulcerations (depth and/or diameter) and luminal stenosis. For capsule endoscopy findings, there are two scoring systems available to describe the extent and severity of small bowel inflammation in CD. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) developed by Gal et al. in 2008 [32] measures inflammation on a 6-point scale ranging from hyperemia to large ulceration, extent of disease on a 4-point scale whether focal or diffuse, and the presence of one or more strictures, as identified in either proximal or distal small bowel segments. The score ranges between 0 and 36, the latter representing the most severe of disease activity [32]. The CECDAI has exhibited an excellent inter-observer agreement amongst reviewers ($k = 0.87$)[32] and has been validated in a multicenter prospective study [33]. The Lewis Index, in contrast, quantifies villous edema, mucosal ulceration, and luminal stenosis [34]. A score of < 135 was designated as normal or clinically insignificant, whereas a score of ≥ 790 was deemed to represent moderate to severe mucosal inflammation. In a retrospective study of 56 patients undergoing CE for suspected CD, only 12.1 % of patients with a score of <135 were diagnosed with CD, compared with 82.6 % of those patients with a score of ≥ 135 [35]. Both scores can be used to measure the degree of mucosal inflammation identified on CE, and therefore be used to describe severity of disease at initial diagnosis as well as evidence of mucosal healing following treatment. Although these scoring systems were devised to standardize CE reporting, their accuracy in measuring mucosal inflammation is not clear. A study comparing levels of fecal calprotectin (FC), an accepted marker of mucosal inflammation, [36] did not demonstrate good correlation between the CECDAI and FC, and the Lewis score only correlated for those patients in whom FC was low, that is, a low FC predicted a negative CE study [36, 37]. Higher levels of FC did not correlate with higher scores of inflammation on

CE [37, 38]. Theories regarding the discordant findings include a heterogeneous population of patients with only 12 patients ultimately diagnosed with CD, a significant delay between FC measurement and CE in some cases, and the fact that the scoring systems do include non-inflammatory findings such as luminal stenosis to characterize disease severity [38]. Another study comparing the CECDAI with levels of C reactive protein (CRP), another accepted serological marker of inflammation in IBD, demonstrated only fair correlation an r=0.58 is actually fairly good correlation ($r = 0.58$, $p < 0.01$). [39] At this time, it seems that the CECDAI and Lewis Scores may be tools with which to compare CE findings amongst patients and in single patients over time, although they may be a complement, rather than a replacement for other markers of inflammation. Also, it is important to note that these scores are not able to discriminate between etiologies of mucosal inflammation; i.e., differentiate CD from NSAID enteropathy.

Comparison of CE and Advanced Endoscopic Techniques

Endoscopic techniques to evaluate the small bowel have included push enteroscopy, ileoscopy, and, in more recent years, device-assisted enteroscopy. Push enteroscopy and ileoscopy are limited to the proximal jejunum and terminal ileum respectively,. The advent of device-assisted enteroscopy has provided the opportunity for complete endoscopy of the entire small bowel, although this modality requires particular expertise to perform, is time consuming, and often requires anesthesia assistance. In addition, usually two separate procedures are required, with antegrade and retrograde approaches to achieve complete endoscopic evaluation of the small bowel. CE, in contrast, is non-invasive, and offers a method to visualize the entire small bowel in one procedure. CE and double balloon enteroscopy (DBE) have comparable yields in diagnosing small bowel CD. One meta-analysis of 11 studies comparing CE and DBE in 375 patients with suspected small bowel disease measured a diagnostic yield of 57 % with CE and 60 % with DBE [40]. Detection of small bowel inflammation was also comparable, with diagnostic yield of 16 % with CE and 18 % with DBE. In cases of capsule retention, deep enteroscopy techniques may be utilized to retrieve the capsule. Deep enteroscopy also offers the opportunity for tissue diagnosis in patients with positive CE, or may be offered to those patients with suspected or documented small bowel strictures in whom CE is contraindicated. Of the two modalities, CE would be recommended as the initial test of choice in the evaluation of possible small bowel CD, as it is noninvasive and allows for complete endoscopy, followed by deep enteroscopy if needed to obtain tissue diagnosis, with antegrade or retrograde approach dictated by CE findings.

CE in Established CD

As an imaging modality with high sensitivity for small bowel inflammation, CE is complementary to standard ileocolonoscopy and upper endoscopy in the evaluation and management of patients with established CD, affecting medical and surgical decision-making. CE can assist in documenting the extent and severity of CD, particularly in patients with persistent or unexplained symptoms [29, 41]. In a prospective study of 28 patients with persistently symptomatic CD, CE identified active inflammation in 82 % of patients compared with only 49 % detected by ileocolonoscopy, demonstrating an incremental yield of 33 %[20]. In a second study of 108 patients with established CD who underwent CE and CTE, 56 % were noted to have jejunal ulcerations not identified on cross-sectional imaging. It is important to note that the presence of jejunal ulcerations in this group was the only risk factor to predict relapse during 6 months of follow-up, and the CE study led to a modification in treatment plan in 20 % of patients [42]. Dussault et al. [43] also described medical decision-making following CE in a prospective study of 71 CD patients. CE was associated with medication changes and/or surgical treatment in 54 % of patients in the 3 months

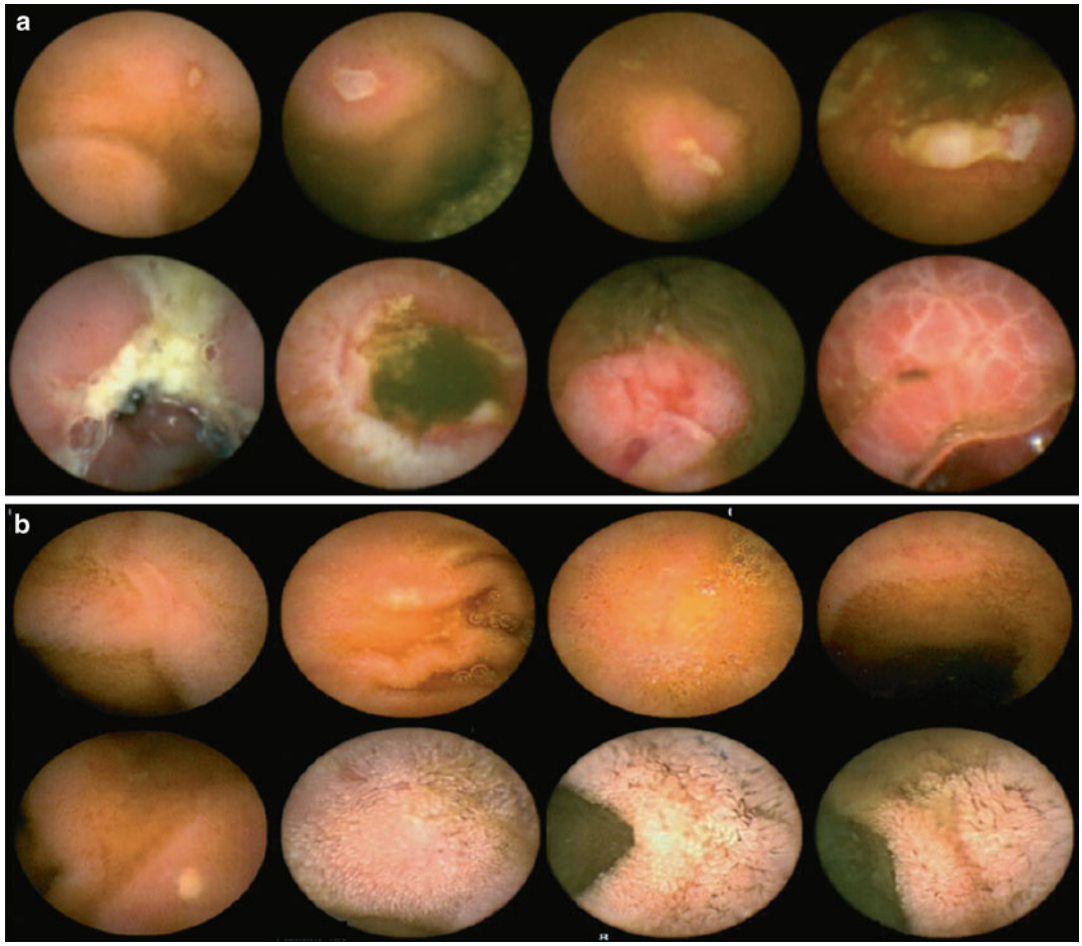

Fig. 7.4 (**a**) Capsule endoscopy images in inflammatory bowel disease. (**b**) Documentation of mucosal healing. Reprinted with permission from Calabrese C, Gionchetti P, Rizzello F, Liguori G, Gabusi V, Tambasco R, et al. Short-term treatment with infliximab in chronic refractory pouchitis and ileitis. Aliment Pharmacol Ther. 2008 May;27(9):759–64

following CE, lending support to the concept of CE as integral to the evaluation and continued management of patients with established CD.

In addition to describing the extent of disease, CE may be useful as well in assessing for mucosal healing once therapy has been initiated (Fig. 7.4) [6, 41, 44]. Legnani and Abreu [41] documented healing of small bowel mucosal ulcers following biologic therapy in a patient with established CD. In a prospective study of 40 patients presenting with a CD flare, Efthymiou et al. [45] demonstrated that CE performed before and after treatment was able to document a significant reduction in the number of large ulcers identified in the small bowel. Mucosal healing of large ulcers correlated with clinical improvement measures such as: the Crohn's Disease Activity Index (CDAI), the Inflammatory Bowel Disease Questionnaire (IBDQ), and C reactive protein (CRP) values in this study.

Lastly, CE offers a non-invasive alternative, or a complement to ileocolonoscopy in the evaluation of postoperative recurrence of CD. Endoscopic recurrence of mucosal inflammation has been reported in the neoterminal ileum in 73–93 % of patients within 1 year of ileocolonic resection for CD [46]. Endoscopic recurrence often predicts symptomatic recur-

rence, and may impact future treatment plans. [17, 47, 48] Traditionally, postoperative evaluation of CD patients involved ileocolonoscopy alone. CE has demonstrated increased yield compared to ileocolonoscopy in identifying postoperative recurrence of CD in the neoterminal ileum following ileocolonic resection [47, 48]. CE may be particularly useful in cases where the surgical anastomosis is not readily accessible by endoscopy.

It is important to note that CE is considered complementary to CTE or MRE in CD, which can visualize transmural inflammation, and extraluminal disease, such as the presence of abscesses or fistulae. In addition, the potential for capsule retention must be considered in those patients in whom small bowel stenosis is identified on radiographic imaging. In cases where stricturing disease is suspected, the patency capsule should be considered prior to capsule endoscopy.

Utility of CE in Cases of IBD Unclassified

Population-based studies have demonstrated that in 4–10 % of adult patients diagnosed with colonic IBD, a distinction between UC and CD cannot be made following standard ileocolonoscopy, biopsy, and small bowel radiology. [5, 49, 50] Establishing the correct diagnosis has important implications for both medical and surgical treatment options as well as expected prognosis. The term "indeterminate colitis," which was initially coined in 1978 to describe such patients in whom diagnosis remained unclear even following colectomy, has been replaced by the term "IBD unclassified (IBDU)" and refers to those patients in whom inflammation is confined to the colon but unclear as to phenotype following the standard evaluation described previously [5, 51]. By providing direct visualization of the entire small bowel, CE may play a role in further defining extent of mucosal involvement in IBDU, ruling out small bowel involvement in cases suggesting UC, or identifying small bowel ulcerations and consistent with underlying CD. [17] Several small studies have demonstrated CE as providing additional information to distinguish CD from UC [29, 52–54]. These studies demonstrated small bowel findings on CE, which changed the diagnosis in 29–40 % of patients [3]. It is important to note, however, that a negative CE does not preclude a future diagnosis of CD. In one study of 25 patients with IBDU and a negative CE, five patients were eventually diagnosed with CD in follow-up. [53]

CE in Ulcerative Colitis

In up to 10–15 % of cases, a change in diagnosis from UC to CD or vice versa is made within the first year [5]. CE may be instrumental in identifying mucosal ulceration of the small bowel, reclassifying patients from UC to CD. Specifically, there are data to support the use of CE in cases of severe, refractory UC prior to planned colectomy, to rule out underlying CD [5]. In one study of patients with UC who underwent CE, up to 61 % of patients (one of whom had an ileal-anal anastomosis) demonstrated findings suggestive of CD [29].

The utility of CE in UC patients planned for surgical management is less clear, however, than has been demonstrated in CD patients. Whereas preoperative small bowel inflammation detected on CE has been found to be an important predictor of pouch outcomes in CD patients, preoperative CE in UC and IBDU patients relegated to colectomy and ileal-anal pouch anastomosis did not appear to predict pouchitis or pouch dysfunction in such patients [55]. Further prospective studies will be required to determine the significance of small bowel findings in UC patients.

Colon Capsule Endoscopy in UC

Mucosal healing in UC is now considered a treatment goal in addition to symptom resolution as documented mucosal healing has been associated with reduced rates of relapse, hospitalization and future need for colectomy [56–59]. In 2006, a capsule endoscope to image the colonic mucosa was developed (PillCam Colon, Given Imaging

Ltd., Yoqneam, Israel). Similar to the small bowel capsule endoscopes described previously, the PillCam Colon is a video capsule equipped with two color video cameras, a battery and a light source, which has the ability to transmit 4 or 35 frames per second for up to 10 h to a recording device worn by the patient. Initially, the colonic video capsule endoscope was devised to screen for colonic neoplasms. However, the PillCam colon has been studied in ulcerative colitis patients as well, to measure its accuracy in detecting colonic inflammation, as compared to the gold standard of colonoscopy [60]. A multicenter, prospective study of 100 UC patients demonstrated a sensitivity and specificity of 89 % and 75 % respectively for colonic inflammation compared with standard colonoscopy. The high sensitivity and positive predictive value suggested the colon video capsule could be used to diagnose UC, however, the relatively low specificity and negative predictive value of only 65 % suggested that CCE could not reliably rule out active disease, and therefore could not be recommended to replace colonoscopy in the diagnosis and follow-up of UC. A second-generation colonic video capsule has been devised with a wider angle of vision and an adjustable frame speed depending on colonic transit, which may improve the capsules specificity. Future study is required to determine whether the new PillCam Colon capsule can adequately monitor patients for mucosal healing in ulcerative colitis.

Pediatric IBD

Similar to figures described in adult populations, up to 38 % of children with IBD will have disease isolated to the small bowel [61]. The number may be higher as this figure is based on conventional ileocolonoscopy and radiographic testing. The impact of small bowel inflammation in the pediatric population has important implications for both growth and development [62]. As a non-invasive imaging test of the small bowel, CE has held particular promise in the evaluation of such patients. A prospective study of 20 pediatric patients, aged 10–18 in whom CD was suspected, but IC and SBFT were negative or non-diagnostic, CE demonstrated a diagnostic yield of 60 % in the identification of small bowel inflammatory lesions [8]. In comparison, IC and SBFT were normal in 15 patients, and with non-diagnostic findings in five patients. Patients tolerated the procedure, with only one patient demonstrating some difficulty in swallowing the capsule. There was one case of asymptomatic capsule retention at 10 days, managed with 5 days of oral steroid, followed by capsule excretion. In a prospective cohort study of 18 pediatric patients with CD, UC, indeterminate colitis or suspected CD, capsule endoscopy led to the reclassification of 50 % of the UC and IC patients as having small bowel CD and 80 % of the suspected CD patients as having CD based on small bowel ulcerations identified on CE. Of those patients with established CD, 50 % were noted to have more proximal small bowel mucosal inflammation than previously identified. In addition to reclassifying patients and documenting extent of disease, CE led to medical management changes in 14/18 (77.8 %) of patients. No adverse events were reported [63]. In a retrospective study of 83 patients with established CD (n = 50), UC or IBDU (n = 16) and suspected CD (n = 17), capsule endoscopy led to a change in management in 64 % of patients with established or newly confirmed CD [62]. Half of the patients with UC or IBDU were reclassified as having CD. Importantly, CD was ruled out in 16 of 17 patients with suspected IBD.

Potential Risks

Capsule Retention

Although capsule endoscopy is considered safe in the vast majority of patients, the risk of capsule retention remains a concern, particularly in a patient population at risk for luminal narrowing in the setting of IBD. The international Conference on Capsule Endoscopy (ICCE) working group has defined capsule retention as the persistence of the capsule in the digestive tract for more than 2 weeks, necessitating medical,

endoscopic or surgical intervention. [64, 65] The incidence of capsule retention reported in the literature varies considerably based on study indication. For those patients undertaking CE for known or suspected CD, capsule retention has been reported to range from 1.4 % up to 13 % [3, 64, 66]. In the pediatric literature, one prospective trial of CE in patients with suspected CD observed capsule retention in 20 % of patients (2 of 10), however, in both cases the capsule passed spontaneously following treatment with oral steroids [8]. It is important to note that patients with obstructive symptoms were often excluded from the early studies, and that the majority of patients had a negative SBFT prior to capsule ingestion [29, 64]. Capsule retention is most commonly due to small bowel strictures caused by CD, diaphragm disease in the setting of non-steroidal anti-inflammatory (NSAID) use, and luminal narrowing in cases of radiation enteropathy. Less commonly, capsule retention is associated with small bowel tumors, prior surgery, and diverticular disease of the small bowel [3, 67]. To date, no long-term sequelae of capsule retention have been reported.

Once diagnosed, options to manage capsule retention include medical management, endoscopic retrieval, and/or surgery. In cases of small bowel stricture, capsule retention may help localize the pathology previously undetected by radiographic means, allowing for a targeted surgical intervention. [64, 65] To reduce the risk of capsule retention, practice guidelines suggest screening patients with abdominal pain or other signs of bowel obstruction with radiographic studies prior to deployment of the capsule [65]. Initially, SBFT was utilized for this purpose; however, multiple studies have demonstrated that SBFT cannot reliably identify those patients at risk for capsule retention [68–70]. In one multicenter review of 733 CE studies, capsule retention was noted in 14 patients despite a preceding normal SBFT [70]. Conversely, Spada et al. [71] demonstrated normal passage of the video capsule in ten patients with radiographically confirmed strictures. Cross-sectional imaging with CTE or MRE, which are particularly useful in identifying luminal stenosis, may be obtained prior to CE to identify those patients at increased risk for capsule retention. Another option to assess for risk for capsule retention is the use of a dissolvable patency capsule, devised for this purpose (PillCam Patency Capsule, Given Imaging, Yoqneam, Israel) [3, 67, 68, 72]. The patency capsule is comprised of a body of lactose and barium, with two side timer plugs with exposed windows. Inside the capsule there is a radiofrequency identification (RFID) tag that can be detected by an external, hand-held RFID scanner included with the system. The pill is designed to disintegrate 30 h after ingestion. If the patient witnesses elimination of the capsule, or if the scanner does not detect the RFID tag, passage of the capsule is assumed, and CE may proceed. In a retrospective study of 42 patients with known or suspected small bowel strictures, the patency capsule exhibited a 91 % negative predictive value for small bowel obstruction and risk of capsule retention [73]. A second study of 106 patients ingesting the patency capsule prior to CE demonstrated a capsule retention rate of zero, when only those patients excreting the patency capsule were selected for capsule endoscopy [68]. Rare complications related to the patency capsule, such as transient intestinal occlusion and abdominal discomfort have been reported [3, 68, 74]. Overall, the patency capsule appears to be safe in the assessment of small bowel strictures prior to deployment of the CE.

Pacemaker Interference

CE uses radiofrequency waves to submit camera images to a data recorder, posing a theoretical risk of interference between the capsule, the data recorder, and implantable electronic devices (IEDs), such as permanent pacemakers (PMs) and implantable cardiac defibrillators (ICDs). Based on this concern, the US Food and Drug Administration (FDA) and the manufacturer (Given Imaging, Yoqneam, Israel) have listed IEDs as a relative contraindication to CE [6, 75]. A number of studies have evaluated the safety of CE in such patients [75–77]. Data from a retrospective study of 118 capsule endoscopies performed in 108 patients (74 with a PM, 30 with

an ICD ± PM, and 8 with an LVAD) demonstrated no alteration of IED function, and no cardiac arrhythmia associated with CE [76]. Of the video capsule studies listed previously, a brief lapse in capsule image acquisition (less than 2 min) was noted in only two cases. Both patients had LVADs implanted, and CE image capture failure occurred briefly when the capsule was in the upper abdomen close to the LVAD device. Patients were asymptomatic during CE, and no adverse outcomes were reported. The combined experience of such studies suggests that CE is in fact safe to perform in patients with IEDs.

Discussion

The diagnosis of inflammatory bowel disease in general and small bowel CD in particular, can be challenging. In the majority of cases, ileocolonoscopy is diagnostic in the setting of typical clinical symptoms and associated laboratory abnormalities. In cases where ileocolonoscopy is negative, but suspicion for IBD remains, further evaluation is warranted. Prior studies of SBFT indicate a limited diagnostic accuracy in the identification of small bowel mucosal lesions found early in the course of CD. In such patients, CTE or MRE provide improved diagnostic yield, identifying mural enhancement, stricturing, abscess formation or lymphadenopathy. If no obstructive symptoms are present, CE may be a more sensitive test for the presence of the more subtle mucosal ulcerations, particularly in the proximal small bowel. CE should be considered complementary to cross-sectional imaging in such patients [78]. A negative CE has a high negative predictive value for small bowel CD, and can complete an initial evaluation for IBD. In addition to its integral role in the adult patient population, CE may play a particularly useful role in pediatric practice, where limiting invasive procedures and radiation exposure is paramount. CE has demonstrated utility in monitoring established CD as well, documenting mucosal healing with medical therapy, and evaluating for early recurrence following surgery, in a manner that may impact future medical management decisions (Table 7.2). One risk to the use of the video capsule endoscope is the risk of capsule retention. In those patients deemed to be at particularly high risk due to known or suspected structuring disease, a patency capsule study may be considered to identify those patients in whom CE may be safely pursued. Overall, CE has proven to be a safe and useful tool in the armamentarium to diagnosing and monitoring patients with IBD.

Table 7.2 Indications for capsule endoscopy in inflammatory bowel disease

Evaluate for small bowel CD following negative ileocolonoscopy and SBFT when clinic suspicion for CD is high based on symptoms, and serological testing
Evaluate extent and severity of small bowel involvement in established CD
Monitor disease activity or document mucosal healing in established CD
Evaluate for postoperative recurrence of CD
Further classify IBDU
Evaluate the small bowel in patients with severe UC prior to colectomy
Evaluate for small bowel disease in Pediatric patients with established or suspected CD

Modified from DeMelo SW Jr, Di Palma JA. The role of capsule endoscopy in evaluating inflammatory bowel disease. Gastroenterol Clin North Am. 2012 Jun;41(2):315–23

CD Crohn's disease, *IBDU* Inflammatory bowel disease unspecified, *UC* ulcerative colitis

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8 Balloon-Assisted Enteroscopy: Techniques, Diagnostic and Therapeutic Yield and Application in Small Bowel Crohn's Disease

Gary R. May

Equipment and Techniques

Traditional push enteroscopy with a dedicated enteroscope or small caliber colonoscopes allowed only limited access to the small intestine and therefore had a small role in patients with IBD, with the exception of patients with duodenal or very proximal jejunal Crohn's disease. The advent of balloon-assisted enteroscopy has allowed deeper access into the small intestine and provides the ability for both diagnostic assessment and therapy of small intestinal pathology.

Two systems are currently available for balloon-assisted enteroscopy. Double balloon enteroscopy (DBE) uses the double balloon enteroscope (DBE) developed by Fujinon. This is a 200 cm scope with a 140 cm overtube, both the scope and overtube have an inflatable latex balloon fitted to the distal tip (Fig. 8.1). There are two scope sizes: an 8.5 mm insertion tube diameter with a 2.2 mm working channel (EN-450p5/20) and a 12 mm outer diameter overtube, and a slightly larger scope with a 9.4 mm insertion tube diameter and a 2.8 mm working channel (EN-450T5) that uses a 13 mm outer diameter overtube. The balloon inflation for both the scope and overtube is controlled with a balloon pump controller (pb-20). The balloon pump controller inflates and deflates the balloons and ensures the pressure within the balloon does not exceed 6 kPa. Single balloon enteroscopy was developed by Olympus (SIF-Q180) and the single balloon enteroscope is a 200 cm instrument with a 9.2 mm outer diameter and 2.8 mm working channel (Fig. 8.1). The overtube is 132 cm and has a silicone rubber balloon on its distal tip and an outer diameter of 13.2 mm. The scope does not have a balloon. There is also a control unit that, like the double balloon system, controls inflation and deflation of the balloon, ensuring the balloon inflation pressure does not exceed 5.4 kPa.

The technique for double balloon enteroscopy was developed by Dr. Hironori Yamamoto in Japan and was initially described in 2001 [1]. It consists of a series of push and pull maneuvers where the endoscope is advanced through the overtube as far as possible. The balloon on the scope is then inflated, anchoring the tip of the scope inplace. The overtube is then advanced to the end of the enteroscope and the overtube balloon inflated. With both balloons inflated, the scope and overtube are pulled back, pleating small bowel over the system. The scope balloon is then deflated and the scope tip advanced. This series of maneuvers is repeated as the scope is advanced into the small bowel. With single

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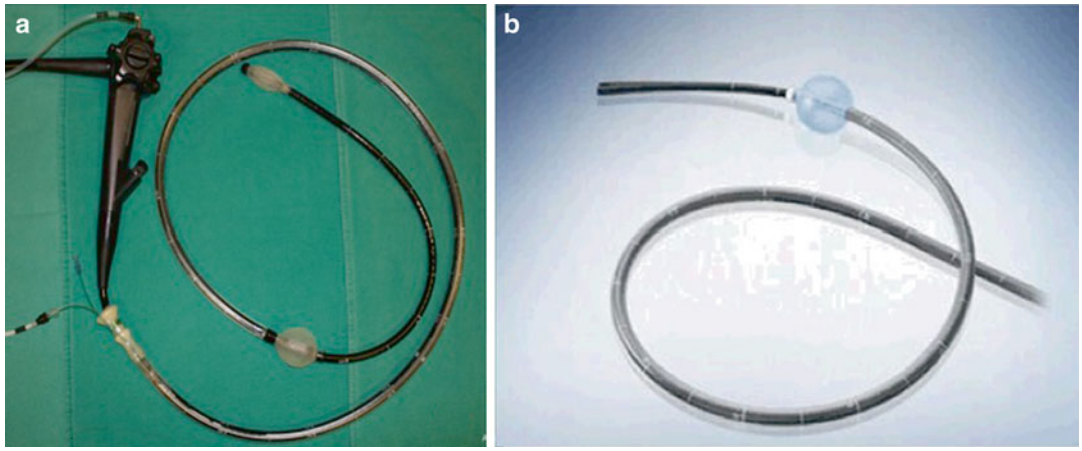

Fig. 8.1 (**a**) Double balloon enteroscope. (**b**) Single balloon enteroscope

balloon enteroscopy there is only the overtube balloon to anchor the system and techniques of suctioning and tip deflection are used to help anchor the tip while maneuvering the overtube and shortening [2].

Both DBE and SBE can be performed via the oral (antegrade) or rectal (retrograde) approaches and thus allows for assessment of a significant portion of the small intestine. In general, both approaches are required to achieve a total enteroscopy as it is rare to be able to traverse the entire small intestine from the oral route alone [3]. Reported total enteroscopy rates using a combined approach range from approximately 18–92 % for DBE [4–7], with an average of 44 % reported in a recent systematic review [3]. DBE has been compared to SBE in two randomized trials showing discordant results: with the trial reported by Domagk et al. showing no difference between DBE and SBE in 130 patients [7] while the trial reported by May et al. showed a total enteroscopy rate three times higher in the DBE group in 100 patients. The diagnostic yield was similar between both groups in this study [6]. Overall, the consensus is that double balloon does offer some advantage over single balloon enteroscopy in the potential depth of insertion.

The choice of the antegrade or retrograde route in part depends on the indication and anticipated location of the pathology. The procedures are usually done under conscious sedation, although general anesthesia has been used in many series. The choice of sedation does not appear to influence the outcome of the procedure and should be tailored to what is most appropriate for the patient. For both DBE and SBE, estimated depths of insertion for the antegrade route are approximately 2.5–2.7 m and retrograde 1.3–1.9 m [2, 8], although ranges vary widely. Average procedure times are in the range of 60–90 min for either approach and it is recommended that the retrograde study not be done on the same day as the antegrade study [9]. Bowel preparation is only required for patients undergoing retrograde studies and it is important to ensure a very good bowel preparation as residual debris can cause undue friction between the scope and overtube making smooth advancement of the scope difficult [9].

Indications for Deep Enteroscopy in Crohn's Disease

Diagnostic Indications

Our ability to evaluate small intestinal Crohn's disease has improved dramatically over the last few decades with the advent of wireless capsule endoscopy, computed tomography (CT) and magnetic resonance (MR) enterography. Although wireless capsule endoscopy (WCE) has been shown to be accurate in defining small bowel Crohn's disease, it is not feasible because

Table 8.1 Indications for deep enteroscopy in patients with known or suspected IBD

Diagnostic indications
• Biopsy of abnormal small intestine in patients with suspected Crohn's disease and abnormal imaging
• Assess abnormal small intestine in patients with known Crohn's disease not responding to therapy
• Assess response to therapy in patients with isolated small intestinal Crohn's disease
• Evaluate obscure bleeding in patients with known Crohn's disease
Therapeutic indications
• Stricture assessment and dilatation
• Treatment of small intestinal bleeding
• Retrieval of retained wireless video capsules

of the risk of capsule retention in up to 40 % of patients [10, 11]. It also does not allow for tissue sampling in cases where the diagnosis is unclear. Several groups have tried to define the role of these various modalities and have published recommendations on their use in Crohn's disease [12, 13]. The role of deep enteroscopy remains to be precisely defined in patients with Crohn's disease, but it does have a role both for diagnosis and therapy in selected patients. Recent consensus guidelines suggest it be used when biopsies are required from suspected involved areas or for dilating strictures when these areas cannot be reachedwith standard endoscopes [14, 15]. A summary of possible indications in listed in Table 8.1.

From a diagnostic standpoint deep enteroscopy should be considered in patients with suspected Crohn's disease who have abnormal small bowel imaging and negative gastroscopy and/or ileo-colonoscopy. In this situation the results may help to confirm a diagnosis of Crohn's disease or rule out other possible infectious or neoplastic conditions. In patients with known Crohn's disease, it can be used to directly evaluate abnormal areas identified on small bowel studies when this information is needed to aid in decision-making regarding changes in therapy or to rule out other mucosal complications such as lymphoma. Repeat examination can help to evaluate for mucosal healing and response to therapy, as CT and MR enterography are not sensitive for the evaluation of mild disease [16–18]. Deep enteroscopy has also been used to evaluate obscure bleeding in

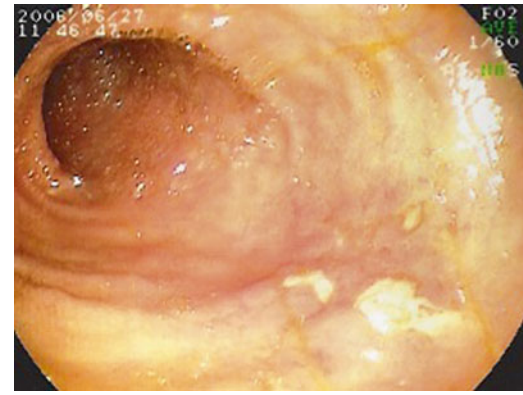

Fig. 8.2 Antegrade DBE showing an isolated Crohn's ulcer in the mid-jejunum

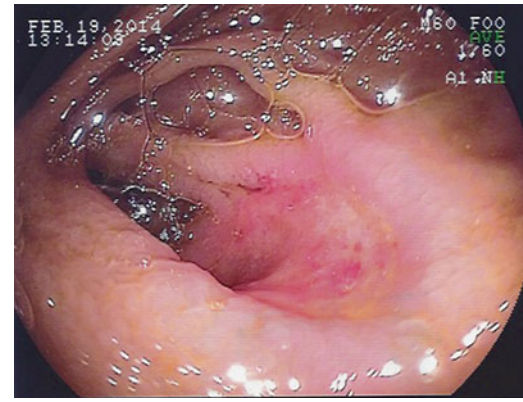

Fig. 8.3 Retrograde DBE showing an anastomotic ulcer in the mid-ileum

patients with known Crohn's, with reported diagnostic yields of approximately 40 % [19]. A variety of mucosal findings have been described with deep enteroscopy in patients with Crohn's disease and include erosions, apthoid ulcers, round and longitudinal ulcers, cobblestoning, strictures and tumors [20] (Figs. 8.2, 8.3 and 8.4).

Several authors have examined the clinical impact of deep enteroscopy in patients with Crohn's diseaseand have found that the findings at enteroscopy have a diagnostic yield ranging from 44 % to 77 % [19, 21]. Results of deep enterosopy can lead to changes in therapy in up to 75 % of patients [16, 22]. The diagnostic yield appears to vary depending on the indication of the deep enteroscopy, with Manes et al. reporting a diagnostic yield of DBE at 40 % for evaluation

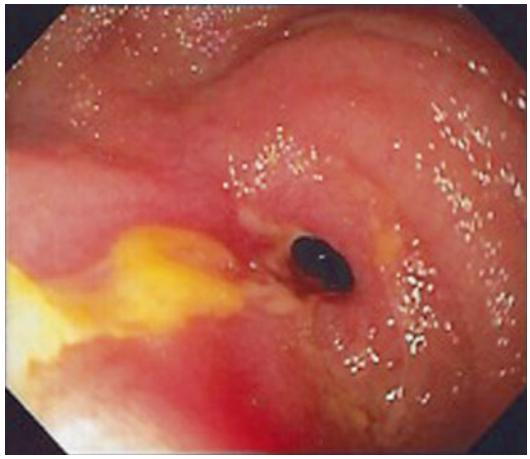

Fig. 8.4 Retrograde DBE showing a fibro-stenotic stricture

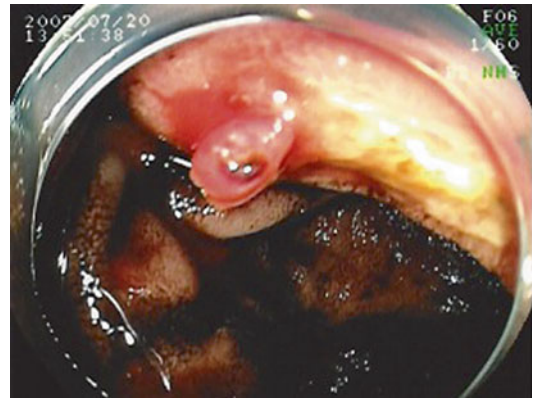

Fig. 8.5 Antegrade DBE showing an anastamotic ulcer with visible vessel

of obscure bleeding compared to 50 % for diagnosis of small bowel lesions and 100 % for the evaluation of small intestinal strictures in patients with Crohn's disease [19]. One study used DBE to confirm mucosal healing after stepping up therapy in patients with isolated small bowel Crohn's [16].

Therapeutic Indications

Balloon dilatation of strictures in Crohn's disease has been shown to be an effective alternative to surgery, with a systematic review showing technical success in 86 % and long-term clinical success in 58 % of reported patients [23]. Although the majority of strictures in patients with Crohn's disease are ileo-colonic in location, a small percentage of Crohn's patients will have strictures isolated to the small bowel and deep enteroscopy provides a means to endoscopically access these strictures and perform through-the-scope (TTS) balloon dilatation. The technique for balloon dilatation has been outlined by Sunada et al. [20]. Fluoroscopy should be used to guide the dilatation. Once the stricture is reached by balloon enteroscopy, if the scope cannot be passed through the stenosis, it is helpful to inject contrast through the scope to outline the stricture and bowel beyond. A guidewire should then be passed beyond the stricture and the balloon subsequently positioned using both endoscopic and fluoroscopic guidance. Initial dilatation size should depend on the severity of stricture, but in general, most authors have dilated to 15–18 mm. For very tight strictures, an initial dilatation of 10–12 mm is recommended, which can then be enlarged to 15–18 mm at a subsequent procedure (Video 8.1). The end point primarily depends on the patient's clinical response. Several centers have reported their results for stricture dilatation in patients with Crohn's disease. Approximately 20–30 % of patients referred for stricture dilatation are not candidates either due to failure to reach the stricture or because the strictures are long or predominantly inflammatory in nature [24]. For those patients in whom dilatation is technically possible, the clinical success ranges from 68 % to 79 %, with approximately 25–35 % of patients requiring a second dilatation [24–26]. Complications have been minimal, with only one reported perforation after DBE balloon dilation in a series of 11 patients [25].

Deep enteroscopy can also be used to treat obscure bleeding in patients with Crohn's disease. Bleeding can result from Crohn's ulcers, anastomotic ulcers or unrelated vascular lesions. Similar to obscure bleeding for other indications, bleeding can be treated with Argon plasma coagulation, endoscopic clips or injection therapy (Figs. 8.5 and 8.6). There is no data on the outcomes of treatment of bleeding using deep enteroscopy, specifically in patients with Crohn's

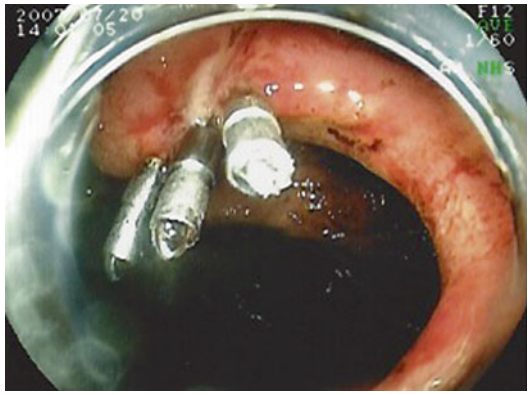

Fig. 8.6 Antegrade DBE showing clips on the ulcer from Fig. 8.5

disease. In unselected patients with bleeding vascular lesions of the small intestine, DBE has been reported to have an initial success of 97 %, with a 46 % rebleeding rate at 36 months [27]. Re-bleeding rates in patients with Crohn's disease would likely be higher and depend on the etiology of the bleeding and if other treatment is available to address the underlying disease (Video 8.2).

Deep enteroscopy has been used to successfully retrieve retained video capsules in patients, some of whom have had Crohn's disease strictures as the cause for the capsule retention [28]. This is usually done via an antegrade approach in patients with symptomatic obstruction since they cannot be properly prepped for a retrograde procedure. Patients with capsule retention without bowel obstruction who can tolerate a bowel preparation can undergo either approach depending on the location of the retained capsule. Stricture dilatation may be necessary to reach the capsule.

Complications of Balloon-Assisted Enteroscopy

The deeply invasive nature of balloon-assisted enteroscopy does appear to confer a slightly higher complication risk compared to standard colonoscopy or push enteroscopy. There have been several large series looking at complications of balloon-assisted enteroscopy and these document overall complication rates ranging from 0.6 % to 1.6 %. A systematic review of diagnostic DBE reported a minor complication rate of 9.2 % (95 % CI, 5.2–14.0 %) and a major complication rate of 0.72 % (95 %CI, 0.56–0.90 %)[3]. The commonest serious complications were bleeding (0.2–0.3 %), perforation (0.2–0.4 %) and pancreatitis (0.2–0.3 %) [29–31].The risk of pancreatitis is felt to be due in part to inflation of the balloons in the duodenum and this risk can be reduced by using a careful technique where the balloons are not inflated until the scope and overtube are beyond the ligament of Treitz [32].

Complication rates are higher after therapeutic procedures, with the risk of bleeding or perforation being reported as high as 4.3 % [29]. A series from Germany of endoscopic interventions performed with DBE procedures suggested that polypectomy carried the highest risk of perforation overall: 10.8 % in 46 patients with 4.3 % having bleeding and 6.5 % perforation. All of these complications occurring in patients with polyps greater than 3 cm [33].

Series of balloon-assisted enteroscopy specifically in patients with Crohn's disease have not reported many complications. To date there have been only two reported perforations: one occurred during a diagnostic study in a series of 53 DBE examinations of patients with Crohn's disease (1.8 %) [34] and a second perforation occurred following balloon dilatation of a Crohn's stricturein a series of 13 DBE procedures with stricture dilatation (7.7 %) [25].This is similar to the reported perforation rates of 1.6–11 % in patients having colonoscopic balloon dilatation of Crohn's strictures [35, 36]. There is a suggestion from a large American series that perforation risk may be higher with the retrograde approach in patients having previous colonic resections. These authors documented a perforation rate of 10 % in this subgroup of patients [30]. Even though reported complications are rare in the reported series of deep enteroscopy in patients with Crohn's disease, given that Crohn's patients are more likely to have had previous surgery and undergo retrograde studies due to the location of their disease, they may have a higher risk of perforation.

Conclusion

Deep enteroscopy with balloon-assisted enteroscopy or spiral endoscopy (see Chap. 9) offers an opportunity to access a part of the intestinal tract that traditionally has not been accessible. The optimal role of these techniques is yet to be determined, but they do offer an option for the direct assessment of the small intestine when other techniques are unable to provide the necessary information or for the treatment of small intestinal complications of Crohn's disease. The preliminary evidence suggests that this can be done successfully with a complication rate that is slightly higher than standard endoscopy in this patient population.

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9 Spiral Enteroscopy: Technique, Diagnostic and Therapeutic Yield and Application in Small Bowel Crohn's Disease

Michael Chiorean

Background, Instruments, and Technique

Spiral or rotational enteroscopy is a device-assisted technique for the endoscopic evaluation of the small bowel. It applies the same principle of pleating the small bowel as the double- and single-balloon enteroscopy (see Chap. 8). However, instead of sequential push-pull maneuvers, it uses a rotational spiral overtube similar to a corkscrew in order to convert rotational motion into linear force that will fold the small bowel, thus "advancing" an endoscope that is threaded through the overtube [1]. The procedure can be performed either anterograde or retrograde using two different overtubes. The anterograde overtube has an overall length of 118 cm, outer diameter of 14.5 mm, internal diameter of 9.8 mm, spiral height 5.5 mm and spiral length 22 cm (Fig. 9.1). The retrograde overtube is shorter at 100 cm, has a larger external and internal diameter (18 mm and 13 mm respectively) and a shorter spiral length (20 cm) (Fig. 9.2) (Spirus Medical LLC, West Bridgewater, MA). Both devices are single use, latex free, and can accommodate a variety of small bowel enteroscopes and some pediatric colonoscopes.

Two operators are usually required to perform the spiral enteroscopy technique given the fact that both the overtube and the instrument have to be manipulated during the procedure. The overtube is installed on the enteroscope using an interlocking device, which can switch between a longitudinal (advance-withdrawal) and rotational axis of freedom for the scope within the overtube. The procedure can be performed with moderate sedation, monitored anesthesia care (deep sedation) or with general anesthesia depending on patient, indication and operator variables. If general anesthesia is used for anterograde procedures, it is advisable to deflate the endotracheal balloon while the spiral is advanced through the upper esophagus to avoid trauma. Infrequently, in patients with significant cervical spine disease or cervical osteophytes, the overtube cannot be advanced past the upper esophagus and an alternative enteroscopy method has to be employed [2]. Once past the upper esophageal sphincter, the fixed overtube-enteroscope unit is carefully advanced through steady rotation through the stomach into the duodenum, keeping in mind the possibility of occult strictures. Non-obstructive esophageal Shatzki's rings are usually inconsequential, but strictures less than 15 mm in diameter should be traversed with caution. Once the overtube engages the pylorus and duodenum, the scope-overtube unit usually advances fairly easily with steady clockwise rotation into the small

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Fig. 9.1 The anterograde Spirus EndoEase Discovery SB overtube utilized primarily for anterograde deep enteroscopy. The same overtube can be used for retrograde procedures but only with a small bowel enteroscope. Reprinted with permission of Spirus Medical LLC

Fig. 9.2 The retrograde Spirus EndoEase Vista overtube is shorter and wider than its anterograde counterpart. It can be used with all small bowel enteroscopes as well as some pediatric colonoscopes with diameter<11 mm. Reprinted with permission of Spirus Medical LLC

bowel. When the entire effective part of the overtube has been inserted in the patient and rotational advancement stops or when the operator encounters unusual rotational resistance, the unit can be unlocked again and the scope advanced independently in the small bowel to the maximal point of insertion or until pathology is found.

For the retrograde approach, the overtube serves primarily to "splint" the endoscope (usually an enteroscope) during insertion into the colon and avoid looping (Fig. 9.3). The retrograde spiral overtube can rarely be engaged through the ileocecal valve. Instead, in a relatively straight configuration and under favorable valve orientation, the enteroscope itself can be advanced relatively easily in the ileum (Video 9.1). In a small study, the terminal ileum was intubated in 100 % of patients and the depth of insertion past the ileocecal valve was estimated at 100 cm (range 50–150 cm) [3]. Controlled visualization and, on a case-by-case basis, endoscopic therapy occurs during system withdrawal, which is essentially the reverse of the process described previously (i.e., counter-clockwise rotation of the overtube with the scope either in "locked" or "free" position to allow a more nimble handling of the scope as well as diagnostic and therapeutic interventions). In order to increase the traction of the overtube on the small bowel, only the minimum amount of gas (air or CO_2) is insufflated during advancement. A more detailed description of the procedure is available [1].

Fig. 9.3 The retrograde Spirus Vista overtube assembled on a 250 cm enteroscope. Note that the distal 20 cm of the scope are extending outside of the overtube during insertion to allow mobility of the scope and avoid excessive tension on the bowel wall. Some endoscopists prefer to have the overtube withdrawn all the way to the scope hub when they introduce the instrument through the rectum. After the scope is introduced for at least 60–70 cm, the colon loops are straightened and the overtube is advanced through the anus by gentle rotation while the colon lumen is kept in the field of view of the scope. Reprinted with permission of Spirus Medical LLC

Technical Success

The technical success rate defined as the ability of the instrument to advance past the proximal jejunum in patients with normal anatomy is approximately 95 % [2]. The most common reasons for failure are luminal strictures, abnormal or unusual anatomy (J-shaped stomach or narrow duodenal sweep) and anesthesia instability [2]. The depth of insertion is on average 200–250 cm post-pyloric (range 10–600) and likely corresponds to the limit between the distal jejunum and proximal ileum, although these measurements have not been adequately validated [2, 4–6]. No clear predictors of the depth of insertion have been identified, although this is an important aspect of these procedures [7]. The average time to reach the maximum depth of insertion is variable but in general it is shorter than either single- or double-balloon enteroscopy [8–10]. Akerman et al. reported an average insertion time of 18.7 min and total procedure time of 29 min [4]. In the US multicenter trial, the maximal extent was reached in an average of 22.1 ± 11.5 min, whereas the mean total procedure time for diagnostic studies was 34.4 ± 10.1 min and 11.4 min longer (range 0–73 min) for therapeutic procedures [2]. However, the depth of insertion and the rate of complete or pan-enteroscopy achieved with spiral enteroscopy appears to be inferior to that of double-balloon enteroscopy (DBE). In a small study using a combined anterograde and retrograde approach, pan-enteroscopy was accomplished in only 8 % of patients using spiral enteroscopy versus 92 % with DBE [10]. The learning curve with this system seems to be relatively quick. A selected group of experienced gastroenterologists were able to acquire the skills for spiral enteroscopy with fewer than 10 procedures in a dedicated training environment [11].

Diagnostic and Therapeutic Yield

The diagnostic and therapeutic yield of spiral enteroscopy in non-IBD patients is similar to other device-assisted deep enteroscopy techniques. Significant small bowel abnormalities are found in 33–75 % of symptomatic patients [2, 8, 9, 12]. Selecting patients via preliminary non-invasive studies such as capsule endoscopy

Table 9.1 Performance comparison of the three most popular deep enteroscopy techniques

	Spiral enteroscopy	Single balloon	Double balloon
Depth of insertion	Medium	Shorter	Best
Procedure duration	Shortest	Medium	Longest
Bi-directional approach	Fair	Fair	Best
Ease of use[a]	Fair	Easiest	Easy
Platform used	Any	Olympus	Fuji
Diagnostic yield	Good	Good	Good
Therapeutic yield	Good	Good	Good
Ability to remove the scope	Good	Good	Poor
Complication rate	Lower	Average	Average
Investment cost	Lowest	Medium	High

[a]Includes the need for two trained operators

increases the yield [2, 6, 8]. Diagnostic and therapeutic interventions can be performed in over 70 % of patients with positive findings [2, 8]. One potential advantage of spiral enteroscopy over other methods is that the endoscope can be withdrawn completely from the patient while maintaining the overtube in a stable position, thus allowing repetitive maneuvers such as piecemeal polypectomy or foreign body retrieval.

Comparison with Other Deep Enteroscopy Techniques

Several small studies compared the technical performance and diagnostic yield of spiral enteroscopy with double-balloon (DBE) or single-balloon enteroscopy (SBE) [8, 10, 13, 14]. The only randomized trial found that the depth of insertion and the ability to perform bi-directional panenteroscopy (combining oral and anal approach) was significantly higher with DBE compared to spiral enteroscopy (92 % versus 8 %, $p=0.002$) but at the expense of a longer procedure duration. However, the diagnostic and therapeutic yields were similar [10]. In contrast, a multi-center larger prospective cohort study found no difference in insertion depth, procedure duration, and diagnostic and therapeutic yields between the two techniques. Panenteroscopy was not attempted in this study and, as mentioned earlier, the depth of insertion is very subjective, technique-dependent and difficult to validate [8]. In a retrospective single-center study, the average depth of maximal insertion was found to be higher with spiral enteroscopy than SBE (301 cm versus 222 cm, $p<0.001$) but procedure duration and diagnostic yield were not significantly different, although there was a trend for longer procedure time with SBE [9]. A comparison of the three most popular deep enteroscopy modalities is provided in Table 9.1.

Complications of Spiral Enteroscopy

Despite its unique characteristics, spiral enteroscopy appears to be very safe, with a complication rate similar to other deep enteroscopy techniques [2, 3, 15]. In the largest, single endoscopist experience with the anterograde procedure encompassing 1,750 patients, the rate of severe complications was 0.4 %. Of the seven patients with complications, six were perforations of which, interestingly, half involved the duodenum. All perforations in this series occurred during scope advancement and not overtube torsion. Intestinal perforations have been reported in patients with pre-existent bowel pathology such as radiation injury or altered anatomy [10, 16]. No cases of pancreatitis have been described in multiple series, but hyperamylasemia is common [17]. Very limited data exists regarding the safety of retrograde enteroscopy [3, 10].

Usefulness in Inflammatory Bowel Disease

No studies have specifically evaluated the usefulness of spiral enteroscopy in inflammatory bowel disease. However, in the multi-center US study, Crohn's disease was the most common diagnosis among the 141 patients evaluated (15 %) [2]. No complications occurred during spiral enteroscopy in this subgroup. Similar results were reported in other smaller studies [3]. In the experience of the authors, spiral enteroscopy can be utilized to perform the same diagnostic and therapeutic interventions as any of the other deep enteroscopy methods. The only caveat relates to patients with intestinal strictures. Given the fact that the external diameter of the overtube is larger than with double- and single-balloon enteroscopy and that the spiral overtube is more rigid, one has to exert great caution in advancing the spiral through strictures (before or after dilation) and particularly if they are less than 10 mm in diameter, more than 2 cm in length, and are angulated or ulcerated. Particularly with the latter two, only the unlocked scope should be carefully advanced through these strictures before or after dilation if this appears to be safe and diagnostically or therapeutically warranted.

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Part IV

Pathologic Diagnosis/ Differential Diagnosis IBD

Diseases That Can Mimic IBD

10

Peter Rubin

Introduction

Malfunctioning of the gastrointestinal tract can present in only a finite number of ways. Thus patients with many maladies may complain of similar abdominal pain, nausea, vomiting, distension, gassiness, diarrhea, and constipation. As described elsewhere in this volume, these could be symptoms of ulcerative colitis (UC), Crohn's disease (CD), or indeterminate colitis. Yet there are a number of other diseases that can mimic inflammatory bowel disease (IBD). It is with this differential diagnosis that this chapter deals.

In broad categories these IBD-simulators can be grouped into:

- "Non-IBD" inflammatory
- Infectious
- Vascular
- Iatrogenic
- Motility
- Other idiopathic conditions

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Non-IBD Inflammatory

Diverticular disease of the colon can present with hematochezia similar to ulcerative colitis or give rise to a segmental inflammatory colitis that can be confused with the colitis of CD. When the rectal bleeding is from diverticulosis it is generally gross blood rather than the bloody diarrhea of UC. Sigmoidoscopic inspection of the rectum should readily diagnose UC and be spared in bleeding of diverticular origin.

Diverticulitis, on the other hand can be more difficult to differentiate from CD colitis. Both can give rise to fever, abdominal pain, abdominal tenderness, inflammatory mass, leukocytosis, elevated ESR and CRP, colonic obstruction and fistulization to surrounding mesentery and urinary bladder. And both are likely to improve with bowel rest and antibiotics. Both entities tend to be rectal-sparing. Computed tomography (CT) or magnetic resonance imaging (MRI) studies may be helpful in differentiation: Inflammatory changes or stricturing of small bowel or several separated segments of colitis suggest CD, as does the demonstration of multiple fistulae. On endoscopy a segment of diverticular disease appears erythematous and edematous [1] (Fig. 10.1), whereas Crohn's can be more ulcerated and friable, with irregular, stellate or intersecting ulcerations ("cobble stoning"). On endoscopic biopsy, granulomas are more pathognomonic of CD but, unfortunately, are seldom found. Even more confusing is the entity of "diverticular colitis" [2].

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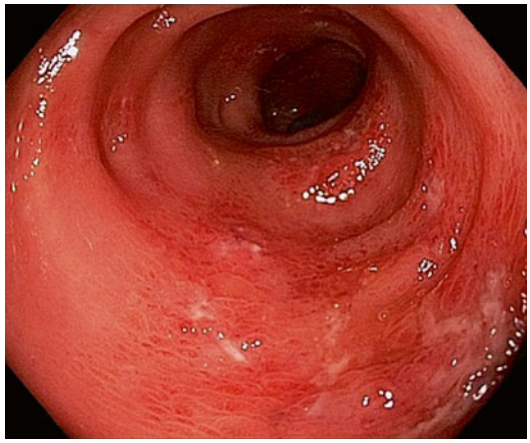

Fig. 10.1 Segmental colitis in the setting of acute diverticulitis

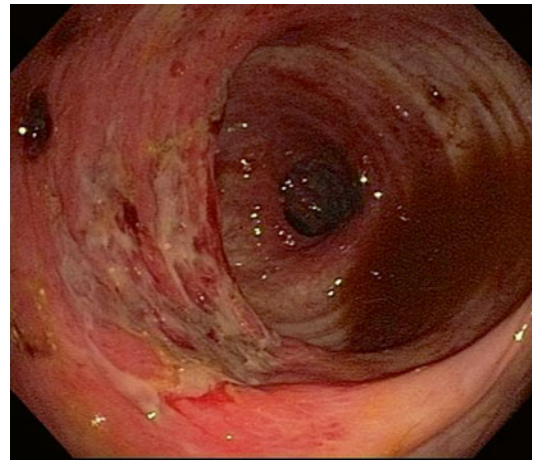

Fig. 10.2 Acute CMV colitis in the setting of HIV infection

These patients, like those with classcal IBD, may have extra-intestinal manifestations such as erythema nodosum and arthritis.

Infectious

A number of infectious colitides can present with bloody or non-bloody diarrhea resembling IBD. These may be due to pathogenic bacteria, viruses, parasites, or fungi. Among these are *Clostridium difficile*, *Salmonella*, *Shigella*, toxigenic *Escherichia coli*, *Campylobacter*, *Yersinia*, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare* (MAI), *Neisseria gonorrhea*, *Cytomegalovirus* (CMV), human immunodeficiency virus (HIV), herpes virus, *Entamoeba histolytica*, *Cryptosporidium*, *Isospora*, microsporidia, *Aspergillus*, *Cryptosporidium*, strongyloides, *Candida*, *Histoplasma*, and *Toxoplasma* [3–12]. These infectious processes should be considered early in patients afflicted with HIV and those with graft versus host disease after transplantation. They should be thought about also in patients who have received antibiotics, imunomodulators or biologic agents—including those with previously documented IBD. Many patients who present with seemingly severe exacerbations of their IBD have acquired a superimposed infectious process, the diagnosis and treatment of which can dramatically alter their course.

Appropriate stool cultures or biopsies are needed to diagnose many of these infections since the macroscopic endoscopic appearance may simulate UC or CD. *Clostridium difficile* may give rise to creamy plaques of "pseudomembranes," most often in recto sigmoid but sometimes only in more proximal colon or not at all. Biopsies of inflamed rectal mucosa may reveal the inclusion bodies characteristic of CMV.

Diarrhea is a common symptom in HIV. Although frequently associated with CMV infection (Fig. 10.2), investigation may reveal inflammation of the large intestine without any demonstrable pathogen [17–19]. Abdominal pain, diarrhea, weight loss are typical of this "HIV colitis," just as seen in IBD. On colonoscopy the mucosal pattern may show diffuse proctocolitis with friability, ulcerations, exudate and edema.

Tuberculosis can resemble CD in every respect including biopsy (Figs. 10.3 and 10.4) [20–23]. It most often involves distal ileum and right colon. In fact, prior to the seminal description by Crohn, Ginsburg and Oppenheimer, the entity we now call CD was considered tuberculosis. Now the opposite is true: The diagnosis of intestinal tuberculosis can be mistaken for CD, with dire consequences. Consideration of tuberculosis is heightened by travel to or from endemic areas and immunocompromise. Investigation for

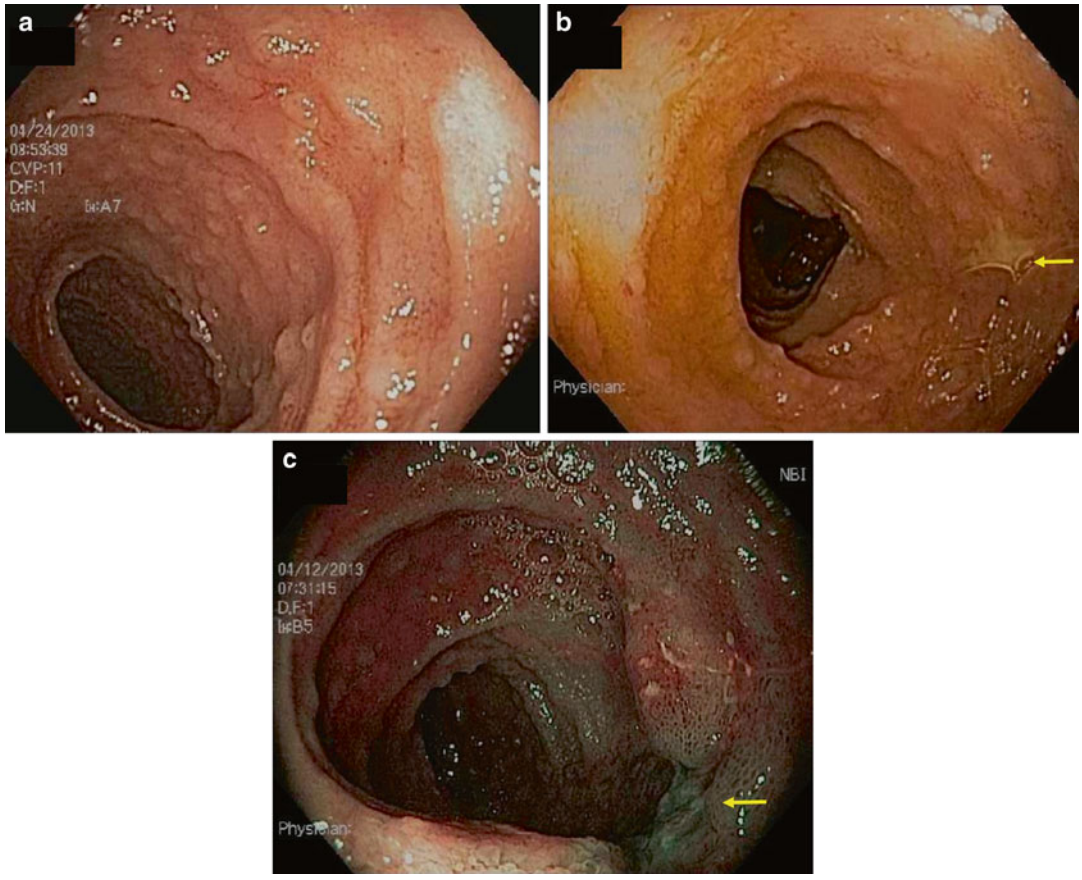

Fig. 10.3 (**a**) Peyer patch hypertrophy and aphthoid ulcers in patient with ileal tuberculosis. (**b**) Note larger ulcer visualized with white light and (**c**) narrow band imaging

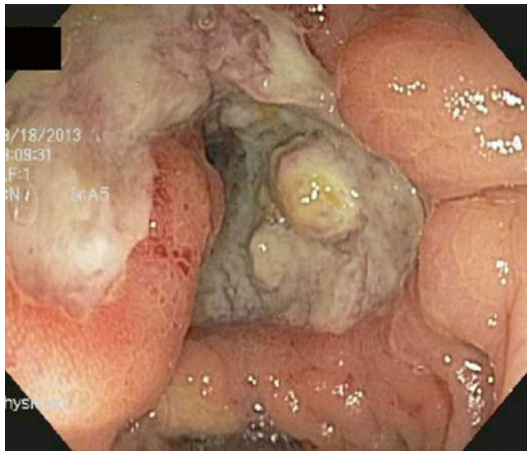

Fig. 10.4 Deep small bowel ulceration related to atypical mycobacterial infection

pulmonary involvement, caseating granulomas, and culturing for *M. tuberculosis* will eventually reveal the correct diagnosis.

Vascular

Ischemic colitis typically presents with pain, diarrhea, and bleeding. Unlike UC, it is usually rectal-sparing [24–30]. Like CD, it is segmental, tending to occur at "watershed" transitions of colonic vasculature serving descending-sigmoid colon or around the splenic flexure. The natural course of ischemic colitis is usually spontaneous resolution, but a minority of patients will have a fulminant course progressing to gangrene, necrosis

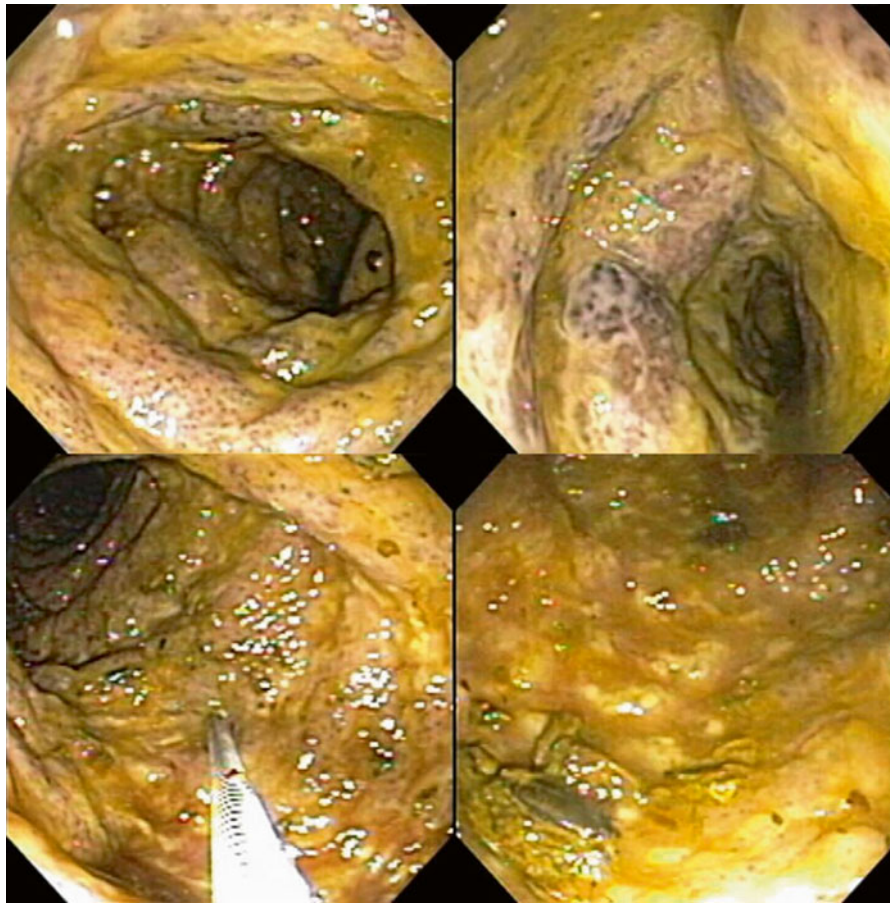

Fig. 10.5 Segmental ischemic colitis following aortic aneurysm repair. Note submucosal hemorrhage, diffuse edema

and perforation, or go on to eventual scarring and stricture.

Ischemia is suggested by onset in the elderly or those with hematologic or cardiologic impairment, or those with peripheral vascular disease, recent aneurysm repair or other vascular bypass surgery (Fig. 10.5).

Endoscopically, ischemia may appear as any other segmental colitis or sometimes as the more diagnostic purplish nodules due to submucosal hemorrhage, corresponding to the "thumb-printing" seen on radiographic studies. Mucosal biopsies often reveal non-specific colitis, but sometimes the more diagnostic mucosal necrosis with cell sloughing.

Iatrogenic

Prominent in this category is the *C. difficile* colitis described previously that may follow a course of antibiotics [13–16]. There have been reports of *C. difficile* colitis without antecedant antibiotics administration, perhaps transmitted by health care workers or from antibiotics in consumed food.

Besides antibiotics, other medications can cause gastrointestinal symptoms that simulate IBD. High on this list is the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) [31–33]. These preparations, available without prescription, and often taken liberally for headaches,

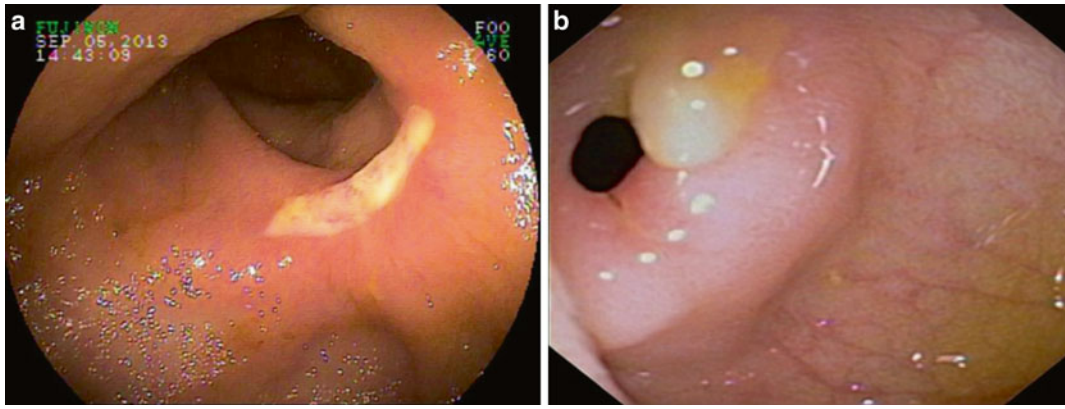

Fig. 10.6 (**a**) NSAID ileal ulcer in patient with multiple additional NSAID-induced small bowel strictures. (**b**) High-grade ileal stricture as a consequence of chronic NSAID ingestion

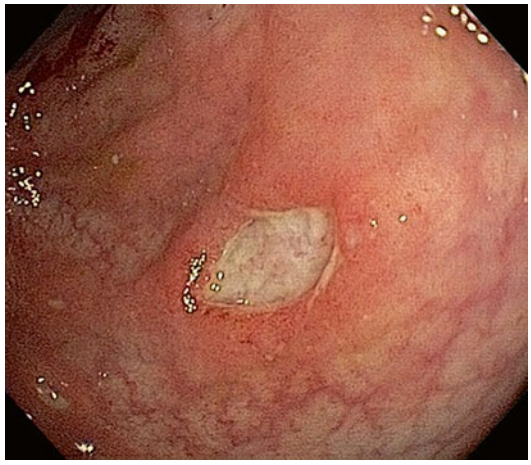

Fig. 10.7 Acute colonic ulceration in patient treated with bevacizumab for breast cancer

myalgias, and arthralgias can injure the intestine at many levels. Potential adverse effects on esophagus, stomach and duodenum are better known, but they can cause ulceration and inflammation of other portions of the intestine as well. Sometimes they are dispensed in "enteric coated" or "sustained release" forms that liberate active drug in jejunum, ileum, or colon.

Patients with NSAID-associated enteritis may present with diarrhea and abdominal pain. Examination of small bowel by capsule endoscopy and large intestine by colonoscopy in non-IBD patients has revealed erosions and ulcerations virtually identical to those of CD, often in patients taking NSAIDs who have no gastrointestinal symptoms (Fig. 10.6a, b). Biopsies of these lesions reveal inflammatory cells suggestive of microscopic colitis. These lesions disappear upon discontinuation of the NSAIDs.

NSAIDs have been implicated also in flares of IBD activity in patients with UC and CD. Patients will recognize these symptoms from previous exacerbations of their IBD. Complications may include bleeding, obstruction, perforation, fistulization and stricturing. Physical, laboratory, radiologic, and endoscopic findings are indicative of active IBD and treatment should include elimination of NSAIDs and appropriate escalation of IBD therapy.

A number of medications given topically or systemically can cause inflammation of small or large bowel. These include chemotherapy (Fig. 10.7), enteric-coated potassium, isotretinoin, oral contraceptives, endoscopic cleaning solutions, and phosphosoda-based laxatives [34]. Occasionally and paradoxically, sulfasalazine and mesalamine prescribed to treat mild to moderate colitis can actually produce diarrhea suggestive, wrongly, of active IBD.

Adhesions from prior surgery can cause an obstructive presentation like Crohn's disease. This can be particularly difficult to differentiate when the surgery was performed for CD. Recurrent Crohn's commonly occurs around anastomoses. On endoscopy and radiographic imaging, narrowing from adhesions tends to be

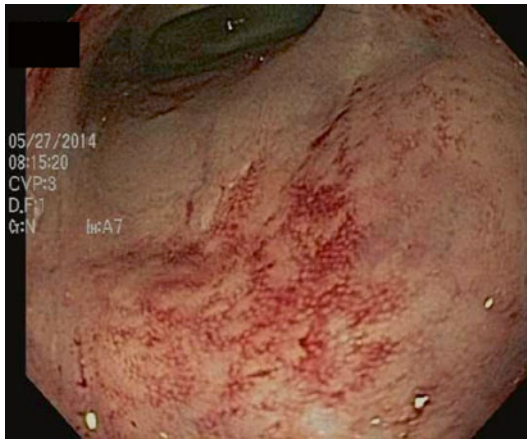

Fig. 10.8 Bypass colitis with atrophy and marked mucosal friability

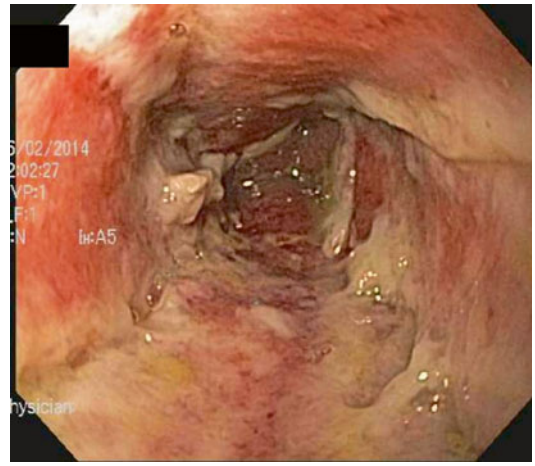

Fig. 10.9 Acute radiation colitis persistent at 6 weeks post irradiation

more localized, as opposed to the longer strictures of recurrent CD. On endoscopy, hypervascularity and circumferential ulceration may be evident at the narrowed anastomosis but the surrounding mucosa appears normal, whereas in Crohn's there may be the characteristic aphthoid lesions of recurrent IBD. Both anastomotic and CD strictures can be dilated endoscopically using through the scope (TTS) balloons, although this intervention tends to be more successful when the stricturing is just postoperative.

Another post-surgical scenario that can be mistaken for IBD is that in which a portion of the intestine has been bypassed or diverted (Fig. 10.8) [35–37]. Diversion for small bowel CD, in which the Crohn's segment was left in situ but bypassed had been a popular technique in the mid-twentieth century but is no longer commonly performed for CD. However, temporary diversion of intestinal contents into a colostomy or ileostomy is still performed in multi-staged surgery performed for diverticulitis, cancer, CD, or after colectomy with ileal pelvic pouch. In these instances the bypassed segment of colon or ileum on endoscopic examination prior to closure of the diverting ostomy may appear edematous, friable, and have considerable mucus, raising the specter of IBD. Biopsies may reveal inflammation and lymphoid follicular hyperplasia, just as in IBD. The appropriate and definitive treatment of "bypass enteritis" is to close the diversion and reestablish intestinal continuity.

Radiation injury to the intestinal tract can be a challenging differential diagnosis from IBD [38–48]. Attempts should be made to elicit a history of prostate or gynecologic malignancy radiation therapy. This history can be relatively recent or very remote. Most of the intestinal tract is protected from radiation by peristalsis, but areas fixed by anatomy (such as the rectum) or by prior surgery remain vulnerable. Thus both small and large bowel may be affected. With rectosigmoid injury patients may have bloody stools, diarrhea, mucoid discharge, urgency and tenesmus, just as in distal UC. With small bowel involvement, patients may have diarrhea, malabsorption, stricturing, fistulization and bacterial overgrowth syndrome, just as can be seen in CD.

Endoscopy of post-radiation colitis may demonstrate mucosal edema, friability and ulceration, just as in acute UC (Figs. 10.9 and 10.10). Often, however, there is a characteristic proliferation of telangiectasias that may be the source of the bleeding. With chronic radiation injury there may be loss of rectal elasticity and even stricturing. Effective therapy of bleeding from the discrete vascular malformations can be delivered via electrocautery or argon plasma coagulation. For more diffuse proctosigmoiditis, topical

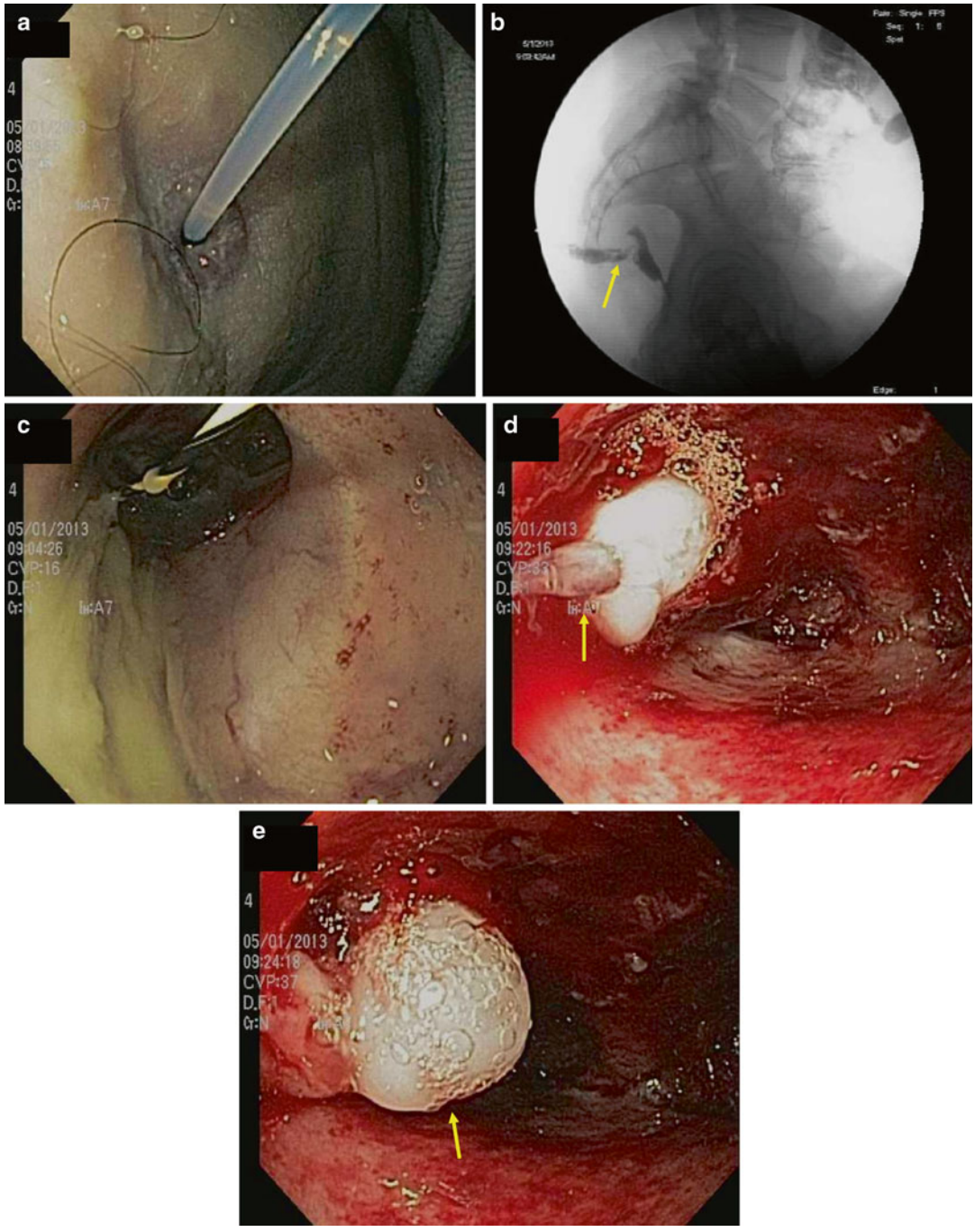

Fig. 10.10 Cutaneous fistula into residual rectum following low anterior resection for cancer followed by irradiation. (**a**) Note cannula demonstrating (**b**) fistulous tract radiographically. (**c**) A guidewire is placed into the rectum. (**d**) Note multiple radiation telangiectasia following cytology brush abrasion of the tract. (**e**) The fistula is closed with 2 cc of fibrin glue

steroids, mesalamine, or short chain fatty acids can be offered. For refractory distal colitis, application of dilute formalin has been useful but may bring about further loss of compliance and stricturing.

Motility

Solitary rectal ulcer syndrome (SRUS) is a misnomer because it is not necessarily solitary or ulcerated [49–55]. The typical history is of chronic constipation, with prolonged straining and use of suppositories or digital manipulation to achieve defecation. It may be associated with rectal prolapse. Patients note blood and mucus associated with tenesmus.

Endoscopic inspection reveals ulceration or localized proctitis with edema, erythema and granularity, just as in idiopathic distal UC. Biopsies of the lesions of SRUS may demonstrate fibroblasts and smooth muscle displaced from muscularis mucosa.

Irritable bowel syndrome (IBS) is always in the differential diagnosis of patients with IBD. Symptoms of bowel irregularity, either predominately constipation or diarrhea, bloating, distension, nausea and malaise all overlap with IBD. Significant rectal bleeding, fever, leukoytosis, elevated ESR or CRP, and extraintestinal manifestations are lacking. In the absence of definitive diagnostic tests for IBS, patients usually are evaluated for IBD with the findings of normal colonoscopy, biopsies, and small bowel imaging.

A subpopulation of patients with IBS may be habitual laxative users. They may complain of alternating constipation and diarrhea, bloating and diffuse abdominal pain. Endoscopy reveals normal mucosa, edema, or melanosis after chronic ingestion of anthraquinones such as senna, cascara, or rhubarb laxatives.

Complicating the issue further is the fact that a significant number of patients with documented IBD have coexistent IBS. For these patients relief of symptoms may require simultaneous therapy with antispasmotics and attention to diet and other potential triggers of IBS such as travel, medications, intercurrent illnesses, and stress.

Other Idiopathic Conditions

Microscopic colitis is a diagnostic term encompassing lymphocytic and collagenous colitis [56–60]. Both can present with watery diarrhea and abdominal discomfort. Patients are usually middle-aged or older. Physical examination and blood tests are often normal, although elevations of ESR and CRP are found. The endoscopic appearance may be normal or show edema. Patients are often diagnosed as having IBS of the diarrheal type, but biopsies reveal either a chronic inflammatory mucosal and submucosal infiltrate (lymphocytic colitis) or a prominent subepithelial collagen band (collagenous colitis). Since these findings may be patchy, a number of biopsies from different portions of the colon may be necessary for accurate diagnosis.

The causes of lymphocytic and collagenous colitis have not been established. Some studies have suggested an association with NSAID ingestion [59, 60]. Others have noted the high coincidence of arthritis and autoimmune markers. These mysterious colitides may disappear spontaneously, both clinically and microscopically. Treatment success has been reported with bismuth subsalicylate or with a non-absorbable steroid. In refractory cases, practitioners have had to resort to immunomodulators or even colectomy.

A rare additional idiopathic syndrome mimicking CD is Behcet's disease [61, 62]. Originally defined by the triad of mouth ulcerations, genital ulcerations, and eye inflammation, this malady can affect any portion of the gastrointestinal tract as well. It presents with abdominal pain, anorexia, rectal bleeding, vomiting, and diarrhea.

The mouth ulcerations are described as "aphthous" and the eye lesions include uveitis, just as in CD. The most common gastrointestinal areas affected with ulcerations are distal ileum and cecum. Some patients develop a vasculitis that can lead to bowel ischemia or hepatic vein thrombosis leading to Budd-Chiari syndrome.

Colonoscopy reveals ulcerations of the ileocecal mucosa. If granulomas can be found on biopsy the difficult differential diagnosis can be resolved in favor of CD. Therapy also parallels that of CD with steroids, immunomodulators, or biologics.

Conclusion

In summary there is a vast differential diagnosis to consider in evaluating a patient for UC or CD. Other diseases that can mimic IBD include other inflammatory enteritides, infectious agents, vascular insufficiency, iatrogenic causes, disorders of motility, and other idiopathic conditions. Since treatment and prognosis can be altered significantly it is important to consider the distinctions among this substantial list, then seek to obtain the historical, laboratory, endoscopic, and radiographic information needed to make a correct diagnosis and implement appropriate treatment.

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Histopathologic Diagnosis of Inflammatory Bowel Disease

11

Hejin P. Hahn

Histologic Evaluation of Mucosal Biopsy Specimens

Microscopic evaluation of mucosal biopsies begins with determining whether or not colitis is present. This assessment typically involves the examination of three main components: (1) inflammatory cells, (2) crypt architecture, and (3) epithelial cells. However, in order to recognize aberrant histology, typical variation in normal mucosal appearances should be remembered. In the colon, all three of these histologic features can vary according to anatomic site.

Normal Variations in the Histologic Appearance of Colonic Mucosa

Mucosal Inflammatory Cells

An example of normal colonic mucosa is seen in Fig. 11.1. Chronic inflammatory cells (plasma cells, lymphocytes) are normally present in the lamina propria and are typically more dense in the superficial aspect of the mucosa. The density of the inflammatory infiltrate varies based on anatomic location, with the lamina propria of the cecum and right colon (Fig. 11.1a) being more cellular than the mucosa of the left colon (Fig. 11.1b).

Lymphocytes are normally present as scattered single cells in the lamina propria of the colon. However, mucosal lymphoid aggregates can also occasionally be seen. Additionally, rare intraepithelial lymphocytes can also be present in colonic epithelium, with 5 lymphocytes per 100 enterocytes being considered normal [1]. Slightly increased numbers of intraepithelial lymphocytes are common around lymphoid aggregates.

Crypt Architecture

In a well-oriented biopsy with normal crypt architecture, the crypts are evenly spaced with bases that abut the muscularis mucosa and extend perpendicularly to the surface with an appearance that has been described to be akin to "a row of test tubes." In the rectum, mild architectural distortion is acceptable, with slight irregularity in crypt spacing and mild shortening of crypts.

Epithelial Cell Components

Paneth cells are normally present proximal to the splenic flexure; however, when present distal to this anatomic site, Paneth cell metaplasia can be a sign of chronic injury.

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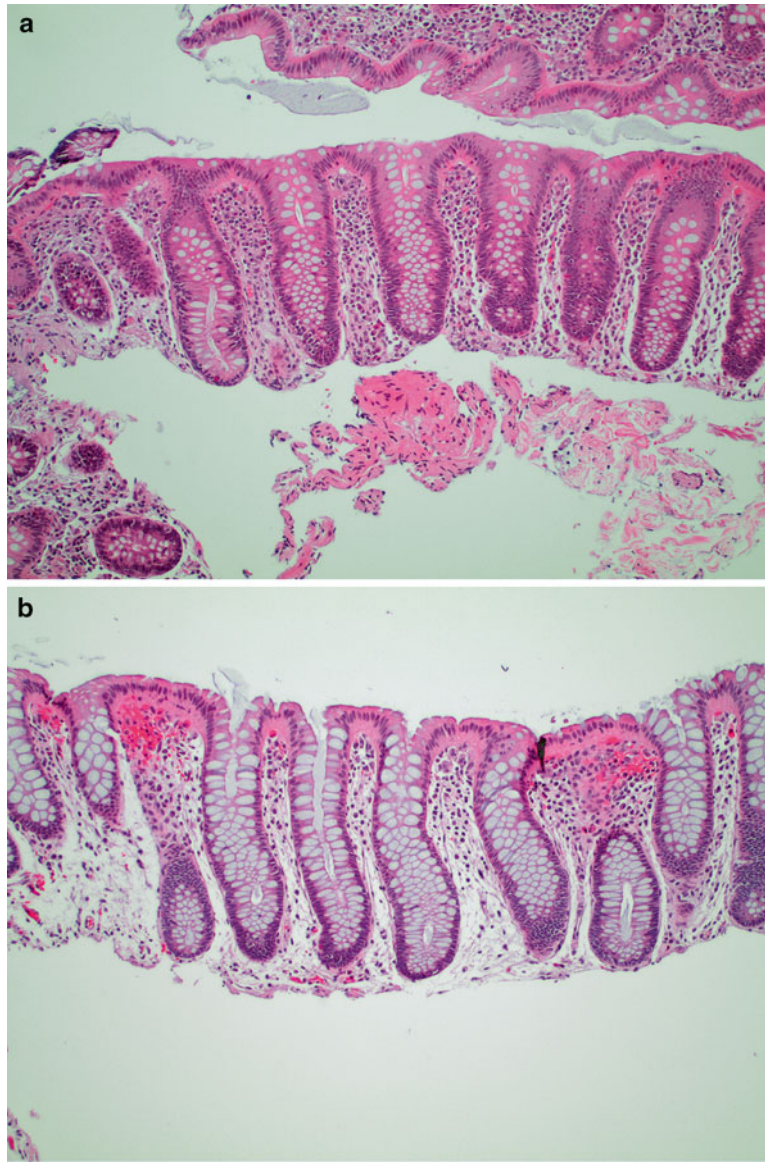

Fig. 11.1 (**a**) Normal right colon mucosa with increased lamina propria cellularity. (**b**) Normal left colon mucosa

Histologic Features of Colitis

Active colitis is considered to be present when there is neutrophilic inflammation and epithelial injury. There may be neutrophilic cryptitis, crypt abscesses, erosions, or ulceration. However, the presence of rare intraepithelial neutrophils (particularly in a superficial location) can be secondary to bowel preparation [2].

Histologic Features of Chronic Colitis

When colitis persists, the chronicity of the inflammatory process is associated with other histologic abnormalities. As inflammatory bowel disease (IBD) is considered a chronic disease process, histologic features of chronicity are considered supportive evidence of IBD and can be helpful in distinguishing between IBD

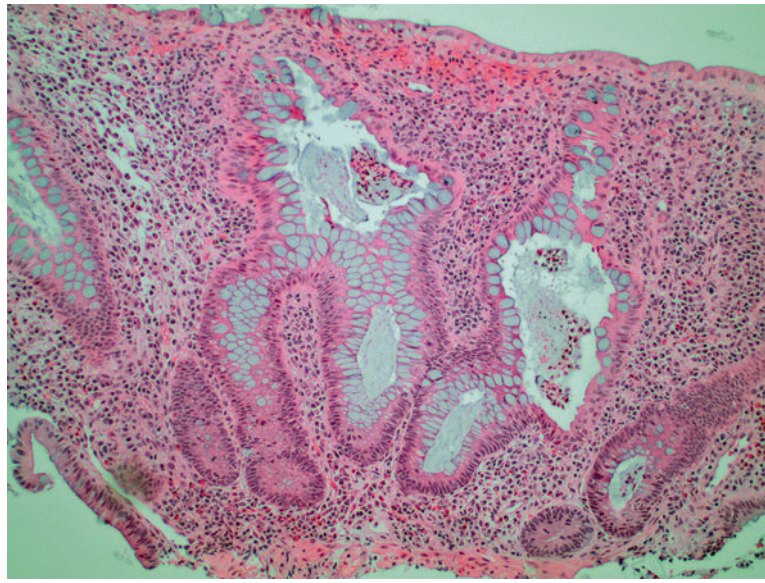

Fig. 11.2 Chronic active colitis with neutrophilic crypt abscesses, crypt architectural distortion, and basal lymphoplasmacytosis

and cases of acute self-limited colitis (which typically resolve in less than a month). An example of chronic active colitis is seen in Fig. 11.2.

Mucosal Inflammatory Cells

Changes of the inflammatory cell infiltrate in the lamina propria can be one of the most reliable features of chronic colitis. Increased density of lamina propria inflammation is often seen in both acute self-limited colitis and in chronic colitis. Basal plasmacytosis, a term used to describe the presence of plasma cells at the base of the mucosa that can separate the crypt bases from the muscularis mucosa, is considered one of the most specific features of chronicity. Basally located lymphoid aggregates are also considered abnormal and can be seen in chronic colitis, but are often difficult to objectively identify. Multinucleated giant cells and granulomata are not normal components of the mucosa, and their presence can raise the possibility of Crohn's disease, although their presence is not pathognomonic.

Crypt Architecture

Changes in crypt architecture indicating chronicity include crypt branching and crypt atrophy (shortened crypts that do not reach the muscularis mucosa, and irregular spacing between crypts). These alterations in crypt architecture are thought to reflect crypt regeneration after mucosal injury. Irregularity of the mucosal surface can also be seen in chronic colitis. There is often dilation of the crypt lumens towards the surface with crypt separation that results in a villiform, undulating mucosal surface.

Epithelial Cell Components

Epithelial cell metaplasia including Paneth cell metaplasia and pyloric gland metaplasia (seen in Fig. 11.3) can also be associated with chronic colitis.

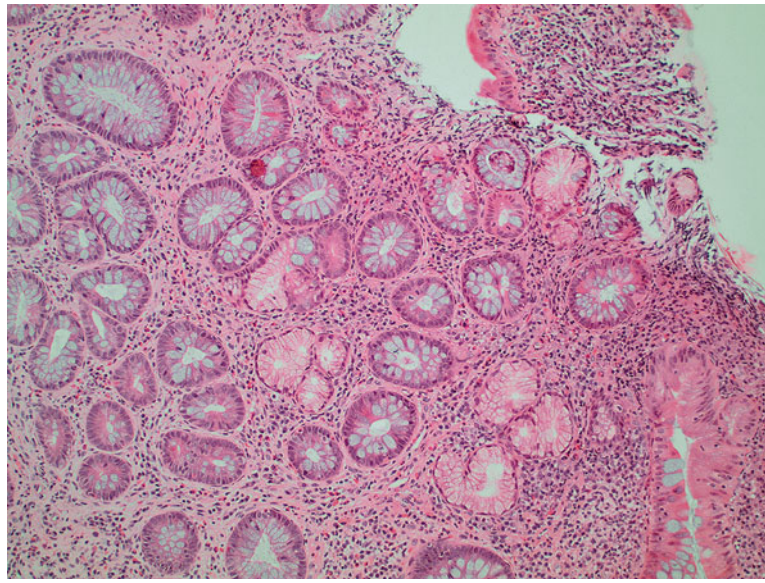

Fig. 11.3 Pyloric gland metaplasia

Reliability of Histologic Findings as a Marker of Chronicity

Although many of the features of chronicity previously listed are useful in differentiating between acute self-limited colitis and IBD, the exact degree of histologic change and number of features of chronicity required for a diagnosis of IBD are not well defined. Several studies have found that the presence of (1) crypt architectural distortion and (2) basal plasmacytosis are the most reliable in distinguishing between IBD and acute self-limited colitis [3–6].

However, it should be remembered that features of chronic mucosal injury are not specific to IBD. Chronic injury secondary to etiologies other than inflammatory bowel disease (e.g., ischemic injury, radiation, etc.) can occasionally have a similar histologic appearance (an example is seen in Fig. 11.4). A discussion of other histologic mimics of IBD is presented later in this chapter.

It should also be remembered that histologic features of chronicity may not be present at time of presentation. While basal plasmacytosis is a relatively early change and can be seen within the first 15 days of symptoms, crypt architectural abnormalities are not present until after 2 weeks of disease. In addition, on first presentation, the findings can be focal, with increased severity and prevalence over time [7]. Thus, a diagnosis of IBD always requires careful correlation of histologic findings with clinical findings.

Correlation of Endoscopic Appearance to Histologic Appearance in IBD Biopsies

Although endoscopic appearances often correlate well with histologic findings, correlation is not absolute. Lemmens et al. compared the endoscopic and histologic appearances of 131 patients with ulcerative colitis. The biopsies were scored using the Geboes and Riley histologic scoring system, and the endoscopic scoring was performed using the Mayo endoscopic subscore. Overall, although endoscopic and histologic scores correlated well with inactive and in severely active disease, there was not good correlation when disease activity fell between the two extremes [7–9].

In other studies that compared endoscopic appearances with histologic findings, although

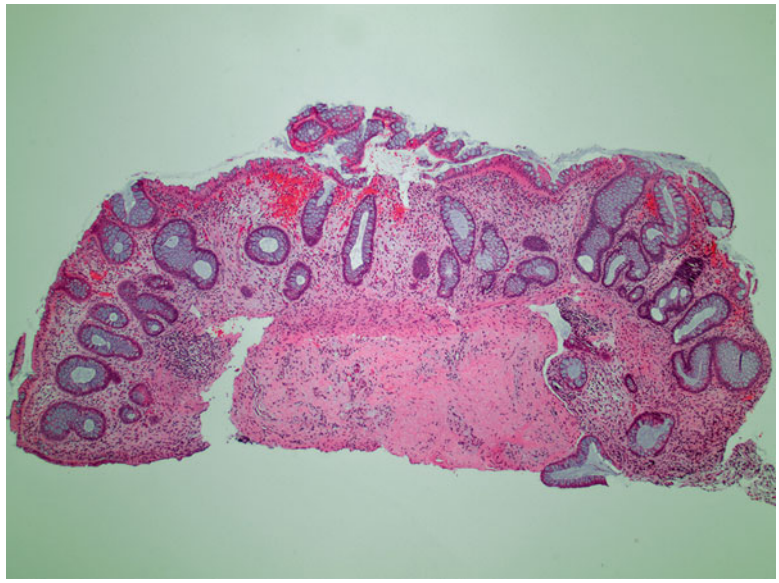

Fig. 11.4 Chronic ischemic colitis with architectural distortion

the bowel appeared endoscopically normal, histologic examination revealed persistent inflammatory activity. In a study of 797 biopsy sites from 41 patients with ulcerative colitis (UC), Kleer et al. described a lack of endoscopic-histologic correlation in one-third of cases. In 25 % of the biopsies, an endoscopically normal appearing biopsy site showed chronic colitis histologically [10]. A subsequent study of 75 UC patients with endoscopically inactive disease showed histologic evidence of colitis in 40 % of patients [11]

In a study of both biopsy and colectomy specimens from 56 patients with ulcerative colitis, Joo and Odze found that an endoscopic appearance of rectal sparing concurred with the biopsy histologic features in approximately 80 % of patients. However, there was no statistical correlation between endoscopic appearance and the histologic findings in the resected colectomies [12].

Compared to ulcerative colitis, endoscopic and histologic appearances are often more difficult to correlate in Crohn's disease (CD), where changes are patchy, and sampling error can be an issue.

Definition of Activity in IBD

In IBD, disease is often categorized as being either active, chronic active, or chronic inactive (quiescent). Active (or acute) colitis would be considered the presence of neutrophilic epithelial injury without features of chronicity. Mucosal biopsies with chronic active colitis would contain features of chronic mucosal injury as well as active epithelial injury. Chronic inactive colitis or quiescent colitis would be the term used when there are features of chronic mucosal injury without concurrent neutrophil mediated epithelial injury.

Grading Histologic Activity in IBD

During the evaluation of mucosal biopsies from patients with IBD, in addition to categorizing colitis as either chronic and/or active, it is recommended that histologic disease activity be graded. However, a single widely accepted grading system does not currently exist. Several different grading systems have been proposed, some of

which were developed specifically for either ulcerative colitis or Crohn's disease.

In some systems [12–14], disease is first separated into various "phases" of disease (e.g., normal, chronic inactive/quiescent, and chronic active disease); then, if active disease is present, it is graded based on the presence or absence of neutrophilic cryptitis, crypt abscesses, surface ulceration/erosion, and amount of mucosa involved. For example, Joo and Odze used a five-tier grading system with 0 = normal mucosa, Grade 1 = chronic inactive colitis, Grade 2 = chronic colitis with mild activity, Grade 3 = chronic colitis with moderate activity, and Grade 4 = chronic colitis with severe activity [12].

A similar grading system put forth by Geboes et al. [8] incorporated both evidence of chronicity and progressively increasing active epithelial injury. In their system, biopsies were given a grade of 0 and/or 1 if they contained crypt architectural changes and chronic inflammatory infiltrates but no evidence of active epithelial injury. Biopsies were given grades ranging from 2 to 5 if they showed both chronic changes as well as neutrophilic and eosinophilic inflammation, crypt destruction, or surface erosion and ulceration of increasing severity.

In other grading systems, different histologic findings are each given a separate grade and a sum of all the grades are used as the final score. For example, a grading system put forth by Riley et al. [7] included the evaluation of six histologic features (neutrophilic inflammation in the lamina propria, crypt abscesses, mucin depletion, surface epithelial integrity, chronic inflammation in the lamina propria, and crypt architectural abnormalities) and each feature was graded on a four-tier system (none, mild, moderate, or severe).

At our institution we consider "mild" activity to be presence of neutrophilic cryptitis without the presence of crypt abscesses, "moderate" activity to be the presence of cryptitis and crypt abscesses, and "severe" activity would be used to describe the presence of marked neutrophilic inflammation with ulceration.

When tested, the reproducibility of scoring systems shows relatively good interobserver agreement. However, the number of these studies are relatively limited. Scoring systems based on phases of activity as well as scoring systems based on the sum of all histologic findings appear to show relatively similar reproducibility. Odze et al. [15] used a histologic disease activity scoring system to quantitate the effect of topical 5-aminosalicylic acid (5-ASA) on the histologic appearance of mucosal biopsies of UC patients. Biopsies were given a histologic score based on the presence or absence of features of chronicity (abnormal crypt architecture, villiform surface contour, mixed inflammation in the lamina propria, basally located plasma cells, basally located lymphoid aggregates, and Paneth cell metaplasia) along with the presence or absence of neutrophilic inflammation. They found that there was only minor interobserver variation occurring in less than 10 % of their biopsy samples. Interobserver variation was also measured in the study by Riley et al. [7] using the scoring system described previously. They found that 82 % of their biopsies were given the same grade by the two reviewing pathologists, and that scoring differed by more than one grade in only 2 % of the sections.

Histologic Activity and Risk of Progression to Neoplasia

There is some evidence that there is an association between increased histologic inflammation and increased risk of progression to neoplasia in patients with IBD. In a case–control study of 68 patients with ulcerative colitis who developed colorectal neoplasia and their matched controls (136 patients total), Rutter et al. [16] found that there was a significant correlation between endoscopic and histologic inflammation and risk of progression to colorectal neoplasia. Similar results were reported by Rubin et al. [17]. Biopsies from 141 UC patients without colorectal neoplasia and 59 UC patients who developed colorectal neoplasia were scored using a six-tier histologic activity index. In univariate analysis, they determined that there was a positive association of increased histologic inflammation with development of colorectal adenocarcinoma. Finally, in a cohort study of 418 patients with ulcerative colitis, Gupta et al. [18] found a

significant relationship between increased histologic inflammation and subsequent development of high-grade dysplasia or colorectal adenocarcinoma.

Histologic Activity as Predictor of Clinical Relapse

Evidence of histologic inflammation may indicate risk of clinical relapse. As mentioned previously, even in endoscopically normal appearing mucosa, there can be evidence of persistent inflammation on histologic examination. Several studies suggest that the finding of histologic abnormalities in endoscopically normal appearing mucosa correlates with earlier relapse. In a 1-year prospective study of 74 patients with clinically and endoscopically inactive ulcerative colitis, Bitton et al. [19] determined that the presence of basal plasmacytosis on histologic examination of mucosal biopsies was an independent predictor of earlier relapse. Similarly, in a cohort study of 75 UC patients with endoscopically inactive disease, Bessissow et al. [11] found that that the presence of basal plasmacytosis was predictive of a clinical relapse. Interestingly, although 40 % of their cases contained active histologic inflammation with a Geboes score ≥ 3.1 ("presence of epithelial neutrophils with or without evidence of crypt destruction or erosions") this was not identified as an independent predictor of relapse. In contrast, Riley et al. [7] found that the presence of neutrophilic cryptitis or crypt abscesses in biopsies of endoscopically normal appearing mucosa correlated with relapse. However, the presence of a chronic inflammatory infiltrate in the lamina propria did not appear to correlate with relapse.

Histologic Activity and Treatment Goals

Histologic disease activity can also be used as a tool for determination of treatment efficacy, and it has been proposed that resolution of histologic inflammation should serve as a possible therapeutic goal [20]. However, several issues still exist that would make this difficult. First, it is not clear exactly which histologic findings should be considered a goal for therapy. Possible targets would include resolution of neutrophilic inflammation versus reversion of the mucosa to a normal histologic appearance. Second, it is likely that defining histopathologic therapeutic targets for ulcerative colitis will need to be determined separately from Crohn's disease. Although mucosal biopsies may accurately reflect disease in UC, because of the patchy disease involvement of Crohn's disease and the transmural nature of the disease, limitations of sampling may also limit the ability of histopathologic analysis of endoscopic biopsy samples to serve as a treatment guide.

Histopathologic Features of Ulcerative Colitis

Classically, ulcerative colitis involves the rectum with continuous extension of disease proximally. On gross-examination "skip-areas" of intervening normal mucosa are not present. Examination of biopsy specimens also reflects the continuous nature of the disease, with a relatively uniform distribution of histologic changes between biopsy fragments.

Histologic findings in ulcerative colitis reflect changes of chronic colitis. There is increased inflammation in the lamina propria, present as a diffuse increase in lamina propria cellularity as well as basal plasmacytosis. Crypt architectural abnormality with crypt branching, crypt foreshortening (or crypt atrophy), and villous architecture is often present (17–30 %) and is seen more commonly in ulcerative colitis than Crohn's disease (12 %) [2, 5]. Other features of chronicity, such as Paneth cell metaplasia, can be present. When there is active disease, neutrophilic cryptitis is more common in ulcerative colitis than in Crohn's disease [2].

When resection specimens, rather than biopsies, are evaluated, the mural extent of inflammatory changes can be assessed. In ulcerative colitis, inflammation is typically limited to the mucosa and superficial submucosa. When present, ulceration is usually non-fissuring and does not extend deeper than the submucosa, although some

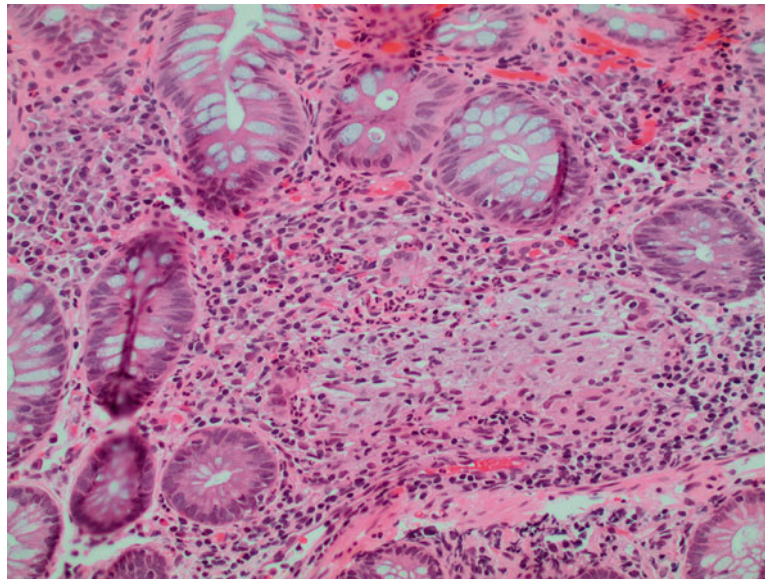

Fig. 11.5 Ulcerative colitis with crypt rupture granuloma

studies have shown that shallow fissuring ulcers can occasionally be seen [21].

Granulomatous Reaction to Ruptured Crypts

Of patients with Crohn's disease, 30–50 % have granulomata in the colonic mucosa. Although this is a useful diagnostic feature in distinguishing Crohn's colitis from ulcerative colitis, the presence of granulomata are not absolutely specific for Crohn's disease. The presence of granulomatous or giant cell reaction to ruptured crypts, also termed mucin granulomas or "cryptolytic" granulomas, can occur in ulcerative colitis as well as in other colitides such as infectious colitis, diverticular colitis, and diversion colitis [22–25]. In ulcerative colitis, it is thought that crypt rupture and release of mucin and crypt luminal contents into the lamina propria can induce a histiocytic, giant cell, and granulomatous inflammatory reaction (Fig. 11.5). In a study of 29 patients whose mucosal biopsy specimens contained granulomas or giant cells, Mahadeva et al. [22] found that 10 of the patients could be given a diagnosis of ulcerative colitis based on the histologic findings in prior and subsequent biopsies and 90 % of these patients also had a diagnosis of ulcerative colitis based on clinical findings. Thus, granulomatous reaction to crypt rupture does not reliably distinguish between Crohn's disease and other colitides [25]. However, careful examination of multiple levels may be required to determine whether granulomas are associated with crypt injury. In the study by Mahadeva et al., the patient whose histologic findings were suggestive of ulcerative colitis, but whose clinical features did not appear consistent with this diagnosis, had a solitary granuloma that did not appear associated with crypt injury [22].

Unusual Variants of Ulcerative Colitis

Although the classic pattern of ulcerative colitis involves the contiguous involvement of the rectum and colon, the evaluating pathologist should be aware of exceptions to this rule in which an unusual, or Crohn's-like, disease distribution can be seen in patients with UC (Table 11.1).

Table 11.1 Unusual patterns of disease in ulcerative colitis and Crohn's disease

Ulcerative colitis
Patchy disease distribution
Treatment effect
"Patch" of cecal or ascending colon inflammation
Peri-appendiceal inflammation present as a skip lesion
Initial presentation in pediatric patients
Ileal inflammation in "backwash" ileitis
Upper GI tract involvement such as diffuse duodenitis
Crohn's disease
Crohn's colitis with mucosa only involvement

Treatment Effects in UC

Patients with longstanding UC may show rectal sparing and a patchy distribution of disease, with normalization of the mucosa on both endoscopic and histologic examination [4, 10]. Reversion of the mucosa to a normal morphologic and histologic appearance can be enhanced by treatment. The 1993 study by Odze et al. [15] found that 36 % of UC patients who were treated with 5-aminosalicylic acid and 12 % of controls showed rectal sparing on post-treatment biopsies. In subsequent studies, other groups reported that 30 % to 59 % of UC patients showed either rectal sparing or patchy disease on follow-up biopsies [26, 27]. Kleer et al. [10] examined sequential biopsy specimens from 41 patients with UC. The histologic appearance of biopsy specimens reverted to normal in 22 of the 41 patients. Thus, a normal appearing biopsy specimen in a patient with treated or longstanding ulcerative colitis should not be misinterpreted as evidence of Crohn's disease. In addition, because normalization of histologic findings can occur in previously treated patients, determination of the distribution of colitis is best made on pre-treatment biopsies.

Pediatric UC Patients

Unlike adult UC patients, pediatric patients may present with relative or complete rectal sparing or with only patchy disease involvement. Markowitz et al. [28] analyzed 17 pediatric patients without a history of treatment and found that 42 % of patients had only patchy rectal disease or a normal rectum. A subsequent study by Washington et al. [29] reported that only 32 % of children (in contrast to 53 % of adults) presented with diffuse rectal disease. Glickman et al. [30] evaluated biopsies from 73 pediatric patients and 38 adult patients and showed that 30 % of children had either only patchy inflammation in the rectum or complete rectal sparing at time of presentation. In this study only a single adult had relative rectal sparing and no adult patients showed complete rectal sparing. In addition, 21 % of the pediatric patients had only patchy involvement by inflammation, while no adult patients had this finding.

The difference in disease distribution and the severity of inflammation in pediatric patients may be more common in younger patients. Robert et al. [31] studied biopsies from 15 pediatric patients and 25 adult patients at time of presentation, and found that there were fewer histologic features of active and chronic disease in pediatric patients, but that this difference was more common in patients younger than 10 years.

Cecal, Ascending Colon, and Appendiceal Involvement in UC

Even in patients with left-sided UC, a "patch" of endoscopic and histologic disease activity can occasionally be seen in the cecum and right colon, and can even be present at initial presentation [32–35]. In a prospective study, Ladefoged et al. [33] discovered endoscopic evidence of periappendiceal inflammation in 27 % of patients with UC without evidence of cecal or ascending colon involvement. D'Haens et al. [34] evaluated both the endosocopic appearance and colonic resection specimens from 20 patients with UC and found that 75 % of patients with left-sided disease had an area of cecal involvement, always including the area around the appendiceal orifice, that was separated by an area of uninvolved mucosa. In a case control study by Mutinga et al [35], 12 patients with left-sided UC and patchy right colonic inflammation were compared to 127 case controls with only left-sided disease. There

was no significant difference in age, gender, extraintestinal involvement, progression to pancolitis, or severity of disease. In follow-up, none of the patients developed features of Crohn's disease.

Discontiguous Involvement of the Appendix

Appendiceal disease, unassociated with periappendiceal or cecal involvement, has been reported in 12-87 % of patients with UC [36–41]. In 1990, Davison et al. [38] reported that discontinuous appendiceal involvement was present in 21 % of their UC patients. However, a subsequent study by Goldblum and Appelman [39] found that appendiceal involvement in UC was present only if contiguous cecal involvement was present. Still, subsequent studies have described discontinuous appendiceal "skip" lesions in UC patients. Groisman et al. [40] examined 160 consecutive colectomy specimens from adult and pediatric UC patients. Ulcerative appendicitis was identified in 82 of 94 cases of pancolitis, as well as in 12 of 14 cases where disease involvement was otherwise only present distal to the hepatic flexure. In another retrospective study, Kroft et al. [41] evaluated 39 resection specimens, and found that 15 % of the examined specimens showed appendiceal disease with normal or nonspecific cecal histologic findings.

Thus, focal cecal, ascending colon, or appendiceal disease activity, present as apparent "skip" lesions, should not completely exclude a diagnosis of ulcerative colitis.

Ileitis in UC: Backwash Ileitis

Although ulcerative colitis is classically defined as an inflammatory process of the colon, ileal inflammation has been described in a subset of patients with ulcerative colitis. It has been presumed that the mechanism of distal ileal inflammation in ulcerative colitis is pan-colitic associated reflux of colonic contents into the ileum through an incompetent ileocecal valve with subsequent ileal inflammation, or "backwash" ileitis. In contrast to the more extensive ileal involvement of Crohn's disease, ileal inflammation in ulcerative colitis is generally limited to only a few centimeters proximal to the ileocecal valve. In addition, other features of Crohn's disease such as granulomas, fissuring ulcers, and transmural inflammation are not seen.

To better outline the histopathologic features of backwash ileitis, Haskell et al. [42] examined colectomy specimens from 200 UC patients. Ileitis was present in 17 % of the cases and the inflammation was generally limited to the distal 1 cm of ileum. The histologic features of the ileal inflammation in these cases consisted of mild, patchy neutrophilic inflammation in the lamina propria, focal cryptitis or crypt abscesses, and patchy villous atrophy and regenerative changes.

Backwash ileitis may be becoming less common with current treatment regimens. To see if the features of backwash ileitis have changed over time, Goldstein and Dulai [42] examined 250 UC colectomy specimens from three different time periods (1960 through 1979, 1980 through 1997, and 1998 though 2004). Overall, 82 (32.8 %) of the cases showed backwash ileitis. However, there was a decrease in the prevalence of both cecal activity and backwash ileitis over time. Although 28 % of cases resected in 1960–1979 had only mild or quiescent cecal disease, 44 % of cases from 1998 to 2004 showed mild cecal disease and 54 % of cases from 1998 to 2004 showed quiescent colitis. There was correspondingly less backwash ileitis seen in the more recent resection specimens. While 72 % of cases from 1960 to 1979 showed moderate to marked backwash ileitis, no cases from 1998 to 2004 contained moderate to marked backwash ileitis and only 1 case had mild backwash ileitis.

Upper GI Tract Involvement

Although upper GI tract (esophagus, stomach, duodenum) involvement is classically associated with Crohn's disease, rare cases of gastric and/or duodenal involvement have been described in patients with ulcerative colitis. In particular,

upper GI tract involvement has been documented in several pediatric patients with ulcerative colitis [43, 44]. Kaufman et al. [43] described five children with pancolitis without granulomata who underwent subtotal colectomy, all of whom had chronic active gastritis and some of whom had duodenitis. In subsequent follow-up, none of these patients developed Crohn's disease. In a study comparing 14 children with ulcerative colitis to 28 children with Crohn's disease, Tobin et al. [44] found that a significant number of pediatric patients also showed upper GI tract inflammation (50 % had esophagitis, 69 % had gastritis, and 23 % had duodenitis).

Interestingly, studies seem to indicate that, in UC patients with upper GI tract disease, the duodenum may be the most common site of involvement. Valdez et al. [45] described four patients with ulcerative colitis who also exhibited diffuse duodenitis. More recently, in a study comparing esophageal, gastric, and duodenal biopsies from patients with ulcerative colitis to matched controls, Lin et al. found diffuse chronic duodenitis was unique to the ulcerative colitis patients and was present in 10 % of the duodenal biopsies from ulcerative colitis patients. Several cases of duodenitis in UC parients have also been described in the Japanese literature [46, 47].

Histopathologic Features of Crohn's Disease

In patients with Crohn's disease, 30–40 % will have only small bowel involvement, 30–40 % will have ileocolonic disease, and 10–20 % will have colonic involvement only. In contrast to ulcerative colitis, Crohn's colitis typically shows areas of segmental involvement with intervening areas of uninvolved colon (skip lesions). In addition, unlike ulcerative colitis, many patients with Crohn's disease will have complete or relative rectal sparing.

On histologic examination, Crohn's colitis shows changes of chronic injury with increased inflammation in the lamina propria and basal plasmacytosis. However, inflammation can be heterogeneous, both between biopsy fragments as well as within a single biopsy fragment. Other features of chronicity such as crypt architectural abnormality, Paneth cell and pyloric (mucous) cell metaplasia may also be present and show heterogeneity in distribution. Similarly, neutrophilic epithelial injury can be variable between biopsy specimens. Occasionally, injured and inflamed crypts can be seen immediately adjacent to normal appearing crypts. This patchy distribution of chronic changes and active epithelial injury can be helpful in favoring a diagnosis of Crohn's colitis over ulcerative colitis [48, 49].

Two types of ulceration are also thought to be relatively characteristic of Crohn's disease: aphthous ulcers and fissuring ulcers. Aphthous ulcers are seen as small, shallow areas of superficial erosion and neutrophilic inflammation overlying lymphoid aggregates. Fissuring ulcers are deep, "knife-like" ulcers that extend deep into the bowel wall. Although they are not absolutely specific for Crohn's colitis, their presence would favor a diagnosis of Crohn's colitis over ulcerative colitis. However, the presence of fissuring ulceration is determined only on the examination of resection specimens, and cannot be appreciated in mucosal biopsies.

As mentioned previously, 30–50 % of patients with Crohn's disease have granulomas in the colonic mucosa. The presence of non-cryptolytic granulomas is considered a relatively specific feature of Crohn's disease that can help distinguish between ulcerative colitis and Crohn's disease. Granulomas in Crohn's disease can be present as pericryptal granulomas (Fig. 11.6a) not associated with crypt rupture or mucin extravasation as well as well-formed non-necrotizing granulomata in the submucosa (Fig. 11.6b).

When resection specimens are assessed, the transmural inflammation of Crohn's disease can be appreciated. Grossly, serosal inflammation may result in "fat wrapping" or "creeping fat" with extension of the mesenteric adipose tissue onto the anti-mesenteric surfaces of the colon. Histologically, the transmural inflammation of Crohn's disease can be seen in the form of transmural lymphoid aggregates, particularly lymphoid aggregates away from areas of ulceration. As mentioned, deep fissuring ulcers

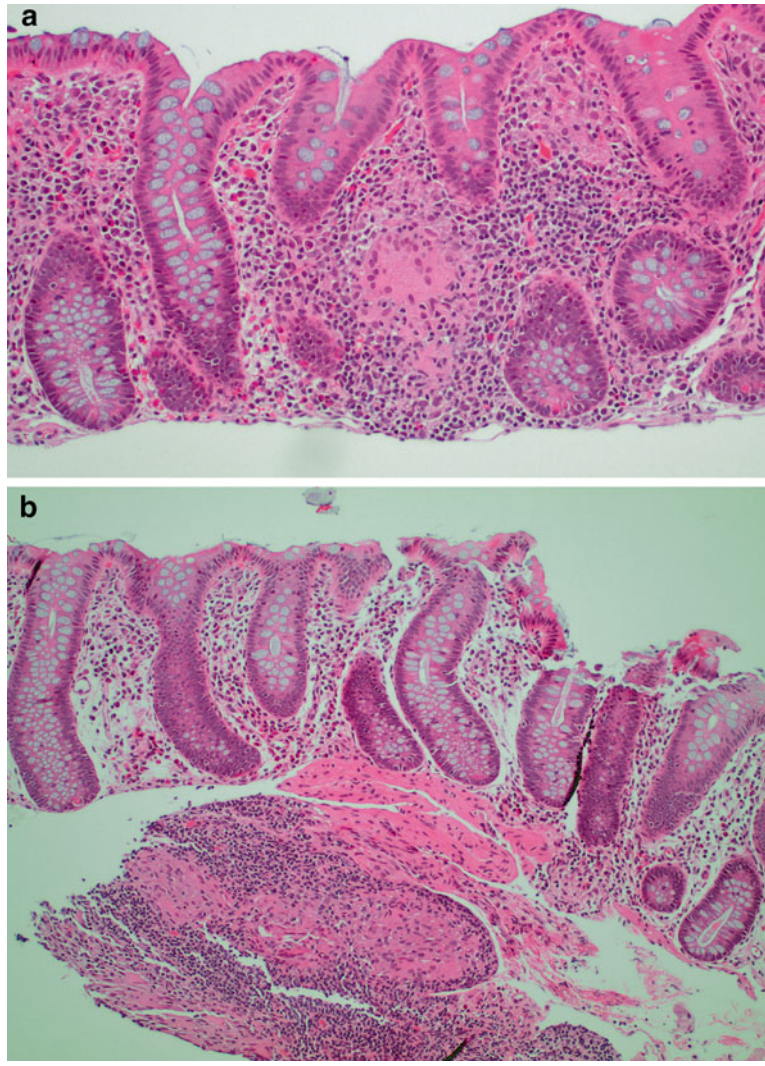

Fig. 11.6 (**a**) Crohn's colitis with mucosal granuloma. (**b**) Crohn's colitis with submucosal granuloma

extending beyond 50 % of the thickness of the muscularis propria are also more commonly seen in CD. Other evidence of the transmural inflammatory pattern of Crohn's disease would include the presence of fibrostenotic lesions, and the presence of fistula and sinus tracts. Granulomas and patchy inflammation in biopsy specimens, and evidence of transmural inflammation would all support a diagnosis of Crohn's disease over ulcerative colitis (outlined in Table 11.2).

Unusual Disease Distribution

CD Limited to the Colonic Mucosa

Although very rare, several cases of UC-like Crohn's disease or superficial Crohn's colitis have been reported in the literature [50–54]. Ten cases of superficial Crohn's colitis were described in an abstract by McQuillan and Appelman [50]. These patients had small bowel disease, but

Table 11.2 Histologic findings helpful in distinguishing between ulcerative colitis and Crohn's disease

Histologic finding	Comment
Favoring ulcerative colitis	
Diffuse distribution of disease	Most reliable in pre-treatment biopsies of adult patients
Favoring crohn's disease	
Patchy inflammation with variation within and between biopsy fragments	
Granulomas not associated with crypt rupture	"Cryptolytic" or mucin granulomas can be seen in UC
Ileal involvement	Needs to be distinguished from "backwash" ileitis in UC
Deep fissuring ulceration	Requires evaluation of resection specimen
Transmural lymphoid aggregates away from areas of ulceration	Requires evaluation of resection specimen

inflammation that was primarily limited to the mucosa and submucosa. In a study of 100 IBD resections, Harpaz et al. [51] described 10 patients with granulomata, but also with macroscopic features of UC and inflammation that generally did not extend deep to the superficial mucosa on histologic examination. Two of the patients had ileal disease, eight developed Crohn's-like complications, and two developed pouch failure.

In a study of 118 patients with Crohn's disease, Soucy et al. [54] found that 14 % of patients with Crohn's colitis (10 of 73 patients) and 13 % of patients with Crohn's ileocolitis (6 of 45 patients) had superficial disease that was limited to the mucosa. Seven of the 16 patients had granulomas. Similar to the findings of Harpaz et al. they found that these patients presented at a younger age. However, other features or clinical outcome of these patients was not significantly different from patients with traditional transmural Crohn's inflammation.

These studies suggest that in patients with UC-like colitis but severe anal/perianal disease, a diagnosis of CD should be suspected. Conversely, in patients with an irrefutable history of Crohn's disease, but superficial inflammation in resected specimens, a diagnosis of superficial Crohn's disease should be considered.

Upper GI Tract Involvement

As mentioned previously, upper GI tract involvement has been reported in 30–65 % of patients with Crohn's disease. The histologic finding most commonly associated with *H. pylori*-negative Crohn's gastritis is often referred to as "focally enhanced chronic active gastritis." Evaluation of mucosal biopsies reveal focal areas of neutrophilic inflammation with surrounding lymphoplasmacytic infiltrates that are separated by normal appearing mucosa. These lesions are found in 30–70 % of CD patients [55]. However, this histologic pattern of "focally enhanced gastritis" can also be seen in the gastric biopsies of some UC patients, and is not a specific finding for Crohn's gastritis [45].

Gastric granulomas have been reported to be found in 9–15 % of CD patients [56, 57]. In gastric CD, gastric granulomas appear to be more common in the antrum, with focally enhanced gastritis more common in the corpus [58]. However, granulomatous gastritis is also not specific to CD. Other etiologies of granulomatous gastritis include infection, foreign bodies, and involvement by other systemic granulomatous diseases. Thus, accurate diagnosis of gastric Crohn's disease requires careful correlation with clinical and laboratory findings.

Duodenal involvement by CD is relatively rare, with an estimated rate of involvement of 1–7 % [59]. When there is duodenal involvement, concurrent involvement of the terminal ileum and colon by Crohn's disease is common, with isolated Crohn's duodenitis being very unusual. In most CD patients with involvement of the duodenal bulb, there is contiguous involvement of the gastric antrum. The histologic appearance of duodenal CD is similar to what is seen in the terminal ileum and colon with patchy transmural involvement by chronic active inflammation with or without non-necrotizing granulomas.

Histologic Mimics of IBD

Many other forms of colitis can mimic IBD both histologically and endoscopically (Table 11.3). It is important that these other causes of chronic colonic injury be excluded before a diagnosis of IBD is made. In addition, IBD patients may have superimposed ischemic, drug associated, or infectious injury, making accurate classification very difficult.

Table 11.3 Histologic mimics of inflammatory bowel disease

Disease	Helpful distinguishing features
Infection	History, cultures, PCR
Salmonella	
Shigella	
Yersinia	
Mycobacterium tuberculosis	
Aeromonas	
Amebiasis	
Diverticula associated colitis	Disease limited to segment with diverticula. Rectal sparing.
Diversion colitis	History
Microscopic colitis	Normal endoscopy
Ischemic colitis	History
Radiation colitis	History
Systemic diseases	
Behcet's disease	Presence of oral and genital ulcers, iritis, and vasculitis
Common Variable Immunodeficiency	Plasma cells absent
Drugs	
Non-steroidal anti-inflammatory medications	History
Mycophenolate mofetil	History

Infectious Colitis

In most cases, histologic features distinguish cases of acute infectious colitis from IBD. However, acute infectious colitis can occasionally mimic the acute onset of IBD.

Biopsies of acute infectious colitis typically show preservation of crypt architecture with neutrophilic inflammation. There is increased lamina propria inflammation, but early in the infectious process, the inflammatory infiltrate is primarily comprised of neutrophils and histiocytes. As the infection begins to resolve, there is an increased mononuclear cell component in the lamina propria infiltrate, however, prominent basal plasmacytosis is not seen. More prolonged courses of infectious colitis can be histologically indistinguishable from IBD, requiring careful correlation with clinical, endoscopic, and microbiologic findings, as well follow-up endoscopy and biopsy.

Severe, prolonged infectious colitis, particularly with *Campylobacter*, *Shigella*, *Entamoeba histolytica*, and *Aeromonas* can induce crypt architectural distortion and an appearance that can overlap with that of either ulcerative colitis or Crohn's disease [60–64]. As the infection begins to resolve, there can be patchy inflammatory changes, which can be difficult to distinguish from Crohn's disease in some cases. In addition, infection with some organisms can be associated with a granulomatous pattern of inflammation, which can also resemble Crohn's disease.

Granulomatous colitis can be seen in infection by *Yersinia*, *Mycobacterium tuberculosis*, *Histoplasmosis*, and occasionally *Salmonella typhimurium*. *Yersinia* preferentially involves the terminal ileum, ileocecal area, appendix, and ascending colon—a disease distribution that can be mistaken for ileocecal Crohn's disease. *Yersinia* infection can result in neutrophilic and granulomatous inflammation. There is often prominent lymphoid cuffing around the epithelioid granulomas, lymphoid hyperplasia with lymphadenopathy, and transmural lymphoid aggregates. Skip lesions and fissuring ulcers can occur. Features that would favor *Yersinia* infection over CD would include the presence of granulomas with prominent lymphoid cuffing as well as the absence of creeping fat [60].

Mycobacterium tuberculosis most commonly involves the ileocecal and jejunoileal areas. Infection can result in ulcerating and structuring disease with skip areas. Confluent necrotizing granulomas (Fig. 11.7a, b) are classically associated

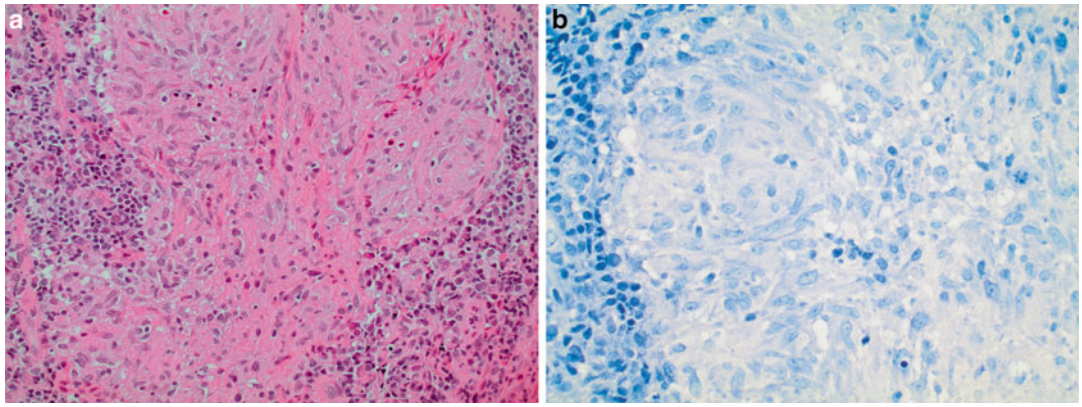

Fig. 11.7 (**a**) Granuloma in *M. tuberculosis* infection. (**b**) AFB stain highlighting *M. tuberculosis* organism

with *M. tuberculosis* infection; however, granulomas can also rarely contain areas of dystrophic calcification and hyalinization. Features that would favor CD over *M. tuberculosis* infection would include the presence of transmural lymphoid aggregates and evidence of chronicity away from areas of granulomatous inflammation [60]. However, distinction between these infectious etiologies and CD is often impossible on histologic examination alone and often requires correlation of histologic findings with clinical history, cultures, serologic studies and polymerase chain reaction (PCR) assays.

Diverticula Associated Colitis

Diverticular disease is common in patients 60 years of age or older and most commonly involves the sigmoid colon. Some patients develop chronic active colitis of the interdiverticular mucosa "diverticular disease-associated colitis (DAC)" or "segmental colitis associated with diverticular disease (SCAD)" [65–68]. The clinical course and histologic appearance can closely resemble IBD. Patients can present with abdominal pain, hematochezia, and diarrhea or constipation. An important diagnostic clue in differentiating DAC from IBD is that the area of inflammation is limited to the area of colon involved by diverticulosis (most commonly the sigmoid colon).

The histologic appearance of biopsy specimens is often indistinguishable from ulcerative colitis. Biopsies can contain increased lamina propria inflammation, mild basal plasmacytosis, Paneth cell metaplasia, architectural distortion, and cryptitis. However, unlike UC, the rectum is typically spared in DAC of the sigmoid colon. Thus, comparison of biopsies from the interdiverticular mucosa as well as the rectum may help differentiate DAC from UC.

Resection specimens may mimic changes of Crohn's disease with cobblestone ulcerations, mural thickening, and "creeping fat" on gross examination and with transmural inflammation, scattered granulomas and fissuring ulceration on histologic exam [69–71]. However, follow-up studies have shown that patients with DAC and a Crohn's-like appearance of their resected bowel do not go on to develop CD elsewhere in the GI tract [72–74].

Diversion Colitis

In segments of colon that have been surgically excluded from the fecal stream (e.g., a "Hartman's pouch"), an inflammatory process can sometimes occur, and is termed "diversion colitis" [74, 75]. These patients can present with abdominal pain and mucoid and/or bloody discharge. The pathogenesis of diversion colitis is thought to be a deficiency of short-chain fatty acid production by colonic bacteria, due to the decreased fermentation of dietary starches in the excluded segment of bowel [76]. Treatment with either short-chain fatty acid enemas or re-anastomosis of the

diverted segment and re-establishment of the fecal stream has been shown to result in resolution and regression of this inflammatory process [74].

On histologic examination, there are often numerous prominent lymphoid aggregates with germinal centers within the mucosa. There can also be architectural distortion, patchy cryptitis, aphthous ulceration, a variably dense chronic inflammatory infiltrate in the lamina propria, and even occasional granulomas, mimicking the histologic features of inflammatory bowel disease [77]. Thus, without the knowledge that the biopsy specimens were obtained from a diverted segment of bowel, the appearance can be easily mistaken for IBD.

In patients with a history of ulcerative colitis or Crohn's disease and colonic diversion, a diagnosis of diversion colitis should always be considered in addition to recurrent IBD. Korelitz et al. [78] reported that in patients with Crohn's disease, despite the development of ulcerations and stricture in the diverted segment of bowel, re-anastamosis and re-establishment of the fecal stream resulted in regression of these changes.

In addition, diversion colitis in the rectal stump of patients with ulcerative colitis should not be misinterpreted as evidence of Crohn's disease. In a study of 15 ulcerative colitis patients by Warren et al., [79] although examination of the rectal stump revealed areas of transmural inflammation, prominent lymphoid aggregates, and occasional granulomas, none of the patients developed subsequent clinical, radiologic or pathologic evidence of Crohn's disease.

Microscopic Colitis

Microscopic colitis is a term used to describe patients with watery diarrhea and a normal colonoscopic appearance, but with evidence of inflammation on histologic examination [80]. Microscopic colitis encompasses two relatively distinct histopathologic entities: (1) lymphocytic colitis and (2) collagenous colitis. Patients with microscopic colitis typically present at middle-age or older, with a median age of 64. There is a slight female predominance, particularly in collagenous colitis. Microscopic colitis is most commonly associated with celiac disease, as well as with other autoimmune disorders. In addition, association with drugs, particularly NSAIDs, and some infections have been reported.

On histologic examination, biopsies of collagenous colitis show an intact crypt architecture and increased cellularity of the lamina propria with increased numbers of lymphocytes, plasma cells, and scattered eosinophils. There is injury of the surface epithelium with mucin depletion. The subepithelial collagen table is thickened (≥10 μ[mu]m) and irregular, and entrapped capillaries and inflammatory cells can often be seen. Because of the abnormality of the subepithelial collagen, the surface epithelium often detaches from the mucosa during processing. Thickening of the subepithelial collagen table can be patchy and is often less prominent in the rectum and sigmoid. Trichrome staining can be used to highlight the thickened and irregular subepithelial collagen table, and can help confirm the diagnosis.

Lymphocytic colitis (Fig. 11.8) is characterized by increased intraepithelial lymphocytes in the surface epithelium and crypts. As colonic mucosa can normally contain some intraepithelial lymphocytes (less than 5 lymphocytes per 100 enterocytes), the presence of 20 or greater lymphocytes per 100 enterocytes has been suggested as a diagnostic threshold. Similar to collagenous colitis, there is increased lamina propria cellularity and the crypt architecture remains intact. There is no abnormality of the subepithelial collagen table.

Occasionally, microscopic colitis can show IBD-like histologic features (Fig. 11.9). In a study of 150 patients with microscopic colitis (79 patients with collagenous colitis and 71 patients with lymphocytic colitis), Ayata et al. found that neutrophilic crypt inflammation was commonly present (30 % of patients with collagenous colitis and 38 % of patients with lymphocytic colitis). In addition, surface ulceration, Paneth cell metaplasia, and crypt architectural abnormality could also occasionally be seen [81, 82]. Pathologists should also be aware of atypical forms of microscopic colitis that have been described, including microscopic colitis with giant cells as well as microscopic colitis with granulomatous inflammation [83]. Overall, in

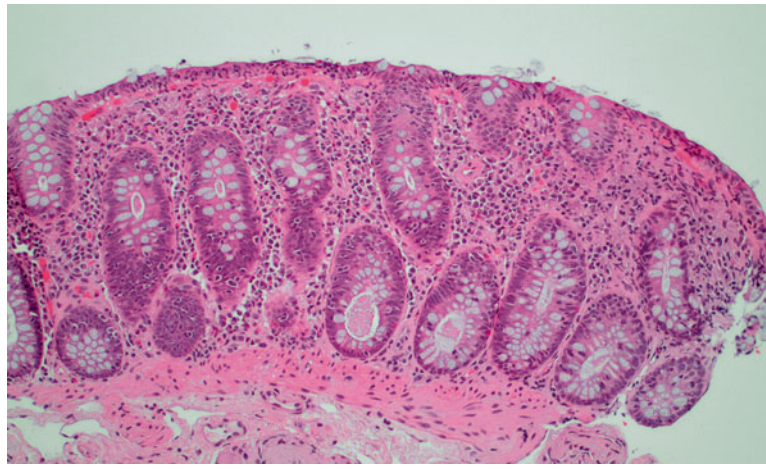

Fig. 11.8 Lymphocytic colitis

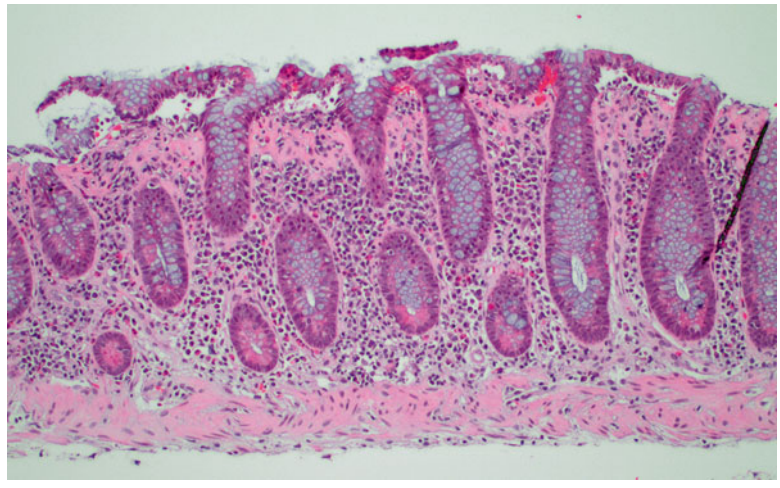

Fig. 11.9 Collagenous colitis with neutrophilic inflammation, Paneth cell metaplasia, and mild architectural distortion

cases that appear to have histologic features of microscopic colitis as well as superimposed IBD-like histologic changes, correlation with clinical findings and endoscopic findings will be helpful in accurate diagnosis.

Behcet's Disease

Intestinal involvement by Behcet's disease can be mistaken for Crohn's disease. Intestinal Behcet's disease most commonly involves the area around the ileocecal valve, and can show patchy disease, including rectal sparing, with deep linear ulcerations. Vasculitis is characteristic of Behcet's disease, but can occasionally be seen in CD as well. Helpful findings to distinguish between Behcet's disease and CD would include the presence of granulomas (which are not seen in Behcet's disease), and prominent stricture and sinus tract formation (which are also uncommon in Behcet's disease). A clinical history of extraintestinal manifestations of Behcet's disease (oral and genital ulcers, eye lesions, and evidence of

generalized vasculitic disease) would also allow differentiation between IBD and intestinal Behcet's disease [84].

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is an immunodeficiency syndrome characterized by hypogammaglobulinemia involving several antibody classes. Patients can present at any age, most often with recurrent bacterial infections. Approximately 20 % of patients with CVID also have chronic GI disorders. CVID in the GI tract can show a variety of histologic lesions and CVID in the colon can have features that can overlap with inflammatory bowel disease [85–87].

In colon biopsies from patients with CVID, neutrophilic cryptitis, epithelial lymphocytosis, mild architectural distortion and granulomata can be seen, and can be confused with Crohn's disease. In a study of 20 patients with CVID, Daniels et al. [85] found that seven patients had a diagnosis of inflammatory bowel disease (three as Crohn's disease) prior to the diagnosis of CVID. In addition, patients with CVID can often respond to the same medications used to treat inflammatory bowel disease. However, the absence of plasma cells in biopsies from patients with CVID is a distinguishing histologic feature and can be used to make the correct diagnosis.

Ischemic Colitis and Radiation Colitis

Other causes of chronic mucosal injury such as ischemia and chronic radiation injury can induce histologic changes such as crypt architectural distortion and pyloric metaplasia that can overlap with the chronic features of inflammatory bowel disease. However, chronic ischemic injury and radiation injury typically do not have increased lamina propria cellularity and the absence of significantly increased lamina propria inflammation or basal plasmacytosis can help distinguish from IBD.

Drug-Induced Injury of the Gastrointestinal Tract

Nonsteroidal Anti-Inflammatory Drugs

Drug-induced colitis can have a variety of clinical and histologic presentations and is often difficult to distinguish from IBD. One of the most common causes of drug-induced colitis are nonsteroidal anti-inflammatory drugs (NSAIDs), due to their extensive use in the general population. NSAIDs can cause mucosal erythema, ulcerations, and ischemic injury. In retrospective studies, NSAID-associated intestinal ulcerations were found in 0.2–0.45 % of patients undergoing colonoscopy [88, 89]. In addition, chronic NSAID use has been linked to the development of collagenous and lymphocytic colitis [90, 91]. It is thought that the main mechanism of NSAID injury in the colon is due to inhibition of prostaglandin synthesis and decreased cyclooxygenase activity [92, 93].

NSAIDs can induce patchy ileocolonic ulceration and inflammation as well as ileal stricture formation and can easily be mistaken for Crohn's ileocolitis. Histologic features of chronicity, such as architectural distortion, granulomata, and pyloric metaplasia can also be seen in chronic NSAID use [94–97]. Because of the marked overlap of histopathologic findings, careful correlation with clinical history is necessary.

Mycophenolate Mofetil

Gastrointestinal tract injury associated with the immunosuppressive agent mycophenolate mofetil can also be mistaken for IBD. GI toxicity is the most commonly observed side effect of mycophenolate and symptoms include nausea, vomiting, and diarrhea. Patients with mycophenolate GI toxicity can also have a spectrum of histologic changes, with biopsy appearances that can resemble graft-versus-host-disease, IBD, or Crohn's disease [97–103]. Although changes can be seen throughout the GI tract, in the colon, the

histologic features of mycophenolate toxicity include crypt architectural distortion including crypt atrophy and crypt branching, increased lamina propria cellularity and edema, neutrophilic cryptitis, and increased intraepithelial apoptosis with formation of apoptotic abscesses. In cases where the appearances greatly overlap with IBD, a trial of drug withdrawal and possible re-biopsy may be needed for definitive diagnosis.

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Part V

Use of Endoscopy to Follow Clinical Course in IBD

Role of Mucosal Healing

12

Arthur M. Barrie III and Miguel Regueiro

Introduction

The clinical evaluation of inflammatory bowel disease (IBD) patients has historically relied on symptoms alone, which often poorly correlate with objective markers of inflammation. Today in the era of biologic therapy, potent immunosuppressive and biologic medications are being prescribed earlier in an IBD patient's course to suppress potential disease progression, thereby limiting tissue destruction and preserving gut function.

Mucosal healing (MH), defined by the complete endoscopic healing of all inflammatory lesions, has become a relevant measure of IBD status and an important treatment goal [1], and endoscopy is the gold standard to evaluate MH and treatment response [2]. In this chapter we review the significance of MH in the two main types of IBD, ulcerative colitis (UC) and Crohn's disease (CD), the various endoscopic scoring systems for each, and clinical applications of MH for the care of IBD patients.

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Significance of Mucosal Healing in Ulcerative Colitis

As UC is limited to the mucosa and submucosa, mucosal healing is at the core of UC disease remission [3]. Pioneering studies by Truelove and Richards demonstrated that clinical symptoms in UC patients do not correlate with mucosal disease activity, as 60 % of examined patients in clinical remission had active endoscopic disease [4]. Interestingly, they and subsequent investigators found additional discordance between endoscopic and histologic findings. For example, Truelove and Richards found active histologic inflammation in 38 % of specimens from endoscopically normal appearing colonic mucosa, while Matts found in his study that 51 % and 79 % of patients reporting clinical remission had active endoscopic and histologic disease respectively [5].

MH on endoscopy and histology has proven to lead to improved clinical outcomes for UC patients. In the Norwegian IBSEN (Inflammatory Bowel in South Eastern Norway) population-based cohort study that investigated the clinical impact of MH, UC patients who achieved both endoscopic and histologic remission one year after their UC diagnosis significantly decreased their 5-year risk for colectomy (1.7 vs. 7.4 %, $P=0.02$) [6]. Histological healing appears to be essential for long-term disease remission, as an early study by Wright and Truelove demonstrated that 40 % of UC patients with no significant inflammation on

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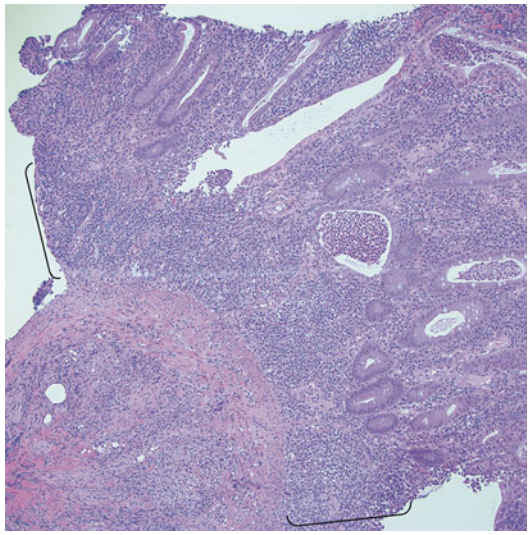

Fig. 12.1 Representative image of basal plasmacytosis in severely active chronic colitis. This image demonstrates colonic mucosa with marked crypt distortion, crypt abscesses, expansion of lamina propria by a chronic lymphoplasmacytic infiltrate with prominent basal plasmacytosis (*outlined by brackets*). (Hematoxylin and eosin, ×100)

rectal biopsies after corticosteroid treatment were symptom-free 1 year later compared to only 18 % of patients who had persistent histologic inflammation [7]. Riley and colleagues subsequently found that UC patients with no symptoms and normal appearing mucosa but with acute inflammation on biopsies were 2–3 times more likely to have a disease flare in the next 1 year compared to patients with no acute histologic inflammation [8]. Interestingly, several more recent studies have identified the presence of basal plasmacytosis, a histologic marker of chronic inflammation (Fig. 12.1), as a strong predictor of disease relapse in patients with quiescent UC [9, 10]. Additional new translational studies have demonstrated the exciting capability of confocal laser endomicroscopy to perform real-time evaluation of histology during endoscopy, including the detection of specific in vivo intramucosal changes that correlate with disease flares in UC patients in clinical and endoscopic remission [11].

The clinical importance of MH in UC is independent of treatment type and is true across all drug classes. Meucci and colleagues showed that UC patients who attained clinical and endoscopic remission treated with oral and topical mesalamine for 6 weeks had a 23 % 1-year relapse rate in contrast to an 80 % relapse rate for patients who only went into clinical remission ($P<0.0001$) [12]. Ardizzone et al. found that patients who achieved endoscopic remission at 3 months after their first course of corticosteroids were less likely to be hospitalized (25 vs. 49 %, $P=0.015$) or require a colectomy (3 vs. 18 %, $P=0.027$) over a 5-year follow-up period compared to patients who were in clinical remission but had persistent mucosal disease [13]. Similar results were observed in the ACT1 and ACT2 UC infliximab trials, in which MH at 8 weeks of infliximab treatment significantly decreased the 1-year risk of colectomy compared with treated patients without MH ($p<0.001$) and correlated with increased rates of clinical and corticosteroid free remission at 30 and 54 weeks ($p<0.0001$) [14].

Significance of Mucosal Healing in Crohn's Disease

MH appears to be important for CD, but its significance and application in CD is less clear-cut than in UC. CD involves transmural injury and locations in the intestine that may not be accessible to endoscopy [3]. As in UC, multiple studies, particularly from the Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestive (GETAID), have found that clinical symptoms and mucosal disease activity do not often correlate in CD. For example Modigliani and colleagues found that only 29 % of colonic and ileocolonic Crohn's disease patients who achieved corticosteroid-induced clinical remission also attained endoscopic remission [15]. Accordingly, the objective nature of MH may prove to be a worthwhile treatment goal rather than subjective clinical remission to decrease the risk of progressive and irreversible tissue destruction seen in CD, such as intestinal strictures and penetrating complications. Ultimately a measure of structural damage that accounts for the transmural process of CD would be a valuable tool for assessing disease progression or improvement to

treatment. Lemann and colleagues have initiated such a CD scoring system that accounts for disease involvement beyond endoscopic mucosal assessment [16].

The IBSEN cohort study demonstrated that Crohn's patients who developed MH at 1 year after diagnosis were less likely to require intestinal resection by 5 years compared to patients without MH (11 % vs. 20 %) [6], and this difference became significant by 10 years and translated into a 60 % risk reduction [17]. Similarly, Baert and colleagues found that complete MH at 2 years after CD diagnosis and treatment initiation was the only predictive factor that correlated with a sustained corticosteroid-free clinical remission, as 71 % of patients with MH were in remission at 3 and 4 years of follow-up compared to only 27 % of patients who had persistent disease activity at 2 years (P = 0.036) [18].

As in UC, the clinical significance of mucosal healing appears to be independent of treatment choice. In a study detailing the superiority of azathioprine versus budesonide at inducing and maintaining complete or partial MH after 1 year of treatment (83 % vs. 24 %, p = 0.0001), azathioprine-treated patients also had a higher rate of clinical remission over an 18 month follow-up period (76 vs. 36 %, respectively, P = 0.03) [19]. Regarding tumor necrosis factor (TNF) inhibitors, Schnitzler and colleagues prospectively investigated a cohort of CD patients treated with infliximab and found those patients who achieved complete or partial MH required fewer hospitalizations (42 vs. 59 %, P = 0.0018) and less major abdominal surgery (14 vs. 38 %, P < 0.0001) than CD patients with no MH [20]. Likewise, in a subgroup analysis of the randomized maintenance infliximab ACCENT 1 trial (**A** **C**rohn's Disease **C**linical Trial **E**valuating Infliximab in a **N**ew Long-term **T**reatment Program), 18 % of CD patients in endoscopic remission at either 10 and/or 54 weeks of treatment had CD-related hospital admissions compared to 28 % of patients with no healing at either time point, and none of the 9 patients who had MH at both time points required hospitalization at 1 year follow-up [21].

Table 12.1 Rutgeerts postoperative Crohn's disease endoscopic scoring system

Endoscopic score	Endoscopic findings
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis (i.e.:<1 cm in length)
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

The importance of MH or endoscopic remission in CD has been further appreciated in the postoperative setting. Rutgeerts and colleagues found in their initial seminal study of the natural history of postoperative recurrent CD that 72 % of examined patients (21 out of 29) had recurrent endoscopic CD within 1 of year of curative resection and that a remarkable number of these patients were asymptomatic [22]. In a subsequent prospective cohort 8 year follow-up study of 89 patients after resection, Rutgeerts and his team found that only 20 % and 34 % of patients were symptomatic 1 and 3 years after surgery, respectively, despite endoscopic disease found in 73 % and 85 % of these patients [23]. Regueiro and colleagues observed similar findings in their postoperative randomized placebo-controlled infliximab trial, as they determined the kappa coefficient of agreement between the patients' endoscopic scores and their clinical Crohn's Disease Activity Index (CDAI) scores was only 0.12 [24].

Rutgeerts and colleagues went on to show that the degree of endoscopic disease severity at 1 year, as judged by the now classified Rutgeerts score (Table 12.1, Fig. 12.2a–d), directly correlated with the progression to symptomatic recurrence and that the endoscopic score was the most statistically significant variable in predicting outcome [23]. For example, only 8.6 % of patients with no or only mild endoscopic disease at 1 year, as defined by Rutgeerts score i0 or i1, had clinical symptoms at 8 years, while 100 % of patients

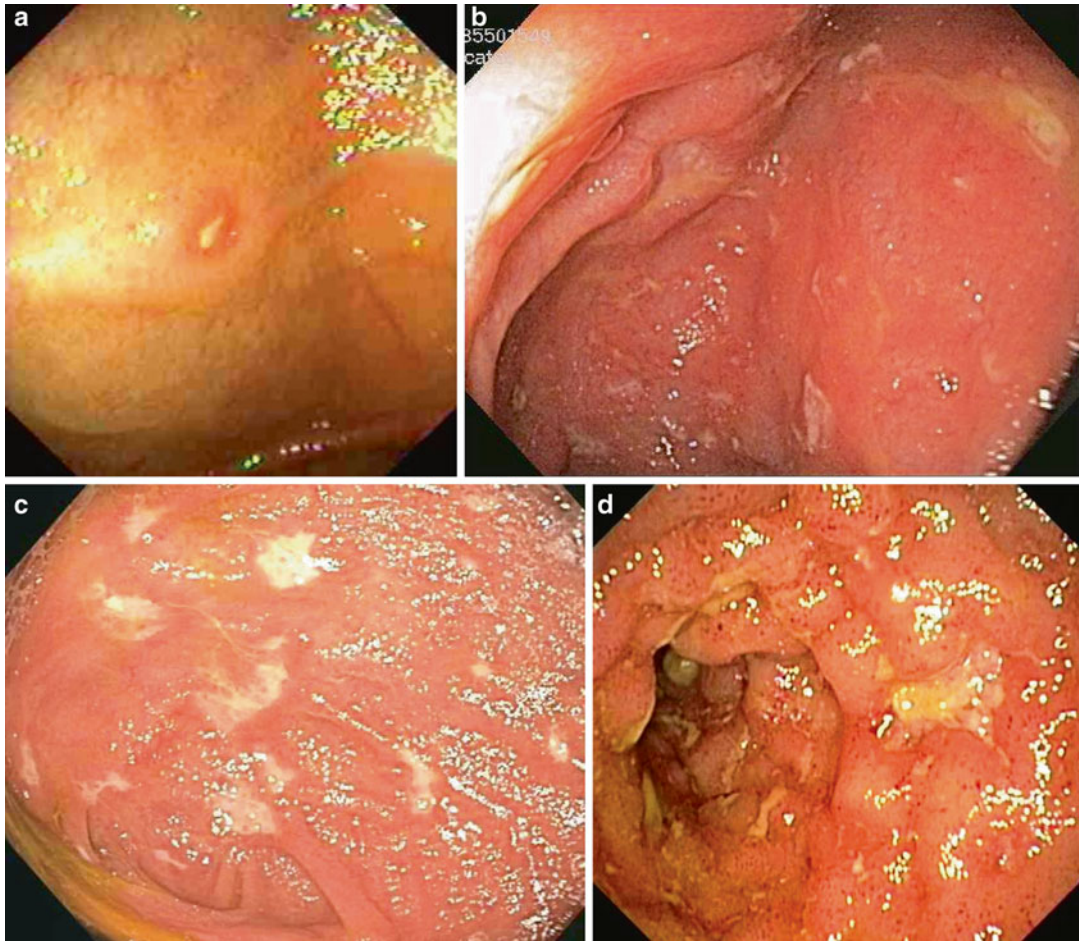

Fig. 12.2 Representative images of the Rutgeerts postoperative Crohn's disease endoscopic scoring system: (**a**) i1 with <5 aphthous lesions, (**b**) i2 with >5 aphthous lesions, (**c**) i3 with diffuse aphthous ileitis, and (**d**) i4 with diffuse inflammation and narrowing

with severe endoscopic disease, as defined by Rutgeerts score i4, had symptomatic recurrence by 4 years.

Endoscopic Assessment of Mucosal Healing

Despite the increasing emphasis on MH in IBD research and patient care, there is yet no true validated instrument for measuring MH. Numerous endoscopic scoring systems have been proposed for both CD and UC [1]. There have been at least ten disease activity indices developed for UC including the Baron score, which was the original endoscopic grading instrument for UC and focuses on bleeding severity. The Baron score was followed by the development of several other indices including the Mayo endoscopic subscore, which is more extensive and analyzes erythema, vascular pattern, friability, erosions and ulcerations (Table 12.2, Fig. 12.3a–d).

The newest developed instrument for UC is the UC endoscopic index of severity (UCEIS) [25]. The UCEIS evaluates three descriptors that the developers concluded were sufficient to measure disease severity: vascular pattern, bleeding, and erosions and ulcers (Table 12.3). The worst segment of the

Table 12.2 Mayo score for UC

Score	0	1	2	3
	Normal or inactive disease	Mild (erythema,decreased vascular pattern,mild friability	Moderate (marked erythema, absent vascular pattern, friability, erosions)	Severe (spontaneous bleeding, ulceration)

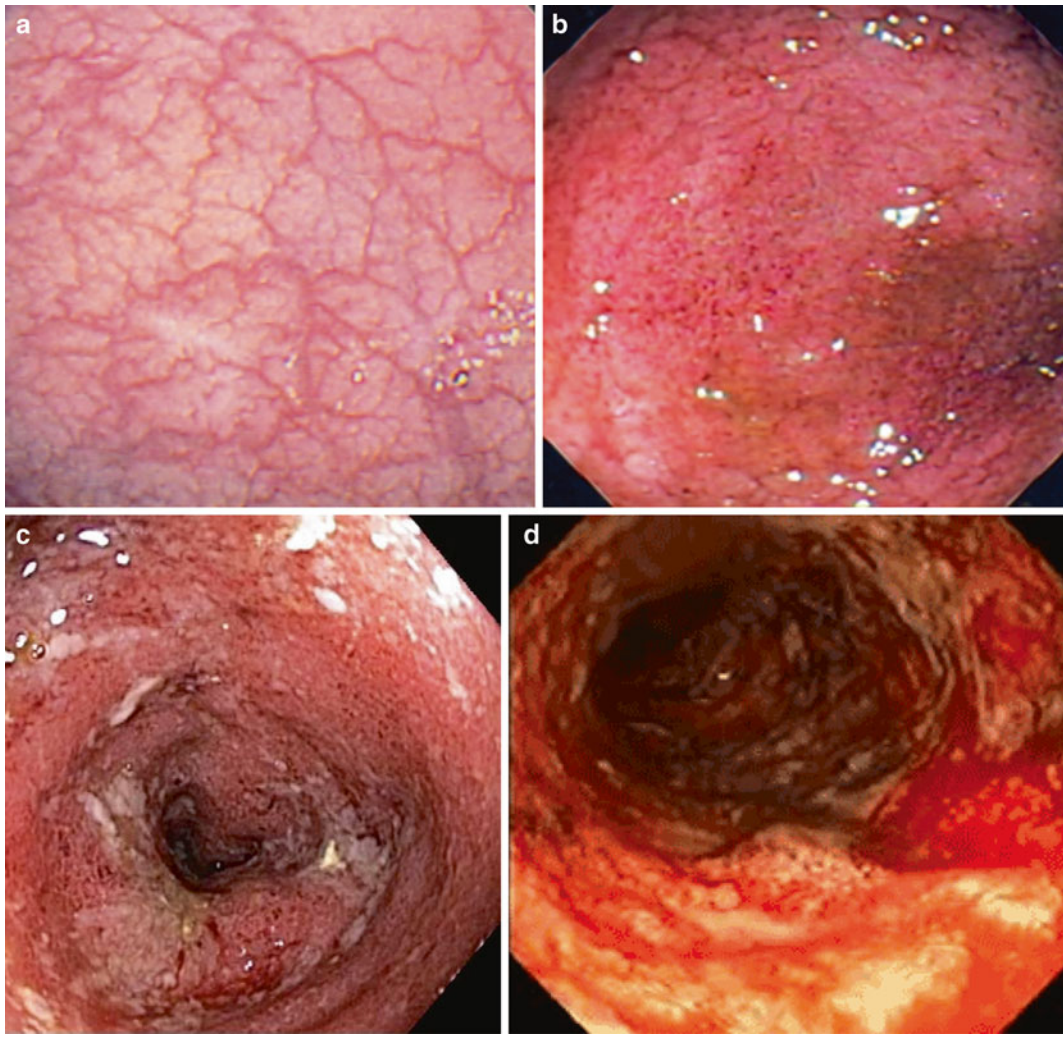

Fig. 12.3 Representative images of the Mayo endoscopic scoring system for ulcerative colitis: (**a**) score 0 with no disease, (**b**) score 1 with mild disease, (**c**) score 2 with moderate disease, and (**d**) score 3 with severe disease

diseased colon is scored for each variable on a ranked 0–2 or 0–3 scale and a sum score from 0 to 8 is then generated. The reliability and validity of the UCEIS were recently published, and it was found that there was satisfactory intraobserver and interobserver reliability as defined by a good overall Kappa (K) score of 0.72 for intraobserver agreement and a moderate overall K score of 0.50 for interobserver agreement [26]. The authors also reported that the correlation of UCEIS scores and overall assessment of severity was high as defined by a Pearson correlation coefficient of 0.93.

The current gold standard for measuring MH in CD is the CD endoscopic index of severity or

Table 12.3 Ulcerative colitis endoscopic index of severity (UCEIS)

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (1)	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (2)	Patchy obliteration of vascular pattern
	Obliterated (3)	Complete obliteration of vascular pattern
Bleeding	None (1)	No visible blood
	Mucosal (2)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (3)	Some free liquid blood in the lumen
	Luminal moderate or severe (4)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a haemorrhagic mucosa
Erosions and ulcers	None (1)	Normal mucosa, no visible erosions or ulcers
	Erosions (2)	Tiny (≤5 mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (3)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (4)	Deeper excavated defects in the mucosa, with a slightly raised edge

CDEIS [27]. The CDEIS involves a complicated and somewhat subjective assessment of the ileum, colon, and rectum in a segmental fashion. A score is generated using the complex formula in Table 12.4. The CDEIS has proven to be too complicated for routine patient care. Consequently, the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) was developed by the CDEIS investigators [28]. The SES-CD scoring system involves four variables: (1) ulcer size, (2) % ulcerated surface, (3) affected surface, and (4) presence of narrowings. Each variable is scored, in segmental fashion from ileum to rectum, on a ranked scale 0–3, and then added together to generate a sum score (Table 12.5).

The CDEIS and SES-CD disease activity indices have been reported to have good to excellent reliability as defined by an intraclass correlation coefficient (ICC) of 0.96 for the CDEIS [27], and interobserver agreement κ scores ranging from 0.791 to 1.000 for the SES-CD [28]. The validity of the CDEIS and SES-CD instruments has recently been examined by Ferrante and colleagues in a post hoc analysis of 172 patients from the SONIC trial ((**S**tudy **o**f Biologic and Immunomodulator **N**aïve patients **i**n **C**rohn's Disease) that investigated the treatment effects of infliximab and/or azathioprine for corticosteroid dependent CD patients [29]. The authors examined multiple cutoff values of endoscopic response for the two systems at week 26 of treatment compared to week 0 scores and relative to corticosteroid-free clinical remission rates at week 50. They found that an endoscopic response defined by at least a 50 % reduction in SES-CD and CDEIS scores correlated with corticosteroid-free remission at week 50 with 74 % and 75 % sensitivity and 48 % and 45 % specificity, respectively, for each index.

The only endoscopic instrument for the evaluation of postoperative ileal CD is the aforementioned Rutgeerts scoring system, which defines severity of disease on a 0–4 scale based on the extent of aphthous ulcerations in the neoterminal ileum [23]. As defined by Rutgeerts and colleagues, complete endoscopic remission with no lesions is classified as i0, while mild disease consisting of 5 or fewer aphthous ulcers is classified as i1. Moderate disease defined by > 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis is classified as i2. Diffuse aphthous ileitis with diffusely inflamed mucosa is classified as i3 and the most severe

Table 12.4 Crohn's Disease Endoscopic Index of Severity (CDEIS)

Variable No.	Variable description	Weighing factor	Total
1	Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that deep ulcerations are seen in divided by the number of segments examined	12	
2	Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that superficial ulcerations are seen in divided by the number of segments examined	6	
3	Segmental surfaces involved by disease. The degree of disease involvement in each segment is determined by examining each segment for the following nine lesions (pseudopolyps, healed ulcerations, frank erythema, frank muscosal swelling, apthoid ulcers, superficial ulcers, deep ulcers, nonulcerated stenosis, ulcerated stenosis) and estimating the number of cm of involvement (one or more lesions present) in a representative 10 cm portion from each segment. The average segmental surface involved by disease is calculated by dividing the sum of each of the individual segmental surfaces involved by disease by the number of segments examined	1	
4	Segmental surfaces involved by ulcerations. The degree of ulceration in each segment is determined by examining each segment for ulceration (apthoid ulcers, superficial ulcers, deep ulcers, ulcerated stenosis) and estimating the number of cm of intestine involved by ulceration in a representative 10 cm portion from each segment. The average segmental surface involved by ulceration is calculated by dividing the sum of each of the individual segmental surfaces involved by ulceration by the number of segments examined	1	
5	Presence of a nonulcerated stenosis in any of the segments examined	3	
6	Presence of an ulcerated stenosis in any of the segments examined	3	
Total CDEIS			

Table 12.5 Simplified endoscopic activity score for Crohn's disease (SES-CD)

	0	1	2	3
Presence and size of ulcers	None	Aphthous <0.5 cm	Large, 0.5–2 cm	>2 cm
Extent of ulcerated surface	0 %	<10 %	10–30 %	>30 %
Extent of affected surface	0 %	<50 %	50–75 %	>75 %
Presence and type of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

disease characterized by diffuse inflammation with already larger ulcers, nodules, and/or narrowing is classified as i4 disease. Many studies now define endoscopic postoperative remission as i0 or i1 and recurrence as i2, i3, or i4 [30]. The reliability of the Rutgeerts score has not been formally validated; however, the instrument has become the gold standard for assessing postoperative CD recurrence given its ease of use and ability to predict disease course.

Though the Rutgeerts score was developed for ileocolonoscopy, several studies have begun to evaluate a possible role for wire capsule endoscopy (WCE). Bourreille and colleagues compared WCE versus ileocolonoscopy for the diagnosis of postoperative CD recurrence in the neoterminal ileum defined by a Rutgeerts score of i1 or greater, with a reported recurrence rate of 68 % in their study population [31]. They found that the sensitivity and specificity of ileocolonoscopy were 90 % and 100 %, while the sensitivity and specificity of WCE were 62–76 % and 90–100 %, depending on discordant results. These operating characteristics did not significantly change if recurrence was defined by a Rutgeerts score of i2 or greater. The investigators

concluded that WCE is inferior to ileocolonoscopy in diagnosing postoperative CD recurrence, but noted that WCE detected small bowel lesions beyond the reach of ileocolonoscopy in two-thirds of patients. In contrast, a similar study by Pons Beltran and colleagues found that WCE detected CD recurrence, defined by a Rutgeerts score of i2 or greater, in 62 % of patients compared to a detection rate of only 25 % for ileocolonoscopy, and WCE detected proximal small bowel disease in over one-half of patients [32]. A third study by Biancone and colleagues investigated WCE and small intestine contrast ultrasonography (SICUS) for the diagnosis of CD recurrence, using ileocolonoscopy and a Rutgeerts score of i1 or greater as the gold standard [33]. Of the 17 patients who had all three procedures performed, ileocolonoscopy and WCE detected recurrence in 16 patients while SICUS detected recurrence in all 17 patients with one patient considered a false positive. These studies combined suggest that WCE is capable of evaluating postoperative CD, however, before it can be applied in clinical practice, an alternative scoring system taking into account proximal small bowel lesions will be necessary to more accurately determine prognosis, as well as additional studies correlating WCE findings with subsequent clinical course.

Role of Mucosal Healing in Clinical Practice

MH is an ideal treatment goal for IBD patients, but may not be achievable for all patients [3, 34]. For example, only 44 % of treatment naïve CD patients achieved MH compared to a clinical remission rate of 56 % after 26 weeks of treatment with combination infliximab and azathioprine therapy in the SONIC trial [35]. As De Cruz and colleagues point out in their review, further escalation of potent immunosuppressive therapy in order to achieve MH may increase the risk of malignancy and infection. Thus in some cases it may be more realistic to focus on mucosal improvement in asymptomatic patients rather than complete mucosal healing.

In addition, MH may not be a practical goal in clinical practice if endoscopy is required given its related high cost and procedure risk. Many unresolved details remain before MH can be integrated into the standard of IBD care, including the need for validated definitions and instruments of MH, as well as validated timing of endoscopic evaluations after treatment initiation or surgery. Prospective trials are underway to determine when and how to escalate or de-escalate therapy based on MH, and to establish whether MH is truly associated with limiting disease progression.

Despite emerging data that mucosal inflammation is an important determinant of IBD progression and mucosal healing, a potential goal for prevention of disease complications, there remain many unanswered questions for the clinician. Is it practical and possible to achieve mucosal healing in all IBD patients? Are there noninvasive tests (e.g., fecal calprotectin or C-reactive protein) that can accurately predict mucosal healing? What do we do if a patient has significant but incomplete mucosal healing at endoscopy? We conclude this chapter with our approach to mucosal healing and acknowledge that this is not evidence based.

The Postoperative Crohn's Patient

We routinely perform ileocolonoscopy 6–12 months after surgery for patients receiving medical prophylaxis or 3 months after surgery for patients on no medical therapy (Fig. 12.4). Patients who have no recurrence (i0) or minimal recurrence (i1) are considered in remission and we continue their current treatment but repeat a colonoscopy 1 year later. Assuming the endoscopic findings remain an i0 or i1, we continue treatment and reassess 2 years later. The exception is the patient on no medication who has an endoscopic score of i1 or higher 3 months after surgery. We consider this an endoscopic recurrence and would start medical therapy. Patients on medical therapy with an endoscopic score of i2 or greater at surveillance colonoscopy are considered to have endoscopic recurrence and we recommend optimizing the current treatment or adding/switching therapy. It has been our experience that

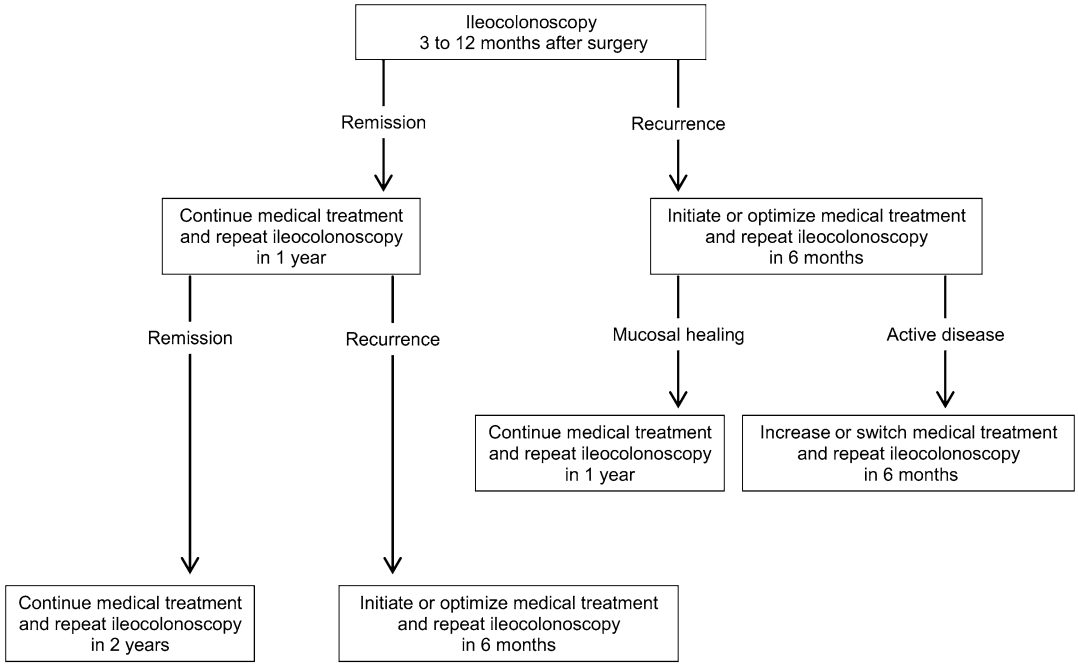

Fig. 12.4 Endoscopic assessment of the postoperative Crohn's patient

patients who progress to i4 with a stricture extending beyond the anastomosis, rarely respond to medication and often require another surgery.

Crohn's Disease and Ulcerative Colitis

Although we are beginning to implement the Mayo subscore for UC and Simplified Endoscopy Score for CD, we remain subjective in our endoscopic assessment of mucosal as well as histologic healing in the majority of our patients (Figs. 12.5, 12.6, 12.7, and 12.8). We suspect that this "real-world" approach is similar to most practitioners caring for IBD patients. Specifically, we qualify disease activity as normal, mild, moderate, and severe, and follow-up endoscopic assessment as improved, worse, or the same as before. It is our practice to perform endoscopic assessment 12 months after initiation or adjustment of treatment for patients who achieve a complete clinical response or within 6 months after treatment change for patients who do not fully respond to treatment (Fig. 12.9). Prior to the endoscopy, we have a discussion with the patient on the implication of active mucosal disease. Patients without endoscopic improvement or worsening inflammation require optimization of current treatment and/or escalation of therapy. Patients with complete mucosal healing (i.e., complete resolution of prior

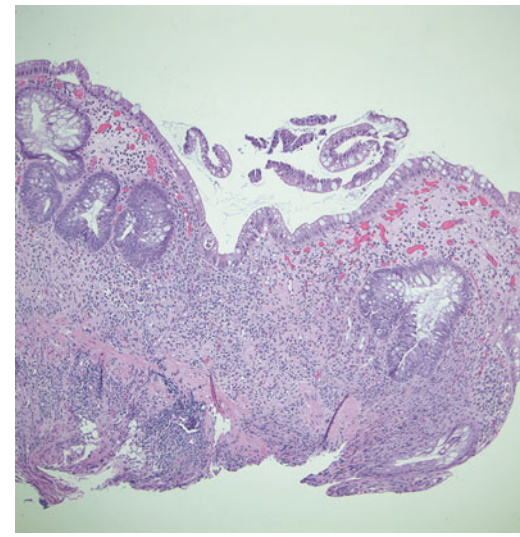

Fig. 12.5 Mildly active chronic colitis. This image demonstrates colonic mucosa intraepithelial neutrophil infiltration, crypt dropout, crypt distortion and expansion of the lamina propria by a chronic lymphoplasmacytic infiltrate. (Hematoxylin and eosin, ×100)

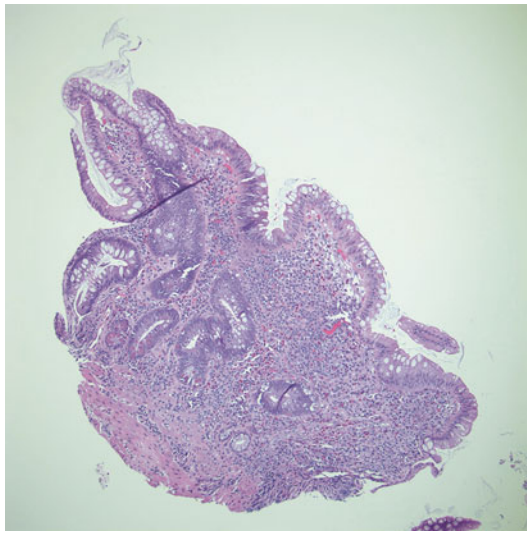

Fig. 12.6 Chronic inactive colitis. This image demonstrates colonic mucosa from the descending colon with marked crypt distortion, expansion of the lamina propria by a chronic lymphoplasmacytic infiltrate, Paneth cell metaplasia and pseudopyloric gland metaplasia. No intraepithelial neutrophil infiltration is present. (Hematoxylin and eosin, ×100)

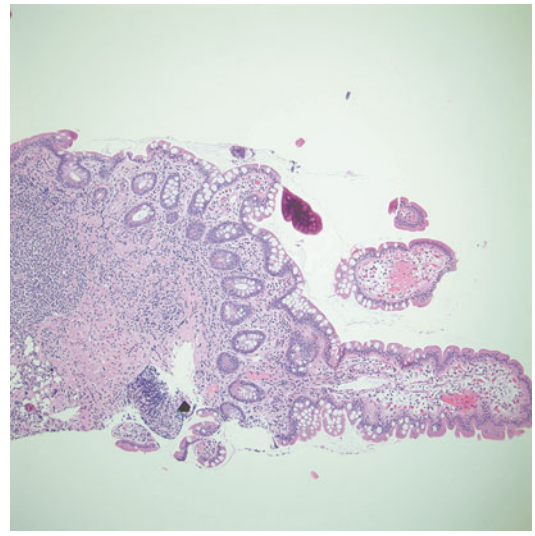

Fig. 12.8 Chronic inactive ileitis. This image demonstrates small intestinal mucosa (terminal ileum) with pseudopyloric gland metaplasia, mild crypt distortion and villous architectural abnormalities (thickening of the villi). No intraepithelial neutrophil infiltration is present. (Hematoxylin and eosin, ×100)

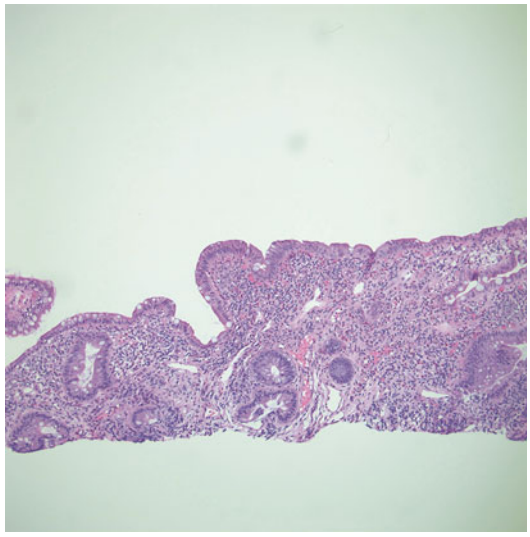

Fig. 12.7 Mildly active chronic ileitis. This image demonstrates small intestinal mucosa (terminal ileum) with intraepithelial neutrophils, crypt distortion, expansion of the lamina propria by a chronic lymphoplasmacytic infiltrate and blunting of the villous architecture. (Hematoxylin and eosin, ×100)

inflammation) continue on their current treatment. Whether the patient in sustained deep remission may stop treatment is unknown and is being investigated.

Patients with improvement in endoscopic inflammation, but not complete resolution of disease, pose the greatest challenge. Such examples would be the ulcerative colitis patient who improves from a severe Mayo subscore of 3 to a mild Mayo subscore of 1, or the Crohn's disease patient who improves from a severe SES-CD score of 3 to a mild score of 1. In these cases, the patient's perspective may vary from the dogma of trying to achieve complete mucosal healing. If the patient has ongoing symptoms, it is easier to justify optimizing treatment. However, it has been our experience that most patients who have had severe disease and achieve *almost* complete mucosal healing feel well and are asymptomatic. For the asymptomatic patient with mildly active disease there are limited data to guide us. In these cases, we optimize the dose of 5-aminosalicylate,

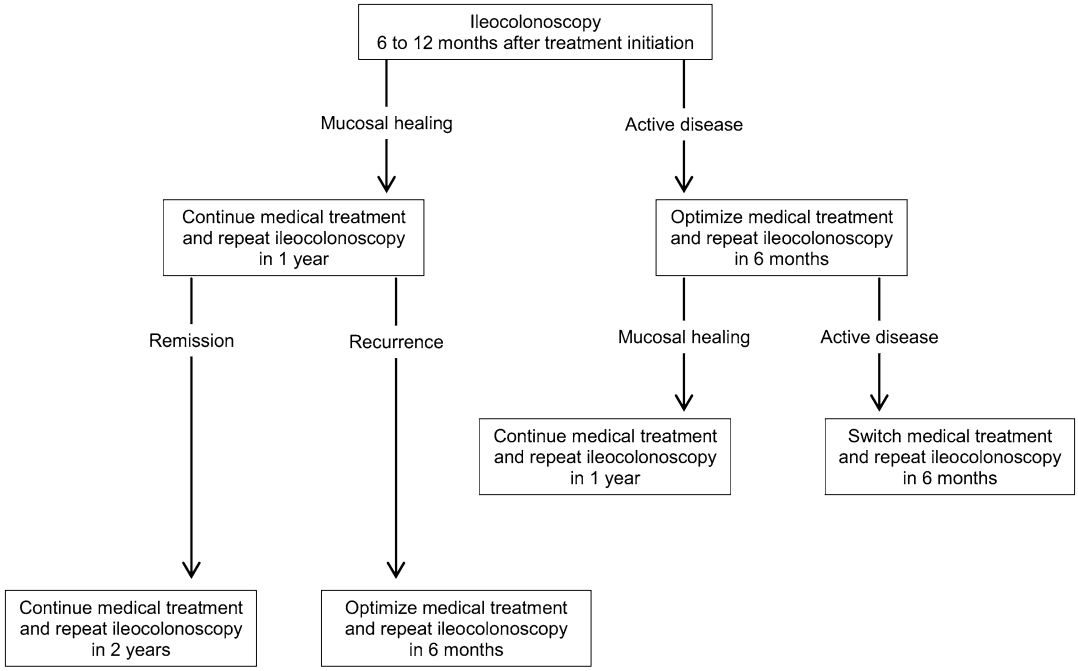

Fig. 12.9 Endoscopic assessment of the IBD patient undergoing treatment

immunomodulator, and/or anti-TNF therapy. We will use thiopurine metabolites and anti-TNF drug levels to guide optimization. The patients who are on maximal therapy (e.g., optimized doses of thiopurines in combination with anti-TNF therapy) may not be able to achieve complete mucosal healing. It is our opinion that minimal disease activity in these patients who previously had severe disease is acceptable and we do not yet recommend switching classes of treatment. Finally, many patients may not want to adjust medical treatment if they are asymptomatic but have residual mild disease on endoscopy.

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Role of Endoscopy to Define Postoperative Recurrence in IBD

13

James D. Lord and Elisa Boden

Role of Endoscopy to Define Postoperative Recurrence in IBD

Until the recent advent of effective pharmacotherapy for inflammatory bowel disease (IBD), surgery has historically been the mainstay of treatment offered to patients. Indeed, even in this modern age of targeted biopharmaceuticals and maintenance regimens, surgery represents the most durable source of remission for Crohn's patients, and the only cure for ulcerative colitis (UC). Surgical techniques have also improved over the years to improve the safety and tolerability of operative IBD management. The use of bowel-sparing stricturoplasties in place of resections has reduced the risk of short-bowel syndrome in Crohn's disease (CD) [1]. Improvements in ileo-anal pull-through techniques, including laparoscopic approaches, have afforded restoration of intestinal continuity to UC patients undergoing proctocolectomy [2]. Perhaps as a consequence, the rate at which IBD patients undergo surgery has only modestly diminished in recent years, despite advances in medical therapies [3].

However, surgery does not necessarily represent an end to the risk of bowel inflammation, particularly in Crohn's disease, where eventual relapse is almost inevitable [4, 5]. Even after curative proctocolectomy, UC patients have a high risk of developing recurrent inflammation in the form of cuffitis, pouchitis or Crohn's disease of the ileoanal pouch [6]. Thus, current strategies for managing IBD postoperatively may involve judicious use of medical therapy postoperatively, even in the absence of symptoms in Crohn's disease. This chapter will discuss the role of endoscopy in diagnosing recurrent disease and guiding therapy in the postoperative patient.

Crohn's Disease

Roughly half of Crohn's patients may undergo surgery within a decade of diagnosis, and up to 80 % of Crohn's patients may undergo surgery at some point in their lives for this disease [7–11]. Just as Crohn's disease is a multifaceted and heterogeneous condition, the surgeries used to treat it are myriad and diverse. However, the most common surgery performed for Crohn's disease is an ileocecectomy or ileocolectomy with ileocolonic anastomosis to remove all inflammation and associated strictures detectable at the time of surgery, leaving a healthy anastomosis if no inflammation is evident at the margins of the

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resected specimen. Consequently, the majority of available data concerning postoperative recurrence of Crohn's disease considers recipients of this surgery. Much like the surgical debulking of a tumor, intestinal resection for Crohn's disease can eliminate all grossly evident pathological tissue, albeit in this case immune effector cells rather than dysplastic cells. However, as with tumor debulking, the resection of all diseased tissue grossly or even microscopically evident at the time of surgery does not preclude postoperative disease recurrence [12]. As a fraction of any intestinal mucosal immune cells, including those believed to cause intestinal mucosal inflammation in IBD, may be in circulation at any given time, it is perhaps these cells that return to the bowel to reinitiate Crohn's disease postoperatively, just as circulating tumor cells can metastasize to cause recurrent disease after surgery.

Indeed, mucosal recurrence of Crohn's disease after ileocolectomy can be documented by colonoscopy in 70–90 % of patients [10, 13], usually within the first year after surgery [4, 14], and sometimes even within the first 3 months [5]. The vast majority of such recurrence will occur in the neo-terminal ileum, just upstream of the ileocolonic anastomosis, to which it will be limited in almost 90 % of cases [4]. Even in patients whose Crohn's disease was limited to the colon prior to surgery, the ileum proximal to the anastomosis is the most common site of endoscopic recurrence [5]. This has been hypothesized to result from increased contact between the colonic microbial flora and the ileal mucosa, due to loss of the ileocecal valve. Endoscopic recurrence is dependent upon mucosal contact with the fecal stream [15], as a diverting ileostomy upstream of the ileocolonic anastomosis has been shown to prevent it, while subsequent restoration of continuity with an ostomy takedown results in prompt endoscopic recurrence [16]. In most cases, endoscopic recurrence may be clinically silent for years, as only 30–40 % of Crohn's patients report gastrointestinal (GI) symptoms for up to a decade after ileocecectomy with primary reanastamosis [10, 13]. However, the severity of endoscopic recurrence is a powerful predictor of subsequent clinical recrudescence [12]. Smoking, penetrating Crohn's disease (e.g., fistulas or abscesses from Crohn's), or a history of prior resections each confers a 1.5- to 2-fold increased risk for accelerated postoperative recurrence, so patients with none of these features may be less likely to warrant postoperative prevention. Efforts to improve upon these predictors, using serologic or genetic testing, have largely been ineffective. Although considerable data concerning the association between IBD-specific antibodies and Crohn's disease behavior has been published, very little information exists on how such test results correlate with disease recurrence after surgery [17]. Antibodies to *Saccharomyces cerevisiae* (ASCA), which have long been associated with Crohn's disease and its behavior, have been found to have no predictive power in identifying patients at risk for postoperative recurrence [18]. NOD2, the gene most strongly associated with Crohn's, has also proven to be a poor predictor of postoperative recurrence in a recent meta analysis [19]. Out of 26 genetic polymorphisms associated with Crohn's disease, only homozygosity for a SMAD3 variant was significantly associated with postoperative recurrence on multivariate analysis [20]. Thus, it remains difficult to preoperatively identify patients who will require postoperative medical prophylaxis.

A number of prophylactic medical regimens have been employed in efforts to alter postoperative recurrence, including probiotics, antibiotics [21], 5' aminosalicylate agents, and thiopurine immunomodulator drugs [22]. However, the most recent and impressive data on postoperative prophylaxis involves the initiation of anti-TNF-α(alpha) biological drugs within the first month after surgery. In 2009, a small, randomized trial reported endoscopic recurrence of Crohn's disease 1 year after ileocecectomy in only 1 of 11 patients who started the anti-TNF agent infliximab less than a month after surgery, compared to 11 of 13 patients in a placebo group [23].

Cost-effectiveness models comparing the various postoperative prophylaxis strategies have suggested that endoscopic risk-stratification prior to anti-TNF initiation is a more efficient use of health care resources than universal administration of anti-TNF agents or less effective medications in the immediate postoperative period [24, 25].

A strategy has therefore been proposed in which initiation of anti-TNF therapy within 2–4 weeks of surgery may be reserved only for patients with risk factors for aggressive recurrent Crohn's [26, 27]. In all others, a colonoscopy performed 6 months after surgery may provide sufficient time for Crohn's to exhibit endoscopic signs of recurrence sufficient to warrant initiation of anti-TNF therapy. This dictates that continued close monitoring of patients after surgery by a physician with access to colonoscopy is essential for optimal care. A uniform definition of what constitutes "recurrence" on colonoscopy is also essential for this approach to succeed.

In all the aforementioned studies, postoperative endoscopic recurrence has been defined using a version of an endoscopic activity scale originally published by Paul Rutgeerts et al. in 1990 [12], now referred to as the "Rutgeerts score." This system is far simpler than the Crohn's disease endoscopic index of severity (CDEIS) [28] commonly used in clinical trials, and ranks inflammation grossly from 0 to 4 in the neoterminal ileum, where inflammation after ileocolonic resection/anastomosis for Crohn's recurs. Thus, Rutgeerts scores are commonly prefaced with an "i" (ileum) as i0-i4 (Table 13.1). A score of i0 requires that no apthous ulcers or other signs of inflammation be present, in which case ileal mucosa should appear completely normal (Fig. 13.1a) [29]. If less than five aphthae are visible, and the mucosa is otherwise normal, the mucosa is scored as i1. A score of i2 reflects five or more aphthae, with normal intervening mucosa, or larger lesions with skip areas, or lesions confined to the anastomotic rim that are under 1 cm in length. A score of i3 indicates diffuse aphthous ileitis with diffusely inflamed intervening mucosa, and i4 refers to diffuse inflammation with large ulcers, nodules, and/or luminal narrowing (Fig. 13.2). Aphthous ulcers feature heavily into this scoring system, as these

Table 13.1 Rutgeerts scoring system

Endoscopic score	Endoscopic findings
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis (i.e., <1 cm in length)
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

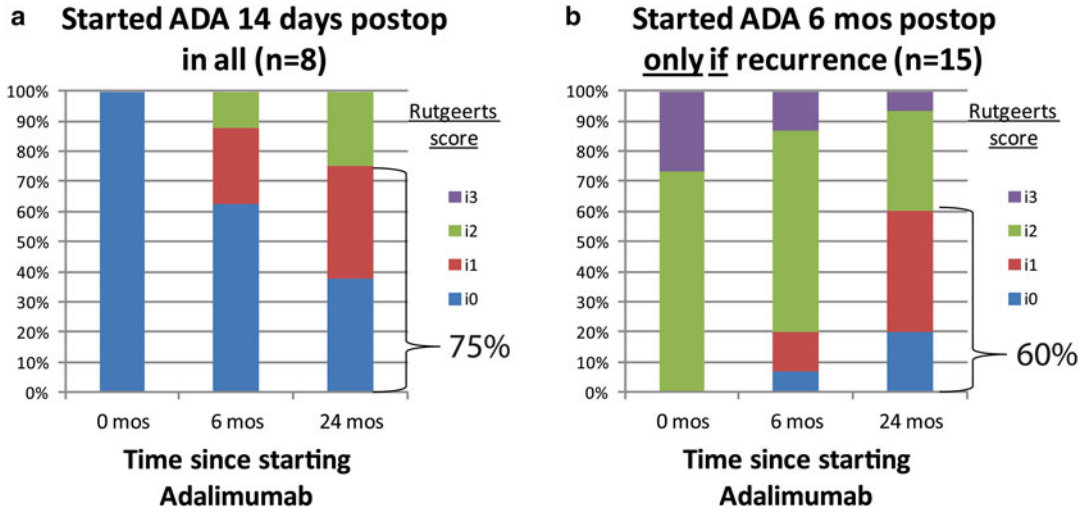

Fig. 13.1 (**a**) Endoscopic outcome of empiric versus (**b**) endoscopically guided postoperative prophylactic therapy with adalimumab (ADA), showing similar rates of endoscopic remission (Rutgeerts i0 or i1) 24 months after initiatingadalimumab [29]

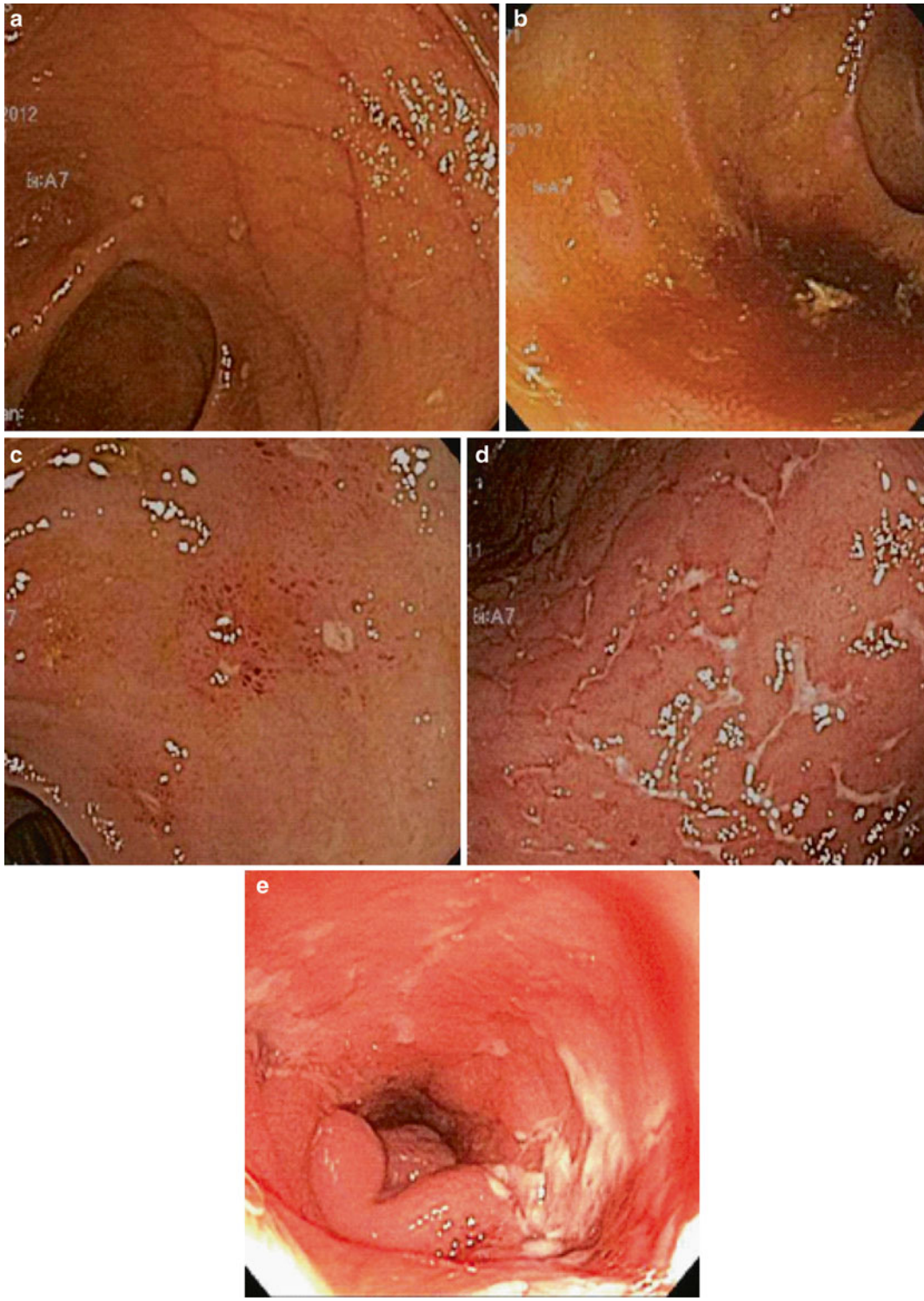

Fig. 13.2 Examples of Rutgeert's scoring in postoperative recurrence of Crohn's ileitis after ileocolectomy with primaryreanastomosis. (**a**) Score of i0, revealing normal ileal mucosa with no aphthous ulcers. (**b**) Score of i1, with rare (<5) aphthous ulcers on otherwise normal mucosa. (**c**) Score of i2, with 5 or more aphthae. (**d**) Score of i3, with diffuse aphthous ileitis and inflamed intervening mucosa. (**e**) Score of i4, with large, deep ulcers and luminal narrowing

small, shallow, "punched-out" appearing ulcers were found to be the most common and earliest endoscopically visible signs of recurrent Crohn's disease after ileocolectomy [5], being present as the only sign of disease recurrence within the first postoperative year in 76 % of Crohn's patients [4]. Aphthous ulcers in the neo-terminal ileum typically occur near the crests of thickened folds, and when multiple, can appear in clusters or a linear array [4].

Other common endoscopic findings after ileocolectomy include mucosal erythema and anastomotic ulcers. Although patchy erythema, sometimes with mucosal friability, was one of the earliest postoperative signs of inflammation to appear after surgery, Rutgeerts et al. deemed it too subjective and irreproducible to be included in a scoring system [4]. In contrast, anastomotic ulcers and stenosis appear to be a later postoperative change, as these changes are rare within the first year after surgery, even among patients with visible recurrence in the neoterminal ileum. Over time, anastomotic changes become much more common, and, at some point more than 3 years after surgery, as many as half of Crohn's patients may develop a rigid, ulcerated stenosis of the anastomosis or neoterminal ileum, with serpiginous or longitudinal ulcers not uncommonly extending distally from the anastomosis into the colonic mucosa [4]. Thus, the endoscopic appearance of postoperative Crohn's disease is not static, but instead progresses over time in the absence of prophylactic therapy [5].

In univariate analyses, the severity of early endoscopic recurrence (within 1 year of surgery, as reported by the Rutgeert's score), predicts postoperative clinical recurrence better than symptoms, indication for surgery, size of colonic resection, disease duration, patient demographics, or whether or not patients had undergone prior resection [12]. If patients were stratified by preoperative disease severity, endoscopic score was found to be the only independent variable with significant predictive value. A score of i0-i1 predicts a risk of clinical recurrence and/or surgery of less than 10 % within the first 8 years after surgery [12], indicating no significant need for chronic prophylactic immunosuppressive or anti-TNF therapy. A score of i2 correlates with a 20–40 % recurrence rate at 5 years, for which the benefits of systemic prophylactic therapy may outweigh the risks and justify its cost. A score of i3 increases this 5-year risk to 50–70 %, while for i4 recurrence at 5 years is a 100 % certainty, with 70 % of recurrences occurring within the first year after surgery (Fig. 13.3) [12]. Thus, for the trials of prophylactic therapy discussed previously, a score of i2 was used as the threshold for endoscopic recurrence.

For surgeries other than ileocolectomy, the natural history of postoperative Crohn's disease is much less clear, but in general the rate of endoscopic recurrence appears to be lower and the rate of clinical recurrence higher than it is after ileocolonic anastomosis. In a retrospective, single-center series, endoscopic or radiographic recurrence, with a median follow-up of 12

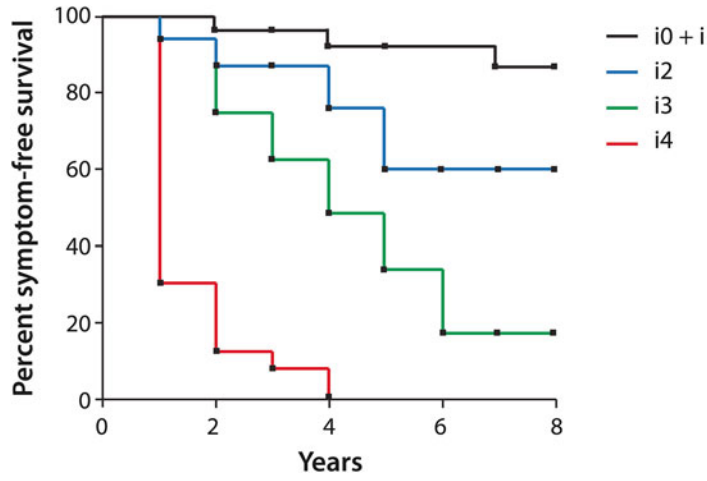

Fig. 13.3 Correlation between Rutgeerts score as assessed within a year of surgery, and subsequent clinical outcome. Adapted from [12]

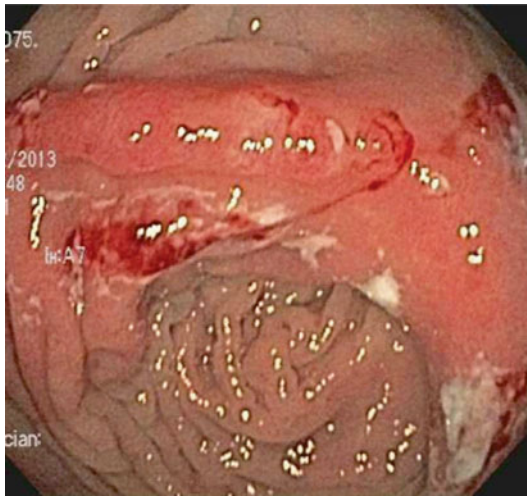

Fig. 13.4 Example of anastomotic ulceration as the sole evidence of recurrent Crohn's disease in a symptomatic patient evaluated within a year of colocolonic anastomosis. Note that colonic mucosa proximal and distal to the anastomosis is normal and uninflamed

months, was only seen in about 40 % of 38 Crohn's patients who underwent surgery other than ileocolonic anastomosis [30]. Ileorectal anastomoses were included in this cohort, and behaved more like typical ileocolonic anastomoses, with five out of five patients demonstrating endoscopic recurrence at both the anastomotic site as well as the upstream neoterminal ileum. If these five patients were excluded from analysis, only one-third of patients showed endoscopic recurrence after ileostomy or colorectal, ileoileal, or more proximal small bowel anastomoses [30]. As with ileorectal anastomoses, all Crohn's recurrences observed after anastomoses involving exclusively small bowel involved both the anastomosis and the adjacent small bowel. In contrast, recurrences after colocolonic anastomoses were limited to the anastomosis alone, with the adjacent colon upstream and downstream remaining healthy and uninflamed (Fig. 13.4). All of these patients with endoscopic recurrence developed clinical recurrence as well [30], so unlike ileocolonic anastomoses, other surgeries do not appear to produce subclinical endoscopic recurrence. Thus, whether endoscopic restaging in asymptomatic Crohn's patients would have predictive value after surgery without an ileocolonic anastomosis is not clear. Instead, endoscopy after such surgery may be more useful to evaluate patients after symptoms have recurred, as a means of diagnosing the etiology of their symptoms and guiding therapy reactively instead of prophylactically.

Thus, if endoscopy is to be used to evaluate for endoscopic recurrence and guide postoperative medical therapy in Crohn's disease, it should ideally be performed within 6 months after surgery. Colonoscopy should be completed to the neoterminal ileum and the endoscopist should pay careful attention to the anastomosis and pre-anastomotic ileum. The pre-anastomotic ileum should be evaluated for evidence of recurrent disease and note should be made of the Rutgeerts score, with a score of i2 or greater indicating endoscopic recurrence. While histologic activity may be patchy and has not been shown to correlate with rates of clinical recurrence, histologic samples may provide supporting evidence of disease recurrence. In addition, the anastomosis should be evaluated for evidence of ulceration and stenosis, although these findings will be uncommon within the first year after surgery. If a severe and short anastomotic stenosis is present, endoscopic balloon dilation (described in Chap. 21) may be used for treatment and to allow evaluation of the pre-anastomotic ileum. It should be noted that ulcerations at the anastomosis alone (marginal ulcers) are not uncommon more than 1 year after surgery, but in the absence of pre-anastomotic ileitis do not constitute Crohn's disease recurrence. While colonoscopy is currently the "gold standard" for identifying postoperative recurrence of Crohn's disease following ileocolonic anastomosis, a number of less-invasive diagnostic techniques have been explored as an alternative. Fecal calprotectin correlates well with clinical recurrence, and better than serological testing, such as C reactive protein [31]. However, the correlation between endoscopic recurrence and fecal calprotectin has been variable [31–34]. Cross-sectional imaging, such as computed tomography (CT) and magnetic resonance (MR) enterography, are able to identify evidence of Crohn's disease recurrence in regions not easily reached by conventional endoscopy, such as the mid small bowel [35]. However, these

modalities primarily detect late postoperative changes, such as stricturing, bowel wall thickening or other anastomotic changes [36], and would be less sensitive than direct endoscopic visualization to identify early aphthous ulcerations predictive of subsequent clinical course. Small intestinal contrast ultrasound (SICUS) performed favorably alongside colonoscopy at 6, 12 or 24 months after ileocolonic anastomosis. Bowel wall thickening of >3.5 mm by SICUS, or the length such thickening extends into the neoterminal ileum, demonstrated excellent correlation with Rutgeerts scores of i2 or greater [37], and hence may have similar predictive power to colonoscopy in highly experienced centers.

Given the fact that Crohn's disease recurrence is almost inevitably in the small bowel upstream of the ileocolonic anastomosis, wireless capsule endoscopy (WCE) has been proposed as a less invasive means to endoscopically visualize the neoterminal ileal mucosa than conventional colonoscopy. Like cross-sectional imaging, WCE has the added benefit of evaluating proximal small bowel beyond the reach of a colonoscope [38, 39]. However, because intestinal strictures increase the risk of capsule retention or impaction, WCE may need to be reserved for patients in whom fibrostenotic disease can first be excluded by cross-sectional imaging or a patency capsule. The latter is a radio-opaque capsule of the same dimensions as a WCE capsule, containing a small radio frequency identification (RFID) tag. If either abdominal plain films or the RFID tag demonstrate retention of the patency capsule in the small bowel 30 h after ingestion, it is presumed to have detected a stricture contraindicating WCE, but will subsequently dissolve, thus preventing obstruction and obviating the need for its removal. In a small, early series of postoperative Crohn's patients with no radiographic or endoscopic evidence of stenosis, WCE appeared to be safe and well-tolerated, revealing mucosal recurrence in most cases [40].

Direct comparison of WCE and conventional colonoscopy 6 months after ileocolonic anastomosis demonstrated significant correlation when both employed Rutgeerts scoring, although WCE tended to report a lower score in a given patient, and thus had inferior sensitivity relative to ileocolonoscopy [39]. This study also revealed significant interobserver variability in WCE scoring, highlighting the subjectivity of WCE results. A smaller study directly comparing WCE, colonoscopy, and SICUS 12 months after surgery demonstrated perfect correlation between WCE and conventional endoscopy, and a near-perfect correlation with SICUS, although this population demonstrated unusually aggressive recurrence, with endoscopic activity in 94 % of subjects, and anastomotic stricturing already present in 23 %, precluding WCE evaluation [38]. Furthermore, aphthous ulcers in the proximal small bowel, beyond the reach of a colonoscope, were identified in 76 % of patients. Thus, WCE may represent an attractive, less invasive mechanism for postoperative risk-stratification than conventional colonoscopy in Crohn's disease.

Ulcerative Colitis

Although recent advances in medical therapies have created more options for the medical management of ulcerative colitis, 10–30 % of patients require colectomy in their lifetime [41–43]. The most common indications for colectomy in UC are medically refractory disease and colitis-associated cancer or dysplasia. Surgical options include total proctocolectomy with end-ileostomy or restorative proctocolectomy, most commonly with ileoanal pouch anastomosis (IPAA). While there can be surgical complications related to total proctocolectomy with end-ileostomy, surgery is curative and recurrence of inflammation postoperatively is generally felt to be reflective of unrecognized preoperative Crohn's disease. Restorative proctocolectomy with IPAA involves formation of the ileum into a reservoir that is anastomosed to the anal transition zone. Post-IPAA inflammation is common and comes in several forms including cuffitis, pouchitis, and Crohn's disease of the pouch. Unlike postoperative Crohn's disease, there are no recommendations for routine endoscopy in the post-IPAA patient to evaluate for the recurrence of inflammation in the absence of symptoms. However, endoscopy is recommended in patients presenting with

pouch dysfunction characterized by increased stool frequency, reduced form, rectal bleeding, urgency, cramping or incontinence. Endoscopic evaluation of the ileoanal pouch is critical to differentiate those entities that can cause postoperative inflammation and to exclude infectious or non-inflammatory causes of pouch dysfunction. Pouchoscopy can generally be accomplished without sedation, although the use of 2 % lidocaine may be helpful in alleviating discomfort in the anal area during the procedure. Preparation is achieved with a phosphate enema or half-dose of polyethylene glycol-based colonoscopy preparation. A narrower-caliber pediatric colonoscope or gastroscope is preferred as there is often mild stenosis at the anal-pouch anastomosis and these scopes have greater flexibility for retroflexion in the pouch. Please refer to Chap. 15 for details on post-IPAA anatomy. During pouchoscopy, the anal canal, ileal pouch-anal anastomosis, pouch and pre-pouch ileum are carefully assessed for evidence of inflammation. The exam should include a digital rectal examination to evaluate for anastomotic stricture and evidence of tenderness in the anal canal that could suggest abscess, fistula or ulceration in this area. In subjects with a stapled anastomosis, where a residual rectal cuff may be present, the length of columnar mucosa present between the anal transition zone and anastomosis should be noted. The anal canal, pouch and pre-pouch ileum should be assessed for endoscopic evidence of inflammation including granularity, friability, contact bleeding, ulceration and pseudopolyps. In addition any sinus tracts or fistulae should be identified. Biopsies should be taken of abnormal appearing mucosa during the exam. However, biopsy of the anastomoses and suture line ulcers should be avoided. These commonly exhibit histologic evidence of inflammation and foreign body granulomas, which may lead to misdiagnosis of pouchitis or Crohn's disease of the pouch. Biopsies of the normal-appearing pouch and pre-pouch ileal mucosa can occasionally reveal histologic evidence of inflammation. Therefore, our practice is to take routine biopsies of these areas even when they appear endoscopically normal

Cuffitis

Cuffitis is the term used to describe inflammation of the residual columnar rectal mucosa left intact after IPAA with stapled anastomosis. During a hand-sewn anastomosis, a mucosectomy is typically performed of the distal anorectum and the pouch is sutured directly to the anal transition zone. A stapled anastomosis, alternatively, uses a stapling device to secure the pouch to the anorectal stump without mucosectomy. This often necessitates leaving a small "cuff" of residual intact rectal mucosa distal to the anastomosis that is at risk to become inflamed. While very uncommon, cuffitis can occur in patients who have undergone mucosectomy if islands of rectal mucosa have been left behind [44]. The frequency of cuffitis following stapled anastomosis is reported to occur in 7–15 % of patients [45, 46]. Cuffitis is probably best thought of as residual, rather than recurrent, inflammation and is thought to represent the same pathophysiologic process present in the preoperative colon of patients with ulcerative colitis.

The symptoms of cuffitis may include diarrhea, urgency, incontinence, rectal bleeding, and anorectal pain. Cuffitis is diagnosed by endoscopic findings of erythema, edema, increased granularity, decreased vascular pattern, friability and contact bleeding in the rectal cuff. Histologic evaluation reveals neutrophilic and chronic inflammatory infiltrates in the retained rectal mucosa (columnar epithelium between the anal transition zone and anastomosis). Cuffitis is more frequently symptomatic with a long segment of in situ rectum, but can occur with residual rectum of any length. Extraintestinal manifestations are more common in patients with cuffitis than other disorders of the pouch [47]. Cuffitis is treated similarly to proctitis, with first-line use of mesalamine and steroid suppositories [48]. However, recent data from a tertiary care center has suggested that up to 48 % of patients may be refractory to topical therapy. Many of these patients were later diagnosed with Crohn's disease of the pouch or surgical complication such as fistula [49]. Thus, in patients with cuffitis who do not

improve on topical therapies, further investigation for secondary causes of inflammation is worthwhile. Surgical revision of the ileal pouch-anastomosis has been reported to be successful in cases of refractory cuffitis with long segment of retained rectum [50, 51].

Pouchitis

De novo inflammation of the ileal reservoir, called pouchitis, is the most common cause of recurrent inflammation in post-IPAA patients. At least one episode of pouchitis is estimated to occur in up to half of patients with ulcerative colitis who undergo IPAA [52–57] and of these, 70 % develop pouchitis within the first year after ileostomy takedown [58]. The clinical symptoms associated with pouchitis overlap with other pouch inflammatory disorders and include increased stool frequency and liquidity, urgency, incontinence, anorectal pain, and/or abdominal cramping. Rectal bleeding and fevers are uncommon. Pouchitis has been classified according to several different clinical parameters. The clinical course of pouchitis can be acute, relapsing or chronic. Forty percent of patients will have only a single episode of acute pouchitis [59], while 5–19 % of patients will develop chronic pouchitis defined as lasting more than 4 weeks [60–62]. Pouchitis can be additionally classified according to antibiotic responsiveness (antibiotic responsive, antibiotic dependent, or antibiotic refractory).

Dysbiosis, or alteration in the composition or quantity of bacteria in the ileoanal pouch, has been strongly implicated in the etiology of pouchitis. This is evidenced by the fact that pouchitis rarely occurs in the absence of the fecal stream and that both probiotics [63, 64] and antibiotics [65, 66] are effective for the treatment of pouchitis. Decreased bacterial diversity and changes in the bacterial composition have been reported in subjects with pouchitis after IPAA, although no specific species or phylotypes appear to be causative [67, 68]. Host factors, including genetics, also appear to play an important role as pouchitis rarely occurs in patients undergoing IPAA for familial adenomatous polyposis [69–71].

Clinical risk factors predictive of development of chronic pouchitis include young age at colectomy, never smoking status, NSAID use, extensive disease and backwash ileitis [58, 72, 73]. In addition, concurrent primary sclerosing cholangitis (PSC) as well as the presence of other immune mediated disorders has [74] been found to be a significant risk factor in the development of pouchitis [58, 75, 76]. Genetic polymorphisms have been associated with risk of pouchitis including those in TLR9, CD14, TLR1 and NOD2 [72, 77, 78]. A recent meta-analysis of eight studies, revealed an association (odds ratio of 1.76) of anti-neutrophil cytoplasmic antibody (ANCA)-positivity with chronic, but not acute, pouchitis. No similar association was seen with anti-*Saccharomyces cervisiae* antibody [79]. Seropositivity for anti-CBir1 [80] and anti-outer membrane porin (OmpC) [72] have additionally been associated with risk of pouchitis development.

The diagnosis of pouchitis is based on the combination of clinical, endoscopic and histologic findings. Characteristic endoscopic findings compatible with pouchitis are diffuse or patchy erythema, friability, edema, hemorrhage, granularity, exudates and ulceration (Fig. 13.5). Linear ulcers can be found at the anastomosis and should not be interpreted as evidence of pouchitis. Endoscopy allows for determination of the severity and extent of inflammation, including evaluation of the rectal cuff and pre-pouch ileum. It should be noted that pre-pouch backwash ileitis has been associated with diffuse pouchitis. Therefore, the presence of ileitis does not necessarily portend a diagnosis of Crohn's disease of the pouch. However, lack of significant pouchitis, deep ulceration or extent of ileitis beyond the distal pre-pouch ileum should raise the suspicion for Crohn's disease of the pouch. In addition, cuffitis may occur in patients with pouchitis [45] and can represent a secondary phenomenon that responds to primary treatment of pouchitis in some cases.

Endoscopic appearance does not necessarily correlate well with histologic severity, likely related to issues of sampling error [81]. Histologic findings associated with pouchitis are non-specific and include acute inflammation with neutrophilic

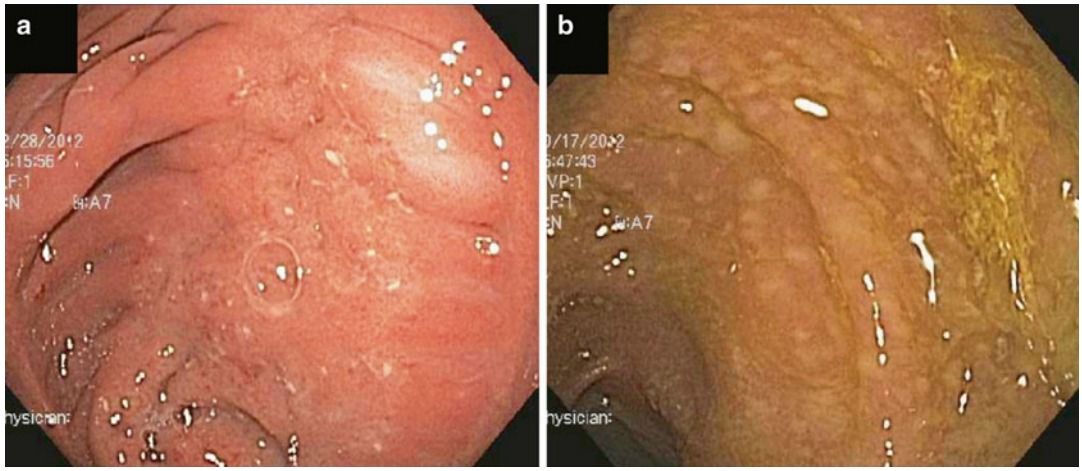

Fig. 13.5 Examples of pouchitis. (**a**) Idiopathic pouchitis. (**b**) Pouchitis secondary to *Clostridium difficile* infection

infiltrates, crypt abscesses and ulceration as well as chronic inflammatory infiltrates. Inflammation is often associated with villous atrophy and crypt hyperplasia [82, 83]. Although histologic findings are not specific for pouchitis, evaluation can alert the endoscopist to alternative causes of pouch inflammation if granulomas, viral inclusion bodies (suggestive of cytomegalovirus) or evidence of ischemic changes are identified. As infections, NSAID use and ischemia can mimic the endoscopic and histologic findings of idiopathic pouchitis; these entities should be considered as causes of secondary pouchitis, particularly in those patients with relapsing and antibiotic-refractory disease.

First-line therapy for the treatment of acute pouchitis is accomplished with a 2 week course of ciprofloxacin or metronidazole. Both metronidazole (15–20 mg/kg/day) [65] or ciprofloxacin (1 g/day) have been shown in randomized controlled trials to be effective for the treatment of acute pouchitis, with ciprofloxacin demonstrating superior efficacy and fewer side effects in a comparative efficacy study [66]. The probiotic VSL#3 has also demonstrated efficacy in randomized controlled trials for the treatment of symptoms from mild pouchitis [63]. Budesonide enemas have also been shown to be equivalent to metronidazole in a randomized comparative efficacy study and were better tolerated [84]. In randomized controlled trials of patients with antibiotic-dependent pouchitis and relapsing pouchitis, VSL #3 was also shown to be effective in maintaining antibiotic-induced remission in 85 % of patients [64, 85]. However, subsequent open-label studies have demonstrated less impressive results [86]. Open-label studies of antibiotics including rifaxamin have also suggested a possible role in maintenance therapy [87, 88].

Chronic antibiotic-refractory pouchitis is difficult to treat and unfortunately remains a major cause of ileoanal pouch failure. In the patient who has failed antibiotic therapy for pouchitis, causes of secondary pouchitis should be sought including evaluation for NSAID use, ischemia, structural disease, infections (particularly *Clostridium difficile* and cytomegalovirus) and Crohn's disease of the pouch. Some groups have suggested stool cultures may be helpful in documenting antibiotic resistance and directing antibiotic therapy in this group of patients [89]. Combination antibiotic therapy with Cipro and Rifaximin [90, 91], metronidazole [92] or tinidazole [93] for 1 month had been used to achieve remission in open-label studies. However, maintaining remission in this group of patients remains a major challenge. Small case series have described the successful use of steroids (beclomethasone [94], budesonide [95]), immunosuppressive agents, topical tacrolimus [96] and anti-TNF [97–100] agents in this population. However, the role of

anti-TNF agents remains controversial as the patients treated in these studies were heterogeneous and included patients with significant pre-pouch ileitis and fistulizing pouchitis, raising a question of whether those who responded to therapy had Crohn's disease of the pouch rather than idiopathic pouchitis.

Several small randomized controlled studies have suggested a role for probiotics in the primary prevention of pouchitis [101, 102]. However, larger studies including high- and low-risk populations will need to be evaluated to determine whether primary prophylaxis of pouchitis provides long-term benefit and is cost effective.

Crohn's Disease of the Pouch

Crohn's disease of the pouch, alternatively called Crohn's-like disease of the pouch, is another leading cause of post-IPAA inflammatory disease. Crohn's disease of the pouch is characterized by fistulizing or stricturing disease of the pouch and/or extensive inflammation of the afferent limb. Crohn's disease of the pouch is reported to occur in 3–13 % of patients undergoing IPAA, with higher rates in patients with indeterminate colitis [103–108]. Crohn's disease of the pouch can be diagnosed early (within weeks) or late (years) after IPAA. Clinical symptoms may be similar to other pouch inflammatory diseases and include increased stool frequency, liquidity, urgency, incontinence, abdominal pain, rectal pain. In addition, patients may have obstruction associated with strictures, draining fistulae or malabsorptive phenomena in the setting of extensive small bowel involvement. Based on the pattern of involvement, Crohn's of the pouch can be classified into inflammatory, fibrostenotic and fistulizing phenotypes.

There is significant debate as to whether Crohn's disease of the pouch after IPAA for ulcerative colitis reflects a missed preoperative diagnosis of Crohn's disease or may occur *de novo* in susceptible individuals. Patients with indeterminate colitis and those with a family history of Crohn's disease have increased risk of Crohn's disease of the pouch, suggesting the former possibility in some patients. Yet many patients who develop this entity have no preoperative clinical features of Crohn's disease or evidence of Crohn's-like pathology on their colectomy specimens. Thus, it is possible that the post-surgical anatomy of IPAA creates a permissive environment for development of *de novo* Crohn's disease in susceptible patients. In addition to family history of Crohn's disease and preoperative indeterminate colitis, risk factors for Crohn's disease of the pouch include young age at time of IPAA and active smoking [73]. Seropositivity for ASCA and CBIr1 also increases the risk of Crohn's disease of the pouch [109, 110]. Interestingly, the presence of PSC appears to protect against the development of Crohn's disease of the pouch [111].

Crohn's disease of the pouch can affect the cuff, pouch and/or pre-pouch ileum, but is most commonly active at the anastomoses and pre-pouch ileum. In addition, inflammation can be present in the proximal small bowel and upper GI tract. Endoscopic findings are characterized by edema, granularity, friability, contact bleeding, pseudopolyps, exudates and deep ulcerations (Fig. 13.6). Features that distinguish Crohn's disease from other inflammatory conditions of the pouch include strictures (particularly non-anastomotic strictures), fistulas and extensive ileitis [112]. Ileitis that is more than 10 cm proximal to the pouch-ileal anastomosis or bears discrete ulcerations or is non-responsive to antibiotic therapy should raise the suspicion of Crohn's disease. Upper GI involvement on esophagogastroduodenoscopy or mid-small bowel disease identified on wireless capsule endoscopy are also suggestive of Crohn's disease. Radiographic evaluation of the pouch with MRI or CT can be of additional benefit in identifying stricturing or penetrating complications of Crohn's disease.

Histologic evaluation can be diagnostic of Crohn's disease of the pouch when granulomas are identified. However, only 10–12 % of patients diagnosed with Crohn's disease of the pouch will have granulomas [113]. Anastomotic biopsies should be avoided during pouchoscopy, as foreign-body granulomas can be present in these areas and may not reflect a diagnosis of Crohn's

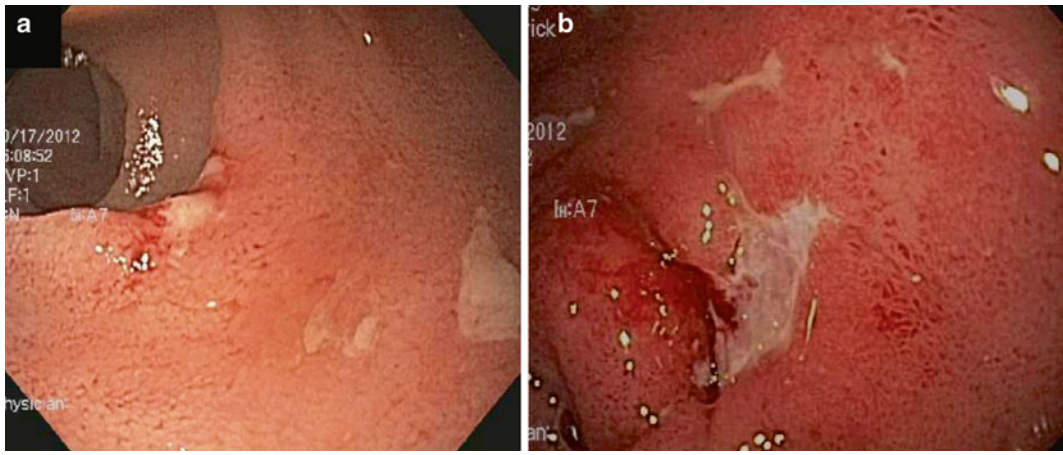

Fig. 13.6 Examples of Crohn's disease of the pouch. (**a**) Discrete ulcerations in pre-pouch ileitis. (**b**) Crohn's disease of the pouch associated with deep ulcerations in the pouch body

disease of the pouch. Other histologic features have been proposed to distinguish pouchitis and Crohn's disease of the pouch including pyloric gland metaplasia (PGM). PGM is more common in Crohn's disease than pouchitis, but the sensitivity and specificity of this finding (77 and 78 % respectively) are not high enough to warrant its use as a diagnostic tool [114].

The diagnosis of Crohn's disease of the pouch can be difficult to make as it shares endoscopic and histologic features with other inflammatory disorders of the pouch. The features that traditionally help distinguish Crohn's disease from ulcerative colitis can be less reliable post-IPAA where surgical manipulation can result in both stricturing and fistulizing complications. In addition, patients with pouchitis may have patchy distribution and transmural inflammation, making these less reliable features of Crohn's disease of the pouch. Furthermore, pouchitis and backwash ileitis can mimic Crohn's disease of the pouch. However, ileitis that is long-segment (>10 cm), or has discrete ulcerations or a different mucosal pattern than inflammation of the pouch or occurs in the absence of pouchitis heightens the suspicion of Crohn's disease. Response to antibiotics can also help distinguish backwash ileitis from Crohn's disease of the pouch. Crohn's disease of the pouch can also affect the rectal cuff and should be considered in cuffitis that is not responsive to topical therapies.

Strictures may be a feature of Crohn's disease of the pouch, but must be distinguished from post-surgical anastomotic strictures. Anastomotic strictures typically lack surrounding inflammation, whereas the presence of mucosal inflammation in the pouch or pre-pouch ileum increases the likelihood of a Crohn's-related stricture. Stricturing at a non-anastomotic site is suggestive of Crohn's disease of the pouch. Fistulae are a feature of Crohn's disease of the pouch, but can be the result of a surgical complication including an anastomotic leak or enterotomy. The most common internal opening sites of both surgical and Crohn's-related fistulae are at the pouch-anal anastomosis and at the stapled end of the J [115]. Fistula openings at other anatomic areas are suggestive of Crohn's disease. The timing of fistula development may be helpful, as surgical fistulas generally occur within 12 months of ileostomy takedown if no leak, sinus or abscess is present. Thus, late development of fistulas is suggestive of Crohn's disease.

Crohn's disease of the pouch may require a combination of medical, endoscopic and surgical therapies. Randomized trials evaluating the comparative efficacy of therapeutics do not exist for Crohn's disease of the pouch. For patients with inflammatory phenotypes, medications used for the treatment of Crohn's disease may be successful, but often have to be continued as long-term maintenance therapy. These include antibiotics

as well as oral and topical 5-ASA and steroids. Given its ileal release formulation, oral budesonide can be used to target the pre-pouch ileum and pouch with less absorption than systemic steroids. Thiopurines and anti-TNF therapies have also been successfully utilized for management of Crohn's of the pouch. Anti-TNFs may be warranted for fistulizing disease or when extraintestinal manifestations are a prominent feature [99, 100, 116, 117].

In addition to medical therapy, strictures and fistulae often require endoscopic or surgical management. Short strictures related to Crohn's disease may be treated with a combination of medical therapy and endoscopic balloon dilation with good efficacy and relatively small risk of complications [118]. At experienced centers, longer strictures have been successfully treated with needle-knife stricturoplasty [119]. Alternatively, longer strictures or those refractory to endoscopic dilation may require surgical stricturoplasty or J pouch revision. For pouch fistulas related to Crohn's of the pouch, a combination of antibiotics, anti-TNF therapy and surgical management may be required. Surgical interventions may include abscess drainage, seton placement, fistulotomy and fistula repair.

Unfortunately, Crohn's disease of the pouch remains an important cause of pouch failure, although aggressive combined medical and endoscopic management are allowing pouch salvage in many cases. In those patients who are unable to control inflammatory, stricturing or fistulizing Crohn's of the pouch with medication, endoscopic or pouch-sparing surgery, diverting ileostomy with or without pouch excision may be necessary. The presence of fistulae and early diagnosis of Crohn's disease appear to be risk factors for pouch failure in this group of patients [120].

Conclusion

Recurrence of inflammatory disease after surgical resection is common in both Crohn's disease and ulcerative colitis. Endoscopy is a critical tool for diagnosing postoperative recurrence and guiding medical therapy. Even in the absence of symptoms, postoperative colonoscopy within 6 months is recommended in patients who have undergone ileocolectomy for Crohn's disease. This allows the endoscopist to stratify the risk of clinical recurrence of Crohn's disease based on the endoscopic appearance and Rutgeerts' score and to devise an appropriate medical treatment plan. In contrast, endoscopic evaluation of the J-pouch following IPAA for UC is not necessary in the absence of symptoms, but symptoms of pouch dysfunction should prompt pouchoscopy to allow for the accurate diagnosis and treatment of postoperative inflammatory diseases of the pouch including cuffitis, pouchitis and Crohn's disease of the pouch.

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The Use of Endoscopy to Follow the Clinical Course of Crohn's Disease

14

Mark A. Samaan and Geert D'Haens

Introduction

The conventional and established goals of treatment in Crohn's disease (CD) until relatively recently have been to achieve and then maintain clinical remission [1, 2]. However, studies have demonstrated that simply ameliorating symptoms is not enough to alter the natural history of this progressive disease [3, 4]. The old dogma remained largely due to the fact that, historically, treatment options amounted to little more than discrete courses of corticosteroids administered during periods of clinical disease activity. The need for (repeated) surgical resections and the occurrence of perianal complications were merely considered inevitable and part of the natural history of the disease. During this period endoscopy had an established role in confirming the diagnosis of CD as well as in defining the pattern, severity and extent of disease. However, endoscopic re-assessment of patients with CD had an ill-defined role, as treatments were known to achieve clinical remission even in the absence of mucosal healing. The poor correlation between symptomatic and endoscopic improvement was demonstrated in a study of corticosteroid therapy in which 71 % of patients achieved clinical remission despite ongoing active endoscopic lesions [5]. The demonstrated lack of sustained mucosal healing is likely to be the reason corticosteroids are ineffective maintenance agents and subsequently resulted in a symptom-driven approach to management rather than one guided by endoscopic results.

More recently, this approach has undergone significant revision with the advent of immunomodulatory and biological agents, which have demonstrated efficacy in achieving and maintaining mucosal healing [6, 7]. Moreover, this property has been shown to be associated with improved clinical outcomes including sustained steroid-free clinical remission, decreased rates of surgery and hospitalization, reduced occurrence of new perianal complications as well as improvement in quality of life and increased work productivity [8, 9]. These associations have given rise to the understanding that mucosal healing represents diminished disease activity and allows deep-tissue healing, thereby affecting the natural history of the disease. This understanding, in conjunction with the longstanding observation that symptoms correlate poorly with objective measures of disease activity [10, 11], has resulted in an increasing emphasis on mucosal evaluation in CD. This change has progressively been reflected in the selection of outcome measures in clinical

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trials, where there has been an evolution from reliance on symptom-based assessments of disease activity [12] to endoscopic assessments of disease activity [13–15]. The benefits of having objective endoscopic endpoints for clinical trials are clear as they reduce placebo rates and allow for video recorded procedures to be centrally read by experienced, expert readers [16, 17].

Although changes in clinical practice have also reflected these developments, several challenges face the clinician when considering how to integrate mucosal healing as a treatment goal in day-to-day practice. These challenges have resulted in a more gradual uptake and more limited use of endoscopy in the follow-up of patients with CD. This could result in the under- or over-treatment of patients, potentially leading to disease progression or unnecessary side effects, respectively, but it also reflects the current lack of knowledge on the clear benefit of an endoscopy-guided therapeutic approach.

In this chapter we will explore the role of endoscopy in following the clinical course of CD. In addition to this, examples of the practical application of using validated endoscopic indices can be accessed online at http://extras.springer.com. By collating and interpreting evidence gained from clinical trials investigating endoscopic goals in the treatment of CD, we will discuss how these may be used to better inform decision-making in clinical practice. Finally, we will consider the challenges of integrating endoscopic treatment goals into clinical practice.

Essential Endoscopic Features of Crohn's Disease

Endoscopy is used to make an initial diagnosis of inflammatory bowel disease (IBD), distinguish CD from ulcerative colitis (UC), assess the disease extent and activity, monitor response to therapy, allow for surveillance of dysplasia or neoplasia, and provide endoscopic treatment, such as stricture dilation. Colonoscopy with ileoscopy (ileocolonoscopy) allows direct visualization and biopsy of the mucosa of rectum, colon, and terminal ileum. Unless contraindicated because of severe colitis or possible toxic megacolon, a full colonoscopy with intubation of the terminal ileum should be performed during the initial evaluation of patients with a clinical presentation suggestive of IBD [18]. Detailed information gained at index endoscopy is important in differentiating CD from UC because, once therapy is commenced, it may obscure discriminating features of CD from UC such as segmental colitis (patchiness) and rectal sparing [19, 20].

The spectrum of mucosal lesions seen in active CD is well characterized and involves a wide range of abnormalities. These include: erythema, swelling, nodularity, strictures, aphthoid ulcerations and ulcers of variable size and depth [21] (Figs. 14.1 and 14.2; Videos 14.1 and 14.2). The contribution of these lesions to the patients' symptoms remains uncertain, although deep ulcerations tend to be associated with abdominal pain and stricturing lesions are more commonly associated with intestinal cramps. The ulcerations in CD tend to be linear and often lead to the classic cobblestone appearance of the mucosa. The most useful endoscopic features to differentiate CD from UC are segmental colitis (i.e., patchiness), rectal sparing, involvement of the terminal ileum and anal or perianal disease [18]. However, none of these are specific for CD. In patients with ileal inflammation it is important to distinguish true CD ileitis from the backwash ileitis seen in 10 % of patients with pancolitis in UC. Features that favor CD ileitis include discrete ulcers or strictures of the terminal ileum or ileocaecal valve [22].

Endoscopy together with other diagnostic modalities can differentiate CD from UC in more than 85 % of patients [23]. In a prospective study of more than 350 patients with IBD followed up for more than 22 months, index colonoscopy and biopsy were accurate in distinguishing CD from UC in 89 % of cases. IBD diagnosis was revised in 4 % of cases, and the diagnosis of indeterminate colitis remained in 7 % of cases [24].

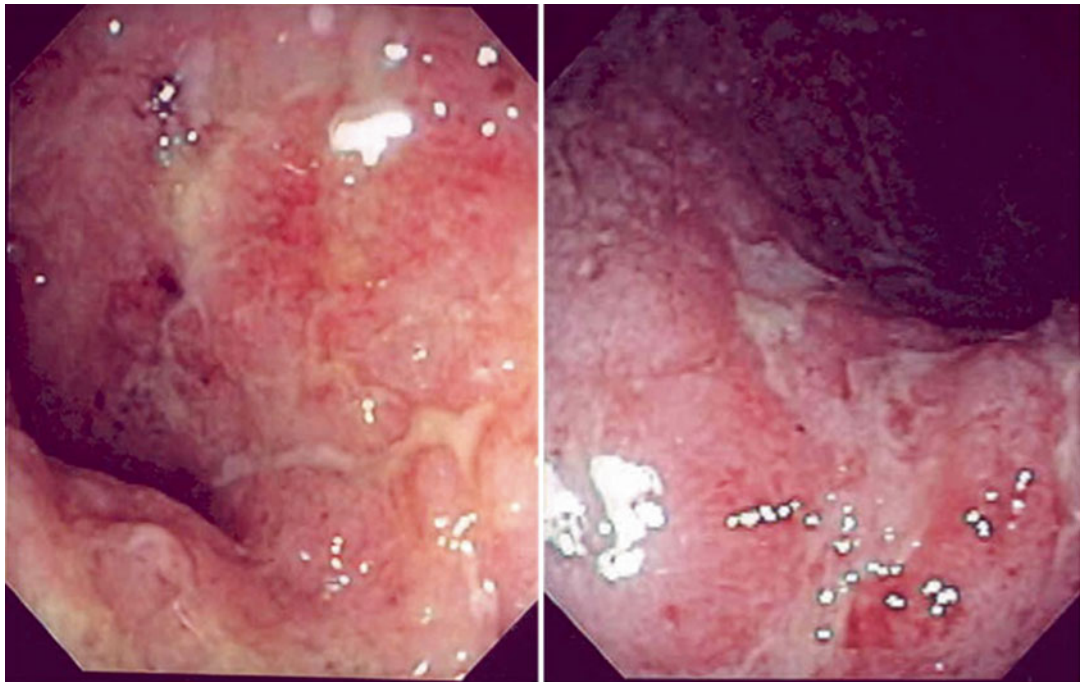

Fig. 14.1 Endoscopic appearance of terminal ileal CD with deep ulceration

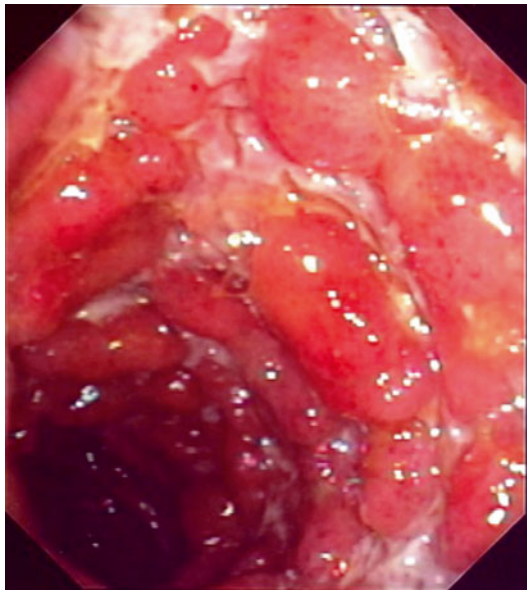

Fig. 14.2 Endoscopic appearance of colonic CD demonstrating the characteristic "cobblestone" appearance with a combination of deep ulcers and inflamed, edematous mucosa

Endoscopic Scoring Indices Used to Evaluate Crohn's Disease

The Crohn's Disease Endoscopic Index of Severity

Index Development, Validation and Utilization

The Crohn's Disease Endoscopic Index of Severity (CDEIS) is the longest standing of the endoscopic indices used for evaluating endoscopic disease activity [10]. It was developed by the GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives) group in 1989 as part of a multi-phase study. In the first phase of developing the index, two endoscopists (one of whom performed the procedure) scored 5 ileocolonic segments (rectum; sigmoid and left colon; transverse colon; right colon; and ileum). In each of these segments data on nine mucosal lesions (pseudopolyp, healed ulceration, frank

	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	TOTAL
Deep ulceration If present, score 12 If absent, score 0	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋⌊_⌋
Superficial ulceration If present, score 6 If absent, score 0	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋⌊_⌋
Surface involved by the disease (measured in cm*)	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋⌊_⌋·⌊_⌋
Ulcerated surface (measured in cm*)	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋	⌊_⌋⌊_⌋·⌊_⌋

TOTAL	⌊_⌋⌊_⌋·⌊_⌋	**A**
Number *(n)* of segments totally or partially explored (1-5)	⌊_⌋	**n**
Total A divided by n	⌊_⌋⌊_⌋·⌊_⌋	**B**
Ulcerated Stenosis If present anywhere, score 3 If absent, score 0	⌊_⌋	**C**
Non-Ulcerated Stenosis If present anywhere, score 3 If absent, score 0	⌊_⌋	**D**
TOTAL *B+C+D*	⌊_⌋⌊_⌋·⌊_⌋	

* For partially explored segments and for the ileum, the 10 cm linear scale represents the surface effectively explored.

Fig. 14.3 Crohn's Disease Endoscopic Index of Severity. (See Fig. 12.3)

erythema, frankly swollen mucosa, aphthoid ulceration, superficial or shallow ulceration, deep ulceration, non-ulcerated stenosis, and ulcerated stenosis) was collected along with the percentage of mucosal surface with disease involvement and the percentage with ulceration, indicated by the endoscopists on a 10 cm visual analogue scale. By dividing the number of segments with endoscopic lesions by the total number of segments explored, a score was also determined for individual segmental rectocolonic frequency (ISRCF). Using multiple linear regression techniques, the CDEIS was derived by correlation between these lesions and an endoscopist's global evaluation of lesion severity (GELS) (also determined using a 100 mm visual analogue scale).

A final score with four lesions (superficial or shallow ulceration, deep ulceration, non-ulcerated stenosis, and ulcerated stenosis) along with estimates of extent involvement were weighted to create the final score with a range of 0–44 (Fig. 14.3).

In each bowel segment, superficial and deep ulcerations are given a score of 6 and 12 points, respectively. These are added to an estimate of diseased surface and an estimate of ulcerated surface (expressed on a 100 mm visual analogue scale). These scores are summed and the total is

divided by the number of bowel segments examined (1–5). An additional 3 points are given if a non-ulcerated stenosis is present and further 3 should be added if an ulcerated-stenosis is seen (i.e., 6 points if both are present). The sum of these variables provides the final CDEIS. Clearly, absent and inaccessible segments (due to impassable stenosis or technical difficulties) are not accounted for in these calculations.

As part of the original study the CDEIS was partially validated and its operating characteristics, with regards to criterion validity, inter-observer agreement and responsiveness were demonstrated. Very good correlation with lesion severity and minimal intra-observer variability suggested the index was representative of disease activity and was also reproducible (though the independence of the endoscopists was limited by them being present in the same procedure room).

Responsiveness was subsequently assessed during the second phase of the study in a trial of prednisolone in a group of 54 patients with active CD. These patients were separate from the group used in the first phase. A strong correlation between changes in the CDEIS and GELS was demonstrated when scores for disease activity at baseline and after 3–5 weeks of treatment were compared.

In a recent study, the properties of the CDEIS were re-assessed amongst a group of four expert, central readers. Fifty recorded procedures were scored three times in random order. Results demonstrated "substantial" to "almost perfect" intra- and inter- observer reliability [25].

Endpoints, Definitions and Cut-off Values

The GETAID group followed-up their pioneering work and continued to investigate the properties of the CDEIS in a prospective, multicenter study of 142 patients with moderately-to-severely active CD [5]. Patients were treated with prednisolone (1 mg/kg/day) and underwent serial endoscopies at baseline and after 3–7 weeks of treatment. In this study remission was defined as: (1) no lesions, (2) only scarred lesions, or (3) minor lesions with at least a two-grade decrease on a five-degree scale of endoscopic severity (grade 1: no lesions to grade 5: very severe) with no residual deep ulceration. Though no numerical cut-off points were defined for remission or response in that study, subsequent collation of data from 5 prospective GETAID studies has made this possible [26]. From a total of 562 colonoscopies performed in 231 patients with active CD the following definitions were suggested:

- Complete remission (complete mucosal healing)—CDEIS <3
- Remission—CDEIS <6
- Response—a decrease in CDEIS by >5

These cut-off values were used in the recent MUSIC trial (Endoscopic **MU**co**S**al **I**mprovement in Patients with Active **C**rohn's Disease Treated with Certolizumab Pegol) when investigating mucosal healing with certolizumab pegol (a pegylated monoclonal antibody fragment to tumor necrosis factor alpha) therapy [15]. This study used the absolute change in CDEIS at 10 weeks as the primary end point with endoscopic response, endoscopic remission and complete endoscopic remission as secondary endpoints. However, these definitions have not been consistently applied in other trials. For example, a 2011 study to investigate the mucosal healing effect of methotrexate in CD used a score of <4 (rather than <3) to define complete mucosal healing [27]. Cut-off values to stratify disease activity into mild, moderate and severe have also been suggested. During the ACCENT 1 trials (**A** **C**rohn's Disease **C**linical Trial **E**valuating Infliximab in a **N**ew Long-term **T**reatment Program) these thresholds were arbitrarily defined as <5, 5–15 and >15 respectively [28].

Until recently, no formal analyses had been carried out to investigate the importance of minimal clinical change in CDEIS. However, in a recent study Ferrante and colleagues attempted to assess the minimal necessary improvement in endoscopic activity that could serve to define endoscopic response and that could predict sustained clinical benefit [29]. To do this they undertook a post-hoc analysis of data from the SONIC trial (**S**tudy **o**f Biologic and Immunomodulator **N**aïve patients **i**n **C**rohn's Disease) [14]. The authors studied several predefined endpoints that have been previously used as outcome measures in

clinical trials. They studied different values for absolute reduction in CDEIS (by at least 3 [30], 4 [26] or 5 [14, 26] points) as well as relative reduction (by at least 50 % [31] or 75 % [13]). Their results suggested that defining endoscopic response as a reduction in CDEIS from baseline of at least 50 % provided an endpoint at week 26, which was predictive of corticosteroid-free remission at week 54. Using a relative, rather than an absolute, decrease has the additional benefit that it accounts for patients with relatively low baseline endoscopic disease activity who cannot achieve large reductions in absolute values. This definition for endoscopic response shows significant potential as a reliable, achievable and meaningful endpoint. However, the authors conclude that prospective trials are necessary to validate the mid-term (1 year) outcomes described as well as to investigate effect on long-term (>3 years) disease-modifying outcomes.

The CDEIS has certain limitations and is somewhat complex to use. Assessments made at endoscopy require conversion from a visual analogue scale to calculate the final score and making accurate assessments requires training as well as experience. Its usefulness in day-to-day practice therefore appears limited. Another limitation is that the final score does not reflect the number of affected segments, the location of stenoses (if present) or the severity per segment. Studies investigating the correlation of the CDEIS with clinical disease activity scores—most commonly the Crohn's Disease Activity Index (CDAI)—have yielded conflicting results. Some studies had suggested a good correlation [32] between the two, whereas others (including the original CDEIS studies) demonstrated the opposite [5, 10, 11, 33]. The apparent poor correlation demonstrated in some of these studies could be explained in several ways. Relatively limited lesions (e.g., proctitis) can cause severe symptoms, whereas patients with diffuse but rather superficial ulceration can present with rather mild symptoms. A single stenosis without further ulcerations can be the cause of severe abdominal pain and a high clinical disease index. Finally, the mucosal appearance may not accurately reflect systemic manifestations of active inflammatory disease. It is also possible that in the case of CD affecting the small bowel proximal to the portion of the distal ileum visualized at ileocolonoscopy, the CDEIS could underestimate the degree and extent of disease activity.

The Simple Endoscopic Score in Crohn's Disease

Index Development, Validation and Utilization

The Simple Endoscopic Score in Crohn's Disease (SES-CD) was devised in 2004 to offer a less complex and more user-friendly alternative to the CDEIS. Daperno and colleagues began by incorporating items from the CDEIS with high interobserver agreement into their novel index [34]. The SES-CD grades four items: ulcer size (diameter 0.1–0.5 cm, 0.5–2 cm, or >2 cm); proportion of ulcerated surface (<10 %, 10–30 %, or >30); proportion of the surface area affected by any disease lesion (<50 %, 50–75 %, or >75 %); and stenosis (single, multiple, impassable with a colonoscope). Each item is scored from 0 to 3 in each of the five ileocolonic segments (as described in the CDEIS: rectum, sigmoid and left colon, transverse colon, right colon, and ileum). As part of their regression modeling analysis it was found that the sum of the scores for the four segments should undergo a relatively minor arithmetic manipulation to give the optimal score. However, for the sake of simplicity the sum of the values for the four variables, for the five bowel segments was decided upon as the final score giving a range of 0–60, with higher scores indicating more severe disease (Table 14.1). Apart from its relative simplicity, another proposed advantage of the SES-CD above CDEIS is its emphasis on ulceration as the most likely lesion to change with therapy [35].

As part of the process of developing the SES-CD, the authors also investigated its operating characteristics. Agreement for each of the items modified from the CDEIS was studied in a series of 71 procedures. Two endoscopists (both

Table 14.1 Simple endoscopic score in Crohn's Disease (SES-CD). (See Table 12.5)

	SES-CD values			
Variable	0	1	2	3
Ulcers	None	Aphthous ulcers (Diameter 0.1–0.5 cm)	Large ulcers (Diameter 0.5–2 cm)	Very large ulcers (Diameter >2 cm)
Ulcerated surface	None	<10 %	10–30 %	>30 %
Affected surface	Unaffected segment	<50 %	70–75 %	>75 %
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

present in the procedure room but not communicating with each other) graded each item from the SES-CD. This exercise successfully demonstrated high intra-observer agreement.

The construct validity of the SES-CD was demonstrated by correlation with the CDEIS. The authors of the original paper demonstrated a strong correlation between their simplified index and its more complex alternative. This finding has been subsequently confirmed in a Finnish cross-sectional study of 86 patients with CD undergoing ileocolonoscopy. Near perfect correlation between the two scores was demonstrated when procedures were examined by a single endoscopist [36]. Near perfect correlation was also seen in a recent study where four expert central readers each graded 50 recorded procedures on three occasions [25]. This study not only demonstrated the close relationship between the two scores and reliability of central readership but also added validity to both scores by reporting a substantial correlation with an endoscopist's global rating of disease (based on a visual analogue scale).

The responsiveness of the SES-CD has also been studied in a number of ways. By performing sub-group analysis on data from the SONIC trial, Ferrante et al. [29] demonstrated an excellent correlation between changes in SES-CD and CDEIS values at week 26. In a smaller, prospective cohort study carried out as part of the Finnish study described previously [36], 32 patients underwent a follow-up endoscopy at an average of 4 months from baseline. This also demonstrated that changes in SES-CD and CDEIS between these two examinations correlated highly.

Correlation between the SES-CD and clinical parameters has also been investigated. While the SES-CD was shown to have only a weak correlation with the CDAI in the study that originally described the simplified score [34], a subsequent trial demonstrated a moderate correlation [36]. However, the changes over time seen in these indices correlate poorly. The same pattern was described for the relationship of SES-CD with C-reactive protein (CRP).

Endpoints, Definitions and Cut-off Values

As with the CDEIS, clearly defined and validated endpoints and cut-off values for disease severity using the SES-CD have not been described. However, through a combination of expert consensus [37] and prior trial experience, boundaries for disease activity have been arbitrarily set. The following cut-off values are generally accepted and have been used as endpoints in clinical trials [37, 38]:

- 0–2 Remission
- 3–6 Mild inflammation
- 7–16 Moderate inflammation
- >16 Severe inflammation

As is seen with cut-off values to describe severity using the CDEIS various, minor alterations have been suggested [39] and used as boundaries for the SES-CD. For example, in a trial comparing the two scores, an SES-CD of >15 was used to define severe disease [36].

The minimal clinically important change in SES-CD values was investigated during post-hoc analysis of data [29] from the SONIC trial (described in the CDEIS section). Though values for absolute change in the SES-CD were not studied in detail (as was undertaken for the CDEIS) the authors demonstrated that a relative reduction of 50 % from baseline score at

the week 26 endoscopy accurately predicted corticosteroid free remission at week 50. Another post-hoc analysis study [40], this time examining data from the EXTEND trial (**EXT**end the Safety and **E**fficacy of Adalimumab **T**hrough **END**oscopic Healing), showed that for CD patients treated with adalimumab, an SES-CD score of 5 measured at week 12 represented the optimal dichotomizing points for predicting clinical remission at week 52.

Owing to its relative simplicity and demonstrated high degree of correlation with CDEIS, the SES-CD has gained favor. It is now in frequent use as an entry criteria [41] and as endpoints [9, 27, 42, 43] in clinical trials. Elsewhere the two scores have been scored alongside one another [44]. However, this strategy may become unnecessary as data demonstrating correlation and experience interpreting the simplified score grows. The SES-CD is also eminently more feasible for application to daily practice than the CDEIS, with some experienced endoscopists advocating its routine use in every ileocolonoscopy where CD is assessed [36]. However, by virtue of the way the ileocolonic segments are divided it is possible that both scores have the potential to overestimate colonic disease or mild changes seen in several segments. Conversely, ileal disease alone, or a limited but severe disease may be underestimated by both systems [1].

Rutgeerts Score

Index Development, Validation and Utilization

The Rutgeerts score is the long-standing and widely accepted scoring system for the assessment of Crohn's disease activity in the postoperative setting [45, 46]. Since its development more than two decades ago and despite limited validation it has been the gold standard and no other scoring systems are in common use for this purpose [47]. It is used to describe the severity of endoscopic changes (recurrence of disease) seen at the ileocolic anastomosis and in the preanastomotic ileum after ileal or ileocolic resection. The authors devised their score based on the observation that endoscopic recurrence, particularly at the anastomosis, precedes clinical recurrence [48]. Moreover, it was noted that the severity of the endoscopic changes seen correlated with the likelihood of subsequent clinical relapse. Lesions seen at endoscopy are graded on a five-degree scale (i0–i4):

- i0 No lesions
- i1 Fewer than five aphthous lesions
- i2 More than five aphthous lesions with normal mucosa in between or skip areas of larger lesions, or lesions confined to ileocolonic anastomosis (that is, <1 cm in length)
- i3 Diffuse aphthous ileitis with diffusely inflamed mucosa
- i4 Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

Endpoints, Definitions and Cut-off Values

When applied to an asymptomatic patient in the year following surgery this index not only provides a real-time assessment of endoscopic recurrence but allows for accurate stratification of patients into groups at high or low risk of developing symptoms. It therefore has significant prognostic value: 80–85 % of patients with a score of i0 or i1 (Video 14.3) will be asymptomatic 3 years after surgery compared with fewer than 10 % of those with a score of i3 or i4 (Video 14.4) [49, 50]. As well as predicting the future development of symptoms, estimates of progression of mucosal changes can be made. In Rutgeerts' original study of 89 patients having undergone ileal resection for CD, 80 % of patients with i0 or i1 lesions at the postoperative endoscopy had unchanged lesions at 3 years. However, mucosal disease progression was noted in 92 % of patients with i3 or i4 lesions. Though this property was validated in the original work, the reproducibility of the score has not been fully and prospectively validated. Nonetheless, it has been extensively used for clinical trials [51–53] and integrated into many postoperative algorithms (Fig. 14.4). For example, the authors of this chapter advocate planning an ilecolonoscopy at 6 months to 1 year after ileocolic resection (assuming patients remain asymptomatic). The Rutgeerts'

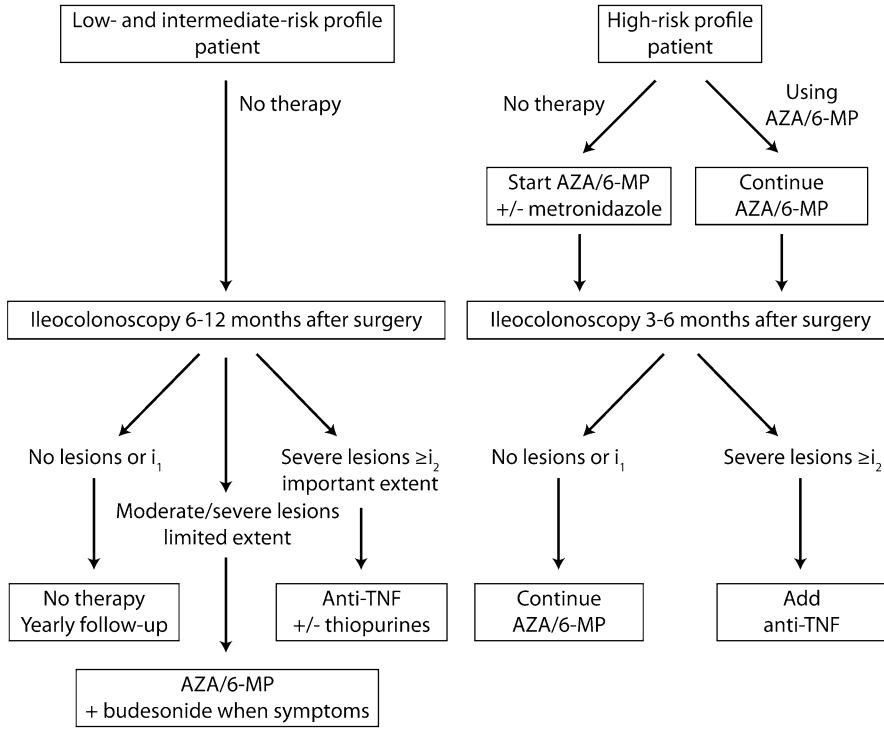

Fig. 14.4 The use of Rutgeerts score in a postoperative surveillance and treatment algorithm for CD. AZA = azathioprine, 6-MP = 6-Mercaptopurine. (See Fig. 12.1) Reprinted with permission of S. Karger AG, Basel from van Lent AU, D'Haens GR. Management of postoperative recurrence of Crohn's disease. Dig Dis. 2013;31(2):222–8

score measured at this procedure, along with clinical, biochemical and imaging (if appropriate) parameters should be used to guide therapeutic decisions. Based on the evidence previously described, there is good rationale that those with i3 and i4 lesions should undergo treatment intensification, even in the absence of symptoms. Equally, for those on no treatment with i0 and i1 lesions, monitoring for the recurrence of symptoms alone is advocated. If treatment had been continued after surgery, there is no clear evidence whether this should remain unchanged or withdrawal should be considered. Assuming an ongoing asymptomatic course, then endoscopic re-evaluation at 3 years post surgery is suggested. The duration of this interval is, in part, arbitrary but also draws on evidence from the aforementioned studies.

A grade of i2 on the Rutgeerts score predicts an intermediate risk of clinical recurrence of disease [35]. Prognosis for this group is more difficult to define than for the other grades and is further complicated by its description, which is more subjective than the alternatives [16]. This has therefore divided opinion in its interpretation when defining disease recurrence for clinical trials. Some studies have defined postoperative recurrence as a score of i2 or above [51], whereas others have opted for i3 and above [54]. Others have even included those with i1 lesions in their recurrence group [55], though evidence would suggest that this is an unnecessarily stringent definition. In an attempt to overcome the uncertainly surrounding this issue some authors have modified the Rutgeerts score to divide the i2 grade into two groups: i2a and i2b. For the purpose of their study investigating recurrence rates in patients treated with azathioprine versus those on mesalazine, Reinisch and colleagues did this [56]: They defined i2a as "moderate endoscopic

recurrence," demonstrated by >5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions. In turn, i2b lesions were defined as those confined to the ileocolonic anastomosis (i.e., 1 cm long). Similar dissonance exists in day-to-day practice with some clinicians preferring to recommence treatment based on i2 images and others taking a more conservative approach. Currently insufficient evidence exists to justify treatment on this basis alone and the authors of this chapter advocate a strategy based on close clinical observation.

These examples serve to demonstrate that further work needs to be carried out to accurately define the postoperative risk of symptomatic recurrence in this group of patients. Such studies are already in progress and this well-established index is likely to undergo further attempts at modification in the near future.

The Definition of Mucosal Healing and Endoscopic Response in Crohn's Disease

Although the characteristic appearances of CD at ileocolonoscopy are well characterized, there is no validated definition of mucosal healing [57]. Endoscopic remission is an alternative, synonymous term sometimes used to describe healed mucosa but is equally without validated definition. A simplistic and perhaps most intuitive definition of mucosal healing relies on absence of any mucosal ulceration. This definition has the clear advantages of its relative ease of use and its property of dividing patients in a binary fashion into those with residual ulceration and those without. Although this definition has been used in designing endpoints for clinical trials, it is less useful in clinical practice where a spectrum of disease needs to be appreciated in context with many other parameters (symptoms, abdominal imaging, serum and fecal biomarkers, for example).

In fact, even within clinical trials, evidence is gathering that such a stringent definition for mucosal healing is less optimal than first imagined. For example, the use of this definition would classify a patient in whom multiple, deep ulceration had improved leaving only a solitary small ulcer as a "non-responder." The difficulty in achieving this definition can be demonstrated using data from the randomized, placebo-controlled EXTEND trial, where mucosal healing was used as a primary endpoint for the first time when studying a biological agent [13]. In this study, mucosal healing was assessed by a blinded central reader and any disagreements between sites and central readers were adjudicated by up to two additional central readers. Mucosal healing was defined as absence of ulceration in patients with ulceration at baseline and a secondary endpoint of reduction in CDEIS by >75 % was also set. Of the 62 patients with CD given adalimumab, 15 (24 %) achieved mucosal healing following the induction phase and the same number maintained this at 52 weeks. Based on this observation, complete absence of ulceration is now often considered by many experts to be too difficult to achieve when assessing drug efficacy in a clinical trial or in daily practice. Though evidence would suggest that achieving mucosal healing is associated with favorable outcomes [58, 59] it remains unclear exactly what degree of healing is required to achieve these long-term clinical benefits.

Recent investigation has attempted to define a more achievable and pragmatic definition for mucosal healing by studying the minimal clinically important improvement in endoscopic disease. Though the SONIC trial [14] used complete absence of ulceration as a secondary endpoint when studying mono- versus combo-therapy (using azathioprine and infliximab, in immunomodulator naïve patients with CD), post-hoc analysis of results [29] led to the conclusion that a reduction in the inflammatory score (as measured by the SES-CD or CDEIS, both discussed in subsequent sections of this chapter) of 50 % at week 26 compared with baseline score was the minimal endoscopic improvement associated with clinical benefit (Video 14.5). The authors described this degree of change as "endoscopic response"—an endpoint that showed good predictive value for maintaining clinical benefit at week 50 using a variety of clinical endpoints. However, it is not yet known whether the mid-term improvement in clinical outcome associated with endoscopic response in this study will translate into disease-modifying, long-term benefits.

Though validation of this endpoint and investigation of long-term outcomes will require further prospective studies, this target has significant potential for trials as well as implications for targets in clinical practice. For example, integrating endoscopic re-assessment at 26 weeks in treatment algorithms may identify patients who would benefit from early treatment intensification.

The previously described evidence demonstrates how using the presence or absence of ulceration alone lacks the sensitivity to describe grades of activity or partial endoscopic responses. Its responsiveness as an evaluative index for dose finding or early phase trials seeking a signal of efficacy is also unknown. To address these shortcomings, endoscopic indices, which allow objective quantifiable assessments, appear useful. An ideal index should detect meaningful changes in mucosal appearance with treatments of known efficacy (responsiveness) and remain unchanged in static disease (reliability). As part of their validation, indices should have limited inter- and intra-observer variability. These indices, along with their development and definitions will be considered in the next section of this chapter.

The focus of this chapter concerns the use of endoscopy to follow the clinical course of CD and this section has, therefore, discussed only endoscopic definitions of mucosal healing. There are, of course, other ways of defining mucosal healing, including the use of histological resolution of abnormalities or examination of mucosa using confocal laser endomicroscopy. These techniques are considered beyond the scope of this chapter but are discussed in the relevant chapters of this book.

The Clinical Relevance of Mucosal Healing in Crohn's Disease

The Relationship between Clinical and Endoscopic Disease Activity

The lack of correlation between clinical measures of disease activity (using the CDAI) and endoscopic assessments for CD has been demonstrated on several occasions [10, 11]. In a study to investigate the relationships between disease activity and serum and fecal biomarkers in patients with CD, no correlation was observed between the CDAI and SES-CD [60]. It is also worth noting that though serum (CRP and interleukin-6 concentrations) and fecal biomarkers showed the same poor correlation with CDAI, they both correlated strongly with SES-CD values. The correlation between symptoms and endoscopic scores is known to be particularly weak when attempting to predict the degree of endoscopic activity present based on clinical scores alone [5]. An example of this was demonstrated in analysis of data from the SONIC trial [14], comparing infliximab or azathioprine monotherapy with a combination of the two drugs. Inclusion to the trial required a CDAI score of >220, suggesting moderate disease at least, but findings demonstrated that 18 % of patients meeting this criteria had no objective evidence of endoscopic disease activity. This disparity has clear implications for research studies (higher placebo rates, lower estimated effect size) as well as decision-making in clinical practice. It is possible that these findings reveal the limitations [47, 61] of the CDAI as an instrument for assessing clinical activity, though alternative explanations do exist, as outlined previously.

The poor predictive value of clinical disease scores when estimating endoscopic disease activity is even more pronounced in the postoperative patient. As discussed in the section describing the Rutgeerts score for postoperative disease recurrence, mucosal changes are usually seen before patients develop symptoms [45, 48]. Along with the limitations of the CDAI considered above, this well-understood pattern of chronology means that the CDAI does not have the appropriate operating characteristics to use in this setting. This was demonstrated in a study of 110 postoperative patients, of which CDAI values could correctly predict endoscopic recurrence in only 65 % [62]. This finding has been confirmed in other, similar studies [63], one of which showed that using a CDAI cut-off of 150 resulted in a sensitivity of only 70 % (though specificity was better at 81 %[64]). Owing to these findings, routine endoscopic revaluation at 6–12 months following surgery remains the gold standard for diagnosing postoperative recurrence of disease. This proactive strategy is essential to guide

management aimed at preventing symptomatic recurrence in patients with endoscopic disease activity.

The Impact of Endoscopic Disease Activity on Outcomes

The association between endoscopic disease activity, however defined, and clinical outcomes is surely the key relationship when considering how to monitor patients with CD based on mucosal assessment. It also forms the driver behind the increasing use of endoscopic outcome measures in trials investigating novel therapies. The natural history of CD is a progression from an inflammation predominant disease (90 % at presentation [35]) to one characterized by structuring and penetrating complications [65]. Surgery is required in the majority (80 % at some point in the disease course) and is not curative, with rates of repeat surgery as high as 70 % in some series [66]. Strategies aimed at the amelioration of symptoms without necessarily demonstrating mucosal improvement have been ineffective at significantly altering this pattern [3]. The advent of biological therapies with the property to heal mucosa renewed hope that better outcomes for patients with CD was possible. The dramatic effect on endoscopic appearances observed led to the prediction that directly targeting tissue damage at the mucosal level could result in rapid and sustained mucosal restitution. It was hoped that this in turn should halt the progression of disease and development of complications. However, to justify the additional resources needed and inconvenience to patients involved in a follow-up strategy based on endoscopic results, evidence was needed to support this prediction.

Following studies carried out in the 1990s demonstrating clearly that mucosal healing was achievable with infliximab [7] the relationship between deep mucosal ulceration and long-term clinical outcomes was more clearly defined. Allez and colleagues revealed that CD patients with deep and extensive (involving at least 10 % of a colonic segment) ulceration at index ileocolonoscopy had a significantly higher rate of colectomy over subsequent years than those without [67]. In their longitudinal series, 62 % of those with deep and extensive ulcers underwent colectomy compared to 18 % without. They concluded that those with severely diseased mucosa had a more aggressive disease course with increased rates of penetrating complications and surgery. The findings of these two fundamental pieces of work taken in conjunction suggested that being able to control disease activity at the mucosal level could indeed deliver beneficial outcomes in CD.

Since the aforementioned studies, evidence has continued to emerge to support the notion that setting and reaching endoscopic targets improves both short- and long-term clinical outcomes. Data from the ACCENT 1 study [12] along with its endoscopic sub-study [32] provided good examples of this principle. Results from the primary trial showed that achieving mucosal healing was associated with a more durable clinical remission. Those reaching this endpoint at week 54 had a significantly longer time to relapse (median 19–20 weeks) than those who did not (4 weeks). In the sub-study, a reduction in hospitalization rates amongst those achieving mucosal healing was also demonstrated. No patient with mucosal healing at both time points (10 and 54 weeks) required hospital admission. This was compared to 4/16 (25 %) of those with healing at one time point only and 34/74 (46 %) of those without healing. These findings have been supported by a large cohort studies. One of these, carried out in Leuven [58], included 183 patients who responded to induction therapy with infliximab and were followed up over a median of almost 6 years while on maintenance treatment. Amongst this cohort, lower rates of hospitalization were again demonstrated along with reduced incidence of surgery in those achieving mucosal healing. Similar results were also generated in an even larger cohort study from the IBSEN (Inflammatory Bowel South-Eastern Norway) group including 227 newly diagnosed patients followed for a total of 8 years [8] in an era when biological treatment was not yet available. In addition to the above, this study also demonstrated that absence of

mucosal ulceration at one year predicted a reduced need for steroids and decreased clinical disease activity over the follow-up period.

The importance of endoscopic monitoring of treatment effect in patients with CD was further underlined in 2010 as part of a study designed to investigate the optimal treatment algorithm for recently diagnosed, treatment-naïve patients. The SUTD trial (**S**tep **U**p, **T**op **D**own) compared the conventional and gradual "step-up" approach of treatment escalation with a novel "top-down" regimen, which involved early use of azathioprine and infliximab combotherapy [68]. When endoscopic re-evaluation was carried out following 2 years of treatment, those without ulceration (SES-CD of 0) had a favorable disease course over the subsequent 2 years when compared to patients who had ongoing activity. Rates of steroid-free clinical remission for the follow-up period was 71 % (17/24) compared to 21 % (6/22) in the two groups, respectively.

Though the majority of evidence supporting the use of endoscopic targets to assess response to CD therapy has been generated in trials investigating infliximab, similar findings have been made with other agents. Post-hoc analysis of patients in the EXTEND trial also demonstrated that early mucosal healing predicted long-clinical benefits in adalimumab-treated patients [69]. Absence of ulcerations, when assessed at week 12, was associated with significantly lower CDAI scores at 1 year (a difference of 46 points was seen between those with healing and those without) as well as reduced rates of hospitalization and improved work productivity and quality of life.

The relationship between improved endoscopic disease status and favorable clinical outcomes is not exclusive to biological therapies. In a trial comparing budesonide with azathioprine for maintenance of remission [70], more patients in the azathioprine group achieved mucosal healing at 1 year and this group also had a higher rate of clinical remission assessed 6 months later (76 % compared to 36 %, $P=0.03$).

These findings taken in conjunction offer compelling evidence to support the proposition that achieving specific endoscopic goals can deliver real and meaningful benefits to patients. In contrast, there is a relative paucity of evidence dictating the optimal timing of endoscopic evaluation and exact nature of these goals. Studies and sub-group analyses (such as the work carried out by Ferrante and colleagues [29]) designed specifically to investigate these questions will more clearly define the role endoscopy should play in the follow-up of CD.

Another important aspect of long-term outcomes in IBD is the incidence of colorectal cancer (CRC). Evidence demonstrating this risk in patients with IBD comes from the CESAME study group (**C**ancers **E**t **S**urrisque **A**ssocié aux **M**aladies Inflammatoires Intestinales **E**n France) [71]. Data was collected from almost 20,000 patients in France, who were followed for more than 3 years for the incidence of CRC or high-grade dysplasia (HGD), which were considered together. Though this study also included patients with UC and IBD unclassified (40 % of the total study population), meaningful results regarding the risk in CD specifically could be drawn. The authors found that patients with IBD and long-standing, extensive colitis (of either variety) were at significantly increased risk of CRC/HGD. However, those without this phenotype were not. The standardized incidence ratios of CRC/HGD were 2.2 for all IBD patients (95 % CI: 1.5–3.0; $P<0.0001$), 7.0 for patients with long-standing extensive colitis (95 % CI: 4.4–10.5; $P<0.001$), and 1.1 for patients without long-standing extensive colitis (95 % CI: 0.6–1.8; $P=0.84$). This issue has been more extensively investigated in UC where there is evidence showing a positive correlation between CRC rates and degree of disease activity (judged endoscopically or histologically) [35]. This relationship has not yet been investigated for CD. Further studies among CD patients are required before a reduced cancer risk in CD can be ascribed to mucosal healing. However, the findings of the CESAME study group would support the use of endoscopic surveillance programs for CD patients with colitis but not necessarily for those without.

The Timing of Endoscopic Assessment in Crohn's Disease

Assuming that the evidence demonstrating the benefit of mucosal assessment is accepted and the lack of clear definition of what exactly is meant by mucosal healing is overlooked, logic dictates the next question is: when to use endoscopy to monitor CD?

Though precise figures regarding the timing of endoscopy (for example, after commencing a biological treatment or undergoing ileocaecal resection) cannot be given on the basis of evidence, there is data suggesting that periodic endoscopic re-assessment does guide management. In a cross-sectional cohort study of 230 pediatric IBD patients, it was found that the result of direct mucosal assessment by endoscopy led to an increased rate of change in management strategy [72].

Guidance on exact timings for endoscopy is lacking and may depend on the treatment patients are offered. If the interval from commencing a treatment and re-assessment is too short and does not allow time for mucosal reconstitution, then a false impression of lack of efficacy is possible. Conversely, a prolonged interval could result in suboptimal treatment and ongoing disease activity, which over time can result in complications.

Perhaps it is therefore more sensible and relevant to clinical practice to consider the timing of endoscopy in the context of clinical scenarios where it may inform decision-making. Generally speaking, these fall into three broad categories: commencing treatment, escalating treatment, and withdrawing or reducing treatment.

Commencing Treatment

Early identification of patients who are likely to have a more aggressive disease course is of value in clinical decision-making and prognostication. As well as the recognized clinical and biochemical parameters, endoscopic features can be used to identify those in whom early combination (immunosuppressive and biologic) therapy would deliver the greatest benefit. Often this information will come from the index ilecolonoscopy, but where this is not the case (due to an incomplete procedure for example) there exist legitimate arguments for endoscopic re-assessment. This rationale is based on data (from the SONIC [14] trial and elsewhere [67, 73, 74]) showing that deep ulceration along with ileal or ileocolonic (Montreal classification L1 or L3) are poor prognostic factors. "Top-down" or an accelerated "step-up" approach to management may therefore be more appropriate for this group of patients than others. The information gained at endoscopy taken in the context of trial data provides robust justification for the excess cost and potential for additional side effects of these aggressive management strategies [75].

Escalating Treatment

Establishing the Effect of Treatment on Mucosal Disease Activity in Those Achieving Clinical Remission

For reasons laid out in the previous section of this chapter, mucosal healing is considered a desirable treatment goal for many reasons. There is, therefore, good rationale for mucosal re-evaluation to establish endoscopic response/remission once clinical remission has been achieved. The demonstrated lack of correlation between clinical symptoms and endoscopic appearance [14, 60], taken in conjunction with the association between mucosal healing and better outcomes, means endoscopy can guide optimal management in this scenario.

For those who fail to make a significant improvement (see earlier Sect. "Essential Endoscopic Features of Crohn's Disease" or [23] for suggested definitions) from index endoscopy, treatment escalation should be considered. Though this paradigm is based on data, it should be noted that prospective studies comparing this strategy with more conventional management are needed before it can be fully endorsed by evidence. One such trial is planned—REACT2 (**R**andomized **E**valuation of an **A**lgorithm for **C**rohn's **T**reatment)—investigating an enhanced

treatment algorithm, which includes endoscopic re-assessment, with conventional step-care based solely on symptoms (quantified using the Harvey-Bradshaw index).

As a general rule, endoscopic response/remission with biologic treatment can be assessed as early as 12 weeks after the start, although 26 weeks is a meaningful alternative. Thiopurines have a more delayed mechanism of actions, therefore endoscopic assessment earlier than 6 months after the start of treatment does not make much sense. Corticosteroids do not offer long-term benefit, making endoscopic reassessment rather useless.

Assessing Mucosal Disease Activity in Those with Symptoms

Symptoms in CD can arise from causes other than active mucosal inflammation and an endoscopy remains the most sensitive way of demonstrating the presence or absence of this. It also allows the clinician to exclude complications such as strictures or infection (e.g., cytomegalovirus diagnosed from biopsy samples, especially important in the context of immunosuppression), which may require specific treatment. These factors are pivotal when considering the management of a symptomatic patient and are certainly best judged at endoscopy.

If mucosal disease activity is confirmed, treatment optimization could be carried out if not already undertaken. For example, by confirming/attaining adequate trough levels of biological agents and/or thiopurine active metabolites. If this is already the case then treatment failure can legitimately be confirmed and treatment should be switched. Declaring a patient to be unresponsive to an agent has obvious implications for their future treatment and, therefore, really should include objective endoscopic evidence. The timing of re-assessment should allow a sufficient interval for mucosal repair to take place with adequately dosed therapy. In patients with pure small bowel disease, magnetic resonance imaging (MRI) may be the preferred method for imaging, but this falls beyond the scope of the current chapter.

Assessing Disease Recurrence in the Postoperative Patient

Endoscopic re-assessment of asymptomatic patients within the first postoperative year is established and accepted practice. The evidence for this approach is discussed in the earlier Sect. "Endoscopic Scoring Indices Used to Evaluate Crohn's Disease": *Rutgeerts Score* [45, 46, 48]. Though we suggest all postoperative patients are reassessed endoscopically, it is reasonable to reassess those with a higher risk of recurrence sooner than those considered low-risk. Reasonable time frames for endoscopy are 3–6 months for high-risk patients and 6–12 months for low-risk patients [76]. Based on the Rutgeerts score, decisions can be made regarding the need for prophylactic treatment, aimed at preventing subsequent clinical relapse [77, 78]. A suggested approach to timing and intervention is given in the algorithm in Fig. 14.4. In cases where disease is limited to the terminal ileum or ileocecal region and treatment is stopped at the time of resection patients with i0 and i1, appearances do not warrant the re-introduction of treatment as they are at low-risk of developing symptoms or endoscopic progression. Conversely, recommencing treatment in those with i3 and i4 lesions is suggested as they are at high-risk of both [79]. Where treatment is continued throughout the postoperative period (usually because the patient is at high-risk of recurrence based on clinical parameters) a similar rationale can be used to make decisions regarding the need for treatment escalation/optimization or addition. Decisions regarding asymptomatic patients with i2 lesions are more difficult to base on evidence and are often at the discretion of the clinician and patient. The 3-year clinical recurrence rate for this group is considered "intermediate" and is in the region of 15–20 % [50]. The POCER trial (**P**ost-**O**perative **C**rohn's **E**ndoscopic **R**ecurrence) was designed to assess the value of a postoperative endoscopic surveillance program. Initial findings are available and show that patients who underwent endoscopy at 6 months (with step-up of therapy if evidence of recurrence was seen) were significantly less likely to have endoscopic recurrence at 18 months

than patients on best drug therapy but no endoscopy at 6 months [80]. The authors also demonstrated the predictive value of clinical risk stratification and based this upon smoking, perforating disease phenotype, or having undergone a previous resection [81]. However, several other factors have been demonstrated to be associated with risk of recurrence [76].

A repeat endoscopy at 3 years is suggested for those with grade i0 or i1 at their first postoperative endoscopy who remain asymptomatic, or at the onset of symptoms suggesting relapse for those whose do not. Similar, but admittedly less evidence-driven, reasoning could be used for treatment decisions at that time point.

Withdrawing or Reducing Treatment

Though many clinicians with a specialist interest in IBD do not routinely withdraw or reduce treatment in patients with well-controlled disease, there are certain circumstances in which this question must be addressed. This issue may be raised by patients themselves, clinicians with concern regarding adverse events or especially in the case of expensive biological agents, from bodies responsible for remuneration. The GETAID group prospectively investigated this in the STORI trial (Infliximab di**S**con**T**inuation in Cr**O**hn's disease patients in stable **R**emission on combined therapy with **I**mmunosuppressors) [82]. A group of 115 patients in steroid-free clinical remission for at least 6 months underwent infliximab discontinuation and after a median follow-up period of 1 year, 45 relapses (39 %) were seen. Multivariate analysis suggested that endoscopic activity (CDEIS >0), CRP, hemoglobin and infliximab trough levels could all be used to predict risk of relapse. Mucosal healing may therefore be used to predict a favorable outcome on infliximab cessation. It should be noted that all were treated with ongoing azathioprine. Hence, when considering the withdrawal of biological monotherapy, immunosuppressive therapy appears to offer protection from future relapse.

GETAID also investigated the withdrawal of azathioprine monotherapy in patients with well-controlled CD [83]. Though they demonstrated the value of azathioprine as a maintenance treatment, only 54 % underwent endoscopy at inclusion. Meaningful conclusions regarding the use of endoscopy to guide this decision could, therefore, not be made on the basis of this study and no others have investigated this specifically.

Colorectal Cancer Surveillance

The increased risk of colorectal cancer (and high-grade dysplasia) in CD patients with extensive and long-standing colitis was demonstrated in the recently published work by the CESAME study group [71]. Their large, prospective, observational cohort study also showed that IBD patients without this phenotype did not have an increased risk. For the purposes of their study they defined long-standing as more than 10 years duration and extensive colitis as estimated cumulative proportion of the mucosal area macroscopically or microscopically affected by IBD > 50 % (both recognized definitions [84, 85]). This increased risk requires surveillance and a suggested approach to this is described in the 2010 British Society of Gastroenterology guideline: *Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups* [84]. Their algorithm suggests that all IBD patients with colitis (regardless of extent) undergo a surveillance colonoscopy (preferably during remission, with pancolonic dye-spray) at 10 years. This allows stratification into low-, medium- or high-risk groups. These groups then undergo follow-up colonoscopy on a 5-yearly, 3-yearly or annual basis. Surveillance is not considered necessary in patients with isolated terminal ileal or small bowel CD.

Factors Limiting the Use of Endoscopy and Possible Alternatives

Endoscopy is an invasive investigation and the procedure, along with the bowel preparation necessary, are understandably disliked by most patients. Each procedure can last between a few

hours to an entire day and can therefore disrupt work, school or social commitments. It is also costly and time consuming for health providers. These factors should be accounted for, along with the possibility of complications, such as perforation and significant bleeding when endoscopy is being considered. Together, these make it difficult to justify repeating the technique for an individual patient unless the findings are likely to lead to a significant change in management.

As well as the endoscopy procedure itself, there are several other factors to be considered when striving to reach predefined endoscopic targets such as mucosal healing. It is likely that the escalation of treatment based on this type of strategy will lead to an increased risk of complications, such as lymphoma and opportunistic infections. This is especially relevant in older patients with co-morbidities, in whom endoscopic targets may be less relevant or safely achievable. The escalation of treatment to achieve these goals also has significant health economic effects. The pattern of spending on CD treatment has changed from hospital-based costs (in patient care and surgery) to outpatient care, predominantly due to the use of expensive biological drugs [86]. This proportion is likely to increase further if more stringent endoscopic targets are adopted in clinical practice.

There are also an expanding number of alternatives to endoscopy when considering how to monitor patients with CD. These will be discussed in greater detail in other sections of this book but one such alternative is MRI. An externally validated [87] scoring system (MRI activity index, MRIA) has been developed [88, 89] for this modality, which correlates well with CDEIS. This technique has the advantage of providing information regarding transmural inflammation, extra-luminal complications and an assessment of areas beyond the reach of a standard endoscope. These qualities take on significant relevance when considering that the mucosa comprises less than 15 % of the thickness of the entire bowel wall [90]. Fecal biomarkers (such as calprotectin) also offer some promise as a non-invasive marker of intestinal inflammation. A low fecal calprotectin has been shown to reliably predict mucosal healing in CD [91]. However, their role in monitoring response to therapy, especially in isolated ileal disease, remains ill-defined [92].

Despite these limitations and alternatives, based on the evidence presented in this chapter, we believe that endoscopy has a significant role to play in the follow-up of CD. There is also growing evidence that in conjunction with macroscopic healing seen at endoscopy, microscopic healing seen using endomicroscopy [93, 94] or histology [28, 95] may also be desirable. This may signify an increased "depth" of remission and could, in the future, be incorporated into composite endpoints (along with endoscopic, biochemical and clinical scores) for clinical trials. Though prospective trials are needed to judge whether this is a necessary or realistic goal, it may also become a factor that influences the future use of endoscopy in CD.

Conclusion

Therapeutic goals in CD have evolved over time from mere symptom resolution strategies to include mucosal healing as a measure of treatment efficacy. This progress has been driven by the desire to significantly alter the natural history of the disease and preserve gut function. Emerging evidence suggests that these meaningful outcomes are achievable using treatments that result in mucosal healing. This change in the focus of treatment can be seen in the incorporation of mucosal healing as an important clinical trial endpoint. In conjunction with this, it is becoming an increasingly desirable goal in clinical practice.

Currently, there is no validated definition for mucosal healing. Evidence is also limited regarding the minimal clinically relevant change in endoscopic appearance. Future perspectives should involve studies that will help address these issues. Ideally, in such trials emphasis should shift from trials investigating medium-term (1 year) outcomes to include long-term (>3 years) outcomes.

As alternative techniques of assessing disease activity in CD emerge and evolve, the role of

endoscopy may also evolve. However, it remains the gold standard and will be for the foreseeable future. Its use in daily practice is likely to increase as serial endoscopies to assess treatment efficacy are integrated into treatment algorithms. The additional information gained from these procedures, compared with symptoms alone, should allow more optimal treatment and improved outcomes for patients with CD.

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Endoscopy in Crohn's Disease of the Pouch

15

Bo Shen

Introduction

The rapid progress in medical therapy for ulcerative colitis (UC), particularly the availability and wide use of anti-tumor necrosis factor (TNF) biological agents, does not appear to have a permanent impact on the long-term disease course, as approximately 20–30 % of patients with UC still eventually need colectomy. Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for patients with UC who require colectomy. While this technically challenging surgical procedure has been shown to significantly improve patients' health-related quality of life by preserving the natural route of defecation and avoiding permanent ileostomy, adverse sequelae are common. This bowel-anatomy-changing procedure is associated with structural, inflammatory, and functional complications. Crohn's disease of the pouch (CDP) along with pouchitis and cuffitis are the most common forms of inflammatory disorders of the pouch.

CDP can develop in the following settings:

1. CDP may persist from Crohn's colitis in a highly selected patient population who elect to have IPAA, knowing that the diagnosis of CD is a relative contraindication for the surgical procedure. This may be called *intentional* CDP.
2. CDP can develop after pouch construction and peri- or post-surgical pathology specimens reveal histologic features of Crohn's colitis and/or Crohn's ileitis. A pouch is inadvertently constructed. Under this circumstance, CDP develop as a *de novo* disorder in patients with a preoperative diagnosis of UC or indeterminate colitis (IC). Alternatively, restorative proctocolectomy with IPAA appears to change the bowel anatomy, alters the bowel ecosystem, and changes the "immune homeostasis," leading to new disorders, including *de novo* CDP. Based on the timing of occurrence, CDP can be arbitrarily divided into early-onset CDP and late-onset CDP, with the latter occurring more than 12 months after ileostomy closure. It appears the early-onset and late-onset CDP have different disease courses, with the latter having a poorer prognosis [1].

The diagnosis of CDP can be challenging, since there are no pathognomonic features for definitive diagnosis of CDP. On the other hand, the management of CDP has been difficult. Endoscopy or pouchoscopy play an important role for the diagnosis, differential diagnosis, and treatment of CDP.

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Endoscopy in Diagnosis and Differential Diagnosis

There is a wide range of clinical presentations, endoscopic and histologic features, and prognoses in CDP. Based on the clinical behavior CDP is categorized into (1) inflammatory, (2) stricturing, and (3) fistulizing phenotypes (Fig. 15.1a–d). Each of the phenotypes may be associated with different risk factors [2]. The pattern of clinical presentations can be dependent on the disease phenotypes. Patients with inflammatory CDP may have increased stool frequency, fecal urgency, incontinence, nocturnal seepage, abdominal pain, and pelvic discomfort. Patients with stricturing CDP may have dyschezia or partial bowel obstruction symptoms, such as bloating, gas, nausea, and vomiting. Clinical symptoms or signs of fistulizing or penetrating CDP include fever, abdominal mass, fistula, abscess formation, pneumaturia (pouch-bladder fistula), or vaginal discharge of gas or feces (pouch vaginal fistula [PVF]). Those symptoms, however, are not specific for CDP, as they can be present in patients with other pouch disorders, such as surgical procedure-associated strictures, fistula, leaks, pouchitis, cuffitis, or irritable pouch syndrome (IPS).

Patients' gastrointestinal symptoms may be accompanied by extraintestinal manifestations such as uveitis, iritis, and arthralgia. In my personal experience, erythema nodosum more

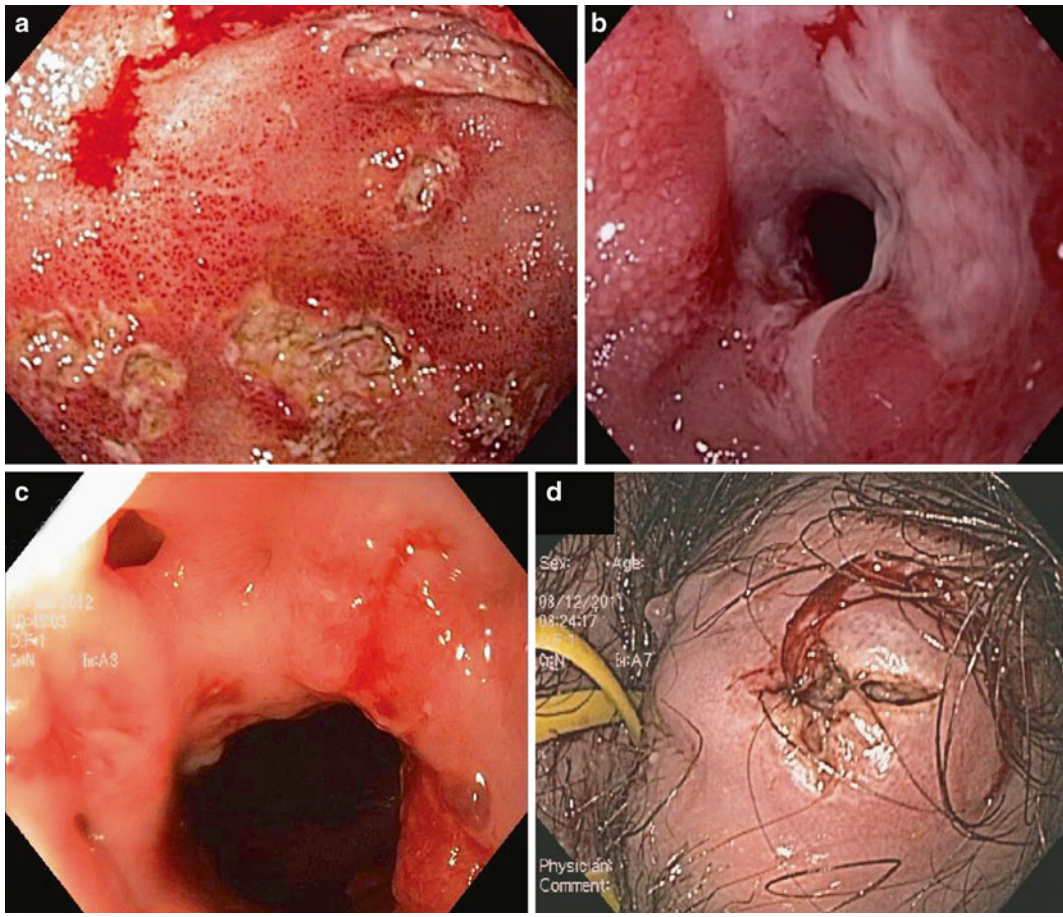

Fig. 15.1 Clinical phenotypes of Crohn's disease of the pouch. (**a**) Inflammatory form (in the afferent limb). (**b**) Stricturing form (at the pouch inlet). (**c**) Fistulizing form (the orifices at the anal transitional zone). (**d**) Fistula with seton in place and drained perianal abscess

Table 15.1 Comparison of endoscopic features of Crohn's disease of the pouch, pouchitis, and cuffitis

	Crohn's disease of the pouch	Pouchitis	Cuffitis
Pattern of inflammation	Discrete ulcers with or without adjacent inflammation	Diffuse homogenous inflammation	Discrete or diffuse inflammation
Distribution	Discrete, can be in the pouch body, cuff, afferent limb, or upper GI tract	In pouch body with or without backwash enteritis	Cuff or anal transitional zone
Stricture	Often	No	No
Fistula	Yes	No	No
Extraluminal disease	Yes, in fistulizing disease	No	No

often occurs in patients with CDP than in chronic pouchitis. In contrast, pyoderma gangrenosum and primary sclerosing cholangitis (PSC) are more often seen in patients with chronic pouchitis than in CDP. In fact, the presence of PSC has been shown to be a protective factor for the development of CDP [3].

While clinical symptoms may provide clues for the diagnosis and differential diagnosis of CDP, pouch endoscopy is the most important diagnostic modality. It should be pointed out that the disease process in CDP is not limited to the pouch body. In fact, it can involve any parts of the gastrointestinal tract, including stomach, proximal and distal small bowel, and cuff. There are other forms of inflammatory disorders of the pouch, mainly pouchitis and cuffitis. The differential diagnosis can sometimes be difficult. A careful evaluation of the pattern and distribution of mucosal ulceration and inflammation on pouchoscopy may yield clues for proper diagnosis (Table 15.1). Endoscopic features of CDP include discrete or segmental small and large ulcers, nodularity, exudate, and/or inflammatory pseudopolyps in the pouch body, afferent limb, or cuff or anal transitional zone (ATZ). Pre-pouch ileitis may be present in patients with pouchitis, and it is not necessarily indicative of CD. The presence of a long segment of enteritis above the pouch inlet in addition to diffuse pouch inflammation suggests that systemic, immune-mediated factors, such as PSC, contribute to the disease process [4]. The key features to distinguish CD ileitis from immune-mediated pouchitis/enteritis is the presence of an ulcerated and/or strictured pouch inlet and discrete (versus diffuse) mucosal inflammation in the former condition.

Non-steroidal anti-inflammatory drug (NSAID)-induced injury to the pouch is common in patients with IPAA, resulting in inflammation, ulceration, and strictures (Fig. 15.2a). Those features overlap with those seen in CDP. The NSAID-induced mucosal inflammation typically does not respond to pouchitis-targeted antibiotic therapy and may resolve after the discontinuation of the drugs [5]. However, long-term use of NSAIDs can cause persistent ulcers or strictures in the small pouch, pouch inlet or outlet, or cuff, even after drug withdrawal. The NSAID-induced ulcers and strictures can be confused with CDP, even with proper evaluation with histopathology. Therefore, clinical history is important and patients should be advised to avoid NSAID use.

Another challenging issue is the presence of the confounding factor of surgery-associated ischemia. Ischemic injury from surgery can result in virtually the same pattern of inflammation, ulceration, stricture, and fistula as in CDP. Like in CDP, the surgery-induced lesions may be present in the distal afferent limb, inlet, pouch body, anastomosis, and cuff or ATZ (Fig. 15.2b). Chronic pouchitis with the contributing factor of ischemia may also be associated with transmural inflammation [6]. Ischemic pouchitis is characterized by the endoscopic appearance of non-diffuse, asymmetric disease distribution, with a sharp demarcation of the inflamed part and non-inflamed part at the suture line (Fig. 15.2c) [7]. Another pattern of inflammation in ischemic pouchitis is the presence of inflammation only in the distal pouch but not in the proximal pouch. This is often seen in obese male patients.

The most common locations for strictures in patients with IPAA include the site of previous

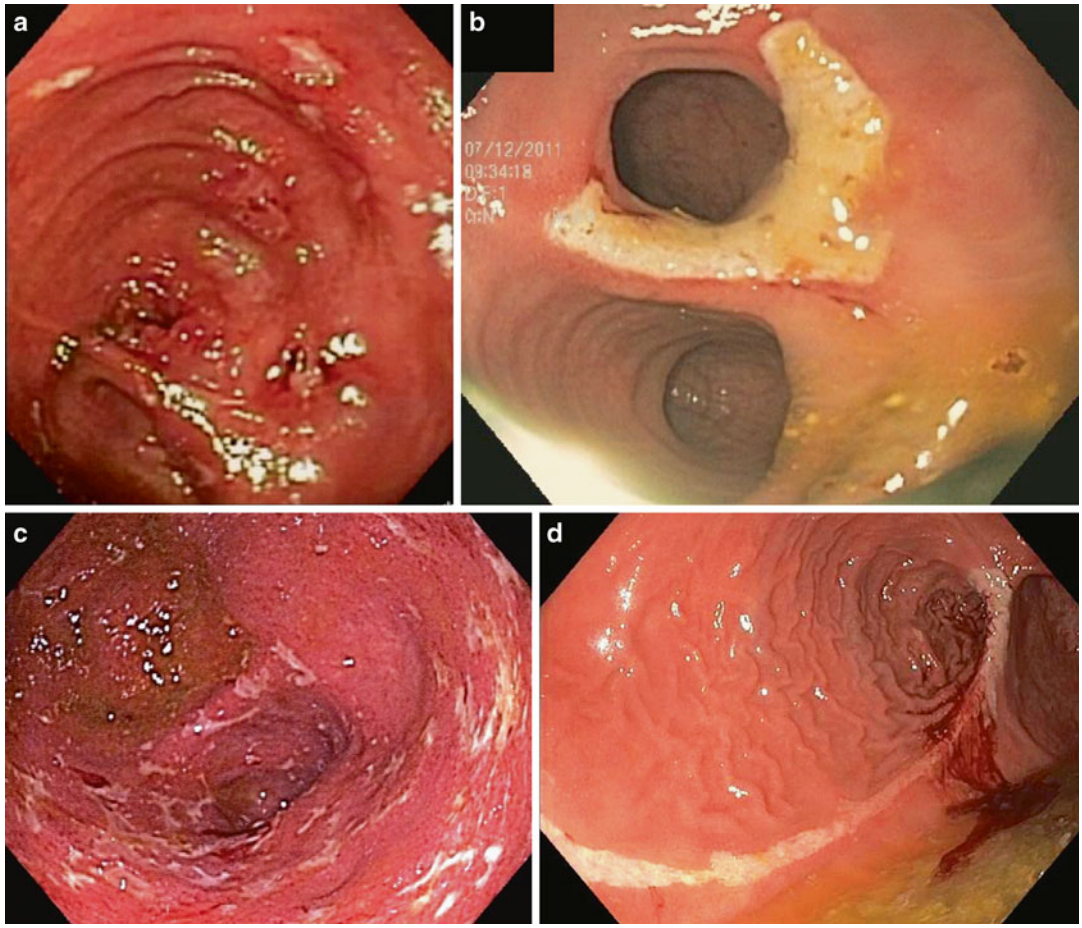

Fig. 15.2 Differential diagnosis of Crohn's disease of the pouch. (**a**) NSAID-induced pouch ulcers that resolved after discontinuation of the agent. (**b**) Isolated ischemic ulcer at the pouch inlet. (**c**) Ischemic pouchitis with asymmetric distribution of the pouch body inflammation with a sharp demarcation at the suture line. (**d**) Long superficial ischemic ulcer along the suture line

loop ileostomy, the pouch inlet and the pouch outlet. The main causes for these strictures are CDP, NSAID (Fig. 15.2a), and surgery-induced ischemia (Fig. 15.2b, c). The endoscopic appearance of the stricture is not helpful for the differentiation diagnosis. The presence of strictures outside these 3 common locations may suggest a diagnosis of CDP, such as those in the middle pouch body, proximal afferent limb, and duodenum.

Not all fistulas in patients with IPAA result from CDP. The most common locations in fistula pouch patients are pouch-vaginal fistula (PVF), perianal fistula, and enterocutaneous fistula. The most frequent causes of fistulae are Crohn's disease, ischemia, iatrogenic injury, and cryptoglandular abscess. During a stapled anastomosis procedure, entrapment of the posterior wall of the vagina can result in a pouch vaginal fistula. Anastomotic leaks can cause PVF anteriorly or a presacral sinus posteriorly. A leak at the tip of the "J" leak or loop ileostomy site can lead to enterocutaneous fistula. Inflammation of the anal glands also can result in an abscess and perianal fistula. Those non-CD related conditions are difficult to distinguish from CDP. It is important to identify the fistula opening from the pouch side and delineate the length and configuration of

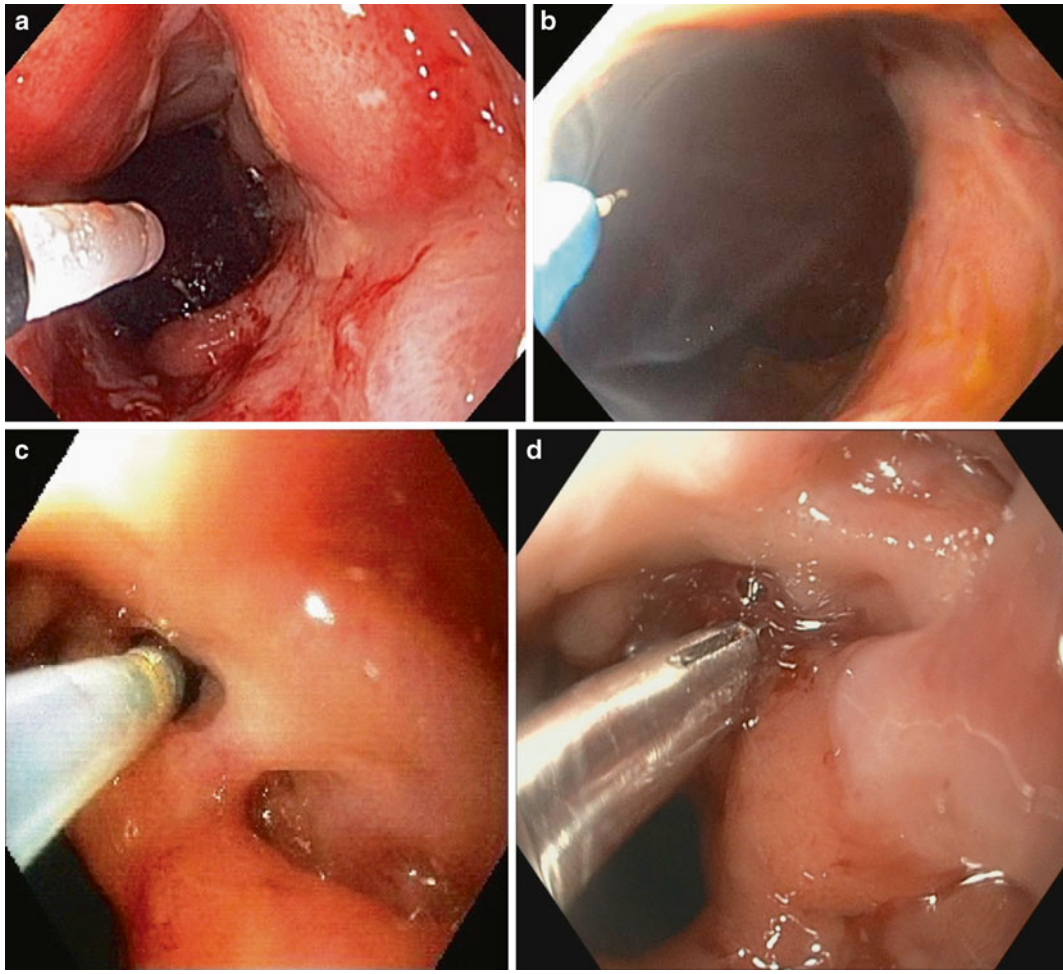

Fig. 15.3 Endoscopic therapy for stricture and fistula: (**a**) Balloon dilation of anastomotic stricture. (**b**) Needle knife stricturotomy of anastomotic stricture. Notice that the therapy was only delivered to the posterior aspect of the anastomotic stricture, not the anterior aspect. (**c**) Infusion of 50 % dextrose through the orifice of pouch-vaginal fistula with a catheter. (**d**) Deployment of an endoclip at the orifice of a vaginal fistula

the fistula. This can be achieved by the use of an endoscopic guidewire or spraying hydrogen peroxide or methylene blue. Magnetic resonance imaging (MRI) of the pelvis or examination under general anesthesia in the operating room may provide confirmatory information. The presence of the following features suggests the diagnosis of CDP:

1. Fistula opening in the mid anal canal, outside of the anastomosis or dentate line
2. Inflammation around the fistula opening
3. Complex fistula; i.e., multiple fistulae or branched fistula
4. Fistula and inflammation and ulcers at separate locations of the pouch (Fig. 15.3).

Mucosal biopsy has been an integral part of the evaluation of pouch disorders. The role of histologic evaluation is several-fold: (1) grading of inflammation; (2) surveillance for dysplasia or cancer; and (3) identification of the etiology for pouch inflammation, such as viral (to include cytomegalovirus) or fungal (such as *Candida*) infection, ischemia, or CD (granulomas). The presence of non-mucinous, non-caseating granulomas on histology usually suggests a diagnosis of CDP. Unfortunately, only approximately 10 %

Table 15.2 Proposed classification of strictures in inflammatory bowel diseases

Criteria	Classification
Etiology	Primary vs. Secondary (Anastomotic); Benign vs. Malignant
Number	Single vs. Multiple
Degree	High-grade vs. Low-grade
Shape	Web-like vs. Spindle-shaped; Circumferential vs. Asymmetric
Length	Short vs. Long
Location	Esophagus, Pylorus, Small Bowel, Ileocecal Valve Anastomosis, Colon, Rectum, Anus
Associated conditions	Fibrosis, Edema, Proximal Dilation, Ulceration, Fistula with or without Abscess, Angulated, Prior Stricturoplasty

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Table 15.3 Proposed classification of IBD-related fistulas

Criteria	Classification
Etiology	Primary (directly related to disease course of IBD) vs. Secondary (iatrogenic or surgery-related, radiation, cryptogenic) vs. Malignant transformation
Location	Entero-enteric vs. Entero-cutaneous vs. Perianal vs. Gut-to-adjacent hollow organs (such as bladder and vagina) vs. Intersphincteric vs. Transsphincteric vs. Extrasphincteric vs. Suprasphincteric
Length	Short vs. Long
Complexity	Simple vs. Branched vs. Multiple
Associated conditions	Mucosal Inflammation of Gut; Stricture vs. Abscess; Cancer; Infections including Tuberculosis and HIV; Radiation; Pilonidal Disease

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of patients with known CD of the pouch have granulomas on mucosal biopsy [8]. Endoscopists should resist the temptation to take mucosal biopsies from a normal or ulcerated suture line (Fig. 15.2d) in order to avoid foreign-body granulomas or pseudogranulomas. In our clinical practice, we have noticed that true non-caseating granulomas on histology may be present in endoscopically normal-looking mucosa and those patients may follow a benign disease course, without overt *clinical* CDP. In this setting we may call this phenotype as histologic CDP.

The diagnosis of CDP, in most cases, is based upon the combined assessment of clinical presentation, and endoscopic and histologic and radiographic features. In cases in which there remains difficulty in differentiating between NSAID-injury, iatrogenic trauma, surgical ischemic injury, and CDP, a diagnostic trial of anti-TNF agent may be needed. Complete mucosal healing on endoscopy or decrease in fistula drainage suggest the diagnosis of CDP.

Endoscopic Treatment

Among the three clinical phenotypes, stricturing or fistulizing CDP may be amenable to endoscopic therapy. The natural history of most patients with CD follows the sequence of inflammation-stricture-fistula-abscess. Therefore, mechanical interventions are often required in combination with medical therapy to treat structural complications of the pouch such as strictures or fistulas.

Preparation for Endoscopy

It is important to delineate the anatomy of strictures with abdominal/pelvic imaging—such as computed tomography enterography (CTE), pelvic MRI, or gastrografin enemas—before endoscopic therapy. Imaging studies may reveal the number, degree, and location of strictures, the presence of proximal luminal dilation, concurrent fistulas or abscesses. We have proposed classification systems for IBD-related strictures (Table 15.2) or IBD-related fistula (Table 15.3). Endoscopic therapy may not be feasible in patients with long strictures (>5 cm), multiple strictures, angulated lumen, or strictures with fistula or abscess in close proximity.

The endoscopy team consists of experienced endoscopists and trained endoscopy nurses and a surgical back up in case procedure-associated adverse events occur. We prefer polyethylene glycol-based bowel preparation the night before the procedure. Conscious sedation is often needed.

We routinely use carbon dioxide insufflation. Before the procedures, we should get all supplies ready, particularly balloons and endoclips.

Endoscopic Balloon Dilation

Balloon dilation is the main therapeutic endoscopic modality for the treatment of strictures in IPAA patients. Despite the variation in the etiology of the strictures, the endoscopic approach uses the same techniques. Non-fluoroscopic through-the-scope (TTS) balloon dilation using an upper endoscope is commonly performed. Wire-guided or non-wire-guided balloons each have advantages and disadvantages. The wire-guided balloon is shorter (5.5 cm) in length and can be difficult to secure across the stricture. However, this type of balloon is useful for antegrade dilation of tight or angulated strictures. The non-wire guided balloon is longer (8 cm) and more easily centered during dilation. It is normally used in strictures that are passable by the scope and for retrograde dilation (i.e., while withdrawing the scope). For pouch strictures, like other IBD-related strictures, the target size of balloon dilation is 18–20 mm. For female patients with an anastomotic stricture, we used the TTS balloon up to 18 mm and rarely 20 mm to minimize iatrogenic trauma leading to PVF.

The recurrence of strictures in pouch patients is almost always the norm. Therefore, intermittent dilations are frequently required after a successful first procedure. We have previously attempted to perform intralesional injection of a long-acting steroid agent after balloon dilation, hoping to maintain the patency of a dilated stricture. Later on we found that the intralesional injection did not make a difference [unpublished data].

Endoscopic TTS balloon dilation is also a feasible alternative in patients with IPAA pouch strictures (Fig. 15.3a). In a prospective study of 150 patients undergoing 646 dilations for IPAA strictures, we reported a technical success rate (i.e., traversable with the scope without resistance after dilation) of 97.8 % with a 97 % chance of pouch retention at 5 years and 85.9 % pouch retention rate at 25 years [9]. The endoscopic approach has been compared with surgical stricturoplasty for pouch strictures. We found that the long-term pouch retention rate was comparable between the endoscopically treated versus surgical stricturoplasty group in a retrospective study [10]. Due to its lower invasiveness, endoscopic balloon dilation is preferred to stricturoplasty or surgical resection with anastomosis.

Endoscopic Needle Knife Stricturotomy

Our group described a novel needle knife stricturotomy technique for the treatment of strictures in patients with IPAA or other inflammation-related strictures [11]. Endoscopic needle knife therapy is less costly than surgical treatment and is therefore an attractive therapeutic option for these strictures. The technique involves the use of Doppler ultrasonography (DopUS) and a through-the-scope needle knife using the endoscopic retrograde cholangiopancreatography (ERCP) setting of Endocut with maximum coagulation and low-degree cut. We use this modality primarily for fibrotic strictures refractory to repeated balloon dilations. The purpose of needle knife therapy is to dissect away fibrotic tissue, with minimal trauma. We found that needle knife stricturotomy has been particularly useful in treating strictures in the lower gastrointestinal tract, since it is easier for the endoscopist to maintain the tip of scope with a short scope and the targeted area of interest is not very mobile. This is particularly true for anastomotic strictures in pouch patients. A tight and fibrotic anastomotic stricture may not respond to balloon or bougie dilation. In addition to discomfort, blind balloon (with a radial force) or a bougie (with a shear force) dilation of a potentially asymmetric stricture may increase the risk for perforation, especially on the posterior wall of the vagina, causing iatrogenic PVF. Needle knife stricturotomy in this setting has been particularly useful. Its advantages include: (1) better tolerance and less trauma; (2) selection of a targeted area to incise in the fibrotic area of the stricture

laterally or posteriorly, avoiding the anterior aspect (next to the vagina or prostate); and (3) avoidance of vascular areas by using Doppler ultrasound guidance (Fig. 15.3b).

Endoscopic Fistula Injection and Clipping

Injection of various substances has been used for CD-related fistulas. In our practice, we use 10 mL of liquid doxycycline (100 mg/10 mL) directly into the fistula from the pouch side during endoscopy. Doxycycline may cause a local inflammatory response with subsequent fibrin extravasation and tissue adhesion. The agent has also been used for pleurodesis in patients with malignant pleural effusions. We found that the injection is particularly useful in pouch patients with a long perianal fistula track [Shen B. Unpublished data]. Highly concentrated sugars have long been used in the management of wound healing. In our routine clinical practice, we inject 10–20 mL of 50 % dextrose into the fistula tract to promote fistula closure (Fig. 15.3c). In patients with a short fistula tract, we have deployed endoclips to temporarily close the fistula opening at the pouch side (Fig. 15.3d). Other agents that have been used to close the fistula include fibrin glue or even adipose-derived mesenchymal stem cells with a modest success rate.

Conclusion

De novo Crohn's disease can occur in pouch patients with a preoperative diagnosis of UC or IC, presumably due to the CD-friendly environment created by the bowel-anatomy-altering surgery. CDP can present with inflammatory, stricturing, or fistulizing phenotypes with a wide range of clinical presentation. There are overlaps of clinical presentation and endoscopic and radiographic features between CDP and other inflammatory disorders of the pouch (i.e., pouchitis and cuffitis), NSAID injury, and surgery-associated ischemia. The diagnosis and differential diagnosis of CDP should be based on a combined assessment of symptomatology, endoscopy, histology, and radiography. In a majority of patients with fibrostenotic CDP, the strictures are amenable to endoscopic therapy with TTS balloon or needle knife stricurotomy. The role of endoscopic therapy in fistulizing CDP warrants further exploration.

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Part VI

Surveillance for Neoplasia

16 Endoscopic Surveillance for Neoplasia in IBD: Random Biopsy

Steven Polyak

Risk of Colorectal Cancer in Chronic Colitis

Epidemiology

The discovery that dysplasia found on random biopsy was associated with colorectal cancer (CRC) in chronic ulcerative colitis (UC) during the mid-twentieth century gave rise to our initial surveillance program [1, 2]. The hallmark publication by Eaden and colleagues [3], cited by most surveillance programs, found the prevalence of CRC in all UC patients to be 3.7 % and those with pancolitis to be 5.4 %. In this meta-analysis, the cumulative risk of CRC in UC patients was 8 % at 20 years and 18 % at 30 years [3]. However, more recent population-based studies report a lower risk of CRC with a varying range of cumulative risk estimates from 1.1–5.4 % after 20 years of UC [4–6]. The decrease in risk could be attributed to variations among studies and study populations, improved patient compliance with maintenance therapy and surveillance colonoscopy, and increased colectomy rates for dysplasia.

Crohn's disease also carries an increased risk of CRC when examining patients with predominately colonic disease [7–10]. In a large population-based study from Sweden, Ekbom et al. [7] reviewed 1,655 patients and reported a relative risk (RR) of 5.6 (95 % CI, 2.1–12.2) for CRC in patients with Crohn's colitis alone. A meta-analysis of 12 studies confirmed this increased risk of CRC reporting a RR of 4.5 (95 % CI, 1.3–14.9) in patients with colonic Crohn's disease [10]. Similar to UC, the risk estimates also increase over time in Crohn's disease to an absolute cumulative frequency of risk of 7 % over 20 years [11].

Risk Factors for Colorectal Cancer

Identification of factors that alter the risk of CRC in chronic colitis can help stratify patients with IBD and allow for more effective surveillance. Risk factors for dysplasia and CRC have been determined mainly in studies analyzing patients with ulcerative colitis, but can be extrapolated to those patients with Crohn's colitis. Duration of colitis had been universally accepted as a significant risk for the development of dysplasia and

This chapter contains video segments that can be found on the following URL:

Electronic supplementary material: Supplementary material is available in the online version of this chapter at 10.1007/978-3-319-11077-6_16. Videos can also be accessed at http://www.springerimages.com/videos/978-3-319-11076-9.

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Table 16.1 Risk factors for CRC in chronic colitis

Risk factors for CRC in chronic colitis
Longer duration of colitis [3, 5, 6, 11]
Extensive colitis [13]
Earlier age of onset [13, 14]
Coexistent PSC [15, 16]
Family history of sporadic CRC [17, 18]
Severe prolonged inflammation [19–21]
Colon stricture [19]
Inflammatory pseudopolyps [19]
Personal history of dysplasia [22–26]

CRC since the meta-analysis by Eaden et al. [3], with most society guidelines recommending initiating screening 8–10 years after the onset of symptoms. However, recent studies report that the risk over time is more linear [4, 5, 12] and utilization of other risk factors may be even more important to stratify patients for screening and surveillance (Table 16.1) [3, 5, 6, 11, 13–26].

Extent of colitis can be divided into disease extending proximal to the hepatic flexure, which is associated with a higher risk of CRC; disease to the splenic flexure (left-side) that carries an intermediate risk; and proctitis or proctosigmoiditis that carries a low risk [13]. It is important to note that the extent of colitis is defined either macroscopically or microscopically, whichever reveals the furthest extent of inflammation. Mathy et al. demonstrated that neoplastic lesions can arise in areas of microscopic colitis that are otherwise grossly normal [27]. Whether early age of onset increases the risk for CRC, exclusive of an association with a longer duration of disease, remains controversial [3, 4, 13]. Increased risk of CRC with a concomitant diagnosis of PSC is clear [28] with estimated risks of 33 % at 20 years, and 40 % at 30 years after the diagnosis of UC [15]. A family history of sporadic CRC in a first-degree relative carries a twofold higher risk of CRC when compared to IBD patients without a family history of CRC [16, 17, 20]. Studies have confirmed that both histologic inflammation and endoscopic evidence of inflammation (i.e., presence of pseudopolyps, strictures, backwash ileitis, etc.) are independently associated with an increased risk of CRC [18–21, 29, 30]. Lastly, the presence of neoplastic change or dysplasia found during screening or surveillance colonoscopy is one of the strongest risk factors for CRC and is discussed in detail later.

Implications and Features of Dysplasia

Classification of Dysplasia

In general, dysplasia itself is known to be associated with an increased risk of CRC [24, 31], and often leads to a recommendation for prophylactic colectomy. To understand the endoscopic findings and surveillance strategies one must understand the classifications of dysplasia. Dysplasia is histologically defined as neoplastic alteration of the epithelium without invasion into the lamina propria, also termed intraepithelial neoplasia [31]. Traditionally the microscopic classification of dysplasia is divided into negative for dysplasia, indefinite for dysplasia, and positive for dysplasia [31]. Indefinite for dysplasia refers to changes in the epithelium that cannot be classified definitively as positive or negative for dysplasia either due to the confounding effects of inflammation and regeneration or to technical factors that impede their pathologic interpretation [32]. Dysplasia is further classified into LGD (also referred to as low-grade intraepithelial or noninvasive neoplasia), HGD (also referred to as high-grade intraepithelial or noninvasive neoplasia) or invasive cancer [31, 33]. It is important that histologic diagnoses of dysplasia be confirmed by a second expert gastrointestinal pathologist.

Grossly, most dysplastic lesions are endoscopically visible and their appearance in chronic colitis is heterogeneous, but is usually described as flat or elevated [34]. Flat dysplasia is the same as invisible dysplasia found on random nontargeted biopsies, and elevated lesions can be described as polypoid, plaque-like, slightly raised (flat), unifocal, or multifocal [35]. The growing use of the term "flat colon polyps" in non-colitic colons, which are now better visible through improved endoscopic imaging, can lead to confusion with flat LGD. Endoscopists must

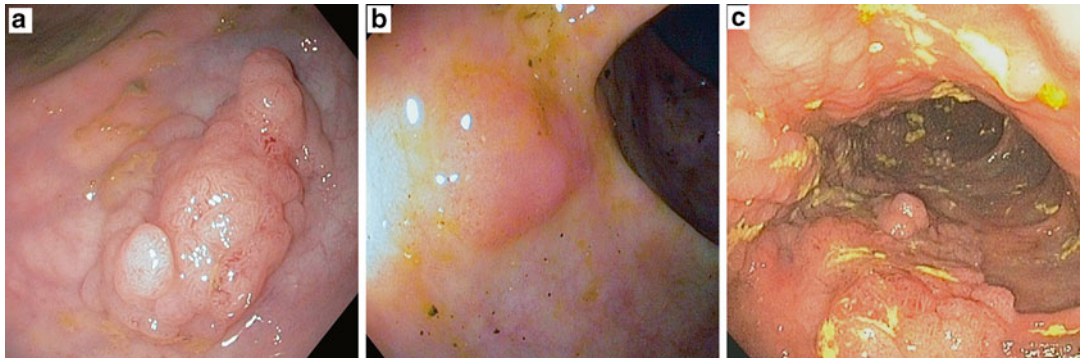

Fig. 16.1 Representative images of raised lesions seen on surveillance colonoscopy in chronic colitis. (**a**) An irregular sessile polyp in a part of the colon without inflammation (sporadic polyp) with clear defined borders that is amenable to complete resection. (**b**) A well-defined small sessile polyp was identified in a region of minimally active chronic colitis (adenoma-like DALM). This should be treated like a sporadic adenoma with goals of complete resection taking margins and biopsies from the surrounding basal mucosa. (**c**) An irregular, broad, nodular polyp (nonadenoma-like DALM) without clear defined borders was found in an area of chronic colitis. Surrounding mucosa was also positive for dysplasia. This was not endoscopically resectable. (Fig. 16.1c is courtesy of John F. Valentine, MD; University of Utah, Salt Lake City, UT.)

be clear whether the dysplasia was macroscopically visible (elevated) or invisible (flat). Raised dysplastic lesions discovered in areas of macroscopic or microscopic inflammation or prior inflammation are also referred to as dysplasia-associated lesion or mass (DALM) [36]. DALMs can then be further characterized into lesions that endoscopically appear to be consistent with sporadic adenomas, called "adenoma-like DALMs" or those that do not, called "nonadenoma-like DALMs." If a well-circumscribed polyp with dysplasia is found outside the area of inflammation it is commonly referred to as a sporadic adenoma (Fig. 16.1a). If a similar appearing lesion is found within inflammation it is referred to as an adenoma-like DALM (Fig. 16.1b). Nonadenoma-like DALMs found in areas of inflammation typically have irregular and indistinct margins [36] (Fig. 16.1c). This terminology can be confusing since there might not be a difference between a sporadic polyp and an adenoma-like polyp when discovered in colitic mucosa; and when present in inflamed irregular mucosa it can be challenging to distinguish from a nonadenoma-like DALM [37]. These distinctions carry important prognostic implications with different management outcomes summarized in Table 16.2.

Dysplasia and Risk of CRC

Unfortunately, carcinogenesis in IBD may not follow a progressive pattern from low-grade dysplasia (LGD), through high-grade dysplasia (HGD), to cancer [30]. Ullman et al. showed that cancer can arise in patients without prior dysplasia, without progression from LGD to HGD [23]. In fact even the diagnosis of indefinite for dysplasia carries risk of advanced neoplasia in 9 % of patients [5, 38].

The degree of risk for associated or synchronous CRC or HGD in patients with flat LGD is varied with studies reporting rates of 0–28 % [23, 24, 39, 40]. A recent meta-analysis examining 20 studies with 447 cases of flat LGD reported that the positive predictive value of flat LGD was 22 % for synchronous CRC and 36 % for synchronous HGD and CRC [41]. Further raising controversy, two large cohort studies from Europe found only a 2–10 % frequency of advanced pathology over a 10-year period in patients with flat LGD [25, 26]. The debate will continue regarding the degree of risk for synchronous or future advanced neoplasia, but there clearly seems to be a risk. There is a better consensus with the risk of CRC from flat HGD with historical cohort studies and reviews indicating a risk of

Table 16.2 Characteristics of dysplasia in chronic colitis

Dysplasia types	Endoscopic appearance	Initial management
Sporadic polyp	A typical dysplastic or hyperplastic polyp with classic features of well-circumscribed borders outside the area of chronic inflammation	Routine polypectomy; if it is uncertain that chronic microscopic inflammatory changes are involved then obtain separate biopsies of the base and surrounding mucosa
Adenoma-like DALM	Similar to a sporadic polyp but within the area of inflammation. These can be sessile, pedunculated, and slightly raised but retain well-circumscribed borders	Polypectomy with goal of snare resection that includes margins; in a separate specimen jar place random biopsies of base and surrounding mucosa
Nonadenoma-like DALM	A slightly raised to visibly raised polyp that can be carpeting or nodular and typically irregular without distinct borders	Colectomy
Flat HGD	Invisible random biopsy	Colectomy
Flat LGD	Invisible random biopsy	Increased surveillance or colectomy

DALM dysplasia associated lesion or mass, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia

synchronous or metachronous CRC in up to 42–67 % of patients [3, 22, 24, 42].

There is also agreement on the risk of advanced neoplasia after finding a raised lesion with dysplasia, although it depends on whether it is found in an area of IBD or not (summarized in Table 16.2). Nonadenoma-like DALMs carry a risk for synchronous occurrence of CRC as high as 43–58 % and thus are referred for total colectomy [22, 36]. Adenoma-like DALMs carry a negligible risk of associated CRC similar to that of sporadic polyps [43, 44]. Additionally the risk of CRC does not change if the adenoma-like DALM is inside or outside the area of inflammation [45]. The key in this situation is to make sure the polyp in the area of inflammation is actually an adenoma-like DALM.

Surveillance Strategies

Efficacy of Surveillance Colonoscopy

Surveillance strategies are aimed at early detection and mortality reduction from CRC in IBD. Evidence for the effectiveness of surveillance programs reducing morbidity and mortality from CRC is not strong due to the limitations of currently available studies, reviewed in Ahmadi et al. [46]. A recent Cochrane systematic review reported that there was no strong evidence that surveillance colonoscopy prolonged survival in people with chronic colitis, but there was evidence that suggested CRC found at an earlier stage led to a better prognosis [47]. However, a recent retrospective study of 149 subjects from the Netherlands identified a significant survival benefit for patients diagnosed with CRC during surveillance colonoscopy, with a 5-year overall mortality of 0 % for people undergoing surveillance versus 36 % for those not undergoing surveillance [48].

Current Guidelines

Although there is consensus among international gastroenterology societies that persons with chronic ulcerative colitis and chronic Crohn's colitis undergo surveillance colonoscopy, differences exist on when to start screening, the interval of surveillance, and even the method of surveillance. These differences among American, British, European and Asian societies are summarized in Table 16.3 [49–57].

Current American guidelines do not stratify patients according to risk exclusive of a diagnosis of PSC and disease extent. However, evidence supports that risk stratification to determine surveillance intervals may be a cost-effective approach, and is currently followed by British and European guidelines. European risk

Table 16.3 Comparison of screening and surveillance guidelines in IBD

Recommendation	American	British	European	Asian
Screening initiation				
Extensive colitis	8–10 year after symptoms	10 year after symptoms in all patients to assess disease extent	8 years after symptoms	8–10 year
Left-sided colitis	15 years after symptoms		8 years after symptoms	12–15 years
Proctitis	Standard CRC guidelines		Standard CRC guidelines	Standard CRC guidelines
PSC	At diagnosis	At diagnosis	At diagnosis	No clear recommendation
Ileal pouch	No clear recommendation	No clear recommendation	No clear recommendation	No clear recommendation
Colonoscopic methods				
Random biopsies	Yes (≥33)	Only if chromo n/a (≥33)	Only if chromo n/a (≥33)	No clear recommendation
Chromoendoscopy	Supportive but NR	Recommended	Recommended	
Follow-up surveillance	Every 1–3 years Consider annually for disease greater than 20 yrs No clear recommendation for surveillance in the ileal pouch	Stratified by risk Low risk: every 5 years Intermediate: every 3 years High risk: annually If surveillance desired in pouch then annually in high risk and every 5 years in low risk	Stratified by risk Low risk: every 3–4 years High risk: every 1–2 years No clear recommendation for surveillance in the ileal pouch	Every 1–2 years in Japan

PSC primary sclerosing cholangitis, *NR* not recommended, *yrs* years, *LGD* low grade dysplasia, *HGD* high grade dysplasia, *n/a* not available

stratification is defined as a scoring system, with one point for each risk factor (pancolitis, endoscopic and/or histological inflammation, pseudopolyps, and family history of CRC) with low-risk patient scores of 0–2 and high-risk scores of 3–4 [55]. British risk stratification is defined as: low risk (no endoscopic/histological inflammation or left-sided colitis or Crohn's disease colitis affecting <50 % surface area of the colon); intermediate risk (mild endoscopic/histological active inflammation or presence of post-inflammatory polyps or family history of CRC in a first-degree relative aged 50 years or over); and high risk (moderate or severe endoscopic/histological active inflammation or stricture within past 5 years or confirmed dysplasia within past 5 years in a patient who declines surgery or PSC/post-orthotopic liver transplant for PSC or family history of CRC in a first-degree relative aged <50 years [53].

Limitation of Surveillance Colonoscopy

Colonoscopic screening and surveillance for CRC in chronic colitis is widely accepted, and even though guidelines evolve, several limitations remain. First, a high sampling error exists, with <1 % of the entire mucosal colonic surface area sampled if 32 biopsies are obtained [30]. Despite growing evidence that most dysplasia in chronic colitis is visible, approximately one-third is flat invisible dysplasia requiring optimal sampling or improved endoscopic techniques [34]. Current guidelines are based off the estimate that 33 biopsies provide a 90 % probability of dysplasia detection [58].

Next, adherence to guidelines by patients and providers are paramount to screening success. A large cohort study from California reported that less than one-third of at-risk

patients underwent surveillance colonoscopy in a two-year period. These low rates were also reported by a nested study from the French CESAME cohort that showed a reduced rate (54 %) of surveillance in at-risk subjects with the lowest rates of surveillance in subjects with Crohn's colitis and those not cared for at specialized centers [59]. Studies have also demonstrated that providers often stray from guidelines and take less than 33 biopsies [60–62].

Making an accurate histologic diagnosis is also vital for proper surveillance outcomes. In addition to the reactive atypia that may confound pathologic interpretation, there is a large degree of interobserver disagreement among pathologists when distinguishing between LGD and HGD [63, 64]. As part of the guidelines it is recommended that all specimens concerning for dysplasia be confirmed by a second gastrointestinal pathologist [65].

Finally, as the guidelines evolve to recommend resection of raised dysplastic lesions as an alternative to colectomy, the adequacy of resection is increasingly important [66]. However, anatomical interference can limit the effectiveness of proper identification and complete resection of lesions. Three circumstances encountered during surveillance colonoscopy need to be addressed further: pseudopolyps, UC-associated strictures, and Crohn's-associated colonic strictures. In the setting of multiple or diffuse pseudopolyps, identification of suspicious lesions can be a daunting task. A case–control study by Velayos et al. demonstrated that presence of pseudopolyps was associated with a 2.5-fold increased risk in the development of CRC [20]. Strictures in UC should arouse a high suspicion of CRC as studies have shown that a quarter of them are malignant [67]. In the setting of colonic Crohn's strictures, the risk of underlying malignancy is not as high as in UC, but is still present. A review of 175 Crohn's colon strictures revealed a 6.8 % frequency of colon cancer after 20 years of disease duration [68]. Therefore surgical resection should be considered if one is unable to fully evaluate the stricture or proximal colon [68, 69].

Surveillance Colonoscopy with Random Biopsies

To reduce the risk of CRC or CRC-related mortality it is recommended that patients with UC extending beyond the rectum and extensive Crohn's colitis involving more than a third of the colon undergo surveillance colonoscopy following the timelines suggested in Table 16.3. Since dysplasia in chronic inflammation or healed colitis can be invisible (flat), only slightly raised, or difficult to visualize in a field of active inflammation, current guidelines in the U.S. continue to recommend obtaining random, nontargeted biopsies using white light endoscopy (WLE). This section of the chapter will review the details and evidence that will help optimize WLE endoscopy technique in colitis surveillance, including procedural quality, biopsy techniques and specialized situations.

To improve quality of dysplasia detection during WLE it is recommended that the bowel preparation be of good quality, and that the disease be in clinical remission if possible. Although evidence does not exist for the influence of bowel preparation on dysplasia detection in colitis, it has been reported that patients with colitis have worse prep outcomes [70]. Good bowel preparations will aid in the ability to visualize the heterogenous lesions in IBD. Similarly, the presence of active inflammation may interfere with the ability to visually recognize the subtle lesions commonly found in chronic colitis, and histologically differentiate reactive atypia from indefinite for dysplasia or LGD [71]. Thus current guidelines recommend performing surveillance when disease is quiescent if possible [49]. Equipment may also make a difference in the quality of dysplasia detection. High definition endoscopic video imaging is widely available and when examined in a retrospective cohort study of colitis surveillance it performed better than standard definition WLE with an adjusted prevalence ratio of detecting any dysplastic lesion of 2.21 (95 % CI, 1.09–4.45) [72]. Variation also exists among biopsy forceps and experts have recommended

that jumbo forceps can be used to obtain random surveillance biopsies to increase tissue sampling [73]. Two recent single center studies have demonstrated increased tissue volume using jumbo forceps during random colon biopsies [74, 75]. However, guidelines do not recommend a forceps type since head-to-head studies examining dysplasia detection do not exist.

Traditionally, random biopsies have been performed utilizing a four-quadrant technique sampling the entire colon every 10 cm in addition to biopsies of suspicious lesions. Thus in an 80–100 cm colon this yields a minimum of 32–40 biopsy specimens. It is important to note that this accounts for <1 % of the total colonic surface area, resulting in the potential for false-negative results [30]. As previously discussed these numbers are required to detect dysplasia with 90 % confidence [58]. A recent mathematical modeling study reduced this probability, reporting that 32 random biopsies provide only 80 % confidence that dysplasia involving greater than or equal to 5 % of the colon can be detected [76]. These limited data would suggest that many more random biopsies are required to detect dysplasia. Some experts recommend sampling every 5 cm in the rectosigmoid colon, given the higher frequency of dysplasia in this area. A retrospective study from Mount Sinai reported that the rectosigmoid colon demonstrated the highest percentage of biopsies positive for any neoplastic lesion and advanced neoplasia [77]. Finally, similar to colon cancer screening in noncolitic patients, a slower withdrawal time will increase dysplasia detection rates [78].

Ideally, multi-bite forceps should be used with no more than two mucosal bites taken in a single pass. This technique is demonstrated in Video 16.1. Experts suggest no more than eight biopsies should be placed in separate containers and labeled by location. Locations are best separated into (1) cecum/ascending colon, (2) transverse colon, (3) descending colon, (4) sigmoid colon, and (5) rectum. This time consuming and iterative process could distract the endoscopist from properly scanning the mucosa for subtle irregular lesions. The endoscopist should remain vigilant and utilize all qualified endoscopy staff assisting in the procedure to help monitor for suspicious lesions, which should be sampled separately. Raised lesions that resemble sporadic adenomas or adenoma-like DALMs should be completely resected, with separate biopsies of the surrounding tissue sampled as well. Further details in the management of dysplasia are provided later in this chapter.

There are no formal recommendations regarding surveillance biopsy techniques in the setting of inflammatory pseudopolyps. Pseudopolyps are raised polypoid lesions developed through recurrent epithelial regeneration and can be distinguished, by experienced endoscopists, from sporadic adenomas or raised dysplasia through their pit patterns on high-definition imaging utilizing magnification and contrast [79]. However in fields of active inflammation or with routine WLE this distinction is less clear. Additionally, when pseudopolyps are numerous they may obscure the visibility of adenomas or DALMS [19, 20]. Through communication with experts these lesions are typically targeted during random surveillance biopsy in an attempt to minimize the risk of missing dysplasia in irregular mucosal surfaces. It is important to communicate these limitations with the patients that have numerous colonic pseudopolyps so future surveillance risks can be continued through a joint decision-making process.

Endoscopists may also encounter patients who have had a subtotal colectomy and now are left with a closed rectal pouch. This is mostly encountered in Crohn's colitis. The remaining rectal pouch should be surveyed following precolectomy risk factors to guide surveillance intervals. A small retrospective case control study from the Netherlands confirmed that the risk of CRC persists in closed rectal stumps and was seen mainly in patients with PSC or patients with greater than 8 years of disease [80].

Overall, the random biopsy surveillance technique is a laborious and costly process with historically reduced adherence by patients and providers. Thus a paradigm shift is underway toward a more focused and targeted biopsy approach through visual contrast imaging techniques. However, if specialized training or

resources are not available then random biopsies continue to be an acceptable method for dysplasia surveillance in patients with chronic UC or Crohn's colitis. But should we completely abandon random surveillance biopsies? If targeted biopsies can identify 60–88 % of neoplasia [34, 81–83], it could be extrapolated to a potential miss rate of 12–40 % of neoplastic lesions. Although current data might suggest that targeted biopsies are better at identifying neoplasia as compare to random biopsies, endoscopists might want to consider doing both to optimize detection rates. At present, a prospective randomized controlled trial is underway in Japan, comparing targeted biopsy versus random biopsy approaches [84]. This will hopefully provide better evidence to optimize our current endoscopic protocols.

Management of Dysplasia and Approach to Polypectomy

If we consider the benefits of discovering raised and flat (invisible) dysplasia, the role of the endoscopist is to detect, describe, and biopsy or remove all endoscopically visible lesions; plus obtain biopsies from flat "normal" appearing mucosa. Then after rigorous histologic assessment of several biopsies for a single patient, a diagnosis is made that stratifies the patient into a path of continued surveillance or proper dysplasia management. Table 16.1 outlines the approach to managing dysplasia summarized from the three most current guidelines. In the instance that an "indefinite for dysplasia" diagnosis is made and confirmed, guidelines advise optimization of therapy and follow-up with a repeat colonoscopy in 3–12 months [49]. The greater the number of risk factors the sooner it should be repeated. As already discussed, the risk of synchronous and metachronous CRC after finding flat HGD and nonadenoma-like DALMs (with LGD or HGD) is significant and a colectomy is recommended. However, the elephant in the room is flat (invisible) low grade dysplasia. Consensus has not been reached on how to manage this finding due to its variable natural history in previous cohort studies.

Approach to Flat LGD

If flat or invisible LGD dysplasia is found on colonoscopy the management is not clear primarily because of conflicting data regarding the progression of flat LGD to CRC and the controversial existence of concurrent advanced neoplasia. Studies have revealed a LGD to HGD or CRC progression rate ranging anywhere from 2 to 50 % [22–26]. Therefore, it is important to discuss the risks and benefits of both aggressive surveillance (repeat surveillance colonoscopies every 3–6 months) and the option of a proctocolectomy with patients at the time LGD is identified. If the dysplasia is multifocal flat LGD (identified in different locations of the colon during the same colonoscopy) there may be an increased risk of progression to CRC and perhaps more a push toward colectomy. A prospective study from the University of Washington followed 42 patients with LGD and the rate of progression to advanced neoplasia over a 4-year follow-up period was low, but for those patients with four or more biopsies that contained LGD the risk of progression to advanced neoplasia was greatest, RR 5.8 (95 % CI, 1.29–26.04) [40]. The risk of progression to advanced neoplasia in the setting of recurrent flat LGD (also identified on the subsequent surveillance colonoscopy) is again less clear since sampling error might create a false negative. Thus for multifocal or recurrent flat LGD the Crohn's and Colitis Foundation of America consensus strongly recommends a prophylactic total proctocolectomy [69].

Endoscopic Approach to Raised Lesions

Management recommendations for raised or visible lesions that contain dysplasia on histologic examination (DALMs) depend on their endoscopic appearance and degree of removal. Raised lesions that resemble sporadic adenomas (adenoma-like DALM) should be completely resected with snare polypectomy technique with biopsies obtained from the adjacent flat mucosa surrounding the polyp base, and placed in a

separate container, demonstrated in Video 16.2. If the flat adjacent mucosa contains dysplasia, then these lesions should be treated as nonadenoma-like DALMs and colectomy should be recommended. Otherwise, if there is no dysplasia in the adjacent or distant tissue, a repeat colonoscopy should be performed within 6 months [49]. Then, if no further dysplasia is identified, surveillance can be resumed every 1–2 years. A long-term follow-up study of 34 patients revealed no significant difference in future polyp formation between UC patients with an adenoma-like DALM (62.5 %), UC patients with a sporadic adenoma (50 %), and non-UC sporadic adenomas (49 %) [85]. Two other retrospective cohort studies revealed a 0–2 % risk of developing advanced neoplasia in follow-up after polypectomy [37, 86]. The endoscopic management of adenoma-like DALMs is appropriate and can be safely monitored by surveillance colonoscopy. On the other hand, if the lesion is recognized as a nonadenoma-like DALM, there is a significant risk of concurrent or metachronous CRC (described previously), thus a colectomy should be recommended [37, 85].

Special Considerations

Ileal Pouch Dysplasia Risk and Surveillance

Special situations that endoscopists can encounter include patients with a restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA). Evidence suggests increased risk of dysplasia in the ileal pouch and the rectal cuff in IPAA patients, especially when the colectomy was performed for the indication of colon dysplasia [87–93]. A recent single-center retrospective study from a specialized Pouch Clinic at the Cleveland Clinic in Ohio reported the cumulative incidence for pouch dysplasia at 5, 10, 15, 20, and 25 years post-pouch surgery to be 0.8 %, 1.3 %, 1.5 %, 2.2 %, and 3.2 %, respectively; and for pouch cancer to be 0.2 %, 0.4 %, 0.8 %, 2.4 %, and 3.4 %, respectively [88]. Dysplasia can occur in the ileal pouch mucosa, the rectal cuff and the anal transition zone. It has been suggested that a stapled anastomosis without a mucosectomy carries a higher risk of CRC compared to patients with a hand-sewn anal anastomosis with mucosectomy, but this protection is not absolute likely from residual or retained foci of rectal mucosa [89, 91, 94–97]. Today most surgical approaches favor the stapled anastomosis without mucosectomy in an attempt to avoid anal sphincter injury, thus surveillance is prudent.

Risk factors for the development of pouch dysplasia have historically included a prior history of UC-associated dysplasia or cancer, the presence of ileal mucosal villous atrophy, concurrent PSC, a family history of colon cancer, long duration of UC, chronic pouchitis, and a stapled anastomosis without mucosectomy. The study from Ohio by Kariv et al. determined that the prior dysplasia was the only risk factor for developing advanced neoplasia; reporting an adjusted hazard ratio between patients with preoperative dysplasia and those without of 3.62 (95 % CI, 1.59–8.23) [88].

Guidelines do not offer specific recommendations on the surveillance biopsy approach in IPAA due to lack of evidence, but the group from Cleveland Clinic Ohio recommends that surveillance endoscopy occur annually in high-risk patients and every 1–3 years in intermediate- and average-risk patients [98]. A suggested endoscopic approach is to perform 4–6 random biopsies from the anal transition zone region and 2–6 from the afferent limb and pouch body [98]. Management of ileal pouch dysplasia is also unclear. Coull et al. suggest that patients with LGD undergo closer surveillance, whereas patients with HGD localized to the anal transition zone or rectal cuff should be referred for completion mucosectomy and perineal pouch advancement with a neo-ileal pouch-anal anastomosis [93]. Patients with CRC require complete pouch excision.

Primary Sclerosing Cholangitis

As discussed previously, a concurrent diagnosis of PSC carries a significant risk for dysplasia and

CRC. A meta-analysis reported an increased risk of CRC with an odds ratio of 4.09 (95 % confidence interval, 2.89–5.76) in patients with UC and PSC compared to UC patients without PSC [28]. Interestingly a recent retrospective study from the Cleveland Clinic in Ohio reported a neoplasia detection rate of 45 % using random surveillance biopsies alone compared to 36 % using targeted biopsies alone [99]. Patients with PSC may warrant both targeted and random biopsy techniques. Special considerations to bear in mind in patients with PSC include location of dysplasia and management of patients who receive liver transplantation. A retrospective cohort study from the Netherlands showed that CRC was more prevalent in the right-side of the colon (proximal to the splenic flexure), odds ratio of 4.8 (95 % CI, 2.0–11.8), in UC patients with concurrent PSC compared to UC-only patients [100]. Thus care should be taken to survey the proximal colon carefully in patients with PSC.

Following liver transplantation, there is an increased risk of CRC in PSC patients with IBD compared to PSC patients without IBD [101]. A multicenter study from Scandinavia retrospectively examined 353 patients with PSC and IBD who underwent liver transplantation and found that 25 % developed CRC [102]. The cumulative risk of colorectal neoplasia was higher after liver transplant compared to before liver transplant; hazard ratio 1.9 (95 % CI, 1.3–2.9) [102]. Of these patients, 79 % also had an increased risk of advanced neoplasia in the proximal colon [102]. Thus it is important to ensure strong compliance with an annual colonoscopy surveillance program in PSC patients post-transplant with attention to the proximal colon.

Conclusion

There is an increased risk of neoplasia and CRC in both long-standing UC and Crohn's colitis, but perhaps less than previously suggested. The risk is still significant and warrants colonoscopy surveillance supported by national and international gastrointestinal societies. A better understanding of the risk factors for patients at greatest risk for the development of CRC allows for risk stratification and personalization of the timing for surveillance colonoscopy, which are currently employed by the British and European guidelines. The lack of prospective studies and limited evidence has led to disagreement in the management of dysplasia, requiring expert opinion and consensus to manifest our current endoscopic surveillance strategies. Although random biopsy surveillance is still supported in the U.S., both British and European guidelines advocate chromoendoscopy-directed targeted biopsies as the best means to survey for neoplasia in IBD. At present, the time it takes to complete a colonoscopy with dye spray and targeted biopsies is not significantly greater than current protocols with random biopsies, and learning the technique is not arduous. Endoscopists need to be aware of the proper management of dysplasia, including raised dysplasia that could be amenable to polypectomy.

The ultimate goal is to reduce CRC-related morbidity and mortality through efficient and cost-effective modalities. Current studies are underway examining advanced endoscopic imaging techniques without dye spray, and may one day replace our current protocols. While we await noninvasive molecular markers for CRC surveillance in chronic colitis we must continue to monitor patients closely with surveillance colonoscopy. Without patient compliance and adherence to guidelines, all prevention and surveillance strategies will fail, making patient education and awareness through provider communication a vital part of our practice.

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The Near Future of Endoscopic Screening in IBD

17

Ralf Kiesslich, Johannes Wilhelm Rey, and Arthur Hoffman

Introduction

Patients with long-standing extensive chronic inflammatory bowel disease (IBD) have an increased risk of developing intraepithelial neoplasia and colitis-associated cancer (CAC) compared to the average risk population. Triggers to neoplasia are chronic inflammation and sporadic adenoma [1].

Thus, colonoscopic surveillance is recommended in patients with long-lasting ulcerative colitis (left side and pancolitis) as well as Crohn's colitis [2].

Guidelines recommend performing targeted (visible lesions) and random biopsies. In this setting, two to four random biopsies every 10 cm within the colon should be applied [2] (see Chap. 16 for details). Dysplastic lesions are often multifocal and flat and difficult to detect with white light endoscopy (WLE) [2].

In 2003, the first randomized, controlled trial [3] was published evaluating lesions in the colon according to a modified Pit-Pattern classification after pan-chromoendoscopy with methylene blue (0.1 %), (Pit-Pattern I-II: endoscopic prediction of non-neoplastic lesions; Pit-Pattern III-V: endoscopic prediction neoplastic). Chromoendoscopy enabled unmasking dysplastic lesions and clarifying the borders between neoplastic and normal tissue. This has led to the "smart biopsy" concept, where more targeted biopsies become possible after enhanced endoscopy (chromoendoscopy) (Figs. 17.1, 17.2, and 17.3). Pan-chromoendoscopy has currently evolved as the method of choice for endoscopic surveillance of IBD patients (European consensus guidelines) [2].

Endomicroscopy has also shown to be of benefit for dysplasia detection and differentiation of lesions to optimize their management (differentiation between colitis-associated neoplasia, sporadic neoplasia and non-neoplastic lesions) and to reduce the number of unnecessary biopsies [4]. Confocal laser endomicroscopy (CLE) has for the first time revealed in vivo tissue microscopy to gastroenterologists [4]. Using this technology, changes in vessel, connective tissue and cellular-subcellular structures can be defined during ongoing colonoscopy at subcellular resolution [5, 6].

Confocal endomicroscopy has further decreased the need for random biopsies.

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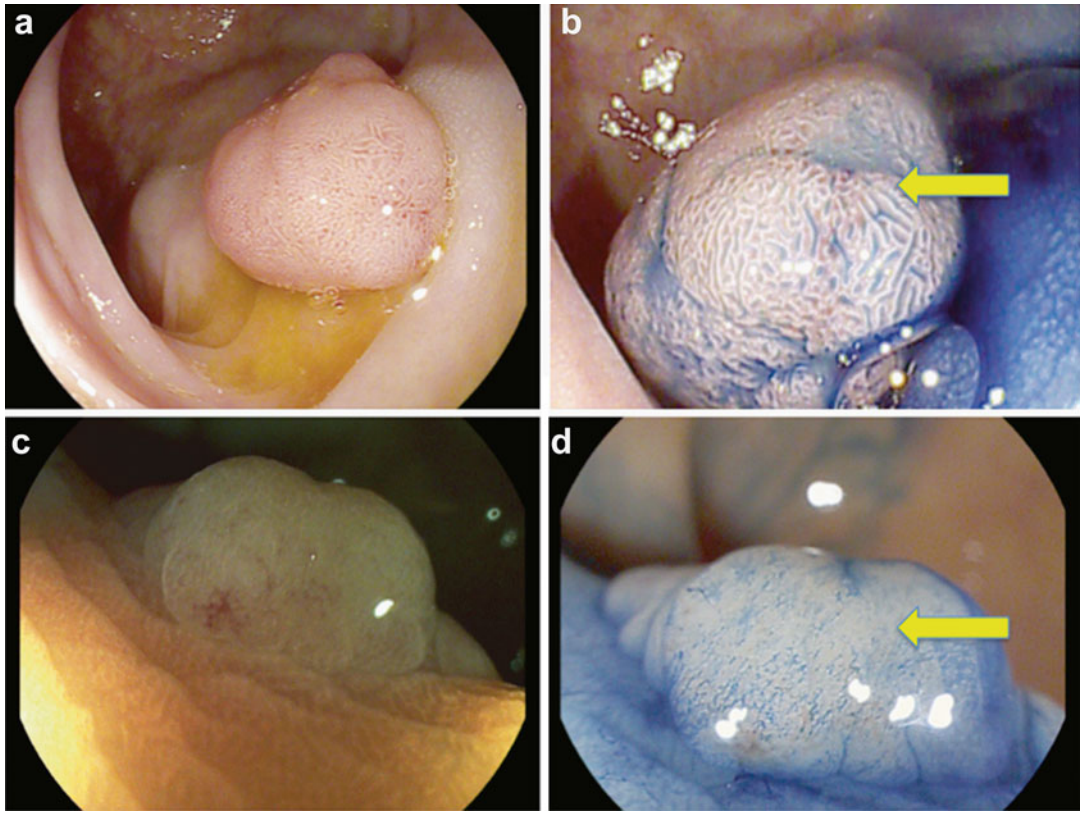

Fig. 17.1 Chromoendoscopy of colorectal lesions. (**a**) A polypoid lesion can be identified in the ascending colon of a 64-year-old patient with 34 years of ulcerative colitis. (**b**) Chromoendoscopy with methylene blue (0.1 %) clarifies the mucosal pattern (pit-pattern IIIL, *arrow*), which predicts a tubular adenoma. Endoscopic resection was performed and final histology confirmed adenoma with low-grade intraepithelial neoplasia. (**c**) A sessile lesion can also be identified. Here wide cryptapertures can be seen (pit-pattern II) using magnification and (**d**) chromoendoscopy. Hyperplastic changes (non-neoplastic) could be confirmed histologically

Endomicroscopy is often combined with chromoendoscopy. Vital staining is used to unmask lesions and targeted endomicroscopy is performed to clarify the need for standard biopsies. Endomicroscopy has a very high negative predicting value. Thus, endomicroscopically normal-looking mucosa does not usually require additional standard biopsies. Neoplastic changes and regenerative tissue can readily be identified using this method. However, significant knowledge about the microarchitecture of the mucosa is necessary to achieve high diagnostic yields [6, 7].

Technical Principles of Confocal Laser Endomicroscopy

The CLE-technique introduced in 2004 has been developed for cellular and subcellular imaging of the mucosal layer [5].

In confocal microscopy a low power laser is focused to a single point in a microscopic field of view and the same lens is used as both condenser and objective folding optical path, so the point of illumination coincides with the point of detection

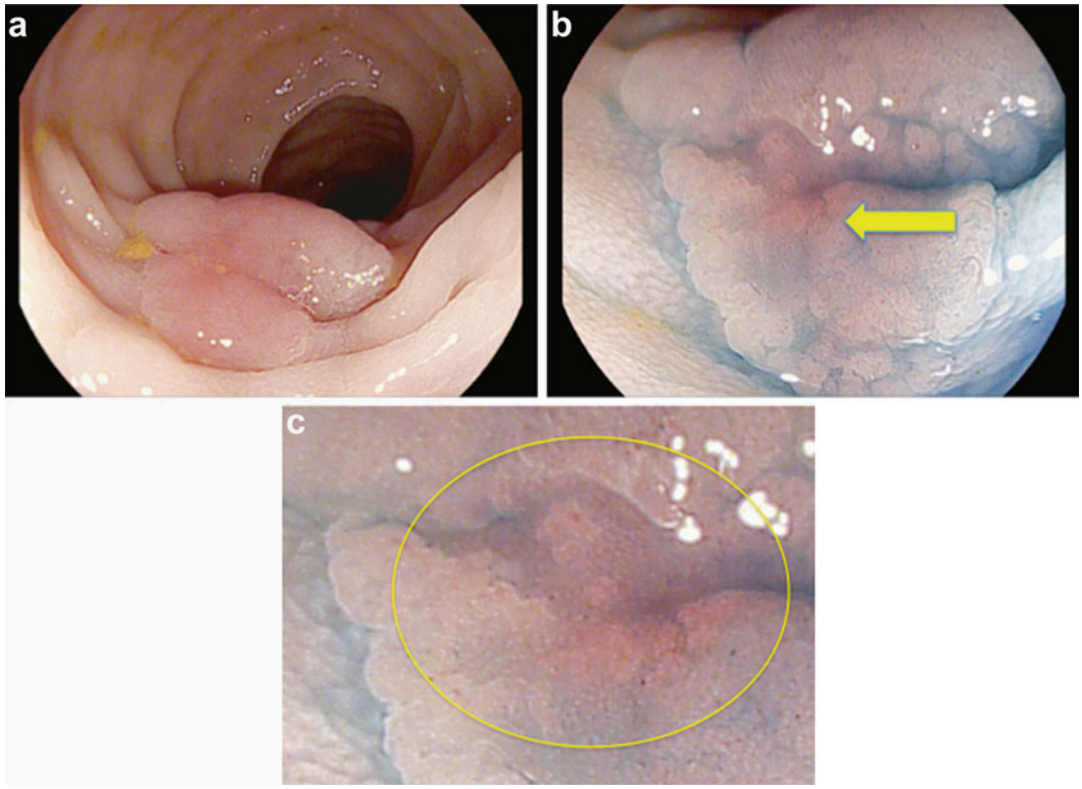

Fig. 17.2 Colitis-associated dysplasia. (**a**) A flat lesion is visible using white light HD colonoscopy. (**b**) Chromoendoscopy with methylene blue (0.1 %) is used to clarify the borders and surface architecture. Irregular pattern with shallow depression (Type IIc, pit-pattern V) can be identified (*arrow*) and (**c**) magnified view. Endoscopic resection revealed colitis-associated early cancer (shallow infiltration of the submucosal layer)

within the specimen [6]. Light emanating from that point is focused through a pinhole to a detector and light emanating from outside the illuminated spot is rejected from detection.

As illumination and detection system are at the same focal plane, they are termed "confocal" [6]. All detected signals from the illuminated spot are captured and the created image is an optical section representing one focal plane within the examined specimen. The image of a scanned region can be constructed and digitized by measuring of light returning to the detector from successive points and every point is typically scanned in a raster pattern [6].

Currently, two CLE-based systems are used in clinical practice and research [6, 7] (see Table 17.1):

1. In confocal laser endomicroscopy (CLE), a miniaturized confocal scanner has been integrated into the distal tip of a flexible endoscope (Pentax Endomicroscopy System, Japan). A blue laser light source delivers an excitation wavelength of 488 nm, and light emission is detected at>505 nm [8]. Successive points within the tissue are scanned in a raster pattern to construct serial en face optical sections of 475×475 μ(mu)m at user-controlled variable imaging depth. Lateral resolution is 0.7 μ(mu)m and optical slice thickness

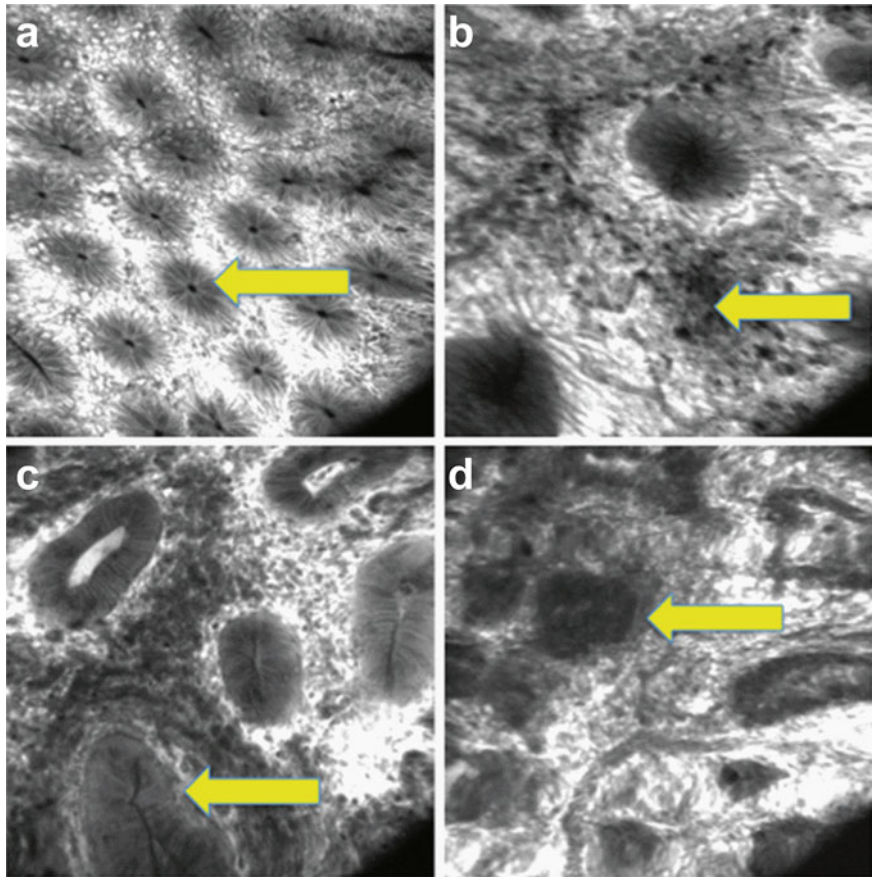

Fig. 17.3 Endomicroscopy in IBD. (**a**) Normal colonic mucosa with regular crypt architecture (*arrow*) can be seen. (**b**) Inflammatory cells can be identified within the lamina propria as a sign of chronic inflammatory changes. (**c**) Inflammatory changes and dysplastic crypts can be seen (*arrow*). The basement membrane is intact. Targeted biopsies confirmed the presence of low-grade intraepithelial neoplasia (colitis associated dysplasia). (**d**) Colitis associated cancer is present. Distorted glands with infiltration of malignant cells into the lamina propria (arrow) can be identified

Table 17.1 Technical aspects of endomicroscopic systems

	Endoscope based	Probe based
Outer diameter (mm)	12.8	1.0; 2.7; 2.6[a]
Length (cm)	120; 180	400; 300[a]
Field of view (μ[mu]m)	475×475	320; 240; 600 μ(mu)m[2a]
Resolution	0.7	3.5; 1.0[a]
Magnification	×1000	×1000
Imaging plane depth (μ[mu]m)	0–250 (dynamic)	40–70; 55–65; 70–130 (fixed)[a]

[a]Dependent on various probes

7 μ(mu)m (axial resolution). Images on the screen approximate a 1,000-fold magnification of the tissue in vivo [8].

2. In contrast, the probe-based system (pCLE—Cellvizio Endomicroscopy System, Mauna Kea Technologies, Paris, France) consists of a 1.5-mm flexible mini-probe with lateral resolution depending on the mini-probe between 3.5 μ(mu)m–1 μ(mu)m and axial resolution 5.0 μ(mu)m and is compatible with the working channel of any standard endoscope [7, 8]. These probes can be fitted through the working

channel of most endoscopes for clinical use. Image acquisition is faster with this probe (12 frames/s) at the expense of resolution being limited by the number of the fibers (30,000 single fibers = pixels).

Compared with probe-based CLE, the endoscopic CLE has slightly higher lateral resolution (approximately 0.7 versus 1.0 μ[mu]m), a larger field of view (approximately 475 versus 240 μ[mu]m) and variable imaging plane depth (approximately 0–250 versus 0–65 μ[mu]m). However, the mini-probe is currently the only commercially available system and can be used in conjunction with any standard endoscope. It is passed through the working channel and endomicroscopic images at video-frame rates are obtained, which allows a dynamic examination of the vessels and micro-architecture (12 versus 0.8–1.6 frames per second).

Endomicroscopy requires contrast agents. The most commonly used dyes are fluoresceine (intravenous application), acriflavine (local application) and cresyl violet (local application) [8–11].

The great potential of endomicroscopy is not only in vivo histology. Endomicroscopy also enables us to display and observe physiologic and pathophysiologic changes during ongoing endoscopy. Furthermore molecular imaging becomes possible [12].

In inflammatory bowel diseases, CLE has been able to demonstrate intramucosal bacteria within the lamina propria [13]. These intramucosal bacteria are much more common in IBD patients compared to normal controls. These new visible details might refine our understanding of IBD, because increased cell shedding is linked with increased intramucosal bacteria as well as with a higher risk to develop a flare within 12 months [14].

Most recently, endomicroscopy has been used for molecular imaging. As such labelled antibodies (adalimumab) have been applied topically onto the affected (inflamed) mucosa in patients with Crohn's disease. The amount of membranous TNF-alpha receptors within the mucosa could be quantified and the response to biological therapy could be predicted with high accuracy based on the fluorescence pattern of the receptors [15].

Thus, CLE is a promising research and clinical tool that will improve our diagnostics and therapeutic algorithms in IBD patients.

Clinical Trials

Endomicroscopy of the whole GI tract is not feasible or possible because CLE covers only a limited field of view with a maximum 475–475 μm. Therefore it is very important to combine chromoendoscopy (for detection) [16] with endomicroscopy (for characterization) [17]. More neoplastic lesions can be detected and neoplastic lesions can be differentiated from non-neoplastic based on surface pattern architecture.

The enhanced ability via chromoendoscopy and endomicroscopy discriminating between non-neoplastic lesions, sporadic adenoma (adenoma-like mass; ALM) and colitis-associated neoplasia (dysplasia-associated lesion masses; DALM) can potentially help reduce the risk of colorectal cancer, lengthen surveillance intervals and reduce the number of unnecessary biopsies [2, 3, 15] (see Fig. 17.3).

Panchromoendoscopy with either methylene blue or indigo carmine has become a valid diagnostic tool for improving the diagnostic yield of intraepithelial neoplasia using the "SURFACE" guidelines in IBD patients [17].

In the first randomized trial of endomicroscopy in ulcerative colitis, 153 patients with long-term ulcerative colitis who were in clinical remission were randomly assigned at a ratio of 1:1 to undergo either conventional colonoscopy or panchromoendoscopy using 0.1 % methylene blue in conjunction with endomicroscopy to detect intraepithelial neoplasia or colorectal cancer [4].

Chromoendoscopy was used to unmask lesions for CLE and compared to standard WLE with random biopsies in this study.

In vivo endomicroscopic prediction of the nature of lesions (neoplastic versus non-neoplastic) was accurate in 97.8 %. In the conventional colonoscopy group, 42.2 biopsies were necessary. In the chromoendoscopy/CLE group, 3.9 biopsies per patient were sufficient, if only circumscript lesions (by chromoendoscopy) with suspicious

micro-architecture (by CLE) would have been biopsied [4]. The negative predictive value for mucosa with a normal appearance using CLE to not harbor intraepithelial neoplasia was 99.1 %. This stresses again the concept of taking "smart" biopsies instead of untargeted, random specimens [4].

Sanduleanu et al. have demonstrated that Acriflavine-guided endomicroscopy differentiates between low-grade and high-grade intraepithelial neoplasia. An adenoma dysplasia score reliably discriminated high-grade dysplasia from low-grade dysplasia (accuracy, 96.7 %). Interobserver agreement was high (K coefficients: pathologist, 0.92; endomicroscopist, 0.88). In vivo histology predicted ex vivo data with a sensitivity of 97.3 %, specificity of 92.8 %, and accuracy of 95.7 % [18].

A meta-analysis of 91 studies, including 11 with CLE reported by Wanders et al. compared the pooled sensitivity, specificity and real-time negative predictive value (NPV) of virtual chromoendoscopy [narrow band imaging (NBI), i-scan, flexible spectral imaging color enhancement (FICE)], confocal laser endomicroscopy and autofluorescence imaging for differentiation between neoplastic and non-neoplastic colonic lesions. This meta-analysis showed that virtual chromoendoscopy and CLE had an overall similar sensitivity and specificity whereas CLE had the best results (sensitivity of 93 % and specificity of 89 %) and only CLE had a real-time NPV of more than 90 % [19]. A further meta-analysis of 15 CLE studies including four in IBD by Su et al. demonstrated the effectiveness of CLE in discriminating neoplastic and non-neoplastic lesions and showed a comparable result in pooled sensitivity and specificity, whereby specificity was even higher (sensitivity of 94 % and specificity of 95 %) [20].

In summary, multiple studies have stressed the concept of taking "smart" biopsies instead of untargeted, random specimens.

Contrast Agents for Confocal Endomicroscopy

For tissue illumination with endomicroscopic low power laser (488 nm—blue laser light) application of fluorescence agents are necessary.

Most studies in humans have been performed with intravenous fluorescein sodium (5 ml, 10 %). Fluorescein quickly distributes within all compartments of the tissue, and CLE is possible within seconds after injection. It contrasts cellular and subcellular details, connective tissue and vessel architecture at high resolution, but does not stain nuclei [10].

Intravenous fluorescein is a nontoxic agent that is safe and mostly well tolerated and only transient discoloration of the skin has been described [10].

CLE with intravenous fluorescein sodium allows analysis of cellular structure, connective tissue and blood cells of the colonic mucosa in vivo. However, the nuclei of the intestinal epithelium are not readily visible because of the pharmacokinetic properties of fluorescein. Acriflavine and cresyl violet are alternative dyes, which are applied topically and highlight nuclei, cell membranes, cytoplasm and to a lesser extent vessels. Acriflavine accumulates in nuclei and carries, therefore, a potential mutagenic risk. Cresyl violet, which enriches the cytoplasm and visualizes nuclear morphology negatively is an alternative.

A 2-step study approach, made in 2007 by Goetz et al., evaluated the staining characteristics and optimal concentration of a single topical contrast agent, cresyl violet (CV) (Merck, Darmstadt, Germany) for simultaneous chromoendoscopy and CLE for straightforward and reliable recognition of lesions and their immediate characterization in vivo [21].

After establishing the optimal cresyl violet dye-concentration of 0.13 % with a pH of 3.8 in an animal preclinical study, 67 sites in 36 patients in a prospective clinical study were topically stained and subsurface serial images were generated at different depths using CLE. The results showed a good resolution for chromoendoscopy for pit pattern classification and good fluorescent contrast for endomicroscopy. Imaging at variable penetration depths permitted high-resolution visualization of tissue architecture and subcellular details, such as mucin in goblet cells and, more importantly, cell nuclei so that in vivo distinction of low-grade versus high-grade IN was demonstrated for the first time. Endomicroscopic

targeting of biopsies in a region of altered nucleus-to-cytoplasm ratio using intravital staining with cresyl violet has resulted in the diagnosis of one additional case of high-grade intraepithelial neoplasia, and the overall prediction rate of neoplastic changes by CLE was excellent, although the small number of sites investigated may limit the significance of this finding [21].

Conclusion

Endomicroscopy is a new imaging tool for gastrointestinal endoscopy. In vivo histology becomes possible at subcellular resolution during ongoing colonoscopy.

Pan-chromoendoscopy with targeted biopsies has become the method of choice for surveillance of IBD patients.

Endomicroscopy can be added after chromoendoscopy to clarify whether standard biopsies are still needed. This smart biopsy concept can increase the diagnostic yield of intraepithelial neoplasia and substantially reduce the need for biopsies.

Endomicroscopy is still mainly used for research, but clinical acceptance is increasing because of a multitude of positive studies about the diagnostic value of endomicroscopy. Different contrast agents are available to identify cellular and subcellular structures. Fluorescent agents can also be combined with proteins or antibodies to enable molecular imaging.

It can be speculated that smart biopsies, functional imaging (e.g., defining local barrier dysfunction) as well as molecular imaging (predicting the response to biological therapy) are future fodder for endomicroscopy.

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Surveillance for Neoplasia in the Patient with an Ileal Pouch

18

Revital Kariv and Bret Lashner

Introduction

The inflammatory bowel diseases, both ulcerative colitis and Crohn's disease, have been suggested as significant risk factors for adenocarcinoma of the colon and small bowel. Professional guidelines have addressed endoscopic surveillance of the colon in patients with colitis [1–8], but post-proctocolectomy surveillance of the ileal pouch has been specifically addressed by only a few [6, 8]. These guidelines advocate stratifying surveillance of the ileal pouch according to risk group. Pouch dysplasia or cancer is infrequent but elevated over what would be expected [9–12]. High-risk groups are those considered to have previous rectal dysplasia, dysplasia or cancer at time of pouch surgery, primary sclerosing cholangitis (PSC), or Type C mucosa of the pouch (persistent atrophy and severe inflammation). However, recent large cohort studies have shown that the risk of neoplasia of the pouch is increased only in patients who had colorectal neoplasia (dysplasia or cancer) prior to surgery [9–12]. No specific protocol is currently recommended for pouch surveillance endoscopy by professional societies.

In this chapter we will review in detail the relevant literature regarding prevalence of pouch neoplasia, surveillance indications, suggested protocols for pouch surveillance, and suggested management of pouch-associated dysplasia or cancer.

Ileal Pouch Neoplasia: Incidence and Prevalence, Pouch and Cuff Neoplasia: Types and Risk Factors

The frequency of dysplasia or cancer of the ileal pouch is low [9–12]. A comprehensive database search of 23 observational studies and case series with a total of 2,040 patients revealed a pooled prevalence of confirmed dysplasia in the pouch, anal transitional zone, or rectal cuff to be 1.13 % (range 0–18.7 %) [10]. The prevalence of high-grade dysplasia, low-grade dysplasia, and indefinite for dysplasia was 0.15 % (range 0–4.5 %), 0.98 % (range 0–15.6 %) and 1.23 % (range 0–25.28 %), respectively.

Recent data from two large cohorts followed for more than 20 years provides the most comprehensive data. A cohort study of 3,203 patients from the Cleveland Clinic demonstrated cumulative incidences for pouch neoplasia at 5, 10, 15, 20, and 25 years of 0.9 %, 1.3 %, 1.9 %, 4.2 %, and 5.1 %, respectively, and cumulative incidence for

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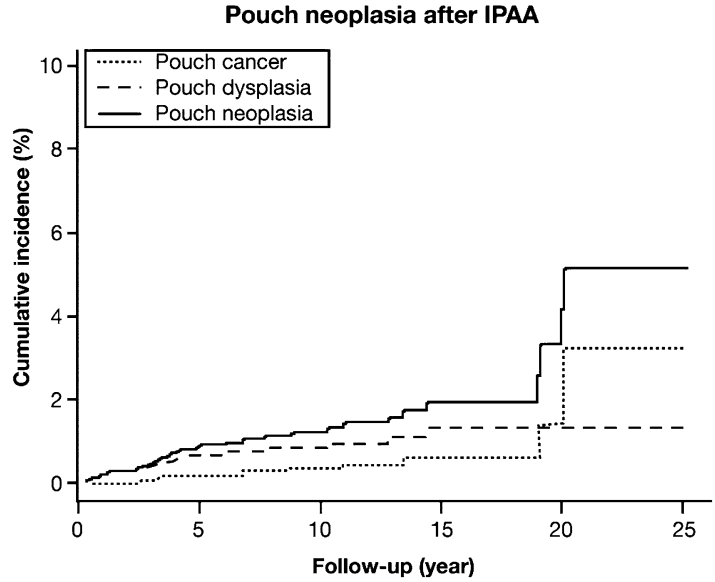

Fig. 18.1 Time-to-event curve showing cumulative incidence of pouch neoplasia (pouch cancer + pouch dysplasia) in 3,203 patients with inflammatory bowel disease and restorative proctocolectomy. Reprinted with permission from Kariv R, Remzi FH, Lian L, Bennett AE, Kiran RP, Kariv Y, Fazio VW, Lavery IC, Shen B. Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. Gastroenterology 2010 Sep;139(3):806–12

pouch cancer (including squamous cell cancer and pouch lymphoma) at 5, 10, 15, 20, and 25 years of 0.2 %, 0.4 %, 0.8 %, 2.4 %, and 3.4 %, respectively [11] (Fig. 18.1). The cumulative incidence for pouch dysplasia at 5, 10, 15, 20, and 25 years was 0.8 %, 1.3 %, 1.5 %, 2.2 %, and 3.2 %, respectively. In that cohort, the overall prevalence of pouch neoplasia was 1.19 % including 11 cases (0.36 %) with adenocarcinoma of the pouch and/or the anal-transitional zone (ATZ), 0.03 % with lymphoma, and 0.72 % with dysplasia of the pouch [11].

A Dutch registry of 1,200 pouch patients found a prevalence of 1.83 % for pouch neoplasia [12]. The respective cumulative incidences at 5, 10, 15, and 20 years for pouch neoplasia was 1.0 %, 2.0 %, 3.7 %, and 6.9 % and 0.6 %, 1.4 %, 2.1 %, and 3.3 % for pouch adenocarcinoma [12] (Fig. 18.2).

Typically, cases of cancer reported in the literature occurred more than 10 years after proctocolectomy, while dysplasia occurred earlier [11] (Figs. 18.3a, b, 18.4 and 18.5).

Pouch neoplasia can be classified as follows [9–11]:

1. Pouch dysplasia (Indefinite/low-grade/high-grade)
2. Cuff dysplasia (Indefinite/low-grade/high grade)
3. Pouch adenocarcinoma
4. Cuff adenocarcinoma

The diagnosis of pouch dysplasia should be confirmed by at least two expert gastrointestinal pathologists, as is done in IBD colonic biopsies with suspected dysplasia. Dysplasia can be flat or polypoid. Polypoid dysplasia can be further divided to a dysplasia-associated lesion or mass (DALM) (Fig. 18.6) or a pouch polyp with no surrounding dysplasia. Often, it is the endoscopic appearance of the dysplastic lesion that is used to distinguish the two types. Pouch and cuff dysplasia have been described to be equally prevalent in some studies [10] while others show that cuff dysplasia is significantly more common [11, 12]

There have been several suggested risk factors for pouch neoplasia. The most important is preoperative ulcerative colitis-associated cancer or dysplasia [9–12]. In both the Cleveland Clinic and Dutch cohorts, preoperative neoplasia was the single most important predictive factor for ileal pouch neoplasia with adjusted hazard ratios of 13.43 (95 % confidence interval (CI): 3.96–45.53) or 24.69 (95 % CI, 9.61–63.42) for prior carcinoma, and 3.62 (95 % CI: 1.59–8.23;) or 3.76 (95 % CI, 1.39–10.19) for prior dysplasia, in the two respective cohorts [11, 12].

Other suspected risk factors for pouch neoplasia, such as long duration of colitis prior to surgery, presence of primary sclerosing cholangitis, type of ileoanal anastomosis (double-

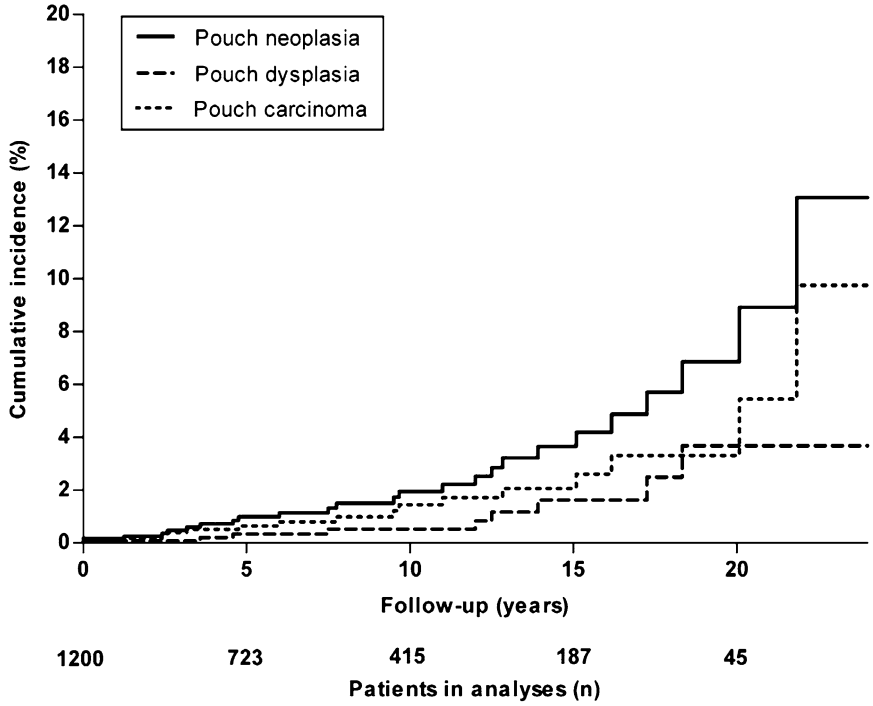

Fig. 18.2 A Dutch registry of 1,200 pouch patients shows cumulative incidence of pouch neoplasia. Reprinted with permission from Derikx LA, Kievit W, Drenth JP, de Jong DJ, Ponsioen CY, Oldenburg B[3] van der Meulen-de Jong AE, Dijkstra G, Grubben MJ, van Laarhoven CJ, Nagtegaal ID, Hoentjen F; Dutch Initiative on Crohn and Colitis. Prior colorectal neoplasia is associated with increased risk of ileoanal pouch neoplasia in patients with inflammatory bowel disease. Gastroenterology. 2014 Jan;146(1):119–128

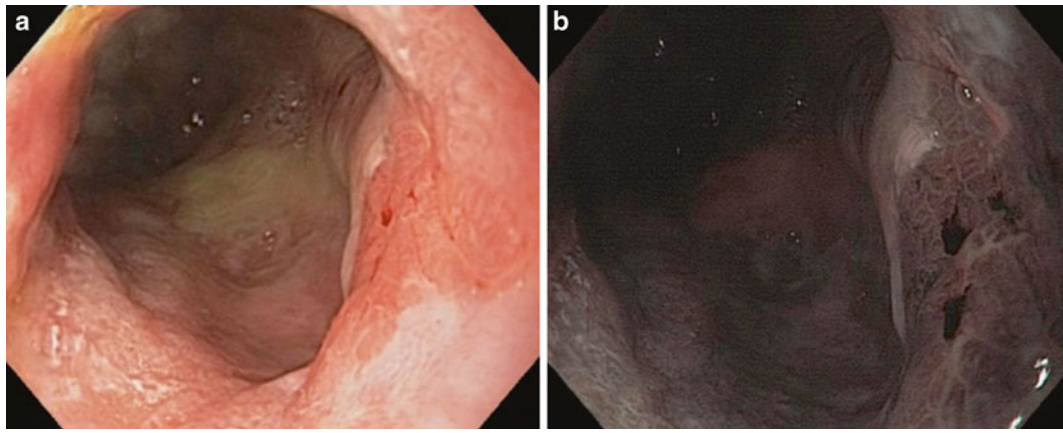

Fig. 18.3 (**a**) Cancer of the ATZ on the right side of the photo with white light imaging. (**b**) Cancer of the ATZ in the same patient with narrow band imaging

stapled versus hand-sewn with mucosectomy), type C (atrophic) pouch mucosa, duration of postoperative follow-up, and chronic pouchitis were examined in pooled analyses, but have not shown consistent predictive ability. Interestingly, these suspected risk factors are still mentioned in some guidelines to suggest more intense surveillance [6]. Mucosectomy but has not been shown to be protective for ileal pouch and ATZ neoplasia [13].

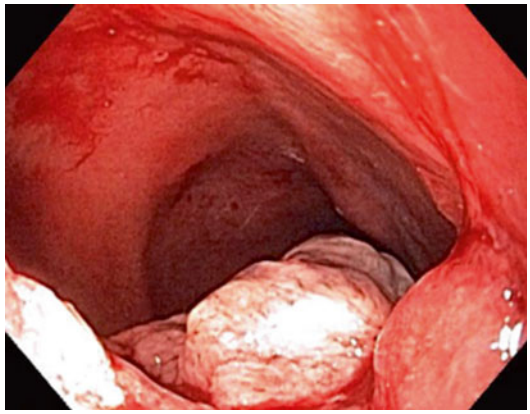

Fig. 18.4 Cancer of the ileal pouch

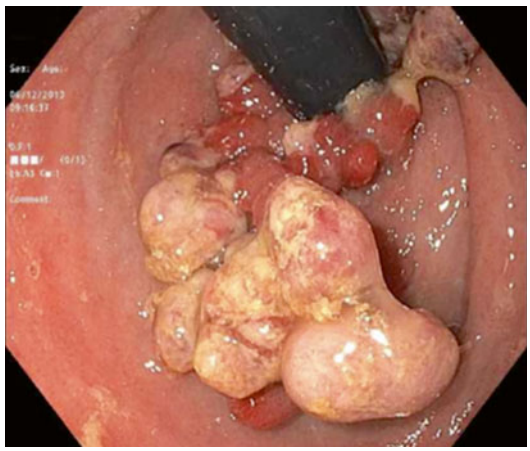

Fig. 18.5 Cancer of the ATZ extending into the pouch

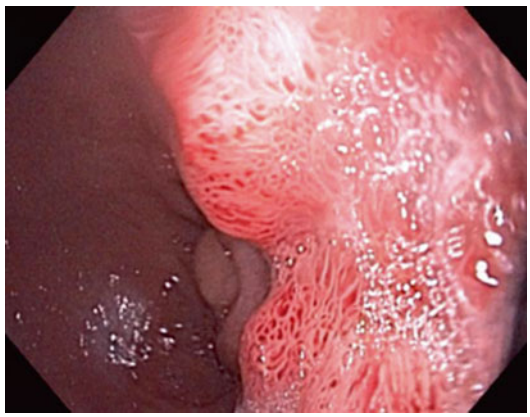

Fig. 18.6 DALM lesion of the ATZ

Pouch Surveillance: An Unsolved Controversy

No guidelines specifically address pouch neoplasia surveillance or define risk groups for increased surveillance. The British Society of Gastroenterology suggests an annual pouch endoscopy for the following high-risk groups: previous rectal dysplasia, dysplasia/cancer at time of pouch surgery, PSC, or Type C mucosa of pouch (persistent atrophy, and severe inflammation) [5, 6]. Surveillance is recommended every 5 years in all others. American Society for Gastrointestinal Endoscopy (ASGE) guidelines do not address pouch endoscopic surveillance [4]. UpToDate suggests a surveillance pouchoscopy every 3–5 years in the absence of inflammation and atrophy [8]. However, in the presence of severe inflammation or atrophy, increasing surveillance to annual pouchoscopy is suggested.

A debate has been ongoing in regard to the clinical justification and cost-effectiveness of pouch surveillance [14–18]. A series of 138 asymptomatic pouch patients who underwent surveillance endoscopy of the pouch demonstrated indefinite dysplasia in only one case with no other neoplastic findings, although 50 % of the patients had endoscopic abnormalities [16]. Pouch polyps have been studied through a large pouch patient cohort [19]. Among 1,094 pouch patients, 96 (8.8 %) had pouch polyps, most (96.9 %) were inflammatory polyps while only 3 (3.1 %) were neoplastic polyps with low-grade or indefinite dysplasia.

A decision for pouch surveillance protocols should be based on the following parameters:

1. **High risk groups** as mentioned previously [11, 12].
2. **Cost-effectiveness analysis** of pouch surveillance was conducted for three risk-level populations: (1) average-risk patients with no preoperative colonic neoplasia; (2) above-average-risk patients (dysplasia of the colon as the indication for colectomy); (3) high-risk patients (cancer of the colon as the indication for colectomy) [14]. For average-risk patients,

the incremental cost-effectiveness ratios (ICER) for no surveillance versus surveillance every 1, 3 and 5 years was **$69,040, $41,325** and **$36,516** per life year gained, respectively. For above-average-risk population the ICER for no surveillance versus surveillance every 1, 3 and 5 years was **$10,071, $5,910** and **$4,911** per life year gained, respectively. For the high-risk population, the ICER for no surveillance versus surveillance every 1, 3 and, 5 years was **$3,456, $2,119** and **$2,036** per life year gained, respectively. For the high-risk patients, the added life years gained between surveillance yearly compared to every 3 years was 1.1 years and the ICER of surveillance every year compared to every 3 years was **$5,279**. Sensitivity analysis revealed robust results [14].

3. **Understanding of the pathogenesis of pouch neoplasia**. In colonic IBD, the surveillance strategy is based on the concept of an inflammation-dysplasia-carcinoma sequence [20–22]. Current data are insufficient to determine whether this sequence also applies to pouch neoplasia. The fact that pouchitis was not found in any of two large cohorts to be significantly associated with pouch cancer suggests an alternative pathway. On the other hand, clinicopathological and molecular features in pouch carcinoma seem to be shared with the IBD-associated CRC inflammation-dysplasia-carcinoma sequence. The strong association of prior colonic neoplasia with pouch neoplasia favors a field effect theory with similar pathogenesis [11, 12, 21, 22].

Currently, there is no clear evidence that pouch surveillance is beneficial and prevents pouch cancer. However, the cost-effectiveness analysis mentioned previously suggests that cancer surveillance pouchoscopy is cost-effective and should be offered.

Surveillance Pouch Endoscopy: Technique, Biopsy Protocol, Interval

Flexible pouchoscopy is a useful investigation in patients with pouch dysfunction such as pouchitis, stricture, pouch malfunction, and iron-deficiency anemia. It can be performed without sedation and has a high diagnostic yield. Pouch surveillance procedures should be routinely suggested to all pouch patients with the testing interval based on individual neoplasia risk mentioned earlier. It is not unreasonable for any pouch endoscopy to address the aspect of surveillance by taking surveillance biopsies [23]. Preparation for pouch endoscopy should include 1–2 Fleet enemas [11].

A surveillance pouchoscopy should include a careful inspection of the cuff, pouch, afferent limb, and tip-of-the-J to document any irregularities. A reasonable biopsy protocol includes four samples from the upper pouch, four samples from the lower pouch, four samples from the rectal cuff, and biopsies of any abnormalities seen in the pouch or afferent limb [11, 23]. Polypoid or sessile mucosal findings should be resected and sent for histological evaluation and the surrounding mucosa should be sampled in a different biopsy container [16]. High resolution endoscopy or narrow band imaging may increase the rate of detection of dysplasia and should be used if available.

Since most of the pouch cancer arises at the residual colonic mucosa of the cuff, this part should be addressed very carefully. Often, since the cuff is short (1–2 cm), this part may be more difficult and require some expertise.

It is advisable to document the Pouchitis Disease Activity Index (PDAI) score [24] in any pouch endoscopy, even in a surveillance examination since up to 50% of asymptomatic pouch patients have abnormal endoscopic findings, especially those with preoperative diagnosis of Crohn's disease or concomitant extraintestinal manifestations of inflammatory bowel disease [16].

The interval between surveillance pouch endoscopies is not clearly addressed in professional guidelines. However, based on the current literature, risk groups for pouch dysplasia and cancer can be clearly defined and offered more intense surveillance. We suggest the following surveillance protocol for IBD pouch patients, based on current data and cost effectiveness analysis [14]:

- Patients with IBD-related CRC or dysplasia: pouch endoscopy yearly
- Patients with significant family history of CRC, PSC and chronic pouchitis and Type C mucosa: every 3 years
- All others: pouch endoscopy every 5 years

Obviously, the frequency of pouch endoscopy depends on other clinical and endoscopic parameters such as pouchitis, pouch stricture, etc. [25].

Management of Pouch Dysplasia and Pouch Cancer

Dysplasia following restorative proctocolectomy with ileal pouch anal anastomosis is rare but can develop in either the pouch ileal mucosa or in any retained anorectal mucosa. The management of pouch dysplasia is unclear, is not evidence based and may be inferred from IBD colonic dysplasia management. Hence, polypoid dysplasia should be totally resected, borders should be carefully evaluated histologically, and surrounding mucosa should be sampled to distinguish DALM from pouch adenoma. Complete resection with no surrounding dysplastic mucosa or any other dysplastic region should be followed with no further treatment, while patients with lesions that have unclear borders that suggest DALM should be considered for surgical treatment of pouch resection.

Patients with flat unifocal low-grade dysplasia of the pouch should have more frequent endoscopic surveillance. Patients with flat multifocal low-grade dysplasia or flat high-grade dysplasia should be offered surgical resection. Dysplasia in the rectal cuff can be treated with a surgical mucosectomy, rather than pouch resection; however, this approach has not been universally accepted [13].

Since mucosal inflammation can prompt a pathological diagnosis of indefinite dysplasia, the finding of indefinite dysplasia requires re-evaluation after the patient has been successfully treated for inflammation of the pouch.

Pouch resection with lymph node dissection and end ileostomy is the best treatment for pouch cancer.

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Part VII

Endoscopic Approach to DALMs

Pathology of Polypoid Dysplastic Lesions in IBD

19

Kyle Viani and Robert D. Odze

Pathogenesis of Neoplasia in IBD

Patients with ulcerative colitis (UC) and Crohn's disease (CD) are at increased risk of colonic adenocarcinoma secondary to the effects of longstanding mucosal inflammation [1–6]. The well-known higher risk of malignancy in UC patients with severe inflammation and long duration of disease highlights the importance of inflammation in colonic carcinogenesis [1, 7, 8]. Our understanding of the pathogenesis of neoplasia in inflammatory bowel disease (IBD) continues to evolve [9–12]. Central to the pathogenetic process is the production of reactive oxygen species within inflamed mucosa, which leads to increased oxidative stress in epithelial and stromal cells and altered intracellular signaling pathways [12]. The end result is a stepwise accumulation of DNA damage. The sequence of molecular alterations differs between sporadic and IBD-associated neoplasia, although many of the same signaling pathways are affected. For example, *P53* mutations are an early event in IBD-associated neoplasia, but occur late in the development of sporadic colon adenocarcinoma [13, 14]. In contrast, while *APC* mutation is a frequent early event in sporadic adenomas, loss of *APC* occurs late, and less frequently, in IBD-associated neoplasia [15, 16]. Chromosomal instability and microsatellite instability occur in 85 % and 15 % of IBD-associated carcinomas, similar to sporadic colon carcinomas [17].

Dysplasia, defined as neoplastic epithelium confined by the basement membrane, is the morphologic manifestation of progressive genomic alterations and dysregulated cell signaling pathways. The presence of an inflammation-dysplasia-carcinoma sequence in IBD forms the basis of current surveillance guidelines in IBD. Dysplasia serves both as a marker of increased risk, and a direct precursor, of adenocarcinoma. Whereas IBD-associated neoplasia is thought to progress from low- to high-grade dysplasia, and then invasive carcinoma, some invasive carcinomas may develop directly from low-grade dysplasia. For instance, low-grade tubuloglandular adenocarcinomas have been shown to arise directly from low-grade dysplasia without an intervening phase of high-grade dysplasia [18]. Nevertheless, "flat" low-grade dysplasia confers a lower risk of synchronous or metachronous adenocarcinoma than high-grade dysplasia [1]. Accurate classification of dysplastic lesions by both endoscopy and histopathology is critical to the management of IBD patients.

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Grading of Dysplasia in IBD

The grading scheme developed in 1983 by the Dysplasia Morphology Study Group remains the most frequently used system in the United States [19]. This scheme classifies dysplasia as negative, indefinite, or positive (low- or high-grade). An alternative system, termed the Vienna Classification, is frequently used in Europe and Asia [20]. This classification system includes five diagnostic categories: negative, indefinite, noninvasive low-grade, noninvasive high-grade, and invasive neoplasia. Noninvasive low-grade and high-grade neoplasia is equivalent to low- and high-grade dysplasia in the Dysplasia Morphology Study Group system.

Low-grade dysplasia is characterized by cytologic atypia, most often composed of elongated, hyperchromatic, pseudostratified nuclei, and a lack of surface maturation (Fig. 19.1). Architectural changes are typically mild. High-grade dysplasia exhibits greater cytologic abnormalities and often shows significant loss of cell polarity, nuclear pleomorphism, full thickness nuclear stratification, and abundant mitoses, some of which may be atypical. Architectural changes of high-grade dysplasia are more pronounced, and these include cribriform and back-to-back crypts, and budding, among others (Fig. 19.2). The same grading system is used regardless of the endoscopic appearance of the lesion.

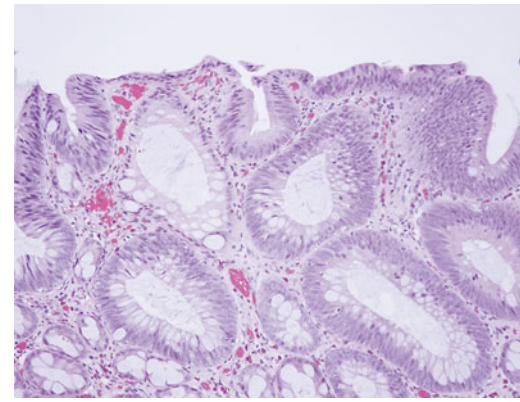

Fig. 19.1 Adenoma-like DALM with low-grade dysplasia, characterized by nuclear stratification and hyperchromasia

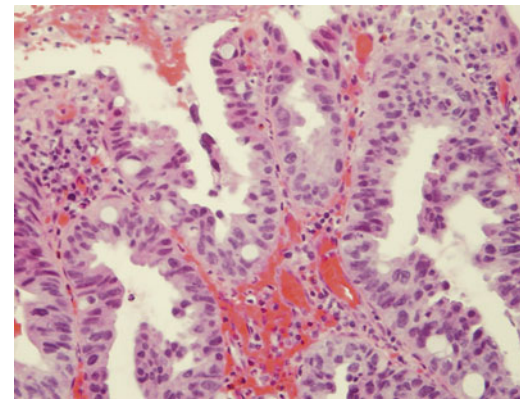

Fig. 19.2 High-grade dysplasia exhibits greater cytologic atypia, loss of nuclear polarity and architectural atypia

Endoscopic Classification and Terminology of Dysplasia in IBD

Historically, dysplasia in IBD has been categorized grossly (endoscopically) as either flat or elevated (DALM), the latter separated into adenoma-like and non-adenoma-like subcategories. In this categorization scheme, flat dysplasia was defined as dysplasia identified in random biopsies of colonic mucosa in which the area of dysplasia was endoscopically undetectable. More recently, particularly with the advent of advanced endoscopic techniques such as chromoendoscopy and confocal laser endomicroscopy, many lesions that were historically considered flat (endoscopically undetectable) can now be recognized endoscopically and, thus, targeted for biopsy. Thus, the term "flat" dysplasia is now considered somewhat misleading and often confusing. Furthermore, separation of elevated lesions (DALMs) into adenoma-like and non-adenoma-like suffers from interobserver variability. As a result, in March 2014, an international group of gastrointestinal specialists—including surgeons, gastroenterologists, and pathologists—convened in San Francisco to discuss, modify, and propose a revised categorization scheme of dysplasia in IBD that would be useful clinically and for future

investigations: Surveillance of Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC). The participants of this meeting agreed that the term "DALM" should be abandoned. The newly proposed endoscopic classification of dysplasia in IBD separates dysplasia into "visible" and "invisible" categories (by endoscopy). Visible dysplasia is subcategorized as polypoid or non-polypoid. Polyps may then be separated into those are pedunculated versus those that are sessile. Pedunculated lesions are those that are attached to the mucosa by a stalk, whereas sessile lesions do not have a stalk. However, in contrast, the entire base of the polyp is contiguous with the mucosa. Non-polypoid lesions (those previously considered flat) are now separated into those that are superficially elevated (lesions that protrude <0.25 mm above into the lumen, which is less than the closed cup on a forced biopsy forceps), flat (lesions without protrusion above the level of the mucosa), depressed (lesions with at least a portion depressed below the level of the mucosa), and ulcerated (lesions with ulceration and depressed fibrinous-appearing base). In contrast, invisible dysplasia is considered lesions that are identified on random (non-targeted) biopsies of colonic mucosa. The results of this meeting in San Francisco, and the classification system the participants proposed, have not yet been published at the time of the writing of this manuscript, so this system is considered tentative. Thus, for the purposes of this manuscript, the traditional endoscopic classification system of dysplasia (flat, elevated) is used.

Although surveillance strategies in IBD were originally developed based on the risk associated with "flat" dysplasia, several retrospective studies have revealed that most dysplasia identified in IBD patients is actually elevated. Blonski et al. [21] reported the endoscopic features of 58 sequentially identified dysplastic lesions in IBD surveillance endoscopies from a single institution. Fifty-one (87.9 %) of the biopsies were from visible lesions, 38 (66 %) of which were described as polyps, 12 (21 %) as ulceration/nodularity, and 1 (2 %) as a "circumferential lesion." Rubin et al. [22] provided the endoscopic features of 75 neoplastic lesions identified in 1,339 sequential UC surveillance endoscopies. They reported that 46 (61 %) of the lesions were visible, including 23 (30 %) polyps, 22 (29 %) areas of "irregular mucosa" and 1 (1 %) stricture. Rutter et al. [23] reported similar findings in a retrospective review of 110 sequential neoplastic lesions identified in UC patients. Eighty-five (77 %) of the lesions were visible and 74 (67 %) were described as polyps. The high relative incidence of polypoid lesions in IBD emphasizes the importance of accurate endoscopic classification of visually identified dysplastic lesions in IBD.

Historically, raised dysplastic lesions have been referred to by the acronym DALM (Dysplasia Associated Lesion or Mass). As mentioned previously, use of this term is discouraged in favor of a new classification system proposed by SCENIC. DALMs have traditionally been subclassified as "adenoma-like" or "non-adenoma-like" based solely on their endoscopic features. Accurate endoscopic categorization of DALMs is critical since the management of adenoma-like and non-adenoma-like DALMs differs considerably. Adenoma-like DALMs resemble sporadic adenomas that occur in non-IBD patients. These lesions are typically well circumscribed with well demarcated borders and a smooth surface contour. In contrast, non-adenoma-like DALMs exhibit features not classically seen in sporadic adenomas. These include a broad plaque-like growth pattern, ulceration, stricture formation, multinodularity, irregular borders, and hemorrhage. Unfortunately there is some degree of interobserver variability in the endoscopic diagnosis of DALMs among practicing gastroenterologists [24]. For management purposes, endoscopically resectable DALMs can be considered "adenoma-like" and non-endoscopically resectable DALMs considered "non-adenoma-like."

Adenoma-Like DALM Versus Sporadic Adenoma

Pathogenetically, adenoma-like-DALMs may represent either sporadic adenomas that have incidentally developed in IBD patients or polypoid dysplasia related to the patient's underlying

chronic colitis. Several studies have investigated clinical, morphologic, immunohistochemical and molecular features in attempts to distinguish "sporadic" adenomas from IBD-related polypoid dysplasia. Although some features, such as young patient age and longer duration of colitis, may favor IBD-related polypoid dysplasia over a sporadic adenoma [25], ultimately it is not usually possible to differentiate between these two entities based on routine pathologic analysis. One exception is that an adenoma-like-DALM arising in a region of the colon without current or prior involvement by colitis can generally be considered a sporadic adenoma. Dysplasia arising in IBD is believed to occur as a direct effect of inflammation. There is no evidence to suggest that mucosa uninvolved by colitis is at an increased risk of neoplasia. However, accurate information regarding the true extent of a patient's disease is necessary before designating a segment of colon as uninvolved by prior colitis, since mucosa may normalize after treatment.

Torres et al. [26] compared the morphologic features of 89 adenoma-like DALMs in 59 IBD patients (51 with UC and 8 with CD) to sporadic adenomas. In this study, adenoma-like DALMs located within an area of colitis were designated probable IBD-associated polypoid dysplasia if flat dysplasia or adenocarcinoma was detected during a median follow-up period of 13 months. Adenoma-like DALMs located in segments of the colon uninvolved by colitis were designated sporadic adenomas. The mean duration of disease was longer in patients with IBD-associated polypoid dysplasia (11 versus 5 years). Morphologic evaluation revealed that lesions designated as IBD-associated polypoid dysplasia were more likely to have increased mononuclear lamina propria inflammation (60 % versus 16 %), tubulovillous/villous architecture (20 % versus 0 %), and mixture of normal and dysplastic crypts at the polyp surface (60 % versus 16 %). Although some differences in morphology were noted there is sufficient overlap between the groups to preclude distinguishing a sporadic adenoma from polypoid IBD-associated dysplasia in an individual case.

Adenoma-like DALMs have molecular features similar to those seen in sporadic adenomas. Fogut et al. [27] compared genetic alterations on chromosome 3p of adenoma-like (n = 18) and non-adenoma-like (n = 12) DALMs in UC patients and sporadic adenomas from non-IBD patients (n = 23). Loss of heterozygosity (LOH) of chromosome 3p markers D3S1766, D3S2409, and D3S2387 was detected in 70 %, 37 %, and 57 % of non-adenoma-like DALMs, respectively. In contrast, a low rate of LOH for these markers was seen in both sporadic adenomas (10.5 %, 7.1 %, and 0 %) and adenoma-like-DALMs (8.3 %, 11.7 %, and 15.3 %). In a similar study, Odze et al. [28] evaluated molecular features of adenoma-like (n = 12) and non-adenoma-like (n = 21) DALMs in UC patients and sporadic adenomas from non-IBD patients (n = 23). A high frequency of LOH for *p16* (56 %) and 3p (50 %) was detected in non-adenoma-like DALMS. Both adenoma-like DALMs and sporadic adenomas exhibited a lower frequency of LOH for 3p (5 % and 28 %) and *p16* (4 % and 5 %), respectively.

Walsh et al. [29] evaluated the immunophenotype of 38 adenoma-like DALMs in patients with UC and 13 sporadic adenomas from non-IBD patients as controls. Adenoma-like DALMs located outside areas of colitis in patients with no adenocarcinoma or flat dysplasia detected during follow-up were designated as sporadic adenomas. Adenoma-like DALMs located within areas of colitis that were associated with the development of flat dysplasia or adenocarcinoma at the same site within one year were designated as polypoid IBD-associated dysplasia. The frequency of p53 positivity was lower in sporadic adenomas from UC patients (5 %) and non-IBD control patients (15 %) than in polypoid IBD-associated dysplasia (29 %). In contrast, nuclear beta-Catenin positivity was higher in sporadic adenomas from UC patients (40 %) and non-IBD control patients (46 %) than in polypoid IBD-associated dysplasia (8 %).

Although some differences have been reported, there is significant overlap in the morphologic, immunohistochemical, and molecular features of sporadic adenomas and polypoid IBD-related dysplasia. However, as will be

described later, the management strategy for an adenoma-like-DALM is the same regardless of whether it represents an incidental sporadic adenoma or polypoid IBD-related dysplasia.

Natural History and Treatment of DALMS

Early studies of DALMs reported a high rate of synchronous or metachronous invasive adenocarcinoma [30, 31]. However, it is now recognized that most initial reports were composed predominantly of lesions that would currently be designated as non-adenoma-like DALMs [32]. In the first description of DALMs in patients with UC by Blackstone et al. [31] in 1981, 7 of 12 (58 %) DALMs were associated with an invasive adenocarcinoma. These DALMs included "multiple sessile polyps" and "plaque-like" lesions. Endoscopic biopsies in many patients represented superficial sampling of an underlying invasive adenocarcinoma. The high risk of malignancy associated with these lesions emphasizes the importance of careful endoscopic characterization of polypoid lesions as adenoma-like or non-adenoma-like. The presence of a non-adenoma-like DALM (non-endoscopically resectable polypoid dysplasia) is an indication for colectomy due to the high risk of invasive carcinoma. However, as will be described later, more conservative management is appropriate for patients with an adenoma-like DALM.

Evidence supporting conservative management of adenoma-like DALMs emerged in the early 1990s with several reports of UC patients treated with polypectomy and continued endoscopic surveillance [33–35]. Subsequent larger studies with longer follow-up confirmed these initial observations. For example, Engelsgjerd et al. [36] evaluated outcomes of 24 UC patients with adenoma-like DALMs located within an area of colitis treated by polypectomy and surveillance compared to a control group of 49 non-IBD patients with sporadic adenomas. Eleven percent of the DALMs harbored high-grade dysplasia. In a subsequent publication, follow-up of this cohort was extended to a mean of 82 months for patients with an adenoma-like DALM within an area of colitis and 72 months for the control group [37]. Of the patients with an adenoma-like DALM, one (4 %) developed an invasive adenocarcinoma 7.5 years after polypectomy. Flat low-grade dysplasia was detected in a resection specimen from one patient (4 %). None of the other patients developed adenocarcinoma or dysplasia. Although the risk of developing adenocarcinoma or flat dysplasia during the follow-up period was low, subsequent adenoma-like DALM(s) were identified in 62.5 % of patients. However, this was not significantly different than the proportion of non-IBD control patients with an adenoma treated by polypectomy who developed subsequent adenomas.

Conservative management of adenoma-like DALMs in UC is also supported by a recent study by Kisiel et al. [38] evaluating 77 UC patients with adenoma-like DALMs inside (57 %) or outside (43 %) areas of colitis treated with polypectomy and endoscopy surveillance. During a median follow-up period of 20.1 months, flat low-grade dysplasia was indentified in four patients (5 %) and one patient (1.3 %) developed an invasive ileocecal valve adenocarcinoma. Twenty-eight patients (36 %) developed another adenoma-like DALM.

Goldstone et al. [39] conducted the largest study to date of adenoma-like DALMs in UC treated by polypectomy and endoscopic surveillance. Outcomes from 89 patients with adenoma-like DALMs were reported with a mean follow-up of 37.5 months. During the follow-up period 4 patients (4.5 %) developed adenocarcinoma. Subsequent high-grade dysplasia was indentified in 3 patients (3.4 %). However, the authors do not specify if the dysplasia was detected in flat biopsies or in additional adenoma-like DALMs.

It is important to emphasize that conservative management of adenoma-like DALMs requires that the polyp be completely removed with negative margins. Vieth et al. [40] compared outcomes of UC patients with adenoma-like DALMs completely removed by polypectomy (n = 87) or only biopsied (n = 60). Of the patients who underwent complete polypectomy, two (2.3 %) developed adenocarcinoma during a mean follow-up period

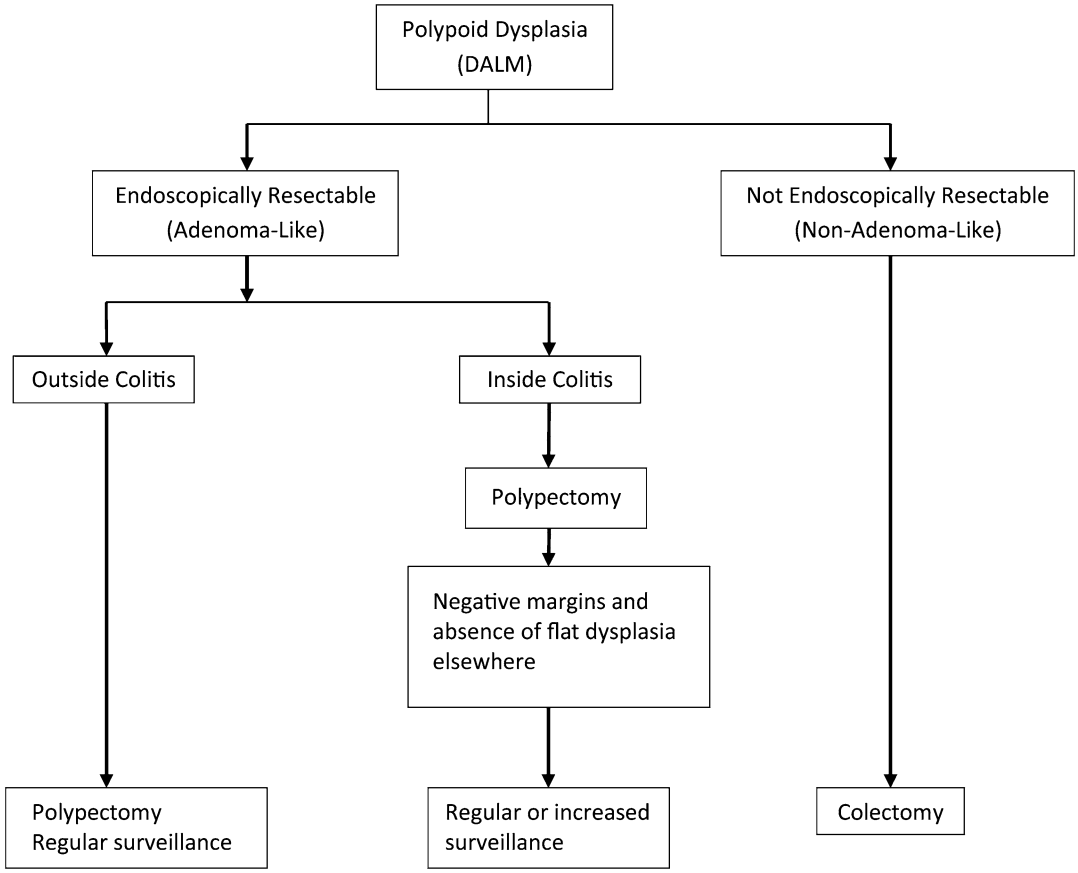

Fig. 19.3 Management scheme for polypoid dysplasia in IBD

of 53 months. In contrast, 10 patients (16.7 %) with adenoma-like DALMs that were only biopsied developed adenocarcinoma during a mean of follow-up of 87 months.

A recent a meta-analysis by Wanders et al. [41] evaluates 10 studies of DALMs treated by polypectomy in patients with UC. A total of 376 patients were included in the meta-analysis with an average follow-up of 54 months. Overall, 2.4 % of patients developed colorectal adenocarcinoma following polypectomy and surveillance. The pooled rate of adenocarcinoma was 5.3 cases per 1,000 patient years of follow-up. The low incidence of adenocarcinoma in this pooled analysis supports polypectomy and endoscopic surveillance as an appropriate management strategy for UC patients with an adenoma-like DALM. A treatment algorithm for DALMs is provided in Fig. 19.3. A summary of follow-up studies of adenoma-like DALMs treated with polypectomy and surveillance is shown in Table 19.1.

Dalms in Crohn's Disease

Most studies of DALMs have been composed predominantly of patients with UC. However, early outcome studies by Rubin et al. [42] and Jess et al. [43] contained a small subset of patients with Crohn's disease, suggesting that DALMs in CD may also be managed by polypectomy and endoscopic surveillance. In a recent paper, Quinn et al. [44] reported outcomes of 50 Crohn's disease patients with adenoma-like DALMs treated by polypectomy over a median follow-up period of 39 months: 43 % of the DALMs occurred in

Table 19.1 Studies of adenoma-like DALMs treated by polypectomy and surveillance

Authors	Year	IBD type	Number of cases	Follow-up	Subsequent carcinoma	Subsequent flat dysplasia
Kisiel et al.	2012	UC	77	20.1 months (median)	1.3 %	5.1 %
Quinn et al.	2012	CD	50	39 months (median)	2.0 %	2.0 %
Goldstone et al.	2011	UC	89	37.5 months (mean)	4.5 %	3.4 %
Vieth et al.	2006	UC	87	53 months (mean)	2.3 %	4.6 %
Odze et al.[a]	2004	UC	34	82.1 months (mean)	2.9 %	2.9 %
Engelsgjerd et al.	1999	UC	34	42 months (mean)	0 %	2.9 %
Rubin et al.	1999	CD or UC	48	49.2 months (mean)	0 %	0 %

Adapted from [32]
DALM dysplasia associated lesion or mass, *CD* Crohn's disease, *UC* ulcerative colitis
[a]This study reports extended follow-up of the same cohort of patient's in the Englesgerd et al. study

areas of colitis and 57 % were located in areas without concurrent or prior involvement by colitis. High-grade dysplasia was present in 7 % of the polyps. During the follow-up period, one patient (2 %) developed invasive adenocarcinoma at a location distant from the polypectomy site. This patient was also noted to have flat dysplasia in her colectomy specimen. No other patients developed flat dysplasia or adenocarcinoma. However, 44 % of patients developed an additional adenoma-like DALM. The relatively high number of patients with CD that develop subsequent adenoma-like DALMs is similar to that reported in UC [37, 42]. The low incidence of subsequent adenocarcinoma and flat dysplasia reported by Quinn et al. [44] suggests that adenoma-like DALMs in CD can also be safely treated by polypectomy and continued endoscopic surveillance.

Dalms with High-Grade Dysplasia

DALMs with high-grade dysplasia can also be treated conservatively by polypectomy and endoscopic surveillance. Blonski et al. [45] reported outcomes of 9 UC patients with adenoma-like DALMs containing high-grade dysplasia treated with polypectomy and surveillance over a mean follow-up interval of 76.5 months. None of these patients developed flat dysplasia or carcinoma during the follow-up period. Other studies of DALMs in UC [36, 37, 42] and CD [44] that contained a subset of polyps with high-grade dysplasia within a larger cohort show similar good outcomes following polypectomy.

Other Polyps in IBD

Patients with IBD may develop a variety of other neoplastic and non-neoplastic polyps that must be distinguished from DALMs. These include inflammatory, serrated, mesenchymal, and lymphoid polyps. Inflammatory pseudopolyps are frequently encountered in IBD patients. These non-neoplastic polyps form when inflamed or regenerating mucosa protrudes above the surrounding mucosa. The polyps often have a glistening frond or finger-like endoscopic appearance. The histopathology of inflammatory pseudopolyps ranges from mucosa with active inflammation and ulceration to non-inflamed regenerative mucosa depending on when the lesion is sampled. In a case control study of 68 UC patients with adenocarcinoma and 136 matched controls Rutter et al. [7] reported that the presence of inflammatory pseudopolyps is associated with a 2.1-fold increase in the risk of adenocarcinoma. In a similar case control study of 188 UC patients with adenocarcinoma, Velayos et al. [46] found inflammatory pseudopolyps to be associated with a 2.5-fold increase in the risk of adenocarcinoma. Inflammatory pseudopolyps may serve as surrogate markers of significant prior inflammatory activity, which leads to an increased risk of neoplasia. However, inflammatory pseudopolyps are non-neoplastic lesions. Only rare cases of

dysplasia [47] or occult adenocarcinoma [48] in a pseudopolyp have been reported.

Benign lymphoid hyperplasia may appear as a polyp in IBD patients. This must be distinguished from lymphoma, which can present as polypoid lesions [49]. Rare benign mesenchymal polyps can also be encountered in IBD patients, including nodular neuronal hyperplasia [50] and inflammatory fibroid polyps [51–53].

Serrated polyps—hyperplastic polyps, sessile serrated adenomas/polyps (SSA/Ps), and traditional serrated adenomas—also occur in IBD patients. Histologically, hyperplasic polyps are characterized by abnormal crypts with "saw-tooth" or "star-fish" architecture without cytologic dysplasia. These polyps are more frequently small (<0.5 cm) and located in the left colon. Hyperplastic polyps in IBD patients have similar morphologic and molecular features as those occurring in patients without colitis [54]. In contrast to hyperplastic polyps, SSA/Ps are more often right-sided and larger (>0.5 cm). They exhibit architectural abnormalities including basal crypt dilation and branching due to expansion of the proliferative zone. Cytologic dysplasia can develop in SSA/Ps and is often associated with MLH1 loss and a microsatellite unstable phenotype [55]. SSA/Ps are not well studied in IBD. Srivastava et al. [56] report 3 IBD patients with numerous (>20) SSA/Ps and hyperplasic polyps, reminiscent of serrated polyposis syndrome. Two of the patients developed adenocarcinoma, suggesting that some IBD patients with a large number of SSA/Ps may be at high risk of malignancy. Solitary SSA/Ps have been reported in IBD [57]. However, a comparison of SSA/Ps in IBD patients to those arising in patients without colitis has not been performed. Similar to SSA/Ps, traditional serrated adenomas (TSAs) are established precursors in the serrated pathway or colorectal carcinogenesis. TSAs are more frequently pedunculated and left-sided. Histologically, TSAs are characterized by polypoid growth, eosinophilic cytoplasm, cytologic dysplasia, and architectural abnormalities including ectopic crypts that are not in contact with the muscularis mucosae. Although TSAs have been reported in IBD [58], it is unknown if these lesions differ from their counterparts in non-IBD patients. Serrated polyps in IBD patients may develop sporadically unrelated to colitis. However, some flat dysplasia in IBD patients exhibits a serrated phenotype. This suggests that a subset of serrated polyps may develop secondary to underlying colitis. The pathology and management of polypoid serrated lesions in IBD are poorly defined and is an area of ongoing research. Thus far, studies of adenoma-like DALMs have been limited to polyps with conventional-type dysplasia.

Conclusion

Polypoid lesions are frequently encountered during IBD surveillance colonoscopy. Accurate endoscopic and pathologic classification of these lesions is essential for appropriate management. Polypoid dysplastic lesions, historically referred to by the acronym DALM (dysplasia-associated-lesion or mass), are classified as adenoma-like (endoscopically resectable) and non-adenoma-like (non-endoscopically resectable) based on endoscopic features. Adenoma-like DALMs are a heterogenous group of polyps that include both sporadic adenomas incidentally arising in IBD-patients and polypoid IBD-associated dysplasia. Regardless of etiology, studies have demonstrated that adenoma-like DALMs can be treated conservatively with polypectomy and continued surveillance provided that the lesion is completely removed and no flat dysplasia is identified in the colon. In contrast, the presence of a non-adenoma-like DALM is an indication for colectomy.

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Endoscopic Approach to Resection of Polypoid and Non-Polypoid Dysplasia in IBD

20

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Introduction

The concept that dysplasia discovered during surveillance in patients with inflammatory bowel disease (IBD) can be treated by using endoscopic resection rather than by surgery is a new concept, which is included in the most recent practice guidelines [1, 2]. Although endoscopists have reported good outcomes of resection of polypoid lesions since the 1990s, only recently has this concept been accepted as a management strategy. The primary hesitation for accepting endoscopic resection relates to concerns about the risk of "undetected" synchronous carcinoma and the risk of "field cancerization," which the finding of a dysplasia may signify [3–5]. More recent data, as well as substantial improvements in endoscopic imaging, suggest that the risk of cancer in IBD, and "undetected" neoplasia, is generally lower than previously reported [6, 7]. The risk of cancer also remains low after polypoid dysplasia has been completely resected [8].

Critical to the concept of endoscopic resection of dysplasia in IBD is the absolute requirement for the lesion's need to be circumscribed, as seen through the endoscope, and without dysplasia in the immediate surrounding mucosa around the lesion, as proven by histology. Outcomes data after endoscopic resection of circumscribed non-polypoid lesions is currently being collected, but many expert centers now offer this resection, which is performed with close follow-up.

The management options for patients after dysplasia has been detected vary from continued surveillance without any resection, endoscopic resection, and proctocolectomy. The option is contingent on a wide range of factors including patients' preferences, co-morbidities, cancer risks, and availability of local or regional endoscopic expertise. This chapter aims to examine these factors.

Pre-Assessment

We recommend chromoendoscopy with targeted biopsy, ideally performed in conjunction with a high definition endoscopy system, for detection of dysplasia in all patients with colitic IBD [1, 2, 9–12]. High definition chromoendoscopy is associated with a two- to threefold increase in dysplasia detection on a per patient basis and a three- to fourfold

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increase on a per lesion basis [13]. As the use of chromoendoscopy becomes widespread, it can be expected that an increasing number of dysplastic lesions will be detected and resected. Guidelines from the United Kingdom, Europe, and Australia all now recommend chromoendoscopy with targeted biopsies [1, 2, 10, 11]. In North America, chromoendoscopy is a recommended option for surveillance [12].

A careful and thoughtful assessment is required to determine the need, timing, and appropriate strategy of resection when a suspected dysplastic lesion is detected during screening or surveillance of patients with colitic IBD. This assessment relates to the characteristics of the lesion, the status of the patient's disease activity, their preferences on future colorectal cancer (CRC) risk, and the morbidity and mortality of surgery, especially the quality of life post-surgery. Three main options exist:

Management Options

1. Endoscopic Resection

Endoscopic resection is appropriate for circumscribed mucosal neoplasia, especially the polypoid morphology (circumscribed Paris 0-Ip or 0-Is, previously described as adenoma like lesion [ALMs]) [9, 14]. The border of the lesion must be clearly identifiable with chromoendoscopy and biopsies from around the lesion negative for dysplasia. The risk of colorectal cancer following such a resection is estimated at five cancers (95 % CI: 3–10) per 1,000 years of patient follow-up [8]. Circumscribed non-polypoid lesions (Paris 0-II) lesions may also be safely and effectively resected endoscopically [15]; however, data on their long-term follow-up is currently lacking. The non-polypoid lesions can be more technically difficult to resect and require close colonoscopic surveillance. Endoscopic resection may be used for circumscribed polypoid and non-polypoid neoplasia containing high-grade dysplasia as long as the lesion can be completely resected and the pathology can be fully ascertained.

2. Pan-Proctocoloectomy with or Without Ileal-Anal Pouch in Patients with Ulcerative Colitis and Segmental Resection in Patients with Colonic Crohn's Disease

Surgery is appropriate for cancer or where there is a strong suspicion of cancer, a large mass lesion with high-grade dysplasia, and neoplasia with indistinct edges. It may also be an appropriate strategy for patients with poorly controlled colitis and dysplasia where the resection may offer cure for both. Note that patients with high inflammatory burden are at higher risk of dysplasia. Young patients with dysplastic lesions will have a significant lifelong burden of intensive surveillance and may also consider colectomy, as may patients whose background disease makes surveillance so difficult as to be unsafe (e.g., large numbers of post-inflammatory polyps). A segmental resection is an option for patients with limited colonic Crohn's disease, although there are studies showing a high rate of metachronous dysplasia or CRC in colectomy specimens [16], with more than a third of patients developing a metachronous colorectal cancer [17].

The approach to endoscopically invisible dysplasia—that is dysplasia not seen by an experienced endoscopist with chromoendoscopy under good surveillance conditions (excellent bowel preparation, patient in remission, ideally high definition endoscopy system)—is not the subject of this chapter; however, the risk of a surveillance strategy of invisible (termed "flat" in this chapter) low-grade dysplasia in the pre-chromoendoscopy era was 14 cancers (95 % CI 5–34) per 1,000 years patient follow-up [18]. Whether or not this risk is acceptable needs to be individualized. Endoscopically invisible high-grade dysplasia, however, appears to carry a worse prognosis and colectomy is preferred in most cases [3]. The higher grade of "endoscopically invisible" lesions detected on biopsy only is thought to represent a "field cancerization" where the entire colonic epithelium becomes genetically unstable, thus the need to remove all at-risk epithelium with colectomy. Molecular data supports this concept in some, but not all, cases [4, 5].

Table 20.1 Potential risks and benefits of endoscopic and surgical resection

	Endoscopic	Surgical
Risks of complications of resection	Low	High
Risks of future cancer	Continues	Nil in proctocelectomy
Needs of continuing surveillance	Yearly at least for 5-years post-resection	None in UC Continues in Crohn's Colitis
Potentials for bowel habit change	Nil	Significant change in patients with controlled disease

The polypoid circumscribed lesions do not appear to manifest field cancerization given the low cancer risk during follow-up [8].

Multiple dysplastic lesions have also been suggested as an indication for proctocolectomy, as they are considered evidence of field cancerization. If endoscopically invisible dysplasias were detected at multiple sites on biopsy only, most clinicians would accept this as an indication for colectomy, even if low grade. The finding of multiple circumscribed polypoid lesions should not necessarily lead to colectomy as an endoscopic resection strategy with close surveillance may equally be appropriate. Multiple sporadic circumscribed lesions are common in the general population, particularly in older age groups. Three or more adenomas were seen in 1.1 % of a bowel cancer screening population aged 55–66 years, which represented 7 % of those with any adenoma or cancer [19].

3. Clinical Observation Without Resection

This strategy might be appropriate for a patient with very significant co-morbidity and a limited life expectancy where the risks of even endoscopic resection and the burden of follow-up outweighs the likely improvements in quality and length of life that resection might offer.

IBD Multi-Disciplinary Team Meeting (IBD MDT)

The decision making for patients with IBD and dysplasia is complex and the stakes are high. Many centers, including ours at the University of Oxford, approach this complex decision by having a weekly meeting where patients with dysplasia and other complex IBD cases are discussed. Thus, the risks and benefits of the different approaches can be carefully weighed (see Table 20.1) by a team. Our team includes gastroenterologists specializing in IBD (usually the primary gastroenterologist), therapeutic endoscopists, IBD surgeons, GI pathologists, GI radiologists, IBD specialist nurses, dieticians, and trainees. The risks and benefits of each strategy can be weighed by the group and specific questions answered in a rapid and collegiate fashion, with the patient confident that all views were taken into account, rather than a specific agenda or viewpoint being served.

Lesion Assessment

Determination of Lesion Margin

Accurate assessment of the lesion margin is a critical first step. Endoscopic resection is only appropriate for lesions that have clearly defined borders; i.e., they are clearly circumscribed. For small lesions where immediate resection is often preferred, photo-documentation after chromoendoscopy, and after lesion resection, with biopsies around the resection site are appropriate. For larger lesions, where there is concern regarding high-grade dysplasia or cancer and the dysplastic nature of the lesion needs to be confirmed, a single biopsy of the lesion itself would ideally be taken to avoid "welding" the lesion to the submucosa even further due to biopsy-associated fibrosis. This should be taken from the most suspicious area of the lesion such as a depression or an area with loss of pit pattern (see later). The

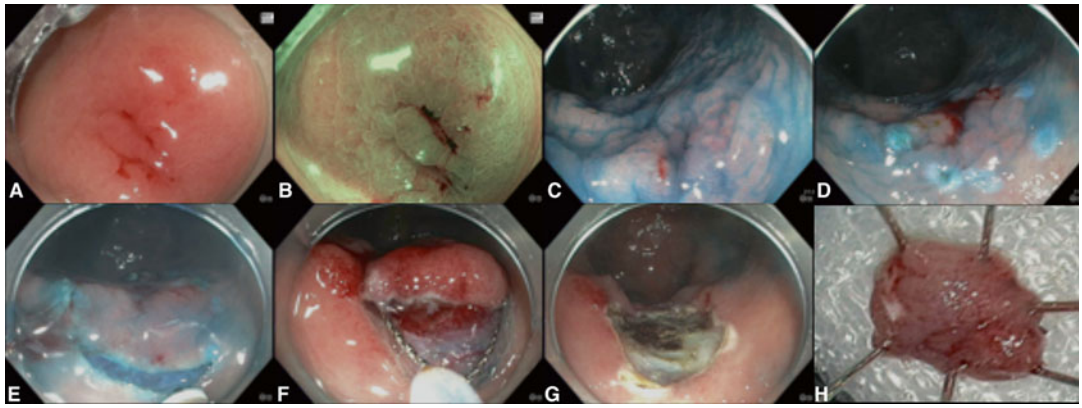

Fig. 20.1 The resection of a superficial flat (Paris 0-IIb) lesion can be challenging. (**a**) The lesion was detected because of its reddish appearance. The spontaneously bleeding site was the site of prior biopsy, which showed low-grade dysplasia (LGD). (**b**) The neoplasm appeared slightly more brownish under Narrow Band Imaging (NBI). Note, however, that NBI is not beneficial to detect the nonpolypoid colorectal neoplasms in patients with inflammatory bowel disease. Pit-pattern analysis under NBI or indigo carmine is also not useful to differentiate neoplastic and non-neoplastic. (**c**) The circumscribed edge of the lesion is well seen with chromoendoscopy. (**d**) Periphery of the lesion was marked prior to submucosal injection. (**e**) Circumferential incision was performed using the Dual Knife. (**f**) The isolated lesion was resected using a snare. (**g**) The site of resection. (**h**) The resected specimen. The pathology showed low-grade dysplasia

endoscopist who found the lesion should provide photo-documentation and pathology results. Image-enhanced endoscopy using chromoendoscopy or other techniques are typically necessary in order to visualize and confirm that the lesion is circumscribed (Fig. 20.1a–c). Even if a clear border can be seen, it is appropriate to take biopsies around the resected site or the lesion when the lesion is discovered to look for endoscopically invisible dysplasia.

Assessment of Potential Invasion

Accurate assessment of the potential for invasive cancer follows the assessment of lesion margin. The lesion should be carefully examined once completely clear of stool and mucus. Typically, a higher concentration of dye for chromoendoscopy is used in order to improve visualization of subtle changes [20], which may indicate the presence of invasive cancer: a large nodule, a depression, loss of pit pattern (Kudo type V), and a mass-like appearance [21]. The presence of any of these signs is a red flag of whether endoscopic resection is appropriate. A perforation of a T1 or T2 cancer during ill-advised resection due to mistaken assessment leading to a by-definition T4 cancer is a clinical tragedy, and usually an avoidable one. Unfortunately these observations, which are reasonably reliable in non-colitic colons for experienced operators, perform less well in colitis as the scarring may lead to pseudodepression and inflammation distorts crypt openings and pit patterns. While the non-lifting sign has a good specificity for invasive cancer in non-colitic neoplasia, the non-lifting sign is often of limited value because of the sub-mucosal scarring due to chronic colitis [22].

Lesion Location in Difficult Areas of the Colon

Location of the lesion close to areas that might make resection more difficult should also be considered such as the appendix orifice, around the ileocaecal valve, at a flexure, especially on the inside of the bend, and near the dentate line [23]. Although polyps in all of these positions can be resected in non-colitis colon scan by experienced endoscopists, the technical difficulty is substantially increased. In

combination with the other difficulties that lesion in colitis represents, this may make the likelihood of a curative resection so low that an endoscopic attempt may not be appropriate.

Endoscopic Access

The final stage to consider is endoscopic access. This is one of the few areas where working in a colitic colon may have advantages as a scarred and tubular colon makes for a straight endoscope, allows accurate tip deflections, and a lack of haustral folds to be negotiated. Before starting, the endoscopist should be satisfied that he/she could easily reach all areas of the lesion with precision.

There is no specific combination of factors or scoring system that suggests whether lesions are or are not safely and effectively resectable. The risk needs to be individualized according to patients' preferences and endoscopists' skills. Ultimately it comes down to the experience and judgment of the endoscopist. Given the fine nature of these judgments, we would recommend that, if possible, the endoscopist who is going to do the resection procedure should perform the endoscopy for lesion assessment prior to resection unless excellent comprehensive images are available.

Colonic Assessment for Disease Status

It is important to consider the rest of the colon before committing to endoscopic resection of a lesion. Performing chromoendoscopy to rule out other lesions is mandatory and although it is generally assumed that the lesion is single, the referring endoscopist may not have assessed the remaining colon using chromoendoscopy. For example, a young patient with multifocal dysplasia may benefit more from surgery.

It is also important to consider the level of disease activity both past and present. Severe inflammation in the past is likely to lead to significant scarring of the submucosa. Lesions that have undergone a previous attempt at resection, recurrence on a scar from previous EMR or non-granular type laterally spreading tumor (LSTs) are examples from non-colitis resection practice that may mimic the severe scarring and increase risk of resection [24]. If the patient has a very tubular colon with evidence of scarring, post-inflammatory polyps, loss of vascular pattern even in remission, or active inflammation, the sub-mucosal scarring is likely to be severe and typically involves the entire lesion. This impedes lesion lifting and makes identification of the sub-mucosal plane difficult.

Active disease is a risk factor for future dysplasia, makes identification of other dysplastic lesions more difficult, and makes edges more difficult to detect. If at all possible, resection should be undertaken in remission and strenuous efforts to achieve this should be made. If reasonable remission cannot be achieved even for a short time, the decision that endoscopic resection was more appropriate than colectomy should perhaps be revisited.

Co-morbidity

As well as taking into account a patient's wishes regarding colectomy and cancer risk, the endoscopist also needs to weigh the patient's co-morbidities and lesion difficulty against the likely outcome of a perforation, and severe bleeding. Although co-morbidities may preclude surgery, careful thought is needed as to whether a difficult endoscopic attempt at resection, for a low-risk lesion, in a patient with severe co-morbidities is really likely to extend or improve the quality of their life. Such an attempt may, in fact, reduce it. The best option may be masterly inactivity. The decision may need to be made to terminate a resection even during the resection if the risk seems to be increasing.

Endoscopic Resection

Lesions that lie outside the colitis segment, as assessed both endoscopically and histologically, can be viewed as sporadic lesions and approached with standard techniques. Here we consider dysplasia as neoplasia occurring within the colitis segment.

There are three key principles to be considered for endoscopic resection in colitis:

1. The patient's colitis should be in remission.
2. Confirm the lesion is circumscribed with no surrounding dysplasia using dye-spray and margin biopsies.
3. Aim for en bloc resection where possible, which may involve en bloc endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or local surgical excision (TEM or laparoscopic disc excision).

Small Lesions ≤ 10 mm

In general small dysplastic appearing lesions, either polypoid (Paris classification 0-Is or Ip) or non-polypoid (Paris 0-IIa, IIb or IIc), within the segment of colitis can be endoscopically resected at the time of detection, but after assessment of the border and extent with chromoendoscopy. Care should be taken to ensure complete excision. EMR can be very useful to resect small non-polypoid lesions en bloc, although the stiffer mucosa of colitis might make resection more difficult. A digital image of the lesion pre-resection with dye-spray, and biopsies from around the lesion are very helpful when discussing the patient's case subsequently in the IBD MDT.

Larger Lesions > 10 mm

Larger polypoid and non-polypoid, including the laterally spreading tumours (LSTs), are more complex to resect. The risk of residual dysplasia after the resection of non-polypoid lesions is probably higher [25] as in the large non-colitic tumors. The risks and benefits of en bloc versus piecemeal resection need to be carefully balanced. In our experience, the non-polypoid lesions can be very challenging to capture with a snare.

Seeing the edge of lesions once resection has started can be especially challenging in colitis. Although marking is not usually used even for ESD in the lower GI tract, lesions in colitis have some similarities in their subtle appearance to early gastric cancer where marking prior to resection is routine. Endoscopists may therefore choose to use the snare tip to mark the edges of the lesion with cautery "dots" prior to resection to ensure all dysplastic mucosa is resected (Fig. 20.1d).

Lifting

Lifting or the failure of lifting of lesions in colitis is one of the major obstacles to safe and comprehensive resection. This leads to problems with lesion assessment for invasion as outlined previously, but more importantly means that the lesion cannot be safely lifted away from the underlying muscularis propria to allow a safe plane for the snare or endoscopic knife to traverse. Scarring of the submucosa leads to difficulty in finding the submucosal plane, a failure to lift, a "diffuse" lift where fluid tracks laterally rather than resulting in focal elevation, and a rapid loss of any lift achieved. Techniques to counter these problem include the use of dynamic injection technique [26], the use of thinner bore injection needles, 25 gauge rather than 21G or 23G, to help find the submucosal plane, and the use of more viscous and longer lasting injection solutions including colloids—e.g., succinylated gelatine (Braun Medical, Bethlehem PA, USA)—for which there is some evidence of improved performance at EMR in non-colitic colons [27], or sodium hyaluronate, which has been popularized in ESD and provides a very long-lasting lift. Other viscous solutions—e.g., hypromellose or glycerol—might also be considered [28]. Nevertheless, even with the use of these technique and injectants, the submucosal lift can be quite limited. All such solutions are currently not approved by the U.S. Food and Drug Administration for this indication.

Snares

Standard snares can be used for EMR in colitis; however, as alluded to previously, scarred, flat lesions with poor lift can be very difficult to engage into the snare. Furthermore, if a large

piece is successfully engaged there is a risk that the scarring will pull up an area of underlying muscle, leading to damage to the muscularis propria "target sign" or a full thickness perforation [29]. Perforations can be especially difficult to close in scarred mucosa. In order to improve snare grip, braided or spiral snares may be used, which have an additional spiral wire around the main snare cable to improve gripping (Spiral snare 20 mm, SnareMaster, Olympus, Tokyo). An alternative is the flat band or "ribbon" snare (Flat ribbon snare 22 mm, Resection Master, Medwork, Höchstadt, Germany). This comprises a flat band of metal to make the snare loop with the edge of the band orientated vertically to the mucosa. This snare cuts into and grips the mucosa more effectively than standard braided snares, but seems to have less hemostatic capacity. An alternative is to use a smaller braided snare to resect small pieces at a time, reducing the risk that too much mucosa is gathered with associated muscle as one might do for a scarred lesion in non-colitic colons. A final option is the use of a double channel endoscope using a grasper to pull mucosa into a snare, which is in the other channel. Although this technique guarantees the ability to grip mucosa, the risk of perforation is significantly magnified, and experience and extreme care are needed.

En Bloc Resection

Given the difficulties described previously in lesion assessment pre-resection and the need to avoid residual dysplasia or recurrence, en bloc resection of the lesion is preferable to allow precise pathological assessment. ESD offers this possibility and is technically possible in colitis; however, the significant submucosal fibrosis makes ESD extraordinarily challenging, increases the risk, and reduces R0 resection rates even for experts in ESD. Use of small-caliber-tip transparent hoods to facilitate submucosal tunneling can help in severe fibrosis and there is often a need to use sharp-tipped needle knives to cut fibrotic bands; however, use of the hood increases the bleeding risk because it limits the ability to apply hemostatic accessory [30]. The use of ESD in colitis should be limited to those with extensive experience of ESD in scarred lesions.

Other concepts of ESD may be helpful to endoscopists who are not super-specialized ESD practitioners [31]. The EMR with small incision technique can be useful to resect lesions up to 20 mm where submucosal scarring is mild and some lift is possible. Following lifting, the snare tip is used to make a small incision on the oral side of the lesion. This small hole is used to anchor the snare tip to allow definite edge capture and additional downward pressure with the snare in a situation of limited lift, increasing the chances on an en bloc snare resection. The hybrid ESD technique is another potentially applicable technique. Here, after circumferential incision around the lesion with an ESD knife, a snare is placed in the incision and the lesion resected with standard polypectomy technique. The hybrid technique allows the snare to be placed in the marginal groove, thus allowing the lesion to be captured by the snare. In colitis, once resection starts, the lesion margin can be difficult to see, so marginal incision can assist here as well. The "hybrid" ESD can provide a good compromise between the time, risk and difficulty of full ESD, with the need to get a grip on the lesion and a clear margin (Fig. 20.1d–g).

Ablation

The optimum technique to remove dysplasia is en bloc resection using an EMR or ESD technique in order to provide cure and accurate pathological assessment. Use of ablation should be minimized. However, en bloc resection in colitic IBD is often not feasible and piecemeal resection occurs with fragments or islands of dysplasia left at the resection site, often at points of maximal scarring. These areas need to be definitively but safely destroyed. Avulsion of remnant tissue with biopsy forceps is one method to address this challenge. Argon plasma coagulation (APC) has been commonly used for this, with some evidence from the EMR literature that it is effective in reducing recurrence [32]. Precise use of short

pulses of APC can be effective even for larger areas of dysplasia. Further attempts at injection before use of APC may allow the so-called "melt effect" seen with the use of APC for dysplasia ablation in the duodenum [33]. For small fragments the use of the tip of the snare with "soft coagulation" current settings allows effective ablation without over-delivery of energy and risks of a deep mucosal burn.

Post-Resection

For larger lesions not in areas where colonic landmarks are definitive—i.e., not within the cecal pole or within 20 cm of the anal verge—placement of a tattoo may be helpful to aid future localization of the scar, especially on a colitic background that may already be scarred. Injection of carbon particles (Spot, GI Supply, Camp Hill, PA, USA) for tattoo should ideally be placed 2–3 cm away from the lesion to avoid submucosal fibrosis induced by the material. Unfortunately, due to poor lift, tattoos can be rather diffuse and difficult to see. After dye-spray they can even be more difficult to detect. Therefore, we recommended to look for scar sites and their associated tattoos during intubation and assess them then before performing dye-spray to look at the rest of the colon.

Following resection, which should be as complete as possible at the first attempt, careful examination of the scar should be performed at 2–6 months. The use of dye-spray and advanced imaging on the scar can be helpful here to try and detect tiny areas of recurrence. Scar biopsy should be routinely performed even if no recurrence is seen. If recurrence is suspected, and the threshold should be very low, a biopsy of the site followed by the aforementioned ablation methods is appropriate, with a further examination in 2–6 months. Repeated recurrence despite appropriate ablation, high-grade dysplasia in recurrence biopsies, or a large area of recurrence should prompt consideration of surgical resection or ESD salvage. After a complete resection, yearly follow-up for 5 years is recommended.

Team for Endoscopic Resection of Dysplasia in IBD

Endoscopist

For more advanced lesions, those >10 mm especially if non-polypoid, the endoscopist should be an experienced therapeutic endoscopist familiar with surveillance in IBD patients. They should also be experienced with tertiary level endoscopic mucosal resection and/or endoscopic submucosal dissection techniques. Often these endoscopists may have a regional referral practice for large or complex EMR in non-colitic patients. They should be familiar with en bloc resection even for larger lesions and specific techniques (described previously) to facilitate this.

The endoscopist will require extra time on the list to perform these cases, which should not be scheduled as a "standard case" even if within easy endoscopic access; e.g., in the rectum.

Many, if not most larger lesions, will not be suitable for non-sub-specialist endoscopists. Referral to an endoscopic sub-specialist colleague should not be considered a professional failure by the referring endoscopist, but should perhaps be viewed as a "surgical" referral where the referring endoscopist has achieved a difficult diagnostic process and now hands over for specialist resection. This change in mindset is critical if the endoscopic community is to resect larger lesions in colitis comprehensively and safely.

Endoscopy Assistants

The endoscopy assistants supporting the endoscopist need to be experienced in tertiary endoscopic resection with excellent ability to anticipate during the procedure and a deep familiarly with the full range of accessories and equipment needed. An extra team member can be helpful during larger and/or more complex resection, and all should be familiar with working with the endoscopist.

Surgical Backup

A close working relationship with surgical colleagues who have a special interest in IBD surgery in order to provide immediate surgical backup is desirable. The most optimal backup is

with the surgical team who agreed to the approach discussed during the IBD MDT.

Pathologist

Experienced GI pathologists are often necessary to assess dysplastic lesions, as a second opinion on a dysplastic lesion is often sought [12]. There should be clear communication between pathologist and endoscopist about the resection location, techniques, piecemeal or en bloc, specimen recovery and surrounding biopsies. A copy of the endoscopy report with associated images can be helpful. Pinning a lesion resected en bloc out on a board can assist the pathologist, especially when assessing lesion edges, and is recommended (Fig. 20.1h). Getting multiple specimens in the correct container for pathology during a high-risk resection can be a challenge for endoscopy assistants, particularly if there are multiple lesions.

Conclusion

Endoscopic resection of dysplasia is now an accepted management strategy and is increasingly performed for polypoid and nonpolypoid tumors, respectively. The snaring of the lesion is perhaps the simplest part of the process. The more complex part is actually taking into consideration the patient as a whole and their lifetime journey with IBD. It is crucial to ensure that decisions are made with the patient in mind in order to optimize their quality of life and minimize risk in the long term. Effective multidisciplinary approach and advanced endoscopic skills and judgement are imperative.

Key Questions for Future Research

- What is the future cancer risk after resection of non-polypoid dysplasia in inflammatory bowel disease?
- Is en bloc resection necessary for safe management of non-polypoid dysplasia in inflammatory bowel disease?
- What are the risks of complications of advanced endoscopic resection of non-polypoid dysplasia in inflammatory bowel disease?
- Is local surgical resection, either by transanal methods for rectal lesions (transanal endoscopic microsurgery [TEMS]), or laparoscopic disc excision equally valid alternative for lesions that are deemed not endoscopically resectable or where there is a lack of local expertise? If we accept the premise that circumscribed lesions may be locally resected and followed up, then can the resection be performed surgically? This has previously been an anathema to the approach to dysplasia in IBD but is a logical extension of arguments for local resection [34].

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Additional Resources

- Chromoendoscopy in IBD - English. ASGE GI Endoscopy http://www.youtube.com/watch?v=OARkbgwlObI&list=PL4478703E5AABA0C4
- Chromoendoscopy in IBD - Spanish. ASGE GI Endoscopy http://www.youtube.com/watch?v=NjN66JOsNWk&list=PL4478703E5AABA0C4

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Part VIII

Treatment of Complications

Endoscopic Treatment of Complications of Inflammatory Bowel Diseases

21

Siddharth Singh and Todd H. Baron Sr.

Introduction

The incidence and prevalence of inflammatory bowel diseases (IBD) is estimated at 37–39 cases per 100,000 person years and 468–827 cases per 100,000 persons in Western countries, respectively, and appears to be rising globally.[1] While ulcerative colitis (UC) is primarily a mucosal process restricted to the colon, Crohn's disease (CD) is a pan-enteric process, characterized by patchy and transmural inflammation. Phenotypically, CD is classified into three categories according to the Montreal classification: non-stricturing/non-penetrating (pure inflammatory), stricturing and penetrating, or fistulizing. At diagnosis, most CD patients present with predominantly inflammatory pathology; in population-based cohorts, only 19–36 % of incident CD patients had complications such as strictures and fistulae. Over time, the disease phenotype typically evolves from an inflammatory to stricturing and penetrating disease; cumulative rates of progression range from 48–52 % at 5 years and 69–70 % at 10 years after diagnosis, with approximately half of the patients developing a stricture.[2]

Despite advancement in medical management of CD, development of stricturing and penetrating CD has conventionally required surgical intervention. The cumulative risk of surgery in patients with CD at 1, 5 and 10 years is estimated at 16.3 %, 33.3 % and 46.6 %, respectively, based on a recent systematic review of population-based studies.[3] Surgical therapy, although effective for treatment of stricturing and penetrating CD, is invasive and has inherent risks of operative complications as well as long-term sequelae (particularly, if repeated respective surgeries are required). In a systematic review, Yamamoto and colleagues noted a 4 % rate of post-IBD septic events after stricturoplasty, including leaks, fistulae and abscesses.[4] Surgery is rarely curative, and most patients will develop endoscopic, clinical and surgical recurrence on follow-up. Endoscopic recurrence typically occurs just proximal to the anastomosis and is reported in 54 % of patients at 5 years and 75 % of patients by 10 years in population-based cohorts.[5] Clinical recurrence follows endoscopic recurrence, and is reported in up to 28–45 % and 36–61 % of patients by 5 and 10 years, respectively.

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Endoscopy has evolved from its diagnostic role in IBD as a therapeutic alternative to surgery, and as a supplementary tool to medical therapy in some instances. In this chapter, we will discuss the role of therapeutic endoscopy in IBD for strictures (IBD-related and anastomotic), fistulizing CD, IBD-associated gastrointestinal bleeding and colitis-associated colorectal cancer.

Endoscopic Management of IBD-related Strictures

Strictures in CD occur as a result of chronic severe inflammation and resultant attempts to repair tissue damage by intestinal mesenchymal cells with release of several profibrotic mediators. Early during the disease course strictures are primarily inflammatory (associated with significant tissue edema) and are responsive to immunosuppressive therapy. However, over time they evolve into a predominantly fibrostenotic process for which medical management is not effective (Fig. 21.1). Most patients present with obstructive symptoms. Imaging using computed tomography (CT) or magnetic resonance enterography (MRE) can help evaluate strictures. While imaging cannot definitively differentiate inflammatory and fibrostenotic strictures, certain features (absence of active inflammation and presence of pre-stenotic dilation) can suggest fibrostenotic disease. Several classification systems have been proposed for classification of CD-strictures based on etiology (primary versus anastomotic; benign versus malignant), number (single versus multiple), degree (high-grade versus low-grade), length (short <5 cm versus long >5 cm) and location.[6] The frequency and location of de novo strictures resembles the distribution of inflammation: 40–55 % terminal ileum and colon, 15–25 % colon alone, 25–40 % exclusively ileum and up to 10 % in the upper gastrointestinal tract. Strictures are uncommon in ulcerative colitis (UC)—in fact, presence of colonic strictures in a patient with UC should raise a strong suspicion of colorectal cancer.[7] Initial evaluation of all IBD-related strictures involves endoscopic evaluation with biopsy (or brushings) to rule out malignancy. Once a benign IBD-related stricture is confirmed, there are several endoscopic therapeutic interventions that can be considered. The approach to endoscopic management of IBD-related strictures is shown in Fig. 21.2.

Endoscopic Balloon Dilation

Stricture dilation using a through-the-scope (TTS) balloon dilator may be an alternative to surgery for patients with CD-related benign, pan-enteric

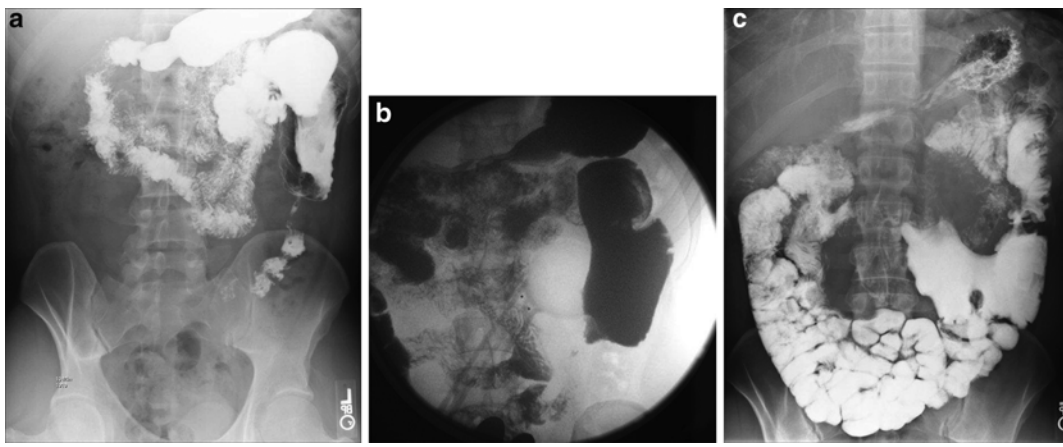

Fig. 21.1 (**a**, **b**, **c**) High-grade jejunal strictures resulting in markedly dilated proximal jejunal loops. Length of stricture/multiple strictures and degree of upstream dilation and damage make surgery a much better option than endoscopic therapy in this patient.

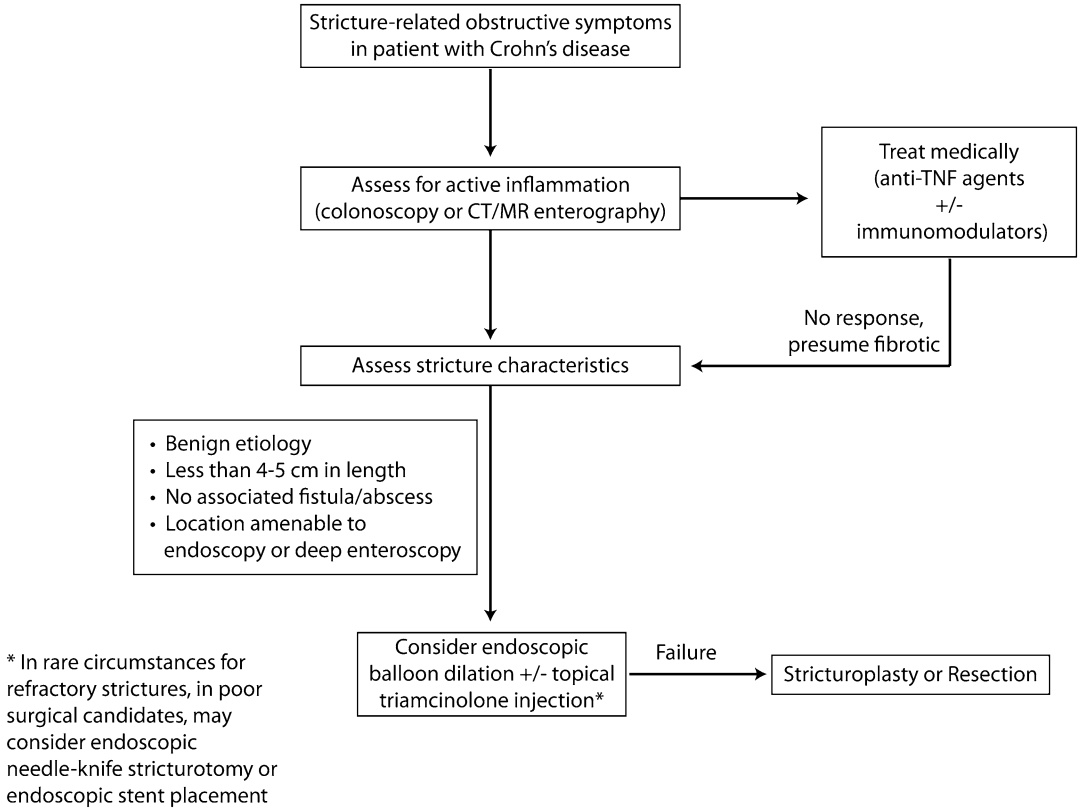

Fig. 21.2 Approach to endoscopic management of IBD-related strictures.

strictures. Typically, this is reserved for patients with short (<4–5 cm), symptomatic (obstructive symptoms), predominantly fibrostenotic or anastomotic strictures, without associated fistulous tracts or abscesses.[8] Hence, initial evaluation should focus on assessing the presence of active inflammation contributing to narrowing of luminal diameter—reduction of transmural edema using anti-inflammatory therapy can significantly increase luminal cross-sectional area and result in marked improvement in obstructive symptoms, obviating stricture dilation. Balloon dilation has also been used for pouch-related strictures after ileal pouch anal anastomosis in UC.[9]

There is no uniform technique of TTS balloon dilation of IBD strictures, but generally follows the same principle of any benign stricture dilation throughout the intestinal tract.[10] Bowel preparation and sedation is the same as for a normal colonoscopy, and periprocedural antibiotics are not required. It is advisable to use balloons 5–8 cm in length to decrease the risk of displacement during insufflation. The balloon is gradually introduced into the stricture, under direct visualization, with or without a guidewire (Fig. 21.3) (Video 21.1). Subsequently, graded dilation using multistep balloons is performed, using water to fill to recommended ideal pressure. Protocols are variable with regard to time of dilation (1–4 min) and frequency of dilation (1–6 times/session). There are no set standards for use of wire-guided versus non-wire guided dilation and use of fluoroscopy. When feasible, retrograde dilation with passage of scope beyond the stricture and working backward is preferred over blind antegrade dilation, to minimize risk of adverse events. Wire-guided stricture dilation is typically used for angulated strictures or tight strictures, through which a scope is not able to pass (Fig. 21.4) (Video 21.2). For small bowel-strictures, deep enteroscopy using balloon-assisted endoscopy has been used to perform

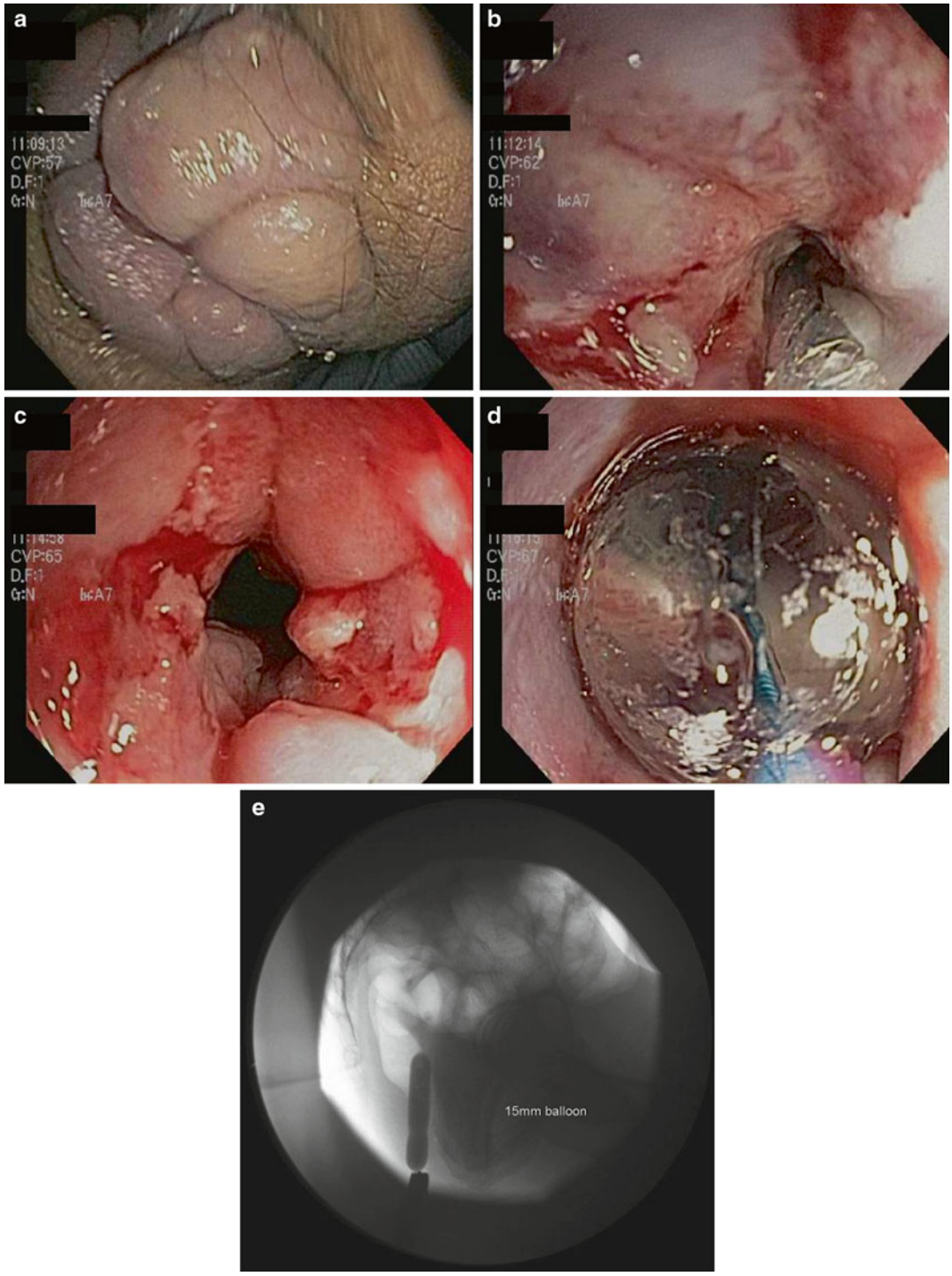

Fig. 21.3 (**a**, **b**, **c**, **d**) High-grade anal stenosis in patient with additional anastomotic Crohn's. (**e**) Anal canal dilated to 15 mm using CRE balloon. Note huge hemorrhoids. Accompanying Video 21.1 demonstrates spontaneous drainage of perirectal abscess following balloon deflation.

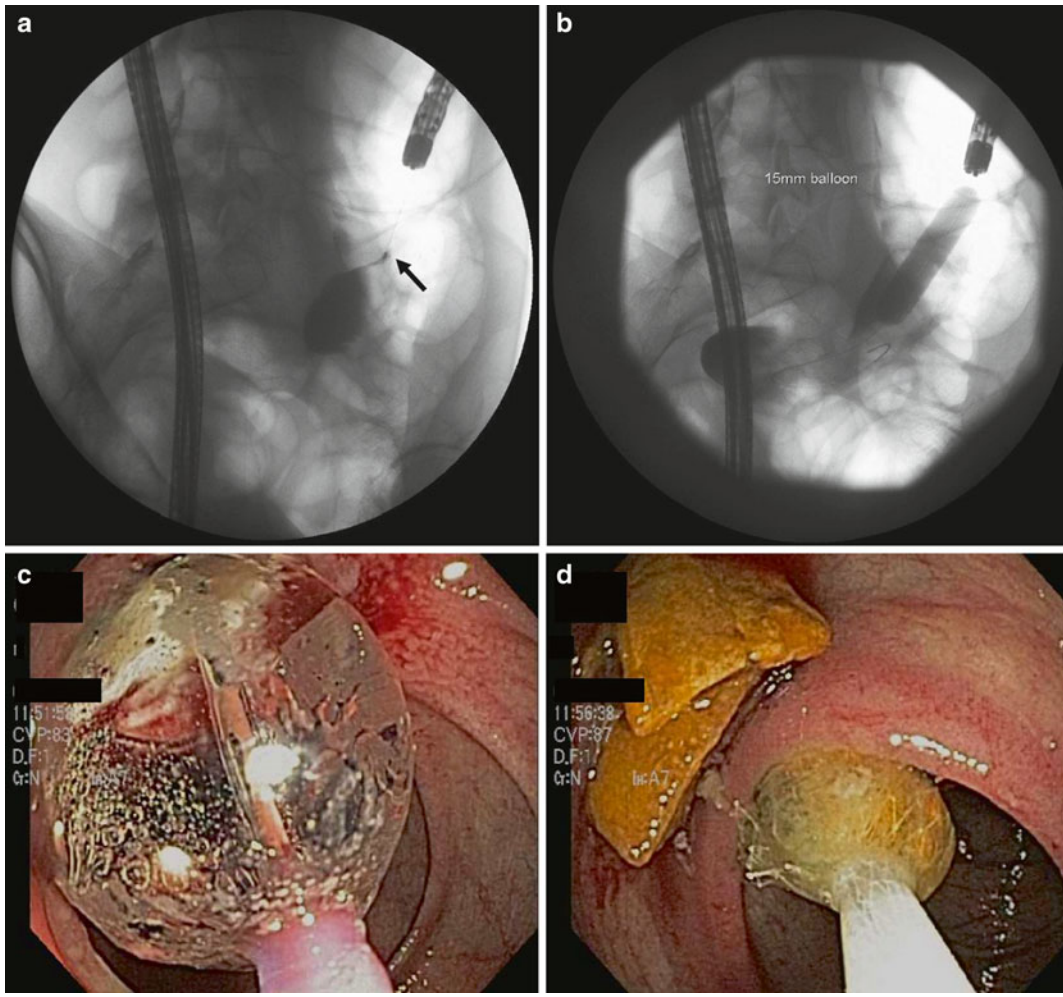

Fig. 21.4 (**a**) Tight anastomotic stricture in an end-to-side ileocolonic anastomosis (*arrow*). (**b**) Contrast injection beyond stricture dilated with 12–15 mm CRE balloon. Accompanying Video 21.2 demonstrates second stricture that was dilated 12–13.5 mm followed by removal of upstream enteroliths (**c**, **d**).

TTS stricture dilation. In a systematic review of 13 studies in 347 patients with CD-related strictures who underwent pneumatic dilation, the technique varied widely across studies with regard to balloon size (maximum, 18–25 mm in studies), use of graded dilation (used in 8/13 studies), duration of balloon dilation (<1 minute to >3 minutes), number of dilations/session (1–4), and number of sessions per patient (average, 2.2/patient).[11]

The technical feasibility and efficacy of dilation is also variable. On systematic review of fibrostenotic CD in 347 patients in 13 studies (mean age, 54 years; 54 % female; mean time from CD diagnosis to development of stricture, 13 years; mean stricture length, 2.7 cm, range, 0.5–20 cm, with 65 % being <3 cm and 84 % being <5 cm), balloon dilation could be accomplished in 86 % (range, 45–100 % in individual studies) of patients.[11] In others, TTS dilation was technically unsuccessful due to inability to reach the stricture with the endoscope or in passing the balloon through an angulated stenosis; 89 % of these patients underwent surgery. Short-term technical success was achieved

in 71–100 % of patients. At mean follow-up of 33 months, long-term clinical efficacy (defined as surgery-free at end of follow-up) was achieved in 58 % of patients (68 % of those in whom dilation was technically feasible), ranging from 50–100 % in individual studies. Approximately 59 % of the responders avoided surgery until the end of follow-up after a single session, 22 % required two sessions, whilst the remaining 19 % required more than two dilatations, ranging from 3 to 18. Surgery was ultimately necessary in 144 (42 %) patients. The mean interval between endoscopic dilatation and surgery was 15 months (range, 1–70 months). Subsequently, in a large series of 138 patients with fibrostenotic CD who underwent 237 dilations (mean age, 51 years; 56 % female; 84 % anastomotic; all strictures <5 cm in length), technical success (defined as ability to pass an adult colonoscope through the stricture after dilatation) was accomplished in 97 %.[12] After a median follow-up of 5.8 years (interquartile range, 3.0–8.4y), 44 % did not require any additional procedures until end of follow-up (dilation- and surgery-free); recurrent obstructive symptoms after the first dilation led to repeat dilatation in 46 % or surgery in 24 %, with a median time to next procedure of 12.5 months (IQR, 6–21.5 m). In another series of 776 dilations in 178 patients of whom 75 patients had >5 year follow-up, cumulative risk of surgery after dilation was 13 % and 36 % at 1 year and 5 years after dilation.[13] In an observational study of 167 patients with ileal pouch strictures who underwent stricturoplasty (10 %) or endoscopic balloon dilation (90 %), there were similar rates of stricture recurrence (56.3 % versus 55.0 %, respectively) after a mean follow-up of 4.1 years, although the response was more durable with stricturoplasty.[14] Factors influencing outcome after endoscopic balloon dilation in fibrostenotic CD are largely unknown. Technically successful dilation, stricture length of 4 cm or less and the absence of ulcer in the stricture have been positively associated with successful dilatation.[8] The data on smoking are inconsistent. In contrast, C-reactive protein, endoscopic disease activity or medical treatment after dilation, seem to influence the subsequent disease course.

Some investigators have advocated intralesional steroid injection after dilation, based on retrospective observational studies (Fig. 21.5). This technique has been used with success in other stricturing gastrointestinal conditions such as peptic, corrosive or anastomotic strictures or fibrosis post-radiotherapy. However, findings from two randomized controlled trials (RCTs) have been conflicting. In an RCT of 29 pediatric patients with fibrostenotic CD, Di Nardo et al. observed that only 1/15 patients with intramucosal triamcinolone injection (40 mg, 4-quadrant injection at 2-cm intervals) required redilation (0/15 required surgery) as compared to 5/14 receiving placebo (4/14 required surgery).[15] The time to redilation was also longer in patients who received steroid injection (steroid versus placebo, median: 11.7 versus 9.4 months). However, contradictory results were observed in another RCT of 13 adult patients with fibrostenotic CD.[16] Five (out of 7) steroid-treated patients required re-dilation, as compared to 1/6 placebo-treated patients. However, all these patients had long-standing (8–30 years), anastomotic strictures. Hence, additional studies are warranted before intralesional steroid injection after balloon dilation can be routinely recommended for patients with fibrostenotic CD. Small, uncontrolled, case series have also suggested that intra-lesional injection of infliximab may be considered for refractory strictures with limited success, although this data is hard to interpret.[17]

Endoscopic balloon dilation is generally safe, but the risk of adverse events is higher than conventionally reported in the general population. In the same systematic review, serious adverse events (defined as bleeding, perforation, infection or other event leading to hospitalization) were observed in 14/695 dilations (rate, 2 % per dilation; 4 % per patient), with perforation rate of 1.9 % per dilation.[11] In another series of 237 dilations in 138 patients, 12 serious adverse events (6 perforations) were observed (rate, 5.1 % per dilation; 8.7 % per patient); all 6 patients with perforation required surgery. In another series of 178 patients who underwent 776 dilations, overall adverse event rate per procedure was 5.3 %, including perforation rate of 1.4 % and major bleeding requiring blood transfusion rate of 1.0 %; there was no procedure-related mortality.[13]

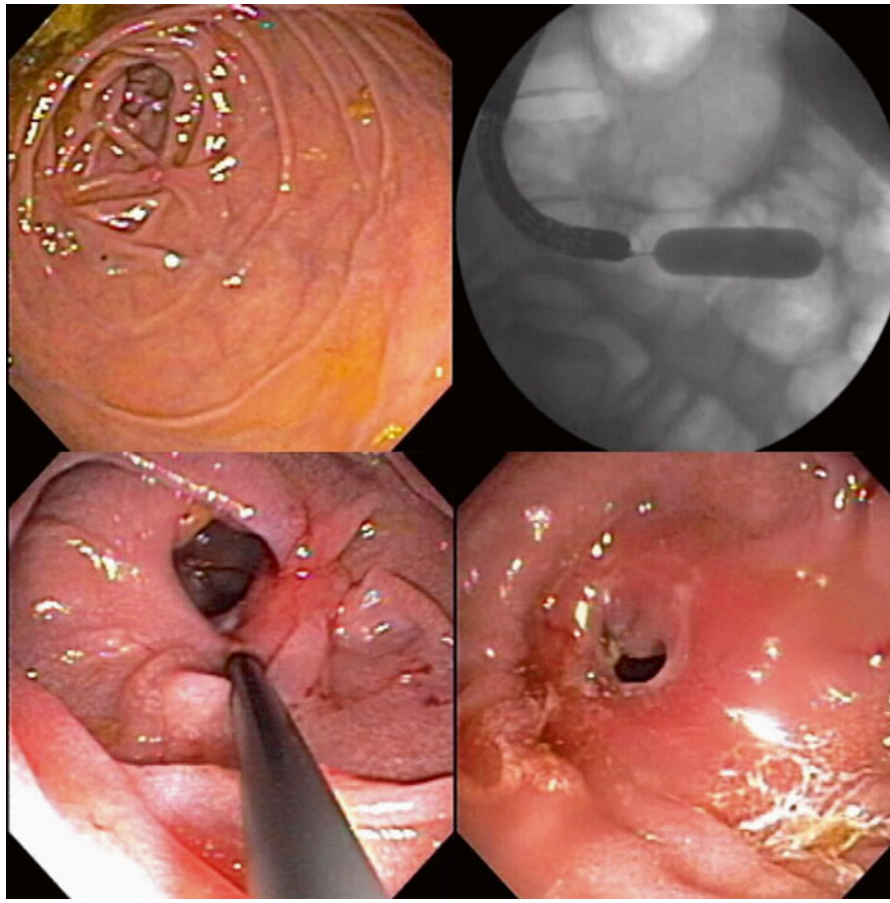

Fig. 21.5 Steroid injection into tight anastomotic stricture following balloon dilation.

Endoscopic Needle-Knife Stricturotomy

Electroincision using a needle-knife has been conventionally used for precut sphincterotomy in patients with difficult biliary cannulation during endoscopic retrograde cholangiopancreatography (ERCP). It has also been used for refractory esophagogastric anastomotic strictures before balloon dilation [18] and in congenital pylori stenosis.[19] In a recent study from Cleveland Clinic, endoscopic needle-knife stricturotomy has been performed for ileocolonic and ileal pouch strictures, in patients with fibrotic strictures refractory to repeat balloon dilation.[20] The technique involves use of a TTS catheter-based Doppler ultrasound probe to localize low-flow areas within the stricture. Then, an ERCP sphincterotome is used to dissect the fibrotic stricture, avoiding areas of high vascularity. This technique has been useful, in highly specialized centers, for strictures requiring repeated balloon dilation, with acceptable rates of adverse events.

Endoscopic Stent Placement

In patients with fibrostenotic CD or with anastomotic strictures, self-expanding metal stents (SEMS) have been used with limited success (Fig. 21.6a). In a series of 17 patients with fibrostenotic CD, 25 stents (21 fully covered SEMS, four partially covered SEMS) were placed in strictures 2–6 cm in length, after failure of repeated endoscopic balloon dilation, and were kept in place for 28 days (range, 1–112 days).[21] SEMS

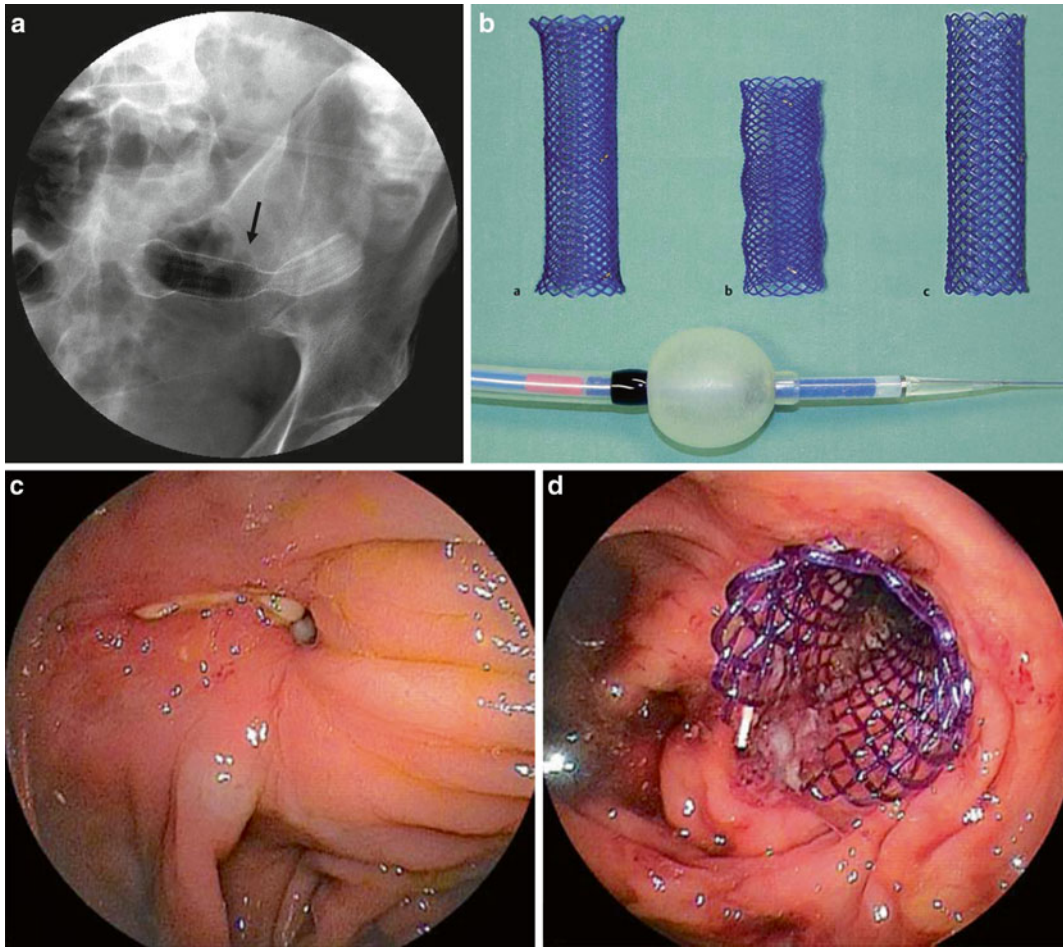

Fig. 21.6 (**a**) *Arrow* demonstrates partially covered Ultraflex placement in patient with high-grade Crohn's stricture. Prosthesis migrated at 10 days upon stricture resolution. (**b**) Variable design biodegradable stents woven from polydioxanone filament. (**c**, **d**) Note delivery system and placement across a high-grade anastomotic stricture. (Images reprinted with permission from Rejchrt S, Kopacova M, Brozik J, Bures J. Biodegradable stents for the treatment of benign stenoses of the small and large intestines. Endoscopy. 2011 Oct;43(10):911-7.)

placement was technically successful in 16/17 patients. After a mean follow-up of ~16 months, the treatment was successful (symptom-free at end of follow-up) in 65 % of patients. The recurrence rate after the therapy in patients with technical success was 44 %, after a mean follow-up of 14 months (range, 3–30 months). While there were no immediate adverse events of bleeding or perforation, four patients developed stent impaction with difficulty in stent removal not unexpectedly with partially covered SEMS. Thirteen of the 25 stents (52 %) spontaneously migrated distally primarily due to resolution of the underlying stenosis, and hence, may not be considered a procedural adverse event. In another French series, SEMS placement was attempted in 11 patients, with technical success in 10 patients.[22] Of these, 60 % had improvement in obstructive symptoms; however, two patients required surgery to address adverse events related to stent placement. Development of an anti-migratory system within the stent may decrease risk of migration; these stents do, however, require removal after intended utility.[23] The use of endoscopic suturing devices to anchor stents in place has not been studied for CD-related strictures.

To overcome the adverse event of stent migration and removal after intended use, biodegradable stents, made of various synthetic polymers, such as polylactide or polyglycolide, or co-polymers, such as polydioxanone, have been developed (Fig. 21.6b, c). These stents are deployed with guidewire assistance through an overtube, and have an average 4-month stent degradation period. Though conceptually appealing, these stents have had limited use in CD; of 11 patients in which this was tried, 7 were symptom-free at end of median 17 month follow-up; 3 patients experienced early stent migration.[24] However, the need to deliver this stent through an overtube using a special introduction system limits its utility in proximal stricturing CD.

Endoscopic Management of IBD-Related Fistula

Transmural inflammation in CD results in penetrating complications, such as intra-abdominal and perianal abscesses, as well as fistulae. Fistulous tracts in CD can form between the intestine and skin (enterocutaneous fistula), bladder (enterovesical fistula), vagina (enterovaginal fistula), or between two loops of bowel (enteroenteric fistula). Perianal disease with abscess, fissures and fistulae develops in 20–40 % of patients with CD, and is a most disabling and embarrassing complication for the patient.[2] Clinically, patients may present with drainage from perianal or cutaneous openings, anal discomfort, air or stool passage through the vagina or bladder, or recurrent urinary tract infections, depending on type of fistulae. Evaluation of fistulae, in particular perianal CD, often requires an exam under anesthesia, combined with MR imaging of the pelvis or endoscopic ultrasound. Medical management of fistulae in CD is not very effective; while anti-tumor necrosis factor (TNF) agents may be helpful in treatment of penetrating CD, the overall success rate is limited. Surgery is often required, involving either resection in case of internal fistulae or placement of draining setons (in case of perianal fistulae), in conjunction with medical management. Endoscopic interventions with injection of various substances have been attempted in management of fistulae in patients with CD, with variable and often limited efficacy.

Injection of fibrin glue in the fistula tract is one such option (Fig. 21.7). Fibrin glue, composed of fibrinogen and thrombin, which when mixed during injection into the fistula tract, form a fibrin clot that seals the tract. Such a clot is thought to enhance wound healing by promoting hemostasis and angiogenesis while acting as a scaffold for fibroblast ingrowth and the deposition of a healing collagen framework. In a short-term multicenter RCT of fibrin glue injection in 77 patients with perianal CD, clinical remission (absence of purulence with gentle compression) was achieved in 38 % of patients who received fibrin glue, as compared to 16 % in the observation group at 8 weeks; at week 16, 2/13 responders to glue injection recrudesced.[25] Importantly, patients included in this trial were highly selected—all patients had a quiescent or mildly active CD, relatively healthy anorectum and no evidence of sepsis, and glue injection was performed in the operating room. Hence, before considering glue injection, proper staging of the extent of active disease, control of local sepsis using surgical drainage, setons, and antibiotics, as well as the institution of medical therapy to decrease intestinal inflammation is warranted. Observational case series of glue injection have also had good short-term success, but durability of response has been suboptimal. Similar to fibrin glue, fistula plug, which is a bioprosthetic absorbable tissue filler, has also been studied in perianal CD, albeit in small uncontrolled settings, with a highly variable 15 %–86 % healing rates.[26, 27]

More recently, addition of adipose-derived stem cells to fibrin glue has resulted in more promising results. In a recent RCT, addition of adipose-derived stem cells to the fibrin glue formulation has resulted in better outcomes as compared to glue alone—5/7 CD patients randomized to adipose-derived stem cells had fistula healing at 1 year, as compared to only 1/7 patients who received fibrin glue alone.[28] In another prospective study, complete fistula healing was observed in 82 % of patients by week 8, and of

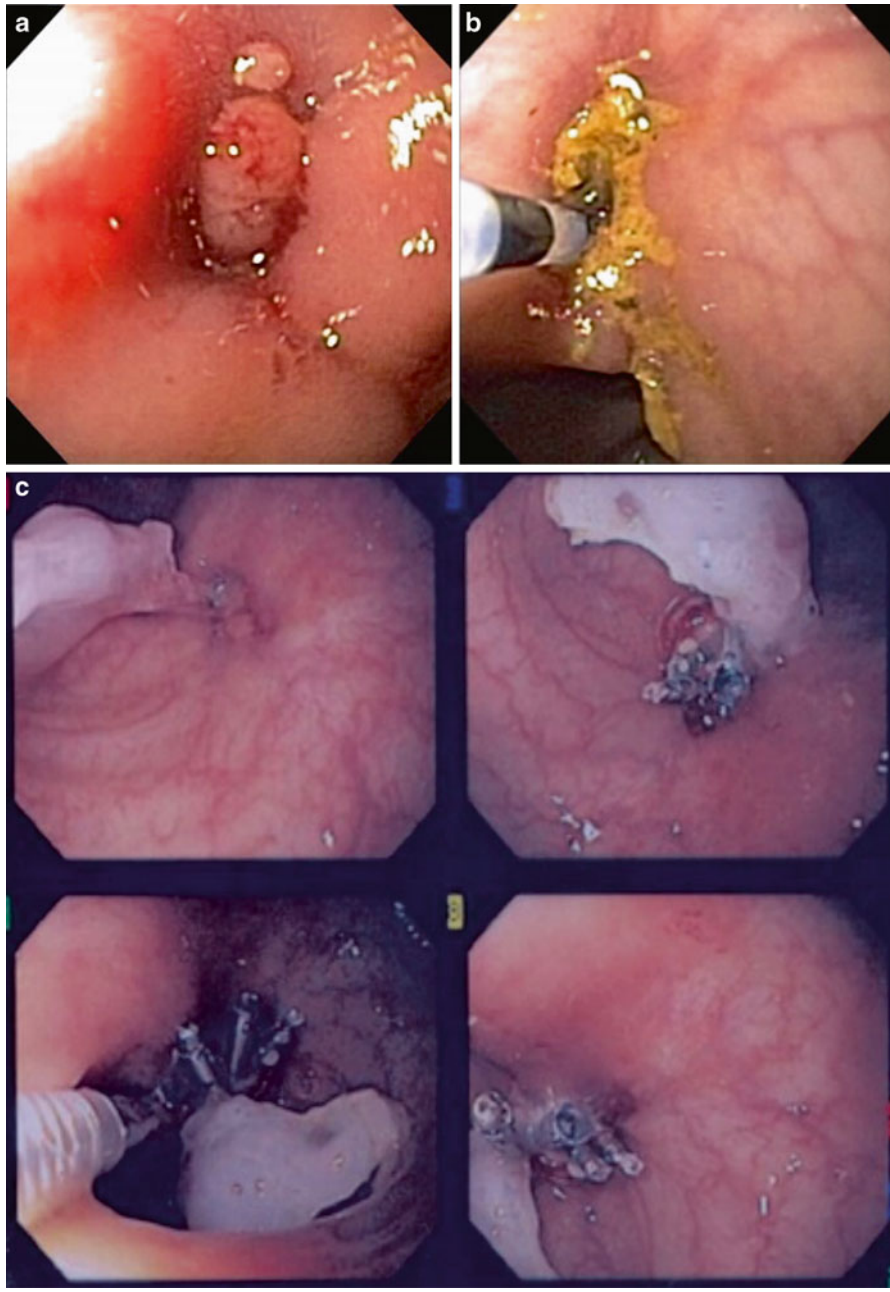

Fig. 21.7 (**a**) Crohn's rectal fistula delineated by contrast injection (**b**) followed by fibrin glue injection, (**c**) and placement of multiple clips to prevent glue extrusion.

those with early fistula healing, over 80 % had sustained fistula closure at the end of 1 year.[29] Similar encouraging results have been obtained with local intrafistula injection of bone marrow-derived mesenchymal stem cells.[30]

Other agents have been instilled endoscopically into fistula tracts to aid closure.[6] These include doxycycline, which incites local inflammation with subsequent fibrin extravasation and promotes tissue adhesion and fistula closure.

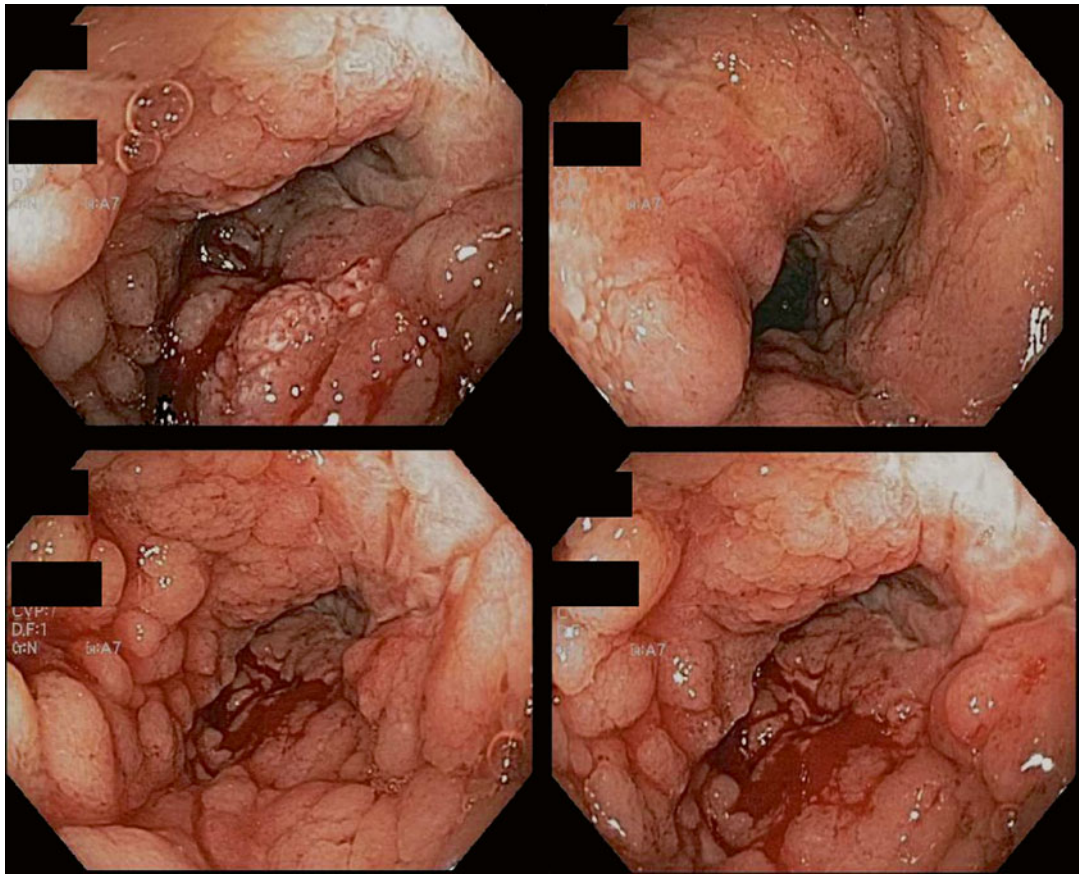

Fig. 21.8 Active bleeding in patient with Crohn's ileitis that ultimately responded to endoscopic control.

While there are no trials for CD-related fistulae, in a small case series of postoperative lymphatic fistulae, rapid fistula closure was achieved in 4/5 patients after instillation of doxycycline. Highly concentrated dextrose solutions (50 % dextrose) have also been used to help with fistula closure, although evidence for use of these solutions is very limited and based on anecdotal reports.

Endoscopic Management of IBD-related Gastrointestinal Bleeding

Gastrointestinal bleeding is a common manifestation of IBD, but major acute bleeding is uncommon; about 1.4–4.2 % of patients with UC, and 0–6 % of CD patients are hospitalized for major bleeding.[31] Most often bleeding is diffuse and there are no foci amenable to endoscopic therapy. Hence, endoscopy has only a limited therapeutic role in the management of bleeding in patients with IBD, but rather a more diagnostic role in identifying the diseased segment (Fig. 21.8).

Endoscopic Management of Colitis-Associated Colorectal Neoplasia

Patients with extensive UC or CD involving at least one-third of the colon have an increased risk of colorectal neoplasia. These lesions can be flat or raised. Endoscopic therapy is not advised in patients with flat dysplasia; in these patients, due to high risk of metachronous dysplasia, colectomy is recommended in presence of high-grade dysplasia or multifocal low-grade dysplasia. On the other hand, polypoid adenoma-like lesions without adjacent flat dysplasia can be managed as endoscopic

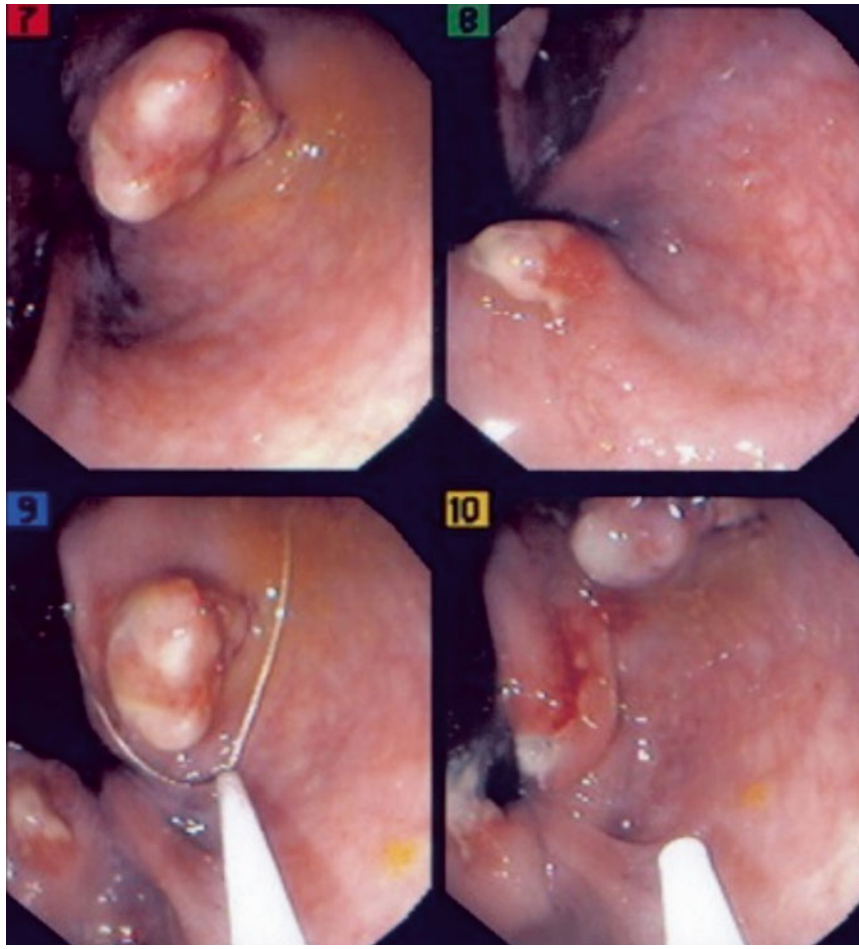

Fig. 21.9 Classic "pseudopolyp" in patient with CUC was endoscopically resected. Pathology unexpectedly demonstrated high-grade dysplasia. Multiple additional biopsies demonstrated diffuse dysplasia leading to a total colectomy.

polypectomy (Fig. 21.9); subsequent risk of dysplasia and cancer is only 4 % after median follow-up of ~7 years.[32] In recent years, endoscopic mucosal resection has been used for flat but endoscopically raised lesions. In a prospective study of 82 flat raised lesions, 76 were resected en bloc whereas another 3 were resected in piecemeal fashion, after indigo carmine-assisted endoscopic submucosal lift. Recurrence of dysplasia was observed in 2.4 % cases after a median follow-up of 2 years. [33] In addition, they also reported successful removal of three laterally spreading tumors using piecemeal EMR, and four laterally spreading rectal tumors removed with cap-assisted EMR. These patients had a higher 14 % risk of recurrent dysplasia after 4 years. In another study, Smith et al. reported an impressive >98 % cure rate at 18 months, with endoscopic submucosal dissection-assisted EMR for the endoluminal resection of flat raised lesions and laterally spreading tumors with complicating submucosal desmoplasis in 67 CUC patients—a difficult group of patients who conventionally would have undergone colectomy.[34] The rates of adverse events were acceptable with 3 % risk of perforation and 10 % risk of bleeding.

Conclusion

In summary, endoscopy is evolving from a purely diagnostic modality in IBD to a potential therapeutic modality complementing medical and surgical approaches. Currently, the primary utility of endoscopy in IBD treatment is for disease-related

or anastomotic strictures and polypectomy for adenoma-like lesions. Emerging therapeutic uses of endoscopy including fistula tract injection, needle-knife stricturotomy, stent placement for strictures and perforations. It is anticipated that the field of therapeutic endoscopy will become an integral part of the care of patients with IBD.

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Part IX

ERCP in Primary Sclerosing Cholangitis

Diagnosis and Treatment: ERCP in PSC

22

Nandakumar Srinivasan and Richard Kozarek

Introduction

Primary sclerosing cholangitis (PSC), first described in the mid 1850s, is a chronic, progressive, and cholestatic disease resulting in multifocal bile duct strictures that can affect the entire biliary tree [1]. Recurrent episodes of bacterial cholangitis, formation of bile duct stones, and development of abscesses in the liver proximal to strictures are common complications of PSC. The lifetime risk for developing cholangiocarcinoma is 10–20 % for patients with PSC [2].

Endoscopic cholangiopancreatography (ERCP) is a diagnostic and therapeutic tool in the management of PSC, used to confirm the diagnosis, to perform dilation of dominant biliary strictures, and to obtain endobiliary biopsy specimens and brush cytology for suspected cholangiocarcinoma [3, 4].

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Epidemiology, Risk Factors and Pathogenesis of PSC

In the United States, the estimated overall age- and sex-adjusted incidence of PSC is 0.9 per 100,000 population with a prevalence of 13.6 per 100,000 population [5, 6]. As a recent systematic review with meta-analysis of the incidence studies of PSC has noted, the incidence of PSC is similar in North American and European countries, with an overall increase in the incidence over time [7]. Approximately 60–80 % of the patients with PSC have associated inflammatory bowel disease (IBD) [6]. Of the patients with PSC, 62–70 % are males and the median age at the time of diagnosis ranges between 35 and 47 years [5–12]. The estimated median survival of patients with PSC was 9.6 years from the time of diagnosis to death or time of liver transplant [13]. No clear clinical or environmental risk factors have been identified for the development of PSC [6]. The pathogenesis of PSC continues to be elusive and it is believed to be a complex immune mediated disease. The most commonly accepted theory is an initial insult to cholangiocytes through environmental exposure to toxins or infection such as bacterial translocation across a leaky gut (e.g., IBD patients), which then results in persistent immune mediated damage with progressive destruction and fibrosis of the bile ducts in genetically predisposed individuals [6]. Genome-wide association studies have shown strong associations of HLA haplotypes, particularly HLA-B8

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(B*0801) and HLA-DR3 (DR B1*0301), in PSC [14]. The genetic predisposition to PSC is supported by studies that have shown almost 100-fold increased risk of PSC in first-degree relatives of the patients with PSC [15]. Several non-HLA type genetic polymorphisms (e.g., genes encoding tumor necrosis factor [16], matrix metalloproteinase [17], and intracellular adhesion molecule [18]) have also shown to influence the susceptibility to PSC. However, most of these genetic associations are weak and difficult to reproduce [6].

Complications of PSC

The majority of patients with PSC develop liver cirrhosis, with 10–15 % harboring or developing cholangiocarcinoma (CCA) [19, 20]. PSC has strong association with IBD, with ulcerative colitis being the most common type (48–86 %) followed by Crohn's disease (13–25 %) [6]. PSC is an independent risk factor for colorectal cancer in patients with IBD. It has been estimated that about 10 % of the patients who have IBD associated with PSC will develop colon cancer, hence recommendations to begin screening at the time of initial diagnosis in patients with both IBD and PSC [21]. Patients with PSC can suffer recurrent episodes of bacterial cholangitis, development of abscesses in the liver, and formation of bile duct stones proximal to strictures (Fig. 22.1) [19]. About 40–60 % of the patients with PSC develop pruritus with significant impairment of quality of life [22]. PSC patients with liver cirrhosis can develop portal hypertension and related complications such as variceal bleeding, ascites and hepatic encephalopathy [6]. Increased risk for metabolic bone diseases (osteoporosis 10–15 %, osteopenia 30 %), fat soluble vitamin deficiencies (50–85 %), and gall bladder neoplasia (estimated prevalence 3–14 % compared to 0.35 % in general population) are also noted in patients with PSC [6]. At early stages of the disease, ursodeoxycholic acid at moderate doses may improve the surrogate markers of the disease progression. However, the only curative therapy available to date is orthoptic liver transplantation [23].

Diagnosis of PSC

The discovery of PSC increasingly is based on the investigations of abnormal liver tests and incidental finding of intrahepatic biliary ductal dilatation on cross-sectional imaging as the majority (44–56 %) of the PSC patients are asymptomatic at the time of diagnosis [5, 6, 13]. A multicenter retrospective Italian study has found up to 17 % of asymptomatic PSC patients may have cirrhosis on liver biopsy at the time of diagnosis [6, 24].

Fatigue and pruritus are the initial presenting symptoms for symptomatic patients with PSC. The patients tend to develop jaundice, abdominal pain and weight loss with disease progression. Bacterial cholangitis is uncommon at presentation in the absence of dominant biliary stricture(s) or biliary intervention [6, 25].

ERCP and transhepatic cholangiography were once thought to be the reference standard for PSC diagnosis [26] before the era of magnetic resonance cholangiopancreatography (MRCP) [27]. The characteristic findings of cholangiography (Fig. 22.2) include short, multifocal, annular strictures alternating with normal or slightly dilated intervening segments called "beads on a string" [28]. A small case series (n = 10) has noted retraction of the major papilla into the duodenal wall in 70 % of the PSC patients (7 out of 10) with typical cholangiogram features [29]. In a recent prospective pilot study, endoscopic ultrasound (EUS) has also proved to be a valuable tool for accurately predicting extrahepatic disease in suspected PSC [30].

In the presence of typical cholangiogram findings, a routine liver biopsy is not required to confirm the diagnosis of PSC. However, a liver biopsy may be required to diagnose small duct PSC and suspected overlapping syndromes such as PSC with autoimmune hepatitis (AIH), and PSC with immunoglobulin G4 associated sclerosing cholangitis [25].

A wide range of auto-antibodies can be detected in the serum of patients with PSC (e.g., anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, anti-smooth muscle, anti-endothelial cell antibody,

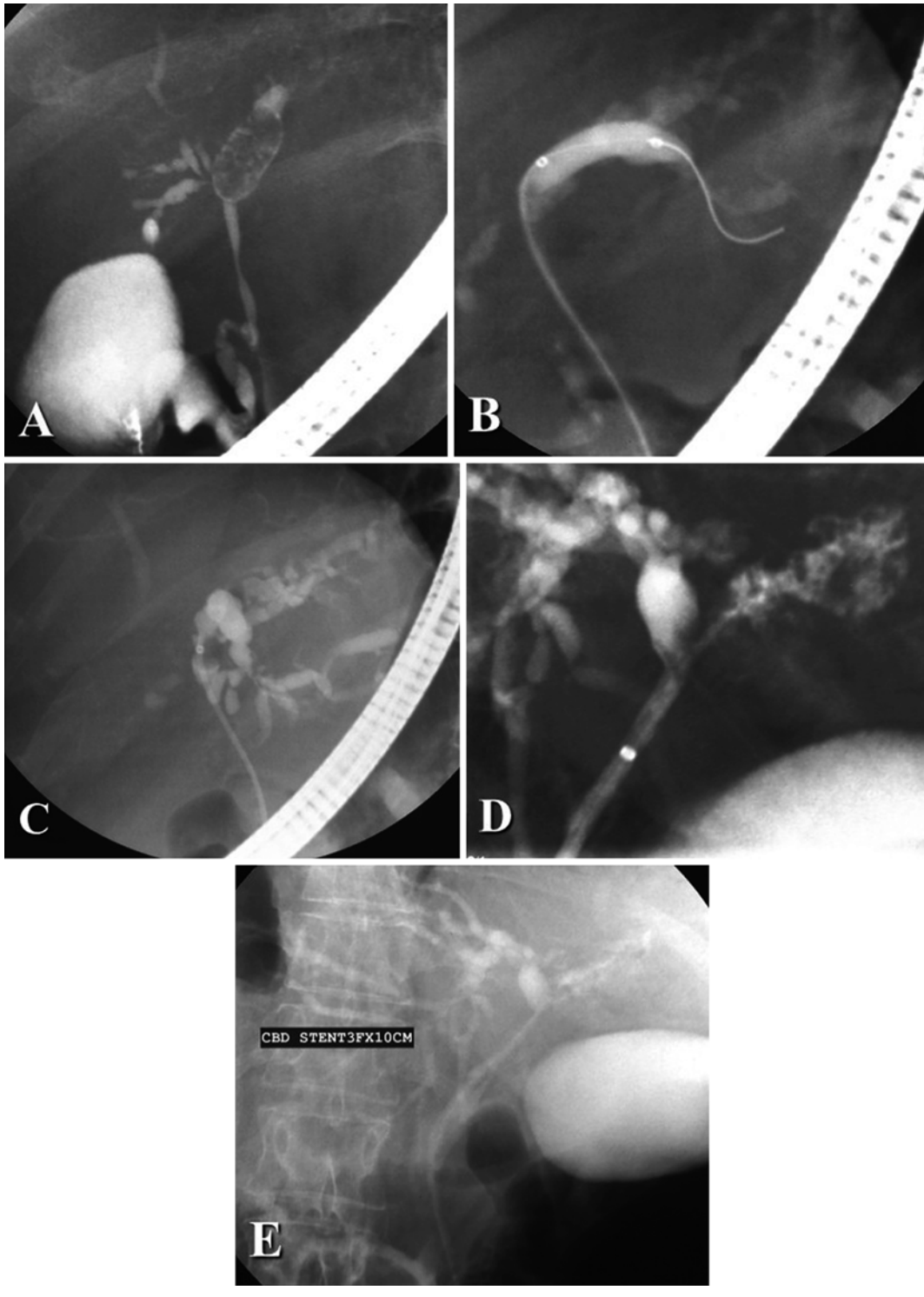

Fig. 22.1 (**a**) Marked intrahepatic right ductal stenosis and a tightly strictured left system filled with stones. (**b**) Patient was dilated with a 6 mm balloon. (**c**) Stone extraction. (**d**) Attempts to dilate the minute right system with a 6 Fr catheter was associated with a local extravasation. (**e**) The duct disruption was stented with a 3 Fr by 10 cm stent

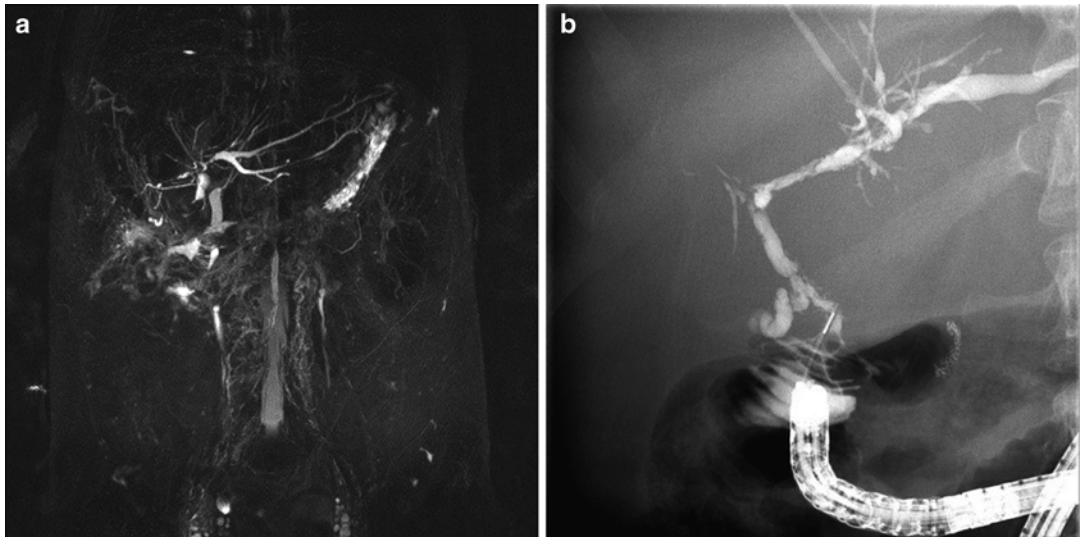

Fig. 22.2 (**a**) MRCP image and (**b**) ERCP image showing recurrent PSC in a patient after liver transplant

anti-cardiolipin antibody, thyroperoxidase, thyroglobulin, rheumatoid factor). However, these antibodies have no routine role in the diagnosis of PSC [25].

Magnetic Resonance Cholangiography (MRCP) Versus ERCP

ERCP is an invasive procedure and can be associated with complications such as pancreatitis, cholangitis, bleeding, perforation (Fig. 22.3), and aspiration [27]. One large multicenter prospective study noted that among 942 diagnostic ERCPs performed there were 13 major complications (1.3 %) and 2 deaths (0.21 %). ERCP may be associated with post-procedural hospitalization in up to 10 % of patients [31]. In contrast to ERCP, MRCP is a non-invasive, complication-free technique, which has the advantages of not using contrast media or ionizing radiation and a relatively shorter time for the examination [32]. Blinded case control, comparative studies have shown, despite an overall better depiction of the biliary tree by endoscopic retrograde cholangiography (ERC), both ERC and magnetic resonance cholangiography (MRC) are comparable in diagnosing PSC [33, 34].

Endoscopic Therapy for Symptomatic PSC

With the improvement in the ability of MRCP in diagnosing PSC, the role of ERCP has changed from diagnostic to therapeutic intervention (Figs. 22.1, 22.4, Video 22.1). A large retrospective study from a tertiary center clinically followed 117 patients with PSC for a mean period of 8 years (range 2–20 years), of which 72 % (n = 84) of the patients with PSC required at least one therapeutic ERCP for symptomatic disease [19]. Of the 84 patients who underwent therapeutic interventions, 70 % (n = 59) had balloon dilation of biliary strictures, 51 % (n = 43) had stone extraction, and 51 % (n = 43) had biliary prosthesis placed to facilitate drainage of infected bile ducts and to improve the bile duct patency on one or more occasions. The overall complication rate was 7.2 % following therapeutic ERCP but there were no procedure-related deaths.

During the course of PSC, dominant (high grade) strictures (Fig. 22.1) may develop in approximately 36–56 % of the patients. These patients have increased risk for cholangiocarcinoma [13, 35, 36] (Fig. 22.5).

Biochemical and clinical improvements have been reported with endoscopic therapy with

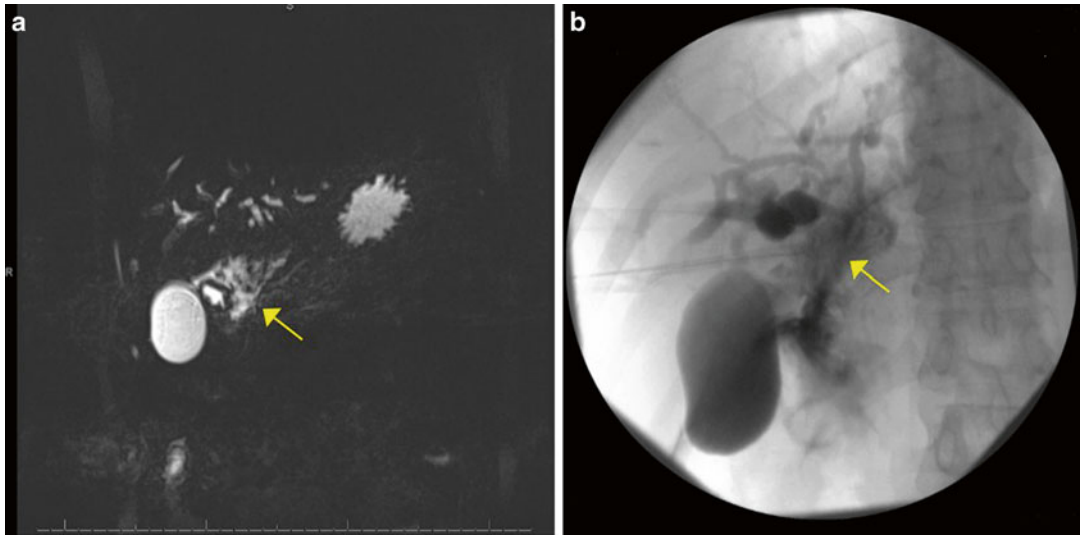

Fig. 22.3 (**a**) MRCP image and (**b**) ERCP image showing guidewire perforation at hilum in a patient with PSC

stenting and/or balloon dilation of dominant strictures [36]. Moreover, there is some evidence to support that secondary liver fibrosis can be reversed by relieving biliary obstruction [37]. Finally, endoscopic therapy has been suggested to improve survival in patients with PSC. A retrospective study of 63 consecutive PSC patients, with a median follow-up of 34 months, noted that the observed survival rate over 5 years following endoscopic therapy (mostly balloon dilation of biliary strictures) was significantly higher than the predicted 5-year survival rate based on the Mayo clinic survival model (83 % vs. 65 %, p = 0.027) [38].

Several non-randomized studies have also noted PSC patients with dominant strictures benefiting from endoscopic intervention, including 81–94 % 5-year liver transplantation free survival rates [35, 38, 39]. Chapman and colleagues, in a large retrospective study, compared long-term outcomes (mean follow-up 9.8 years) of multiple endoscopic interventions (stent alone 46 %, dilation alone 20 %, both stent and dilation 17 %, failed interventions 17 %) in patients with dominant strictures (n = 80) and without dominant biliary strictures (n = 48). Patients with dominant strictures had more interventions (median of 3 [range 0–34]) compared to the patients without dominant strictures (median of 0 [range 0–7]; p <0.001). The major complication rate for ERCP was low at 1 %. Although repeat endoscopic therapies were found to be safe in this study, the overall survival was found to be worse for the patients with dominant strictures (mean survival 13.7 years) compared to the patients without dominant strictures (mean survival 23 years). Much of this survival difference was related to a 26 % risk of cholangiocarcinoma developing only in the patients with dominant strictures [36].

Predictors of Successful Outcome

Published series and case control studies have documented 53–76 % successful clinical outcomes of therapeutic ERCP in patients with PSC [40–43]. A large retrospective study (204 total ERCPs performed on n = 148 patients with PSC) noted clinical improvement in 70 % of patients with PSC following therapeutic ERCP (p = 0.0001). Of the patients with PSC, 53 % had resolution of their presenting complaints and maintained it at 3–6 months, which met the study criteria for clinical success. Endoscopic therapy (OR =4.23, 95 % CI 2.15–8.34) was found to be an independent predictor of the clinical success. Patients who had high bilirubin levels, dominant

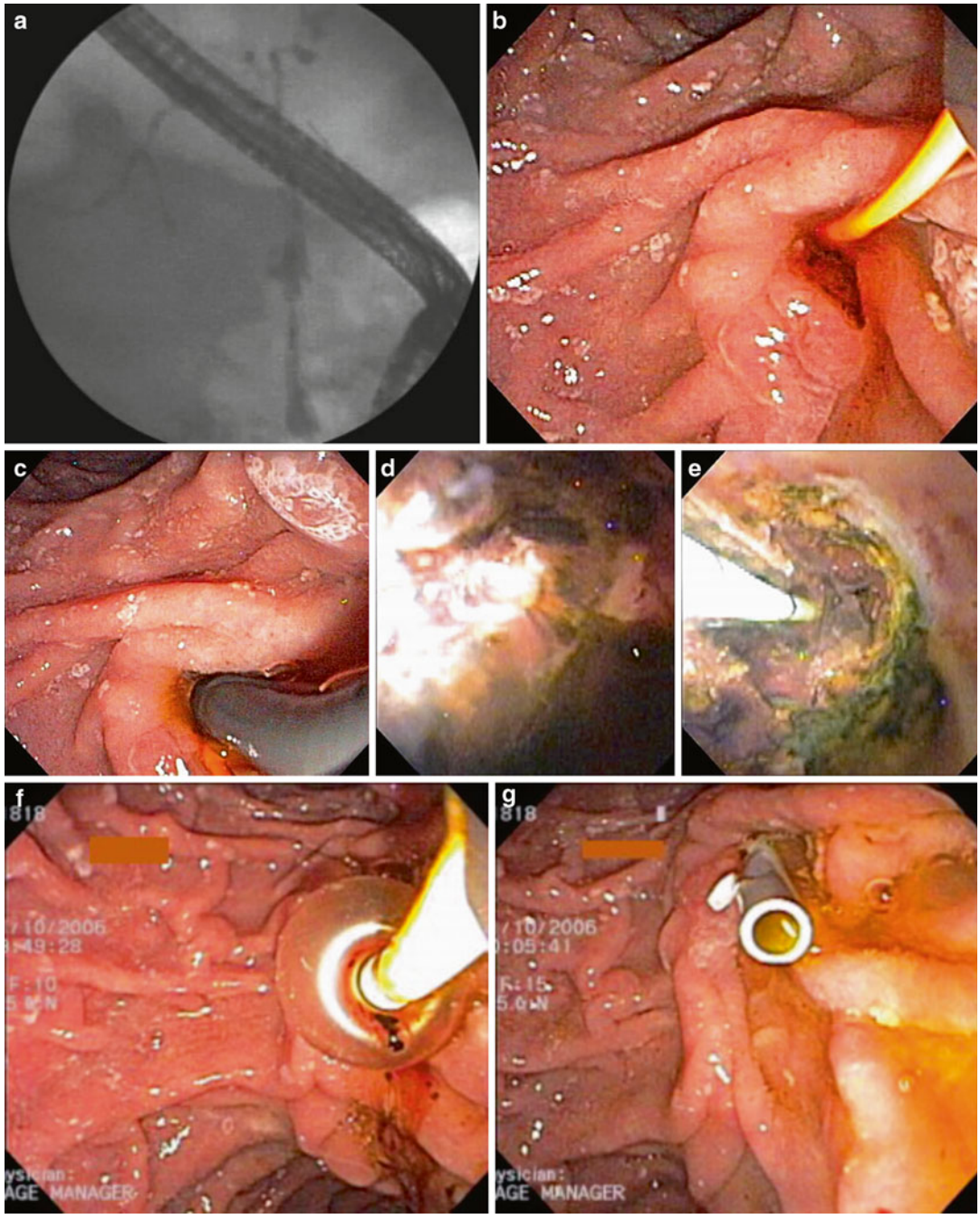

Fig. 22.4 (**a**) Cholangiography demonstrates high-grade extrahepatic and bifurcation strictures. (**b**) Following sphincterotomy, (**c**) a video cholangioscope is inserted to the bifurcation. (**d**) Note inflammatory change at the hilum and (**e**) common hepatic duct stone debris. (**f**) The latter is removed with balloon extraction followed by (**g**) stent placement

biliary strictures compared with those without (OR =3.73, 95 % CI 1.95–7.13), common bile duct strictures versus those who had strictures in other locations (OR =2.47, 95 % CI 1.27–4.81) were all more likely to have successful clinical and laboratory outcomes [44].

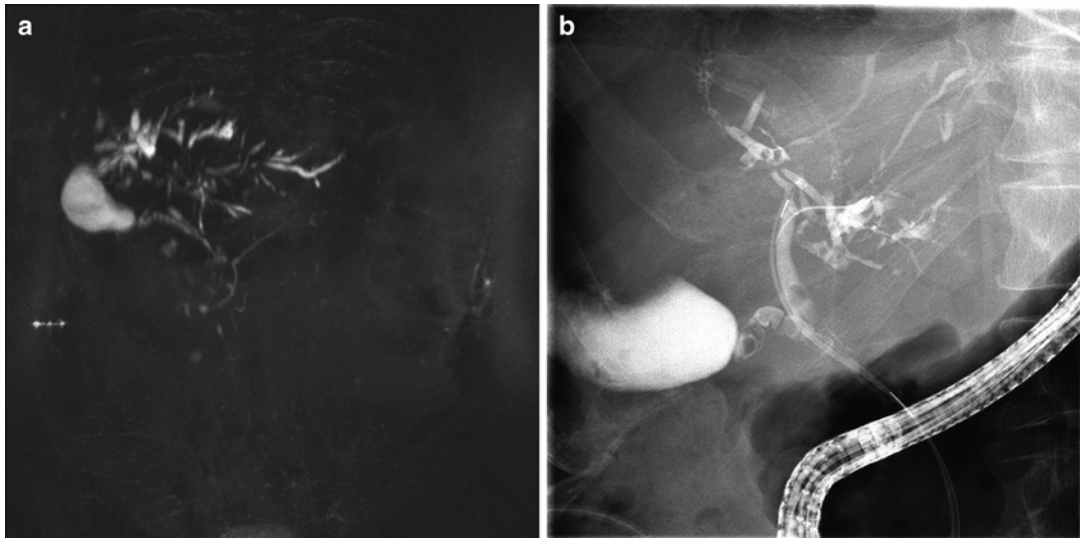

Fig. 22.5 (**a**) MRCP image and (**b**) ERCP image showing diffuse severe biliary strictures in a patient with PSC

Complications of ERCP in PSC Versus Non-PSC

Endoscopic therapy for patients with PSC and dominant strictures has been undertaken for more than 20 years, but there are concerns about the risks versus anticipated benefits in instrumenting a sclerotic biliary tree. A large retrospective study (n = 291 therapeutic ERCPs, and n = 26 diagnostic ERCPs) found that the most common complication following ERCP in patients with PSC was pancreatitis (12 %), followed by cholangitis exacerbation (3 %), sepsis (3 %), duct perforation (2 %), post sphincterotomy bleeding (2 %) and liver abscess (1 %) [19]. A single-center retrospective cohort study comparing consecutive ERCP outcomes in patients with PSC (n = 30, total 85 ERCPs) and those with other biliary strictures (n = 45, total 70 ERCPs) over a 2-year period found no significant difference in the complication rates on a patient-based analysis (PSC 26.7 % [8/30]) versus non-PSC 13.3 % (6/45, p = 0.23) and on a per procedure base analysis (PSC 12.9 % [11/85]) versus non-PSC 8.6 % (6/70, P = .45). However, PSC patients with acute symptoms had a higher rate of complications than those whose procedures were done electively. There was a possible trend toward a higher incidence of cholangitis after therapeutic ERCP in PSC compared to non-PSC patients (7.8 % [5/64] versus 1.4 % [1/69], P = 0.11), despite a significantly higher rate of post-procedure antibiotic usage in the PSC cohort (P = .001) [4].

A retrospective study from Mayo clinic noted that the overall ERCP-related complications in patients with PSC (11 %; 18/168 patients) were not significantly different when compared to non-PSC patients (8 %;76/981; p = 0.2). The duration of hospitalization, complications such as perforation, pancreatitis, and bleeding were not different between PSC and non-PSC groups. However, the incidence of cholangitis was higher in PSC patients (4 %) compared to non-PSC patients (0.2 %), p < 0.0002 despite routine use of antibiotics. Compared to the non-PSC group (n = 981), the PSC group (n = 168) had a longer procedure duration (51 min ± 29 vs. 86 min ± 28, *P* = 0.02), a higher prevalence of portal hypertension (4 % vs. 31.5 %, p < 0.0001), underwent more biopsies (15 % vs. 39 %, p < 0.0001), had more brushings (8 % vs. 37 %, p < 0.001), underwent more balloon dilatations (15 % vs. 48 %, p < 0.0001) and had more intra-ductal ultrasounds (5 % vs. 11 %, p = 0.007) [31].

Predictors of ERCP Complications

A large multivariate analysis of 11,497 ERCP procedures done over a period of 12 years noted a total of 462 complications (4 %), of which 42 were severe (0.36 %) and 7 were fatal (0.06 %). Post-ERCP pancreatitis risk of 2.6 % and bleeding risk of 0.3 % were identified. Overall complications following ERCP were higher among individuals after a biliary sphincterotomy (odds ratio [OR] 1.32). Patients who had a history of chronic pancreatitis and those who received prophylactic pancreatic stenting had fewer complications (OR of 0.78 and 0.69 respectively). Bleeding risk was high after biliary sphincterotomy (OR 4.71]). Severe or fatal complications following ERCP were associated with severe (OR 2.38) and incapacitating (OR 7.65) systemic disease, obesity (OR 5.18), known or suspected bile duct stones (OR 4.08) and complex (grade-3) procedures (OR 2.86) [45].

Risk Factors for Post-ERCP Pancreatitis (PEP) in PSC

A retrospective study from Finland has noted an overall complication rate of 9 % (PEP 7 %, cholangitis 1.4 %, perforation 0.6 %, bleeding or death 0 %) in n = 389 consecutive PSC patients who underwent 441 total ERCP procedures with the guidewire cannulation technique. For patients with an intact papilla, the post-ERCP pancreatitis (PEP) rate was higher compared to those who had previous sphincterotomies (9.2 vs. 2.7 %; $p = 0.01$). Female sex (OR 2.6, $p = 0.015$), guide wire insertion into the pancreatic duct (OR 8.2, $p < 0.01$), and difficulties with cannulation were all associated with PEP. The incidence of PEP was 2.6 % when the pancreatic duct remained untouched compared to 20 % and 31.6 % incidence when the guide wire was inserted into the pancreatic duct twice or five times, respectively. The incidence of PEP was only 1.4 % if cannulation was performed without sphincterotomy. However the risk for PEP increased to 6.8 % with biliary sphincterotomy, 27 % with dual (pancreatic and biliary) sphincterotomies and up to 55.6 % with precut dual sphincterotomies [46].

Differential Diagnosis

Secondary Sclerosing Cholangitis

Secondary sclerosing cholangitis is also characterized by a similar multifocal biliary stricturing process due to identifiable causes (Table 22.1) that can mimic PSC in the both clinical and cholangiographic findings [25].

Table 22.1 Secondary causes for sclerosing cholangitis [25, 72]

Secondary causes for sclerosing cholangitis
Cholangiocarcinoma
AIDS cholangiopathy
IgG4 -associated cholangitis
Ischemic cholangitis
Portal hypertensive biliopathy
Surgical biliary trauma
Choledocholithiasis
Eosinophilic cholangitis
Recurrent pancreatitis
Recurrent pyogenic cholangitis
Hepatic inflammatory pseudotumor
Histocytosis X
Intra-arterial chemotherapy
Mast cell cholangiopathy
ABCB4 associated cholangiopathy
Sclerosing cholangitis of critical illness
Hypereosinophilic syndrome
Sarcoidosis
Graft-versus-host disease
Amyloidosis
Caroli's disease
Other types of ductal plate abnormalities
Hodgkin's disease
Cholangitis glandularis proliferans
Neoplastic/metastatic disease
Hepatic allograft rejection
Combined immunodeficiencies
Angioimmunoblastic lymphadenopathy
Congenital hepatic fibrosis

Small Duct Primary Sclerosing Cholangitis

Population-based studies have noted that small duct PSC represents approximately 11–17 % of all patients with PSC [5, 9]. Small duct PSC patients have clinical, biochemical and histological features of PSC in the setting of a normal cholangiogram, although subtle changes can sometimes be seen in the small branches. The majority of patients with small duct PSC (>80 %) are noted to have associated IBD. Long-term follow-up studies have shown approximately 23 % of small duct PSC can progress to large duct PSC over time. Cholangiocarcinoma does not seem to occur in patients with small duct PSC, in the absence of progression to large duct PSC. Overall small duct PSC has a better long-term prognosis compared to large duct PSC [47].

PSC-AIH Overlap Syndrome

PSC-AIH (autoimmune hepatitis) overlap syndrome is most commonly diagnosed in young adults and children. The term "autoimmune sclerosing cholangitis" (ASC) has been proposed given the typical cholangiography finding of sclerosing cholangitis overlapping with the clinical, biochemical and histological features characteristic of autoimmune hepatitis [48].

This variant of PSC is diagnosed in 1.4–17 % of patients with PSC [49, 50]. Liver biopsy should be considered for the patients with disproportionately elevated aminotransferases (5- to 10-fold increase), increased level of serum auto-antibodies and/or hypogammaglobulinemia, with typical cholangiographic findings of PSC to diagnose or exclude overlap syndrome [6, 25]. Ursodeoxycholic acid has been used in combination with immunosuppressive drugs in the treatment of AIH-PSC overlap syndrome, and the long-term course has been considered favorable [50].

Immunoglobulin G4-Associated Cholangitis and PSC

Immunoglobulin G4-associated cholangitis (IAC) or IgG4-related cholangitis (IRSC) represents the biliary manifestation of a corticosteroid responsive systemic disease entity: IgG4-related disease (IgG4-RD). IgG4-RD could affect multiple organs, and is most often associated with increased serum IgG4 levels and characterized by IgG4 positive plasmacellular tissue infiltrates [51].

IAC affects mostly men (85 %) above middle age (mean age, 62 years), frequently presents with painless jaundice (77 %) and patients are less likely to have associated IBD. IAC has been noted to be associated with autoimmune pancreatitis (92 %), abundant IgG4-positive cells in bile duct biopsy specimens (88 %) and increased serum IgG4 levels (74 %) [52].

The current American Association for the Study of Liver Diseases (AASLD) practice guidelines recommend measurement of serum IgG4 in all PSC patients. If serum IgG4 is elevated, then evaluation for IAC for which a trial of steroid therapy is recommended [25]. Although IAC is usually responsive to corticosteroids, relapse is not uncommon after steroid withdrawal, particularly for patients with proximal bile duct strictures [6].

The interpretation of elevated serum IgG4 can be challenging considering that previous case-series have shown elevated IgG4 in 9–27 % of PSC patients without IAC or IRSC [53, 54]. A recent study from Europe noted that applying four times the upper limit of normal (4 × ULN) cut-off value for serum IgG4 (i.e., serum IgG4 > 5.6 g/L), was associated with the highest specificity and positive predictive value (100 %) for IAC, although sensitivity was low at 42 % (95 % CI 31–55) [51].

Cholangiocarcinoma

PSC should be considered a premalignant condition that warrants close surveillance given the risk of cholangiocarcinoma, which is 160-fold that of the general population [55–57].

A large retrospective study noted the median time from the diagnosis of PSC (n = 128) to cholangiocarcinoma (n = 26) was 26 months (range 0 months to 20.5 years). Forty-eight percent of the cases (n = 10) presented within 4 months of the diagnosis of PSC [36].

Based on the anatomic locations, cholangiocarcinoma can be divided into three subtypes: (1) intra-hepatic cholangiocarcinoma (iCCA), when located within the hepatic parenchyma; (2) perihilar cholangiocarcinoma (pCCA), when located proximal to the cystic duct; and (3) distal cholangiocarcinoma (dCCA), when located distal to the cystic duct [58]. The most common subtype is pCCA. In a large case series of patients with cholangiocarcinoma, 50 % had pCCA, 42 % had dCCA (42 %) and 8 % had iCCA [59].

The most commonly used staging system, the Bismuth-Corlette classification stratifies pCCA on the basis of bile duct involvement but it lacks crucial information such as vascular involvement or distant metastasis. Therefore this classification system was recently extended to also take into account vascular involvement (arterial/venous) and distal metastasis [60].

Cholangiocarcinoma often occurs at the site of dominant strictures in PSC patients [36, 61]. Dominant strictures are defined as stenosis ≤1.5 mm diameter in the common bile duct or ≤1 mm in a hepatic duct [25]. Therefore endoscopic brush cytology of a dominant stricture is advocated to diagnose cholangiocarcinoma (Fig. 22.6). However, the diagnosis of cholangiocarcinoma can be challenging because of its paucicellular nature, anatomic location and also because of the myriad of benign diseases that have clinical features suggestive of malignancy such as jaundice, abdominal pain, sudden change in liver biochemical tests and weight loss [58, 62]. Several studies have documented that positive cytology is highly predictive of presence of malignancy [63–67]. Unfortunately conventional brush cytology has a very low sensitivity (4 %–20 %) and low positive predictive value (≤60 %) despite its high specificity and high negative predictive values [19, 68]. The Mayo Clinic has reported that equivocal cytology results (atypical or suspicious) are much more common

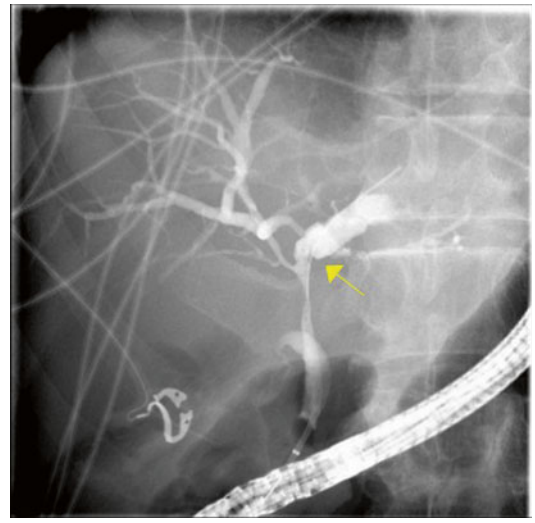

Fig. 22.6 ERCP image showing a dominant stricture in patient with hilar cholangiocarcinoma

(approximately 40 %) than unequivocal positive cytology (<20 %) in diagnosing cholangiocarcinoma from their clinical experience [62]. Fluorescence in situ hybridization (FISH) and detecting aneuploidy using digital image analysis (DIA) are two advanced cytologic techniques that can increase the sensitivity of conventional cytology in diagnosing cholangiocarcinoma. FISH has been shown to increase the sensitivity up to 35–60 % while preserving specificity of cytology when assessing for polysomy (chromosomal gain). The sensitivity and specificity of DIA is intermediate compared with routine cytology and FISH but can have additive value when used along with FISH [62]. A small series, single center study has reported that in expert hands ERCP with probe-based confocal endomicroscopy had 100 % sensitivity (95 % CI 19.3–100 %) and 100 % negative predictive value (95 % CI 71.3.3–100 %) in excluding neoplasia. The specificity and positive predictive values were 61.1 % (95 % CI 35.8–82.6 %) and 22.2 % (95 % CI 3.5–59.9 %) respectively for this study [69]. Another recent, small single center prospective study has reported that cholangioscopy with narrow band imaging (NBI) did not improve the dysplasia detection rate compared to white light imaging despite increasing the biopsies (48 %) of suspicious lesions for patients with PSC [70].

Computed tomography (CT) or magnetic resonance imaging (MRI) may aid in the diagnosis of iCCA but liver biopsy is required for a definite diagnosis [58]. A diagnostic cut-off value of 130 U/ml for serum carbohydrate antigen (CA 19–9) tumor marker has a sensitivity and specificity of 79 % and 98 % respectively for diagnosing cholangiocarcinoma. However, CA 19–9 has a limited diagnostic use because it can also be increased in patients with bacterial cholangitis, significant intrahepatic cholestasis, and is virtually undetectable for those who are negative for Lewis antigen, which includes 7 % of the normal population.

For cholangiocarcinoma surveillance, most experts recommended annual imaging (MRI/MRCP or ultrasound) and serum CA 19–9 level measurement for patients with PSC. For those patients noted to have abnormalities with either one of these tests, further invasive testing with ERCP using conventional brush cytology and FISH is recommended [6, 56]. Recent publications suggest that direct cholangioscopy may play a role in directed tissue acquisition and differentiation of benign from malignant strictures in PSC (Fig. 22.4) [71]. Currently, use of cholangioscopy in PSC is not considered the standard of care. Likewise, the use of confocal endomicroscopy systems (Cellvizio, Mauna Kea Technologies, Paris, France) to differentiate benign from malignant PSC strictures (Video 22.2) should be considered investigational at this time.

Conclusion

Anatomic evaluation of the biliary tree is essential in the diagnosis of PSC. With the improvement in image qualities, MRCP has largely replaced ERCP in diagnosing PSC. Currently, ERCP is largely used as a therapeutic tool in the management of primary sclerosing cholangitis, to improve biliary drainage and to perform biliary brushings/biopsies for suspected cholangiocarcinoma. Establishing biliary drainage with endotherapy in patients with PSC has been shown to improve survival. Liver biopsies are not routinely required to confirm the diagnosis of PSC but should be considered for suspected small duct PSC or overlap syndromes. Cholangiocarcinoma often occurs at the site of dominant strictures in patients with PSC. Because of the increased risk of cholangiocarcinoma in patients with PSC, annual surveillance with MRI/MRCP and serum CA 19–9 is recommended for any concerning findings; ERCP with biopsies should be considered.

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Part X

Future

Future of Endoscopy and IBD

23

Michael Wallace

Focused Biopsy for Dysplasia

The development of advanced imaging systems for endoscopy has been a significant improvement in our ability to detect pathologic states—particularly early cancer and dysplasia. The most notable change has been the use of chromoendoscopy to target biopsies. As outlined in Chap. 17 there is now substantial controlled trial data showing that use of chromoendoscopy, with either indigo carmine or methylene blue, increases the yield for dysplasia. Several societies have now endorsed the use of chromoendoscopy with targeted biopsies as either the preferred method or an alternative method to random biopsy. Recently the British Society of Gastroenterology as well as the European Crohn's and Colitis Organization (ECCO) have recommended use of chromoendoscopy with targeted biopsies [1, 2]. The American Society for Gastrointestinal Endoscopy (ASGE) recently updated the mucosal tissue sampling guidelines and included two possible approaches including the traditional random biopsy or chromoendoscopy and targeted biopsies [3] with similar alternatives recommended by the American Gastroenterological Association (AGA) [4].

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Other red-flag methods to detect dysplasia include narrow band imaging and auto fluorescence imaging, although these have not been shown to significantly increase the yield for dysplasia [5–8]. On the other hand, highly targeted methods of imaging such as confocal endomicroscopy have been shown to be a valuable adjunct to broad field methods [9, 10]. In this setting the areas of abnormality are typically detected by broad field methods such as chromoendoscopy followed by targeted imaging with confocal endomicroscopy. Using this method, Kiesslich and colleagues were able to show a significant increase yield of dysplasia and reduced number of biopsies needed [11]. More recently, the same group has used confocal to demonstrate cellular level gaps in the epithelium, which predicted relapse in patients with IBD [12].

Use of Endoscopy to Facilitate Research and Dysplasia Screening

The unique access of endoscopy to image and acquire tissue in the gastrointestinal tract has been a major reason for the marked advancement in our knowledge of gastrointestinal neoplasia, including our deep understanding of the adenoma-carcinoma sequence. Other major advances have been the use of endoscopy to assess mucosal healing as endpoints in treatment of inflammatory bowel disease. Future advances in imaging are needed to predict and assess response to drug therapy. These can include

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DOI 10.1007/978-3-319-11077-6_23,

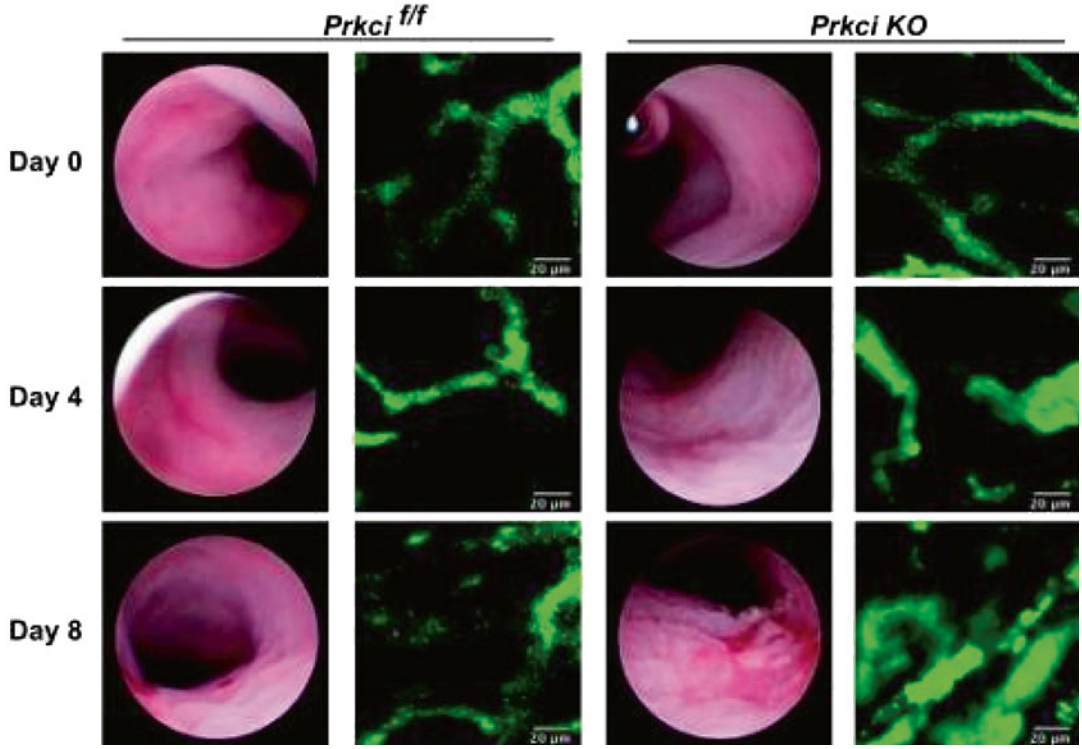

Fig. 23.1 Endoscopic and confocal laser endomicroscopy imaging of a mouse model of colitis. The mouse colitis was induced by ingestion of 3 % Dextran Sodium Sulfate (DSS). Imaging was performed with a small animal endoscope (Karl Storz, Germany) and confocal imaging of angiogenesis performed by using the AngioSpark™ nanoparticles in conjunction with near-infrared CLE (Mauna Kea Technologies, France). Mice with knockout (KO) of their protein kinase C iota (Prkci) gene were more susceptible to colitis compared with intact (f/f) mice. (Reproduced with permission from Calcagno SR, Li S, Shahid MW, Wallace MB, Leitges M, Fields AP, et al. Protein kinase c iota in the intestinal epithelium protects against dextran sodium sulfate-induced colitis. Inflamm Bowel Dis. 2011 Aug;17(8):1685–97.)

molecular imaging methods such as targeted monoclonal antibodies to cancer-associated surface markers and detection of broad field effects of carcinogenesis, even remote from the known areas of histologic dysplasia [13].

Molecular Imaging

High-resolution confocal endomicroscopy has enabled imaging of the intestinal epithelium at a cellular and even molecular level. This has opened an opportunity for imaging of direct molecular events and drug binding. The use of endoscopy and molecular imaging to predict response to specific agents has recently been evaluated in the field of rectal cancer. Specific drugs such as monoclonal antibody inhibitors of epithelial growth factor receptor (EGFR) can be directly imaged with fluorescent-labeled EGFR monoclonal antibodies. In one study in a mouse model of rectal cancer, tumors that highly bound the labeled EGRF inhibitor cetuximab were more likely respond to EGFR inhibitors [14]. Imaging of microvasculature and angiogenesis via CLE is also feasible and has been studied as a method to identify potential anti-inflammatory targets such as protein kinase C [15] (Fig. 23.1).

Inflammatory bowel disease offers a unique opportunity to explore the potential of molecular imaging for both detection and to guide therapy. Because of the increasing array of monoclonal

antibody treatments for inflammatory bowel disease, there is significant potential for molecular imaging using fluorescent-labeled monoclonal antibodies to determine binding density and potentially to predict response to therapy [16]. In a proof of concept of this, Atrya et al. used topically applied fluorescent-labeled adalimumab followed by confocal imaging to assess adalimumab binding. They were able to show that patients with a strong binding of labeled adalimumab had significantly better short-term response to adalimumab therapy [17]. Molecular imaging has been evaluated for cancer and dysplasia detection. For example, molecular imaging probes that are activated by proteases such as cathepsin were found to be significantly upregulated when imaged by CLE in ulcerative colitis patients with dysplasia compared to those without dysplasia [18]. Raman spectroscopy, which evaluates subcellular biochemical changes in the tissue, has also been shown to be promising in detection of inflammatory bowel disease [19].

Other potential future applications include direct drug delivery, which would be most applicable in focal areas of inflammatory bowel disease such as Crohn's disease associated strictures with isolated areas of inflammation.

Conclusion

Future areas for research include:

- The need for randomized controlled trials demonstrating long-term benefit and prevention of colorectal cancer in patients undergoing surveillance, particularly with colonoscopy.
- Methods to teach and train endoscopists to perform chromoendoscopy and to apply this in an outpatient clinical setting apart from tertiary care hospitals.
- Methods to improve the convenience of chromoendoscopy such as using this through integrated water pumps associated with the endoscopic systems or dye delivery in a delayed release tablet.
- Further evaluation of epithelial gaps and other methods to assess microscopic activity and their ability to predict the need for ongoing therapy.
- Further confirmation of the role of confocal endomicroscopy outside of major tertiary care centers to determine if this can be used in practice and how to train endoscopists in image interpretation.

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