Clinical Gastroenterology
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Russell D. Cohen *Editor*

Inflammatory Bowel Disease

Diagnosis and Therapeutics

Second Edition

Humana Press

CLINICAL GASTROENTEROLOGY

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I would like to dedicate this book to the memory of my brother Andy, who dedicated his life to help those less fortunate than us all

Preface

One decade has passed since I first set "pen to paper" to launch the first edition of *Inflammatory Bowel Disease: Diagnosis and Therapeutics*, and yet, it seems that an entire lifetime of progress has been made in the world of "IBD" since that time. We were in the infancy of the biologic revolution; the first IBD gene was identified, and we were just beginning to get a hint that these diseases were sprouting up in people, and in places, where they formerly had never been seen.

Simultaneously, the world was changing as well. The economic roller coaster was perhaps felt strongest in the United States, spurring heated debate over the structure and function of the entire healthcare system, as the economic realities of soaring costs of care in our aging population finally were put on the front burner of political discourse and policy. The terms "cost-effectiveness" and "evidence-based medicine" have suddenly moved from the pages of the medical economic journals to the speeches of politicians, as a new focus on the delivery of health care was born.

The research community expanded further into novel pharmaceuticals, biological agents, and novel approaches of targeting the immune system. Stem cell research held forth the promise of true breakthroughs in our entire approach to disease management, while patient compliance deficiencies have spurred a quest for simpler, better accepted therapies.

This was also the "decade of the patient." Expansion of patient privacy regulations, empowerment of patients through instantly available information (or misinformation) on the Internet, and "direct-to-consumer" marketing of prescription drugs introduced an entirely new two-way communication between the givers and receivers of health care. An unbridled "alternative" health care industry has developed into a very big business, and there is much interest among patients, and even practitioners, about these products. Unfortunately, the lack of regulation (and lack of interest among legislatures to close this legal loophole) leaves the public at the mercy of the unproven, both in terms of product efficacy and safety.

So what does this second version of *Inflammatory Bowel Disease: Diagnosis and Therapeutics, Second Edition* have to offer for its readers? The chapters contained in this book truly bring one to the cutting edge in IBD: the changing epidemiology, the explosion in genetics, and new understanding of the pathogenesis of disease.

Exciting new therapies are explored in both adults and children; updates on optimal uses of currently available therapies, alternative approaches to care, and novel surgical procedures detailed. The reader is then plunged into a truly evolving world of new radiographic, endoscopic, and other techniques utilized in the diagnosis of these diseases and their complications, with fascinating images readily available by today's technology. A new twist in this edition is the "pathology slide show," which clearly shows the major findings and differential diagnoses that one will encounter with patients with suspected or confirmed IBD. Rounding out the tour are new findings in the diagnosis and prevention of colorectal cancer in IBD, economic challenges in the new world, as well as issues specific to women with IBD and those with fecal diversions.

The end result is a culmination of 10 more years of knowledge, a decade of more advances, and the launch pad for the next waves of knowledge in the study and care of patients with IBD. It is my great hope that you as the reader find this second edition of *Inflammatory Bowel Disease* to be as rewarding as it has been to me to have the honor serve once again as editor.

Chicago Russell D. Cohen
July 2010

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Chapter 1
The Influence of Twentieth-Century Biomedical Thought on the Origins of Inflammatory Bowel Disease Therapy

Joseph B. Kirsner

Keywords Ulcerative colitis • Crohn's disease • Psychotherapy • Sulphanilamide • Adrenocorticotropic hormone • Immunomodulators • 6-Mercaptopurine • Azathioprine • Cyclosporine • Tumor necrosis factor • Ileostomy • J-pouch • Strictureplasty • Calomel • Tincture of hamamelis • Boracic acid • Silver nitrate • Kerosene • Lobotomy • Dysentery • Antibiotics • Sulfonamides • Steroids • Heat shock proteins • Trefoil peptides • Helminthic parasites • Nuclear factor κB

The following is a transcript of a lecture made by Dr. Joseph B. Kirsner, at the Falk Symposium 111; June 19–20, 1999; Freiburg, Germany [1]. *Dr. Kirsner considers this talk one of the pinnacles of his long and industrious career, and in celebration of his 100th birthday, he has requested that it be formally published as his foreword to this book.*

Preliminary Personal Remarks

I wish first to thank the organizers of this symposium for inviting me to speak on the origins of inflammatory bowel disease (IBD) drug discovery during the twentieth century. My own involvement with ulcerative colitis and Crohn's disease began in January 1936 [2]. My first patient, a severely malnourished woman of 40 gravely ill with ulcerative colitis, weighed a mere 85 lb. Treatment with the available nutritional supplements, subcutaneous fluids and small blood transfusions, was inadequate and the patient soon died – an experience that stimulated my interest in IBD and in the importance of nutritional support therapy. Between 1880 and 1900, 21 microorganisms had been identified as the specific causes of human disease; more pathogens were recognized early in the twentieth century [3]. So, during the 1930s, we searched unsuccessfully for pathogenic organisms in the stools of

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ulcerative colitis (UC) patients. We also were impressed with the emotional difficulties of IBD patients and yielded to prevailing psychosomatic concepts of disease and endorsed psychotherapy, which, though helpful for some patients, was ineffective. The discovery of sulphanilamide in 1938 [3], the availability of penicillin in the 1940s, and the subsequent sulphonamides and antibiotics were major accomplishments; but for IBD, initial optimism soon ended in disappointment. In the autumn of 1950, the clinical effects of adrenocorticotrophic hormone (ACTH) and the adrenal corticosteroids in rheumatoid arthritis, in IBD, and in other diseases were even more dramatic and suggested the soon-disproved possibility of a hormonal deficiency. Patients with UC improved within 48 h, but recurrences soon followed. Fifty years later, we recognize steroids as useful anti-inflammatory and immunosuppressive agents, but not as long-term therapy. Immunological mechanisms now were being proposed for a variety of diseases, and their implication in IBD soon followed, especially as we became aware of the gut mucosal immune system – you have learned more of this concept from the experts on the earlier program. The benefits of immunomodulators 6-mercaptopurine (6-MP) and azathioprine became apparent later, when persevering physicians prolonged their use in IBD, despite initial concerns about cancer risk. Today, research on the biology of inflammation has produced more potent anti-inflammatory compounds [4], (cyclosporine A and chimeric monoclonal anti-tumor necrosis factor-α [TNF-α] antibody) but they also do not cure IBD.

New surgical approaches improved IBD management and influenced therapeutic decisions. The frustrating ileostomy difficulties of the 1930s and 1940s in UC diminished following the ingenious Brooke–Turnbull ileostomy modification. Today, total colectomy and ileoanal anastomosis with J pouch, adapted from the surgical treatment of familial polyposis of the colon, is the operation of choice for UC [5], although the complication of pouchitis [6] challenges our understanding of intestinal vulnerability. For Crohn's disease (CD), preservation of small bowel through structureplasty and limited bowel resection is now a recognized physiological necessity [7].

Introduction

The (turbulent) twentieth century, in its continuing reexamination of biomedical thought, has been the most productive in the history of medicine, reflecting improved medical education, growth of academic medicine and of medical specialization, increased support of research, and expansion of the basic and Biomedical Sciences [8]. A century of remarkable progress, considering that, at its beginning, the concept of individual disease, recognized by Hippocrates (460–370 BC) 2,500 years earlier and discarded temporarily in America under the influence of Scottish-trained Benjamin Rush (1745–1813), was yet in its infancy. Similarly, pharmacotherapy, beginning with the use of medicinal plants and minerals in the ancient

Chinese, Hindu, and Mediterranean civilizations, recognized in the Society of Apothecaries, London in 1617 and formalized in the Pharmaceutical Society of Great Britain in 1841, established as a science in Germany through Paul Ehrlich early in the 1900s [9], attained scientific respectability chiefly during the past half-century following the adoption of controlled trials [10]. Early in the century, Metchnikoff [11] of the Pasteur Institute (Paris) had condemned the large intestine and its bacterial flora as dangerous to health. Today, we regard the colon more benignly, although we too view the intestinal flora with suspicion, and the IBD (UC and CD), medical curiosities early in the 1900s and neglected in P. Beeson's 1980 list of major digestive diseases [12], now rank among the more challenging problems in medicine.

The absence of an established etiology during the early 1900s [13], limited medical knowledge and scarce medical resources encouraged unusual treatments of ulcerative colitis [14], then the most recognized form of IBD; measures including calomel, tincture of hamamelis, and rectal instillations of boracic acid, silver nitrate, or kerosene, the rectal insufflation of oxygen injection of "extracts" of hog stomach and intestine and the Russian attempts at cooling the rectal mucosa, heating it, or irradiating it [15], all to no avail, of course. Even more surprising, Nobel Prize-winning prefrontal lobotomy [16] (electrocoagulation or procaine injections into the "prefrontal lobe") in France during the 1950s, disrupting connections between the cortex of the frontal lobe and the thalamo-hypothalamic region [16] to "eliminate harmful emotional influences…and pelvic autonomic neurectomy" [17] in the USA "to correct parasympathetic overactivity," reflected extreme and fortunately short-lived supports for psychogenic hypotheses.

Yet IBD treatment today, despite substantial improvement, remains nonspecific and noncurative. The therapeutic problems are numerous [18]: continuing obscurity of etiology, incomplete documentation of patient's status, variable criteria of disease activity and severity, limited knowledge of drug actions, and differing measures of therapeutic efficacy. An additional factor may be in how we view human illness, for CD in particular. A prevailing question is whether we are dealing with one or two diseases or more. For some physicians [19], illness results from the complex interaction of many antecedents, widely separated from each other in time. Because these events often differ for each patient and because even similar events vary quantitatively and temporally, "including the varying capacity of individual patients to adapt to the stress of illness… [20]…every disease, in a sense, comprises numerous illnesses of varying pathogenesis … important in understanding …why a 'disease' responds to a given therapy in one patient but not in another."

None of the current IBD medications evolved from the investigation of UC or CD; each originated in other biomedical circumstances [21]. Thus, IBD was viewed initially as a bacillary dysentery, in the 1930s and 1940s as a psychosomatic disorder [22, 23];and an enteric infection, in the 1950s as an intestinal "protective" deficit or an undefined nutritional deficiency, in the 1960s as an immune or autoimmune disorder, in the 1970s as an intestinal permeability defect

(CD) [24], and in the 1980s and 1990s as an abnormality of the gut mucosal immune system, a defect in oral tolerance, including an excess of proinflammatory molecules [25], and currently as a genetic disorder [26]. Each concept generated its particular therapeutic emphasis.

Much of the advance in IBD therapy has come during the latter part of the twentieth century when in the USA and elsewhere the public, academia, government, and pharmaceutical organization united in the support of biomedical research [27]. Also, technology, having merged with science after the Industrial Revolution in the nineteenth century, became more completely integrated with basic research, creating new pathways of inquiry [28]. While IBD etiology remains obscure, clinical knowledge of IBD (UC and CD) has increased concomitantly with the growth of the basic sciences [29–40] (Tables 1.1 and 1.2).

To illustrate individual pathways of IBD drug discovery I briefly describe the origins of six IBD medications (two older, two intermediate, and two recent products): antibiotics and sulfonamides (Table 1.2 [31–40], Table 1.3 [3, 41–46]; Falk H, 12 March 1999, personal communication, and Table 1.4), steroids (Table 1.5 [47–55]) immunosuppressants (6-MP, azathioprine) (Table 1.6), [56–63] cyclosporine A (Table 1.7 [64–79]) and monoclonal chimeric antibody to human TNF (Tables 1.8 and 1.9 [80–98]). Four of the six won the Nobel Prize during the twentieth century.

Table 1.1 Changing inflammatory bowel disease (IBD) concepts – twentieth century

Early	Late
Bacteria, autointoxication	Molecular microbiology
Bacterial infection	Intestinal flora
B. dysentery	Inflammation
Diplostrep	Biology
Escherichia coli	Molecular
Entameba histolytica	Endothelial biology
Psychosomatic	Neurohumoral-immune-genetic interactions; enteric n.s. (environment)
Enzymes	Cell
Lysozyme	Biology
Pancreatic	Defenses
Deficit	Epithelial
Pig stomach	Metabolism
Intestine	Permeability
Allergy	Immunology
	Systemic
	Intestinal
Familial	Genetics
	Medical
	Molecular

Source: J.B. Kirsner

Table 1.2 Early "antibacterial" era

Nineteenth century		
	L. Pasteur	"Antibiosis" (studies on wine)
	J. Lister	Anti-infection of crude molds
1875	T. Huxley	*Penicillium glaucum*: bacterial inhibition
1885	V. Babes	Bacteria – antibacterial substance
1890	B.Goio	Penicillin versus anthrax (in vitro)
Twentieth century		
1922	A. Fleming	Lysozyme (tears)
1928	A. Fleming	*Penicillium notatum* – (Lysis *Staphylococcus*) ("mold juice")
1938	H. Florey, E. Chain (N. Heatley)	Purification, synthesis penicillin
1943		Penicillin production (USA Department of Agriculture Regional Laboratories, Peoria, IL), *Penicillium chrysogenum*
	R. Dubos	Antibacterials in soil bacteria
1943	S. Waksman (A. Schatz)	Streptomycin (*Streptomyces griseus*)
1944	W.H. Feldman, H.C. Hinshaw	*Streptomyces* versus Mycobacterium tuberculosis
1945–1990s		Numerous antibiotics Aureomycin (1945) Chloramphenicol (1947) Neomycin (1949) Terramycin (1950)

Table 1.3 Sulphonamides

1932	J. Klarer, F. Mietzsch	Prontosil rubrum Chemical affinity for proteins (wool, silk)
1935	G. Domagk	Prontosil rubrum cured bacterial septicaemia *Streptococcus* *Staphylococcuss*
	Dr and Mme Tréfouel (Daniele Bovet)	Prontosil rubrum: effective only in vivo Sulphanilamide (antibacterial)
1938–1947	Bayer Laboratories	5,000 Derivatives of Prontosil rubrum 20 Sulphonamides
1940	N. Svartz	Sulphasalazine (sulphapyridine + 5-ASA)
1977	S.C. Truelove, A.H. Azad-Khan	5-ASA active ingredient (sulphasalazine)
1980	U. Klotz, K. Maier, C. Fischer, K. Heinkel	Confirmed 5-ASA efficacy
1980s	Falk Foundation	5-ASA preparations

Table 1.4 Events in development and availability of Salofalk for IBD

1984 (March)	Salofalk suppositories (Germany) – first 5-ASA product
1984 (November)	Asacol tablets (Switzerland)
1985 (January)	Salofalk tablets (Germany) second 5-ASA preparation
1985, 1986	Salofalk, Asacol (Europe)
1986 (September)	Salofalk enemas, suppositories (Canada)
1988	Rowasa enemas, suppositories (USA), identical with Salofalk
1990	Salofalk tablets (Canada)
1992	Asacol tablets, Pentasa (USA)
1999	Salofalk tablets, enemas, suppositories; 51 countries

Source: Falk H, 1999, personal communication

Table 1.5 Discovery of cortisone ("substance X")

	Male (65), arthritis
P. Hench, 1929	Jaundice → well
1929–1934	16 Patients (rheumatoid arthritis) Jaundice → improved
1931	2 Females, rheumatoid arthritis
	Pregnancy → no symptoms
1938	34 pregnancies (20 rheumatoid arthritis patients) → well
	Treatment with female sex hormones → 0
	"Arthritis reversible" → search for "X"
1930–1938	E.C. Kendall (adrenal gland, "cortin" 1935), thyroxine (1914)
1940, 1941	Hench – treatment with "cortin" for rheumatoid arthritis → 0
Competition	O. Wintersteiner, J.J. Pfiffner (Colombia) (Compound F)
	T. Reichstein (Zurich, Switzerland) (Compound Fa)
	E.C. Kendall, H. Mason (Mayo) (Compound E)
	OSRD Research (9 research contracts)
1930–1940	Kendall, Reichstein 17-hydroxy-11-dehydrocorticosterone (Compound E = Fa)
May 1948	"Compound E" (animal bile, desoxycholic acid) (E. C. Kendall, L.H. Sarrett)
1948	P. Julian – Cortexolone → cortisone
21 September 1948	"Compound E" (100 mg intramuscularly, first patient rheumatoid arthritis), "Remarkable" benefit
1 February 1949	ACTH Armour® (pituitary gland) – "dramatic benefit," rheumatoid arthritis
Autumn 1950	ACTH, cortisone – ulcerative colitis → improved (Mayo Clinic, University of Chicago)

Concluding Comments

"All scientific progress is the result of discoveries of differing degrees of significance [99]. Each discovery, while based more or less directly on previous work, in turn leads to new advances. This forward march, however, is far from regular… often it is obscured…and at other times it is accelerated." As in other disciplines, the pathways of discovery of IBD drugs represent astute clinical observation as well as basic research accomplishment [100] (Tables 1.10 and 1.11).

Table 1.6 Development of 6-mercaptopurine (6-MP), azathioprine (G. Hitchings, G. Elion)

1898	Search for immunosuppressive drugs (>100 chemical agents)
1910	L. Hektoen – search for antibody inhibitors
1942	G. Hitchings → Burroughs Wellcome (Goal: "philosopher's stone")
1944	G. Elion → Burroughs Wellcome (purines, pyrimidines)
1945	F. Hitchings and G. Elion → biosynthesis of nucleic acid antimetabolites
1948	Selective inhibitors dihydrofolate reductase
1951	Tested 100 purines → 6-MP, 6-thioguanine 6-MP metabolism in mice, humans → azathioprine
1958, 1960	6-MP Suppression antibodies Delayed rejection – kidney transplant Slow anti-inflammatory effect Incorporation into nucleic acids
1960s	Early clinical use Leukemia Lupus erythematosus Rheumatoid arthritis
1962	R.H.D. Bean, One UC patient, 300 mg/day → "dramatic improvement"
1970s–1990s	B. Korelitz, D. Present – prolonged 6-MP (2–3 mg/kg) in CD, UC

Table 1.7 Cyclosporine A – discovery, development

1969–1970	B. Thiele	Search for antifungal agents (soil from Wisconsin, Hardanger Vidda, Norway) Two new strains*: Cylindrocarpon lucidum* Booth, *Tolypocladium inflatum* ← Gams cyclosporins A, B, C, D
1972	J. Borel	CyA immunosuppressant Anti-inflammatory Decreased polyarthritis (Freund's adjuvant) Low myelotoxicity
1974–1980	R. Wenger T.J. Petcher	CyA: purified, structure, synthesis
1978–1981	R.Y. Calne, D.J. White et al.	Prolonged allograft survival – kidney, liver, bone marrow
1980s	Multiple investigators	Variable kinetics, poor absorption
1988	John C. Reed et al.	CyA: inhibition transcription genes (IL-2, IL-2R, IFN-γ)
Clinical		
1984	M.C. Allison, R.E. Pounder P.A. Bianchi et al.	Oral CyA – CD (1 patient) Oral CyA – CD (2 patients)
1989	J. Brynskov et al.	Beneficial – CD

(continued)

Table 1.7 (continued)

1990, 1994	S. Lichtiger, D.H. Present	Helpful in severe UC
1992	W.J. Sandborn, W. Tremaine	Helpful CD (fistula) Refractory UC
1993	D. Present, S. Hanauer et al.	Beneficial IBD (CD) Side-effects Nephrotoxicity Hepatotoxicity Hypertension Paraesthesias

CyA Cyclosporine A; CD Crohn's disease; UC ulcerative colitis

Table 1.8 Evolution of knowledge of tumor necrosis factor α (TNF-α) antibody I

1893	Wm Coley (NY)	Bacterial-induced "tumor necrosis" (cancer treatment)
1943	M.J. Shear	*Serratia marcescens* lipopolysaccharide (LPS) Tumor necrosis
1962	W.E. O'Malley	LPS → animals: "endogenous necrosis factor" in serum
1974	A. Theologides	"Cachectin" – mediator of wasting in chronic disease
1977	C. Costa	
1975	E.A. Carswell, Olds	Endotoxin-induced serum factor necrosis of tumors (TNF-α)
1980	D.N. Mannel	LPS/macrophages → TNF-α
1984	D. Pennica	Molecular cloning animal TNF-α
1985	A.M. Wang	
1985	B.B. Aggarwal	Structure human TNF-α
1985	T. Shirai, G.F. Nedwin	Cloning human TNF locus
1985	J. Mathison	Cachectin (high TNF activity)
	B. Beutler	Cachectin/TNF identical
1989	M.J. Eck et al. E.Y. Jones et al.	Crystallization TNF
1990	P. Seckinger, N. Foley, T. Espevik	Identification of TNF receptors
1993	D. Knight et al.	Characterization mouse–human chimeric anti-TNF-α antibody (cA2)
1995	S.A. Siegel	cA2 Neutralizes TNF-α in vitro; protects transgenic mice (cachexia, TNF-α)

Source: Beutler B. Tumor necrosis factor – the molecules and their emerging roles in medicine

Table 1.9 Early clinical-related observations

1990	MacDonald	Increased TNF-α, IFN in inflamed human intestine
1994	Breese et al.	TNF-α cells increased in IBD mucosa (CD > UC)
1997	Targan, Hanauer	Chimeric monoclonal antibody to TNF-α (cA2) effective in CD
1998	Gurmbard et al.	Increased TNF-α in UC, CD Murine antihuman TNF-α chimeric monoclonal antibody derived from cell fusion experiment (Jan Vilcek, NYU)
1998	Maini	Chimeric monoclonal antibody to TNF-α (cA2) + methotrexate for rheumatoid arthritis
1998	Centocor	TNF-α antibody treatment for CD (FDA)

Table 1.10 Pathways of discovery of IBD therapeutic agents

Scientific "climate" – sulphas, antibiotics
Exploitation of clinical observation – sulphasalazine
Flash of insight – 5-ASA
Persevering research – cortisone, ACTH
Inquiring clinician – 6-MP, imuran
Serendipity – cyclosporine A
Application "unrelated" observation – Anti-TNF-α
Ingenuity of prepared mind – biological treatment
Novel technology – genetic treatment

Table 1.11 Biological therapy for IBD

Intervention	Target
IL-1 receptor antagonist	IL-1
Soluble IL-1 receptor	IL-1
IL-2 monoclonal antibody	IL-2
Recombinant IL-4	Multiple
IL-6 monoclonal antibody	Multiple
Recombinant IL-10, IL-12	Multiple
Chimeric anti-TNF-α monoclonal antibody	TNF-α
Humanized anti-TNF-α monoclonal antibody	TNF-α
Soluble TNF-α receptor fusion protein	TNF-α
Recombinant interferon γ	Multiple
Anti (T) CD_4 antibodies	
Antisense oligonucleotides	
Trefoil peptides, growth factors, growth hormone	

Source: Sands [4]

The list of twentieth-century IBD medications is lengthy but lacking. Each seeks to inhibit the production of immune and/or proinflammatory mediators, downregulating the inflammatory process. None cures IBD and none represents a pathogenetic mechanism specific to IBD. While ongoing research, including the novel animal models of intestinal inflammation [101] , and anti-inflammatory advances in pharmacotherapy, including during biomimicry [102], continue to create new compounds (Table 1.12), until the actual cause(s) of UC and of CD, the environmental "triggers" and the initiating circumstances are known, IBD therapy remains nonspecific and palliative (Table 1.13). The question then arises: are other therapeutic approaches to IBD possible? And the answer is yes. Twentieth-century research has already indicated the protective nature of normal oral gastrointestinal tolerance [103], the need to learn more of this process, and how it may be applied clinically.

Related to oral tolerance is the capacity of CD intestinal content to rekindle the disease after intestinal resection and reanastomosis [104], an intriguing therapeutic opportunity if the underlying mechanism can be identified. Additional therapeutic

Table 1.12 New interleukin 2 inhibitors

Microbial source
Cyclosporin (*Tolypocladium inflatum*)
FK 506 (*Streptomyces tsukubaensis*)
Rapamycin (*Streptomyces hygroscopicus*)
Inhibitors of nucleotide synthesis
Leflunomide
Mycophenolate mofotil
Substituted aniline derivatives
Interleukin 2-receptor blockade
Raf-1 blockers
(cxo) Xanthene carboxylase
Compound 9
Inhibitors of Ca^{2+} influx in T cells
SK and F96365
4-Substituted-B-carbolines
Potassium channel blockers
Inhibition of mitogen-activated protein kinase
PD 98059
VD 126

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Table 1.13 IBD therapy – twenty-first century

Area	Potential Therapies
Intestinal flora	Antibacterials, vaccines, "probiotics"?
Inflammation	Inhibitors
	IL-1
	IL-2R
	Inflammatory molecules
	Polymorphonuclear leucocytes, lymphocytes
	Transcription factors
	Anti-TNF-α
	Antibodies
	CDP571
	Thalidomide
	IL-10, IL-11
Oral tolerance	Oral antigens
Epithelial protection	HSP, trefoil peptides, growth factors
Gene therapy	Defective genes
	Repair
	Replace
	Vectors
	Viral
	Nonviral
Pharmacology, biomimicry → new drugs	

Source: J.B. Kirsner

resources emerge from continuing studies of intestinal microbiology [105] (antibiotics, perhaps probiotics [106]), immunology (vaccines specific to T cell [107]), and the CD4+ Type 1 [108] and from the identification of the more complete cytokine profiles and the molecular signaling pathways of intestinal inflammation. The observation of Elliot et al. [109] that exposure to helminthic parasites protects animals against experimental intestinal inflammation (CD) coincides with clinical experience documenting the infrequency of IBD in unsanitary third-world countries.

Other therapeutic possibilities include:

1. Gut mucosal epithelial protection (involving the overlying mucus layer, intestinal sIgA [110], the cytoprotective heat shock proteins, trefoil peptides, and growth factors) [111], the restoration of epithelial tight junctions and possible blockade of transepithelial penetration of potential pathogens [112].
2. The continuing emergence of new human pathogens of disease and the new infective diseases emphasize the continuing possibility of pathogenic microorganisms in the pathogenesis of IBD, now more approachable by advances in molecular microbiology, molecular epidemiology, and vastly improved technological diagnostic resources.
3. In the continuing investigation of host defenses against microorganisms, more than 100 endogenous antimicrobial peptides now have been identified, including the important TAP-like B-defensins expressed in numerous epithelial tissues [113]. Recombinant granulysin, the T cell's antimicrobial constituent, also plays an important role in host defenses [114]. Furthermore, "gastrointestinal cells are literally immersed in a biological sea of physiologically active nucleotides," which, according to Roman and Fitz [115], play a fundamental role in the tissue-specific control of cellular functions and cellular defenses; areas with considerable therapeutic potential.
4. Lastly, the expanding investigation of genetic mechanisms of IBD, including the mutant murine studies, aided by the mapping and sequencing of the human genome projects, enhances the prospect of genetic therapy for IBD. One genetically related target already identified and under investigation is nuclear factor κB (NF-κB) [116–118], representing a family of pleiotropic transcription factors present in the cytoplasm of most cells, NF-κB controls a variety of cellular genes regulating transcriptional activity of various promoters of proinflammatory cytokines, cell surface receptors, transcription factors, and adhesion molecules involved in intestinal inflammation.

In conclusion, the outstanding scientific accomplishments of the twentieth century [119, 120] have established a promising knowledge base for continuing advances in the understanding and the treatment of IBD. We now look to the twenty-first century to finally unravel the multifactorial pathogenesis of UC and CD, an achievement that not only produces the cure for these diseases, but also clarifies other illnesses of yet obscure origins.

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Chapter 2
The Changing Epidemiology of IBD

Anders Ekbom

Keywords Inflammatory bowel disease • Crohn's disease • Regional ileitis • Kenneth Dalziel • Burrill Crohn • Ulcerative colitis • Epidemiology • North–South gradient • West–East gradient • Appendectomy • Smoking

Key Points

- Incidence rates of IBD are increasing in areas of the world previously unaffected by these diseases.
- Among children, the incidence of Crohn's disease (but not ulcerative colitis) has greatly increased.
- Age-specific incidence rates are highest for patients aged 20–40 years old.
- Specific population incidence rates first increase for ulcerative colitis, with an increase in Crohn's disease seen 15–20 years later.
- Environmental factors associated with a decreased incidence of ulcerative colitis include smoking and appendicitis.
- Smoking is associated with a greater incidence of Crohn's disease. A putative "North–South" in Northern America and Europe has been challenged by more recent studies.

Introduction

It has been possible in any given year during the last hundred years to write a review article or a book chapter titled "The changing epidemiology of IBD" which could make the case that what was written last year at least to some extent

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was obsolete. The reason for this is better methodology on how to deal with observational data but foremost is that the disease entities ulcerative colitis (UC) and Crohn's disease (CD) during the last century have affected new populations or new segments of populations. Why should we be interested in such changes? There are at least three different reasons:

1. In order to fulfill our goal of finding primary prevention measures for inflammatory bowel disease (IBD), changes in the descriptive epidemiology could provide hints of the underlying causes of these diseases.
2. These changes should serve as benchmarks when new hypothesis of the etiology are presented.
3. The numbers are of interest for providers of healthcare in order to assure that there is clinical expertise available for these patient groups.

IBD up to 1950

During the nineteenth century, there are scattered cases of UC described especially in the British literature. Already in 1909 there was a symposia held at the Royal Society of Medicine in London, where 317 patients from different hospitals were presented [1]. In 1913, Kenneth Dalziel, a Scottish surgeon, reported nine patients with a new disease entity described as "chronic intestinal enteritis and not tuberculosis" [2]. These nine patients are the first bona fide cases of CD although other patients have been described during the same time period both from Scandinavia and Ireland [3]. However, it was not until 1932 when Dr Burrill B Crohn introduced the term "regional ileitis" [4] and CD as a defined clinical entity was established.

Different case series were presented during the first half of the twentieth century, but they have in most instances one common feature; the lack of a denominator making it impossible to assess any prevalence or incidence figures. It is therefore impossible to describe any temporal trends during this time period. To use only the number of patients as a proxy is also without meaning as it is impossible to disentangle if the increasing number of IBD patients is due to a better awareness among clinicians or reflects a real increase in incidence.

However, there are two retrospective studies in defined populations from 1935 and onward, which have tried to assess the incidence. In one study from Rochester Minnesota, the authors were able to demonstrate an annual incidence for UC of 6.0/100,000 for the period 1934–1944 and an annual incidence for CD of 1.9/100,000 for the period 1935–1954 [5, 6]. In another study from Cardiff, UK, there was an annual incidence of 0.2/100,000 for CD during the period 1935–1945 [7]. Finally, there is one study of data from the US Army where the risk of discharge for an underlying cause of UC was assessed, where Jewish ethnicity was associated with an increased risk of such discharge compared to other ethnic groups [8].

Thus, in 1950 there was a growing understanding of a correlation between UC and CD (see below), the hypothesis of a Jewish ethnicity as risk factor had been formulated, and that IBD at least in some populations constituted a clinical problem of some magnitude.

1950–1975

During this period, there were an abundance of retrospective studies published from different populations, especially in Western Europe [9–12] but also in Northern America [13]. There were some common patterns with regards to the descriptive epidemiology in all these studies; there was a strong correlation between UC and CD, i.e., populations with a high incidence or mortality of UC had also a high incidence of mortality of CD and vice versa [14]. There are at least three possible partly overlapping explanations for these correlations.

1. Misclassification of either UC or CD which would lead to a false high incidence of either one of the disease entities.
2. There are shared genetic or other environmental risk factors for the two diseases.
3. It is the same disease and UC and CD represent opposite ends of a continuous spectra.

Later studies have shown an association between family occurrence of UC and CD, i.e., individuals with a family history of CD are at an increased risk for CD and vice versa [15]. However, such an association is not sufficient to explain the temporal trends for these diseases when they emerge. An increase in UC precludes an increase in CD with around 15–20 years [16]. During this transition period, the increase in incidence and the age distribution will change. Populations with a low annual incidence have an almost flat age-specific incidence, but during the transition from low incidence to high the increase is most pronounced in the age group of 20–40 years both for UC and CD [9, 17]. Although there have been quite a few reports about a second peak in older ages (60+), the existence of such peak remains controversial, and it has been argued that this second peak represents a delayed diagnosis made when the disease relapses [7].

There were also rather small variations in the incidence figures after the transition period 4.0–8.0/100,000 for CD and 15–20/100,000 for UC [16]. Moreover, the age-specific incidence was similar in most populations, such as Sweden and Olmsted County, USA [16, 18, 19]. It is also worth pointing out that due to the differences in the start of the transition period, the prevalence figures could vary substantially in different populations although they had the same annual incidence. This means that prevalence figures are highly unreliable tools to compare the occurrence of IBD in different populations or over time.

Other features which changed during this period were the phenotypes, such as the extent of the disease and localization. In the 1960s, ulcerative proctitis or distal colitis emerged as a specific phenotype [20] as common as pancolitis in patients with UC [16]. In the case of CD, distal ileitis had been the normal feature, but during the 1960s a new phenotype + Crohn's colitis was described [21]. This disease entity had probably to some extent previously been categorized as UC, but it was obvious that this clinical phenotype became more frequent during the second part of the twentieth century.

During this period, the first reports were published of cigarette smoking as a protective factor against UC [22, 23]. Many exposures, especially dietary, such as

refined sugar, margarine, etc., was proposed as etiological exposures, but the results from analytical studies did not show consistent results [24]. Jewish ethnicity and high socioeconomic status were repeatedly shown to be associated with an increased risk of IBD [11, 25]. However, these studies were in most instances small and with a study design, which was not always optimal.

1975–2000

During this time period, an ever increasing number of retrospective studies were published with descriptive data from different parts of the world although mainly Western Europe and Northern America. It then became obvious that some new characteristics of IBD had emerged as follows;

1. There were reports of a North–South gradient in the occurrence of IBD both from Northern America and Europe [26] in the first half of the period an observation which was challenged in the later part of the period [27] and a "new" hypothesis emerged speculating in a West–East gradient.
2. The incidence of IBD seems to respect national borders [28, 29] although there are exceptions such as in Greece where Crete has higher incidence than the rest of the country [30, 31].
3. In some populations, a birth-cohort effect could be demonstrated [16, 32] indicating that early exposures are of importance in the etiology of IBD.
4. In line with this good hygiene during childhood was repeatedly implicated as a risk factor both directly and indirectly [33, 34].
5. Previous findings of high socioeconomic status as a risk factor for IBD was contradicted in studies from this period and even a reverse association was found [35].
6. Incidence studies from Israel did challenge the notion of Jewish ethnicity as an independent risk factor as the incidence of IBD in Israel did not differ from populations in Western Europe and Northern America [27].
7. Immigration studies especially from the UK also showed that second generation immigrants from the West Indies [36] and the Indian subcontinent [37, 38] had the same or even higher incidence of IBD as the background population casting doubts of a special vulnerability among Caucasians.
8. Minorities often with a lower socioeconomic status, such as Maoris in New Zealand [39], Bedouins in Israel [40], and Aboriginals in Canada [41] were found to be at a substantially lower risk for IBD.
9. The pattern of a higher incidence in UC compared to CD turned out not to be a generalized phenomena when studies from France [27] and some parts of Canada [42] were able to demonstrate the opposite.

During this period, the first prospective studies of the incidence in IBD were published [27, 43], highlighting the problem of indeterminate colitis [44] something which can be downplayed in retrospective studies. Indeterminate colitis

turned out to be much more common than previously thought [45] and it still remains to be established if it is an entity of its own. The most prominent prospective study was a collaborative effort from 20 European centers 1991–1993. The study was able to demonstrate that the North–South gradient seemingly was history and that the incidences of IBD in different populations throughout Europe were remarkably uniform [27].

Smoking remained the only environmental factor which consistently was associated with IBD; as a protective factor for UC and a risk factor for CD [46, 47], in the latter case smoking also seems to aggravate the disease course [48]. Ex-smoking status, on the other hand, seems to increase the risk of UC [49]. Oral contraceptive use was also implicated as a risk factor for CD [50], especially in the USA [51], but a female predominance of CD in high incidence areas was already present before the introduction of oral contraceptives in the 1960s. Mycobacterium paratuberculosis, already hypothesized as an etiological factor by Dalziel in 1913 [2], was proposed repeatedly [52, 53] and studied extensively during this period but no causal association could be established [54]. A new association was also identified for UC as appendectomy was shown to be protective against UC [55, 56]. However, in-depth studies seemingly revealed that it was the underlying appendicitis at a younger age that was protective not the appendectomy as such [57]. This is of great interest as the change for the incidence for appendicitis also remains an enigma similar to that of IBD and interestingly early hygiene exposures has been hypothesized to be an underlying cause [58].

Thus, in the end of the last century, we were facing an epidemic of IBD so far mainly affecting Western Europe and Northern America, where it had become one of the most common patient groups for gastroenterologists. The scientific community had failed to identify any primary preventative measures as the underlying etiology remained elusive. Smoking, as a protective factor for UC, identified already in the 1950s was the only environmental factor, where a casual association had been established.

2000 and Onward

The beginning of the twenty-first century meant that some of the established facts of the descriptive epidemiology of IBD were challenged again. The notion that the maximum annual incidence for CD in high incidence population was below 10.0/100,000 was contradicted by findings from Canada, where incidence figures as high as 20/100,000 were reported [59]. However, the data source can be questioned, but incidence figures from Norway [60] and New Zealand [39] also yielded higher numbers than previously experienced. IBD in children had, during the twentieth century, been seen as a rarity [61], but reports starting in Scotland [62] and later from Sweden [63, 64] could show a remarkable increase in incidence in CD in children but a stable incidence for UC.

Outside Western Europe and Northern America, we can now follow a pattern in the incidence of IBD similar to that we experienced around 1950:

1. Eastern Europe: Incidence figures from Hungary [65] clearly indicates that the transition period is over and that Hungary now has a pattern similar to Western Europe, while Croatia seems to be in the transition period [66]. This is contrast to the neighboring countries, such as Poland [67], Romania [68], and Slovakia [69], all of which still have a low incidence.
2. Southern America and Caribbean: Puerto Rico [70] and Barbados [71] have started to show an increase in incidence, and there are indications that a similar phenomenon is under way in Chile [72] and Brazil [73].
3. Africa: With the exception of South Africa, where those with a Caucasian background have an incidence similar to that of Western Europe [25], information is scarce but there are no indications of a rise in incidence.
4. Middle East with the exception of Israel: Although there is still a low incidence, there are signs of an increase in Lebanon [74], Saudi Arabia [75], and Iran [76].
5. India: In a very thorough cross-sectional study in Punjab, the authors could report an incidence figure for UC of 6.0/100,000 [77] perhaps indicating a start of a transition to a higher incidence.
6. China: There is almost a total lack of descriptive epidemiologic data, but there are indications of an emerging raise in the urban population for UC [78] and the consensus at the 2004 Asian Pacific Week in Beijing, China was: "A progressive rise in the prevalence of IBD is discernable in most Asian Pacific countries, more so for UC than CD" [79].
7. Korea and Japan: Incidence and prevalence figures of IBD during the twentieth century indicated a low incidence [80, 81], but the number of patients which have been presented especially from Japan [82] indicates that the incidence is substantially higher than previously thought.
8. Australia and New Zealand: The incidence figures and temporal trends seem to be same as in Western Europe and Northern America [39].

The analytical studies which have been done in these low incidence populations have not yielded any new information; smoking, family history of IBD, oral contraceptive use, and appendectomy have emerged as risk or protective factors with risk estimates similar to those reported from high incidence populations [82–84]. The only exception is high socioeconomic standard which is associated with an increased risk similar to that in Western Europe and Northern America 25–50 years ago.

Conclusions

The last hundred years have taught us a lot of the descriptive epidemiology of IBD, and we can now with some certainty postulate what will happen in the next 20 years in what is at present low incidence population. There will be an increase and there

will be reasons to believe that IBD patients will, in the future, constitute a major part of the patients for gastroenterologists in Asia, Southern America, as well as East Europe. Hopefully, the access to these patient groups will enable the research community to find the underlying etiology in order to find strategies for primary prevention, but such an endeavor urgently needs new hypothesis. We do not need etiological studies of smoking, oral contraceptives without better characterization of the underlying phenotype and potential interactions with different genotypes.

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Chapter 3
Recent Advances in the Genetics of IBD

Russell D. Cohen

Keywords Crohn's disease • Ulcerative colitis • Inflammatory bowel disease • *NOD2* • MHC HLA class II • *5q31* • TNF • Pharmacogenetics • NF-κB • Leucine-rich repeat • Lipopolysaccharide • Toll-like receptor • IL-10 • *MyoIXb* gene • *Multidrug-resistance* gene • *IBD5* • Genome-wide association studies • *Interleukin-23 receptor* • *ATG16L* • *IRGM* • *5p13* • Wellcome Trust Case Control Consortium

Key Points

- The *NOD2* gene's role in Crohn's disease has been verified in ancestry cohorts of European, but not Asian or African descent.
- Although homozygous or compound heterozygous carriage of *NOD* confers a 17-fold increased risk of Crohn's disease, less than 10% develops CD, due to genetic penetrance.
- The class II MHC gene association that have been identified have been specifically for colitis (Crohn's or ulcerative), rather than small bowel Crohn's disease.
- Genome-wide association studies (GWAS) have resulted in the rapid identification of multiple previously unknown or unverified IBD-related alleles, with the promise of many future findings.
- The *interleukin-23 receptor gene (IL-23R)* has been identified as an IBD susceptibility gene for both Crohn's and colitis, and may be involved in signaling between luminal bacteria and fungi.
- *ATG16L* and *IRGM* have been identified as important IBD genes involved in cell autography, important in cell-mediated inflammatory pathways.

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- Until recently, there were very few GWAS-identified gene loci specific to ulcerative colitis, raising the possibility that environmental interactions play a more important role that in the predominantly genetic-based Crohn's disease. However, now there is more overlap between the two major types of IBD.

Introduction

The genetics of inflammatory bowel disease (IBD) has exploded since the first edition of *Inflammatory Bowel Disease: Diagnosis and Therapeutics* was published in 2003. Extensive gene-wide association studies (GWAS) have led to the identification of new, robust genetic associations within Crohn's disease (CD), ulcerative colitis (UC), or general IBD. Much has been discovered about the first IBD gene definitively identified, the nucleotide oligomerization domain (*NOD2*) gene, with extensive studies on *NOD2* polymorphisms, clinical phenotypes, and predictive course of disease. Subsequent studies have identified CD associations with chromosome 5q31, MHC HLA class II, TNF superfamily of genes, and most recently the interleukin-23 receptor (IL-23R). The implications of linking genetic families with therapeutic agents currently in testing or in production for the treatment of IBD brings us closer to the "holy grail" of pharmacogenetics, which is of particular importance in the new world of costly biological treatment options and limited economic resources.

NOD2: What's New?

The *NOD2* gene, identified as the CD susceptibility gene at IBD1, was simultaneously discovered by a consortium of US [1] and European investigators [2], and is located on chromosome 16q12. The NOD2 protein activates NF-κB as well as mitogen-activated protein kinase pathways after being stimulated by peptidoglycan, which is found in bacterial cell walls [3, 4]. The last portion of NOD2 contains the leucine rich repeat (LRR) domain, which is required for lipopolysaccharide (LPS) activation of NF-κB. The LRR is the location of various mutations identified in CD patients. The three best studied variants are *Arg702Trp*, *GLy908Arg*, and *Leu1007fsinsC*. Analyses have linked each of these (independently) to an increased risk for isolated ileal CD or to ileocolonic CD (but not colonic CD or UC) [1, 2, 5]. The heterozygous carriage rates of any of these three alleles is estimated to increase the risk of CD 2.4-fold, while homozygous or compound heterozygous carriage increases the risk to 17.1-fold [6]

However, some important caveats require mention. The first is that even among the latter group of homozygous or compound heterozygous carriers, less than 10% ultimately develops CD, due to genetic penetrance [7, 8]. A large Danish study of

43,596 persons found the penetrance to be extremely low at only 0.30% for heterozygotes (95% CI 0.29–0.31%) and 1.5% (95% CI 1.4–1.6%) for compound heterozygotes and homozygotes, casting great doubt upon the value of genetic testing in this population [9]. The other important points are that the forementioned studies were done in patient populations descendant from European ancestry. The genetic basis of CD is not the same worldwide, as these three major CD mutations have not been implicated in CD patients of African [10] or Asian descent [11, 12].

The clinical implications of *NOD2* polymorphisms have been the focus of many investigations. The *NOD2* mutations have been linked to CD with the early age of onset, small bowel disease (ileal or ileocolonic) [1, 2, 5, 13], and an increase in fibrostenotic, stricturing [14], and penetrating disease [15, 16]. *NOD2* variants have been linked to faster progression to surgery, especially in smokers [15], as well as reoperation following CD surgery [17, 18]. However, there has not been a clear relationship between *NOD2* and CD disease progression [19].

Many investigators have also studied the relationship between the *NOD2* mutations and therapeutic response to therapy. There was no such relationship found with infliximab [20], although the mutants did predict failure of antibiotic therapy in perianal CD [21].

The NOD2 story fits in well with the long-standing hypothesis that CD results from a dysregulated immune response to the gut luminal bacteria. Stimulation of NOD2 results in an array of immune-mediated events, such as stimulation of the release of cytokines, the release of reaction oxygen species and antimicrobial peptides, as well as impacting intracellular trafficking and killing of intracellular microbes [22]. The importance of NOD2 directed responses against "common" intestinal pathogens may be specific for oral, but no systemic exposure [23]. NOD2 has been identified as important in host defenses against *Streptococci* [24], *Salmonella* [25], *Listeria* [26], and mycobacterium species [27]. There may also be an altered epithelial permeability, with relatives having *NOD2* variants showing increased mucosal permeability compared to wild-type relatives [28]. Mouse models have shown that a deficiency in NOD2 results in excessive intestinal inflammation when not only challenged with pathogenic, but also with commensal bacteria, leading to the chronic intestinal inflammation characterizing CD [22].

Beyond *NOD2*: Other Intriguing IBD Genetic Associations

There are numerous other genes that have been identified as being involved in some patient groups with IBD; a few of the major ones are discussed below. In addition, there has been much attention directed at *NOD1* [29–31], alleles within the Toll-like receptor (TLR) 4 [32], the IL-10 receptor [33], the *MyoIXb* gene [34], and the *multidrug-resistance gene* [35]. For more comprehensive list, readers are directed to some recent review articles in the field [36–39].

HLA Class II MHC Genes

There has been much attention to the major histocompatibility complex (MHC) region in the search for IBD-related genes, as many associations have been identified in this area. This is particularly true for the class II region, where there are genes that encode the heterodimeric receptor on antigen-presenting cells [36]. As opposed to the *NOD2* variants, the class II MHC gene associations are mostly for colitis (ulcerative colitis, or colonic CD). *HLA-DRB1*0103* is unique in that it has been identified as a risk factor for both CD and UC [40, 41], while *HLA-DRB1*1502* is associated solely with UC [42].

IBD5

The *IBD5* gene has been identified on chromosome 5q31, and has been linked to CD, possibly to UC. While these alleles are frequently observed in Ashkenazi Jews, the association with IBD is exclusively with the non-Jewish population. Furthermore, there has been no clear association identified with CD type or location, although there is some data to suggest a possible association with UC [43]. *IBD5* does not appear to play a role in Japanese IBD patients [44], but has been linked with CD in a Swedish IBD population [45]. The University of Manitoba IBD Registry identified an independent association of *IBD5-IGR2230* with CD in that province's Canadian population (OR 2.16; 95% CI 1.30–3.59), with a penetrance for *IBD5* of 0.27% for heterozygotes and 0.44% for homozygotes [46]. There also may be a possible epistatic interaction between *IBD5* and *NOD2* in the development of UC [47].

The *IBD5* gene has been associated with colonic disease [48], perianal disease [49], CD progression [50, 51], CD severity [50, 51], as well as possible associations with UC [47, 51–53]. The *Leu503Phe* variant in *SLC22A4* has been of particular interest, and the topic of ongoing investigations into the functional variants of the region [36].

Genome-Wide Association Studies

One of the most notable breakthroughs in the past 5 years has been the emergence of new technologies that has allowed for GWAS to be utilized in the search for genetic relationships in biology, including the medical classification, treatment, and possibly the prevention of disease. The first major finding that was reported was the identification of polymorphisms in the tumor necrosis factor superfamily gene *TNFSF15* on chromosome 9q32, important in upregulating inflammatory cells in intestinal lamina propria [54, 55] in Japanese (and not European) CD patients. Early studies by a few consortiums verified the genetic breakthroughs of the previous decade, as well as

slowly opened a spigot of new genetic loci for CD, ulcerative colitis, and "IBD" in general. A few of the more notable findings are discussed below:

IL-23R

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Genetics Consortium of American and Canadian investigators identified the *IL-23R* gene as an IBD susceptibility gene [56]. Case-control and cohort studies have identified *IL-23R* as playing a role in CD (Jewish and non-Jewish), and in UC adults and children [56–65]. The strongest association within the *IL-23R* family is the *Arg381Gln* polymorphism, which is strongly protective against non-Jewish CD (OR 0.26; 95% CI 0.15–0.43) [36]. The University of Manitoba IBD Registry identified an independent association of *IL-23R-rs10889677* with CD (OR 2.13; 95% CI 1.39–3.28), with a penetrance of 0.37% [46].

The role of the *IL-23R* in IBD has not been replicated in studies of Japanese CD cohorts [66], once again showing the complexity of the genetic relationships in IBD, as well as the difficulty in applying GWAS data culled almost exclusively from European cohorts to other racial groups.

As IL-12/23 targeted therapies are now available for the treatment of psoriasis, and under investigation for other inflammatory diseases, including IBD [67], there has been much attention paid to IL-23R, as well as the IL-23 cytokine's interactions within the immune response. The IL-23R is composed of the IL-23R subunit (chromosome 1p31), and the IL12RB1subunit (chromosome 19p130) [36]. The IL-23 cytokine also is heterodimeric; its p19 subunit is encoded on chromosome 12q13, and the p40 subunit on chromosome 5q33. IL-23 is thought to have an essential role in the development of Th17 cells, which have recently been implicated as critical components in the inflammatory response characteristic of IBD and other related conditions [68–70].

What is particularly intriguing about the IL-23 system is the role that it plays in the innate immune system, and induction of the p19 subunit by bacteria and fungi [71, 72]. There has been a suggested mediation of the stimulation of IL-23 via NOD1 [73], giving further credence toward the interaction of the innate immune system with luminal microbes as an important underlying pathogenic mechanism in IBD.

ATG16L and *IRGM*: Autography Genes

The NIDDK consortium also first presented findings of the autography gene, *ATG16L1*, in the early throes of the GWAS era. Essential for all forms of autophagy, the *ATG16L1*300A* has been associated with CD susceptibility through a single SNP *Ala197Thr*, while the *ATG16L1*300T* is a protective allele *against* the development of Crohn's disease [74–77]. The University of Manitoba IBD Registry

identified an independent association of *ATG16L1* with CD in the Canadian population (OR 1.8; 95% CI 1.09–3.24), with a penetrance of 0.27% for heterozygotes and 0.35% for homozygotes [46]. *ATG16L1* is specific to CD; there are conflicting studies regarding an association with *NOD2* loci, adding speculative fuel to the fire of an altered host–microbe interaction as the underlying pathogenesis of CD mediated inflammation [36, 77, 78].

The other autography gene of interest is *IRGM*. Expression of *IRGM* has been linked to the efficacy of autography, with CD associated with multiple SNPs around *IRGM* [60]. The CD-associated SNP has been identified to be at a 20-kb deletion polymorphism immediately upstream from *IRGM* [79]. The association with *IRGM* with CD needs further studies. Analysis in a Canadian pediatric Crohn's cohort failed to show such an association, while verifying an *ATG16L1* link [80]. Phylogenetic analyses suggest that most of the *IRG* gene family was deleted early in primate evolution, perhaps 50 million years ago. Subsequently, it has been hypothesized that the gene family was "resurrected" through a complex process of insertion of an endogenous retrovirus, altering the initiation of transcription and splicing of *IRGM* [81].

5p13

At about the same time, a French–Belgium consortium announced a novel CD locus on chromosome 5p13.1, an important modulator of the expression of the prostaglandin receptor EP4 (PTGER4) [64]. Mouse models suggesting a protective role of PTGER4 fueled initial excitement in this area; however, it is unclear whether the subsequent studies of the various SNPs have truly uncovered the exact relationship with IBD, specifically CD [82]. More recently, a Spanish analysis of 709 CD, 662 UC, and 1,360 controls validated the association of *5p13* in CD (OR 1.23); there was no association with either UC or an additional group of 605 patients with rheumatoid arthritis [83].

Wellcome Trust Study

The initial GWA findings, along with the initial genetic studies identifying *NOD2* and *IBD5* as candidate genes in CD, were all part of a large "summary" trial by the Wellcome Trust Case Control Consortium [62]. This meta-analysis of the NIDDK, French–Belgium consortium, and Wellcome Trust GWAS looked at 3,230 cases, and 4,829 controls, with 633,548 SNPs. The study identified 32 regions with significant replication evidence, with a combined genome-wide significant "*p* value" of 5×10^{-8}. Genes were classified into groups by function; some imparting innate immunity (such as *NOD2*, *ATG16L1*, and *IRGM*) while others identified as part of the IL-23/IL-17 pathway (such as *IL-23R*, *IL-12B*, *JAK2*, *STAT3*, and *CCR6*).

These findings were replicated in an analysis of 2,731 IBD patients (1,656 CD; 1,075 UC) and 1,086 from Dutch and Belgian populations. Associations were confirmed with *IL-23R*, *ATG16L1*, *IRGM*, *1q24*, *5p13*, *10q21*, and *NKX2-3*. In addition, associations were found with *cyclin Y*, *Hect domain*, and *RCC1-like domain 2* [84].

Additional Novel Loci

GWAS analysis in 393 German CD cases and 399 controls identified a novel SNP *rs1793004* in the gene encoding nel-like 1 precursor (*NELL1*, chromosome 11p15.1). This finding was subsequently replicated in an independent sample of 454 French/Canadian trios, and then confirmed in a large German UC sample (OR = 1.66, 95% CI: 1.30–2.11). In addition, the *NOD2*, *5q31*, and *5p13.1* loci were confirmed in both the German CD while the *5p13.1* loci replicated in the French/Canadian CD group as well as a UK CD patient panel [85].

The Quebec Founder Population family trio study, which included the replication of findings in two independent German cohorts, confirmed previous findings for CD loci at the *NOD2* and *IBD5* region, as well as the *IL-23R* loci [86]. Novel associations were also identified on 4p16.1, 17q11 and 17q23. The 4p16.1 included two important candidate genes: *JAKMIP1* (involved in IL-23 signaling) and *LOC285484*. In addition, several possible candidate genes were identified on 3p21.

Ulcerative Colitis GWAS Studies

Far fewer robust genetic associations have been established in UC than in CD. While some of the genes discussed above had SNPs with associations in ulcerative colitis, many times the data was conflicting and difficult to reconcile, suggesting that the relationships were inconclusive, at best. For example, the *Arg381Gln* allele of *IL-23R* is protective against the development of ulcerative colitis, although most of the genetic relationships for *IL-23R* have been with the Crohn's loci [56, 61]. In the case of the HLA Class II region, there are stronger associations with colonic disease (notably ulcerative colitis) with *HLA-DRB1*1502* (*HLA-DR2*) and *HLA-DRB1*0103* [40–42]. The NIDDK IBD Genetics Consortium identified ulcerative colitis-related genetic loci on chromosomes 1p36 and 12q15. However, until recently, there are still very few GWAS-identified gene loci specific to ulcerative colitis, raising the possibility that environmental interactions play a more important role that in the predominantly genetic-based CD.

The dearth of genetic linkage findings in UC has subsequently been supplemented by numerous findings within the past 2 years. A GWA study in 1,052 UC patients and 2,571 controls (all of European descent) identified loci on 1p36, 12q15, and 6p21, as well as at the *IL-23R* loci on 1p31 [87, 88]. Subsequently, a two-stage GWA study in 1,384 Japanese patients with UC and 3,057 controls not only confirmed the association with the MHC, but also identified three new loci: the immunoglobulin receptor FCGR2A, the glycoprotein gene *SLC26A3*, and a loci at 13q12 [89]. Simultaneously, the UK IBD consortium identified three other new loci, 20q13, 16q22, and 7q31, in a genotyping of 2,321 UC patients and 5,417 controls, after an initial GWA scan in 2,361 UC cases, and 5,417 controls [90]. Of great interest was the *16q22 CDH1* locus, as *CDH1* has also been implicated in an increased susceptibility to colorectal cancer.

In 2010, a breakthrough article was published in Nature Genetics consisting of a joint analysis of two distinct GWAs in UC [91]. The researchers identified 59 SNPs from 14 independent loci, seven of which met the GWA statistical significance level of $p < 10^{-5}$. These were then tested in a cohort of over 2,000 patients with UC and 1,580 controls, leading to the identification of 13 loci associated with UC. Prominent among the findings were the *5p15*, *2p16*, the immunoglobulin receptor gene *FCGR2A*, and *ORMDL3*. The group also determined that approximately one-half of the known CD loci were shared with UC.

The Genetic Future

We are truly just at the dawn of the GWAS-directed studies; as more large data sets become available, it is anticipated that many of the initial findings described in this chapter become more refined and additional relationships with other candidate genes confirmed, or refuted. Many of these findings, such as the *NOD* family of genes, *IL-23R*, and the autography gene *ATG16L* give further credence to the hypothesis that the core principle behind the pathogenesis of IBD is a dysregulation of the immune responses' interactions with a variety of microbes that inhabit the human gut; potentially "normal" or commensal flora, pathogens, or both … or either!

However, there are potentially other environmental – genetic interactions that may account for the predisposition, pathogenesis, or phenotypic expression of disease that have yet to be discovered. For example, the advances thus far have not adequately accounted for the discordant presence, or presentation, of disease in monozygotic twins, in whom luminal flora and other environmental exposures are typically nearly identical as the persons themselves. The role of certain environmental factors, such as exposure to cigarette smoking also begs further explanation. Many of the proposed explanations center around immune reactions [92]; however, it is less clear how activities such as smoking *cessation* can be so classically implicated as they are in patients with new-onset UC [93–96].

Further expansion of knowledge of the MHC-region of genes holds the promise of unlocking further insights into the basis, and perhaps treatment, of multiple immune-related ailments. In the "IBD-world," this is an area of great interest as the differences between CD and UC are more clearly elucidated, and more precise classifications of IBD are identified and verified. Coupled with this are the exciting new GWA findings in UC that will hopefully unveil some of the complex genetic interactions that must exist for this condition, or conditions, and potentially identify more precise targets for therapeutic interventions.

Our classification of IBD as purely "CD," "ulcerative colitis," or "unsure … indeterminate colitis" also potentially become a footnote in future textbooks as GWAS allow us finally to subclassify these diseases, and potentially their optimal therapeutic approaches … medical and/or surgical. Predicting which patients with UC truly benefits from a total proctocolectomy with ileo-pouch anal anastomosis, as opposed to those who develop chronic unrelenting pouchitis or CD is one example.

The risk of surgical recurrence after CD resection is another, as is the predicted disease course after an ostomy.

The possibilities are truly endless as we unravel the genetic codes behind disease such as IBD, but that does not necessarily mean that all outcomes in fact are due to the genetics, or that they are all revealed. One could hope that GWAS and other genetic advances allow for further understanding, and prediction, for the development of colorectal cancer in IBD, or other neoplasms in related immune diseases; these "pie-in-the-sky" scenarios may seem as far-fetched to us today as many of today's findings were just a decade ago. The promise of tomorrow is what keeps many of those suffering, or caring for the suffering, still moving forward today.

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Chapter 4
New Paradigms in the Pathogenesis of IBD

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Keywords Inflammatory bowel disease • Ulcerative colitis • Crohn's disease • Pathogenesis • Commensal flora • Mucosal immune system • Innate immunity • Adaptive immunity • Microbial clearance • Cytokines

Key Points

- IBD patients are genetically predisposed to a dysregulated interaction between commensal bacteria and the intestinal mucosal immune system.
- Environmental factors trigger the initial presentation and possibly recurrent episodes of disease.
- IBD most probably is the result of defective bacterial clearance from the lamina propria of the gut.
- Proposed defective mechanisms include impairment of the epithelial integrity, defective production of antimicrobial peptides, and flawed intracellular handling of bacterial products.
- IBD pathogenesis is now thought to be due to these flaws in the innate immune system along with "dysbiosis" of the commensal instestinal flora.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are collectively referred to as the inflammatory bowel diseases (IBD). Common features of the two conditions include primary localization to the GI tract, a chronic course with alternating

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periods of remission and recurrence, inflammatory infiltration of the bowel wall, association with systemic and extra-intestinal manifestations, and unknown etiology. However, UC and CD also exhibit several individual features that distinguish them as separate diseases. For UC, these include confinement of disease activity to the large intestine with universal rectal involvement and continuous mucosal inflammation. In contrast, CD is characterized by transmural and discontinuous inflammation that may affect any part of the GI tract, typically with rectal sparing. In addition, fistulous tracts are often formed in CD that allow for abnormal communication between the bowel and internal organs or the skin. The similarities between the two conditions point to a common immunogenetic background, whereas their distinct features indicate the existence of unique pathogenic mechanisms as well.

In recent years, intense research in the field of IBD has generated great progress toward our understanding of the effector mechanisms that mediate intestinal inflammation [1]. At the same time, the predisposing genetic alterations that underlie IBD are being rapidly elucidated [2]. Finally, we have gained considerable knowledge of the environmental factors that trigger the development of intestinal inflammation. The convergence of information from these research areas has led to the synthesis of a novel conceptual framework outlining the pathogenesis of IBD [3].

Sources of Information

Information regarding the IBD pathogenesis originated mainly from the following areas: animal models of intestinal inflammation, genetic association studies, translational research studies in humans, and finally, clinical observations. Each of these investigative arenas has contributed to our current knowledge of the pathogenesis of the disease. Nevertheless, the advantages and limitations of each study have to be kept in mind when interpreting the findings and fitting them into a pathogenetic model for the clinical condition.

Animal models of intestinal inflammation are important investigative tools that allow experimental manipulations that would be impossible to perform in humans. [4, 5] Using mice that are genetically modified to lack or overexpress a particular gene, we can definitively explore the role of single molecules and well-defined pathways in the development of intestinal inflammation. However, the theory of participation of these specific pathways in the human disease is usually derived from the original hypothesis and not necessarily based on clinical evidence. Therefore, caution is required before applying experimental results obtained in genetically modified mice more broadly to the clinical condition in humans, as this does not always prove to be the case. In this regard, information obtained from the few available spontaneous (i.e., nonchemical, nongenetically engineered) models of chronic intestinal inflammation, is far more applicable to the human condition [6–8].

Identification of genetic associations in IBD has been greatly facilitated in recent years due to the availability of genome-wide association studies [9, 10]. At present, at least 30 mutant loci have been associated with CD susceptibility, and the situation is similar in UC. However, due to the level of disease, heterogeneity identified genetic associations that need to be reproduced in multiple patient populations before they can be considered a major contributing factor to pathogenesis.

These drawbacks notwithstanding, there are several important conclusions that can be drawn from both animal and genetic studies regarding the pathogenesis of IBD. *First,* it is clear that defects in several unrelated pathways lead to intestinal inflammation. Indeed, deletion or overexpression of various genes in mice can lead to colitis, and multiple genetic associations have been described in human IBD. *Second*, some homogeneity does exist among the various associations since the identified genes encode molecules that generally fall into a few functional classes: factors involved in the integrity of the epithelial barrier, factors that participate in the clearance of bacteria, and components of the intestinal immune response. *Third*, no matter how diverse the starting points may be, there appear to be some common downstream effector pathways for the induction and maintenance of intestinal inflammation that offer unique therapeutic targets, even when the primary trigger is not known. *Finally*, there is general agreement that the antigenic stimuli that triggers and maintains the inflammatory response in the intestinal mucosa is of bacterial origin, and specifically involves commensals that inhabit the enteric lumen.

These general conclusions have led to the evolution of a new conceptual framework for the pathogenesis of IBD [11]. The central abnormality in IBD appears to be a deficient interaction between the mucosal immune system and bacterial antigens from the commensal flora [12]. Genetic predisposition confers a defect in the way that the innate immune system senses microorganisms and/or in the integrity of the epithelial barrier. Finally, an environmental factor may be necessary for the two counterparts of the dysregulated immune response to come into close contact and the genetic abnormalities to be revealed [13].

Novel Pathogenetic Hypotheses

The most unique characteristic of the intestinal mucosa is its close proximity to a tremendous number of microorganisms composing the commensal flora. In fact, from an immunological standpoint, if one considers one gram of fecal material in the context of 1 g of intestinal tissue, there are approximately 10^{12} microorganisms versus 10^{6} lymphocytes [14]. It becomes therefore obvious that any uncontrolled contact between these two elements would lead to a catastrophic inflammatory reaction [15, 16]. For such an event to be avoided, the enteric mucosal has developed a series of defensive barriers whose function is to prevent or at least regulate the contact between gut bacteria and the mucosal immune system (Fig. 4.1). The first line of defense is the intestinal epithelial barrier, which maintains its integrity

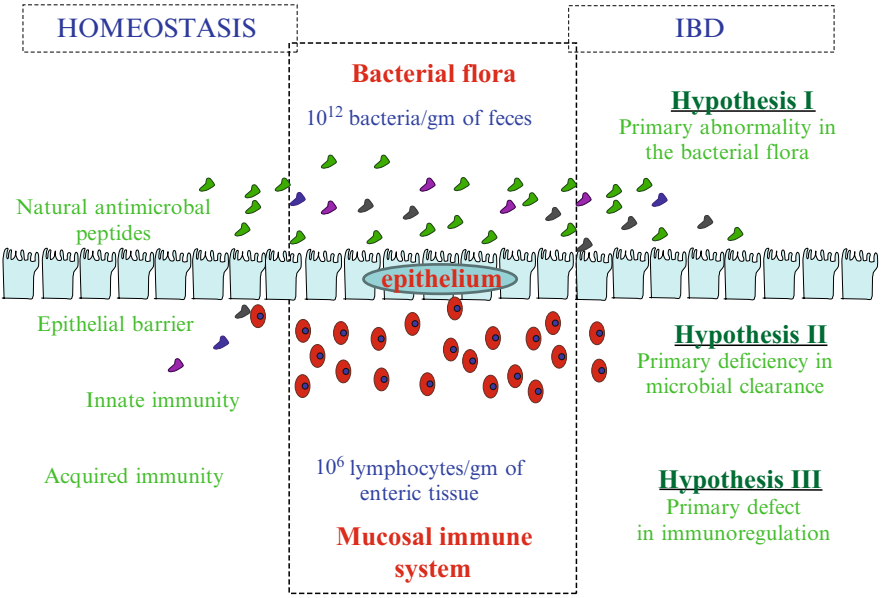

Fig. 4.1 Homeostasis in the intestinal mucosa is maintained through the function of consequent barriers, which act by preventing and controlling the contact between microorganisms of the commensal flora and the cells of the mucosal immune system. In IBD, this homeostasis is broken, either as a result of abnormal composition of the flora or as the consequence of defects in one or more protective barriers

through a layer of epithelial cells joined together by tight junctions between the enterocytes, along with a mucus layer and a number of repair elements, such as the trefoil factors. The role of these factors is to mechanically isolate intestinal bacteria from the immunocytes contained within the lamina propria compartment. Contact between the two is nonetheless unavoidable and to a certain point desirable as it contributes to the proper development and function of the mucosal immune system. As such, the defensive mechanisms of the epithelial barrier are therefore aimed at maintaining this occasional interaction at a subclinical level without inducing deleterious inflammatory responses. Initially, this is achieved by the antimicrobial defense mechanisms of the mucosa. These include the secretion of natural antimicrobial peptides and secretory IgA and IgM, as well as the rapid clearance of invading microorganisms by cells of the innate immune system. The final layer of defense is that of the acquired immune system, which has adopted a unique type of response against microbial products from the bacterial flora. This consists of limited pro-inflammatory and enhanced regulatory responses that result in the confinement of the occasional intruding bacterium without provoking a strong and deleterious pro-inflammatory reaction. This careful mucosal homeostasis is broken during active IBD. The current paradigm for IBD pathogenesis

proposes a primary failure in a single or multiple elements of the innate intestinal mucosal defense, culminating in a dysregulated adaptive immune response and chronic mucosal inflammation.

Abnormal Composition of the Intestinal Flora

In recent years, great advances have been made in understanding the diversity of the intestinal commensal flora, mainly due the introduction of molecular techniques for the identification of the inhabiting microorganisms. Classical microbiological culture methodology recovered only a small proportion of the intestinal microflora. Nowadays, a full molecular armamentarium exists that consists of nucleic acid-based profiling methods, such as PCR-based amplification of bacterial DNA specific for 16s or rRNA regions, fluorescent in situ hybridization (FISH) with species-specific probes, and analysis of 16s RNA gene sequence libraries [17–19]. These techniques have allowed a compositional comparison of the total microbiome between patients with IBD and healthy controls [20, 21]. In addition, isolation of bacterial DNA directly from washed intestinal biopsies, rather than from fecal matter has allowed the identification of microorganisms that are specifically adherent to the intestinal mucosa rather than just components of the intraluminal flora [22]. One conclusion that has been drawn from experiments using these new methods is that no single pathogen appears to be exclusively present in samples from IBD patients. Therefore, the theory that CD result from a latent, chronic infection, most likely with an intracellular microorganism (i.e., MAP), is not supported by strong experimental evidence. In contrast, a broader derangement of the composition of bacterial flora, especially the mucosal-adherent microorganisms, may exist in patients with IBD.

Dysbiosis. Recent studies have indicated that patients with IBD have a relative imbalance between beneficial and potentially harmful intestinal bacteria. These studies have mainly focused on the mucosal-adherent populations. In one study, a detailed phylogenetic characterization of intestinal flora from almost two hundred IBD patients and healthy controls identified a subpopulation of IBD patients with a selective decrease in the proportion of microorganisms that belong to the phyla *Firmicutes* and *Bacteroidetes* [23]. Members of these phyla are involved in the generation of butyrate and other short chain fatty acids. The latter are among the most important energy sources for enterocytes [24]. In addition, they have been shown to act as anti-inflammatory factors in the intestines [25]. It follows that the selective reduction of these microorganisms in patients with IBD may lead to deprivation of valuable nutritional elements, dysfunction of enterocytes, and eventually breakdown of the epithelial barrier. Similar findings were reported in another study, where the concentrations of short chain fatty acids were actually measured in the feces of IBD patients and found to be reduced [26]. Interestingly, the number of *Bacteroidetes* attached to the mucosa was also diminished in this study. These and other studies raise the possibility that at least a subset of patients with IBD has distinct alterations of their flora [22, 27]. However, the enormous diversity of the

human intestinal microbiome makes it extremely difficult to translate these findings into meaningful therapeutic interference at this time.

Adherent-invasive Escherichia coli (AIEC). AIEC is a strain of *E. coli* that has a number of virulent factors, which allow it to successfully invade the intestinal mucosa. These facilitating factors include adherence to epithelial cells via type 1 villi, invasion of macrophages via active microfilament and microtubule-dependent mechanisms, and persistence and survival within phagocytes with subsequent TNF-α secretion but no apoptosis [28–30]. Therefore, AIEC has the ability to act as an intracellular bacterium and causes persistent inflammation with pro-inflammatory reactions at the mucosal level. It was recently shown that this bacterium colonizes the neoterminal ileum of patients with CD. AIEC was found in 36.4% of patients with early recurrence compared to 22% in normal areas. It was also found in 22% of chronic CD lesions. This invasion appears to be specific for ileal CD since only 6.2% of control ilea, 3.7% of CD colon, and 1.9% of control colon harbor the bacterium [31, 32]. In vitro studies have shown that AIEC adhere more readily to ileal enterocytes from CD patients than to those from healthy individuals. In a follow-up study, it was shown that AIEC uses CEACAM6 as a receptor on the intestinal epithelial cells [33]. Interaction between AIEC and CEACAM6 facilitates the specific adherence of the microbe to the terminal ileum. One unsolved problem with the AIEC hypothesis is whether adhesion of this bacterium precedes the development of ileitis or, conversely, the presence of inflammation facilitates upregulation of CEACAM6 and adherence of AIEC [34].

Defective Microbial Clearance

The role of bacteria is one of the most rapidly evolving areas of study regarding the pathogenesis of IBD. Indeed, in recent years a change has taken place in the way we understand the immunological abnormalities that underlie the chronic inflammatory states of CD and UC. The traditional dogma of a primary dysregulation of the acquired immune system was questioned after the discovery of a number of IBD-associated genes whose function relates mainly to the innate immune system [35]. These genetic associations and subsequent functional studies have generated a novel hypothesis, which states that the main defect in IBD is an inability to effective clearance of bacteria [36]. This inability may exist on several levels [37]. It may be the consequence of a defective epithelial barrier that allows for massive entrance of microbes and their products into the lamina propria. Alternatively, it may result from inadequate production of antimicrobial peptides by intestinal epithelial cells. Finally, it may originate from a deficiency of phagocytes to handle and remove intracellular microorganisms due to defective recognition and elimination pathways. The end result of these innate defects, which may occur at single or multiple points in the process of microbial clearance, is the persistence of bacterial products in the lamina propria [38]. This, in turn leads to continuous stimulation of effector pathways, and perpetuation of a pro-inflammatory response, eventually culminating in injury to the bowel wall.

Defensins. One of the most important components of the intestinal mucosal antimicrobial barrier is the secretion of natural peptides with antibacterial properties. Among these molecules, defensins are the best studied and mostly closely associated with IBD. Expression of defensins within the GI tract is location specific [39]. In the small bowel α-defensins (HD5 and 6) are secreted by specialized epithelial cells of the crypts, known as Paneth cells [40]. Recent studies have shown that the expression of HD5 and HD6 is significantly impaired in CD [41]. Interestingly, this impairment is most pronounced in patients with a mutation in the *card15* gene (see below). The β-defensins (HD1-4) are expressed within the large intestine. Of those, the expression of HD1 is constitutive, whereas that of HD2-4 is inducible upon inflammatory or infectious signals [42]. It appears that patients with CD have a deficiency that prevents them from upregulating the expression of HD2 upon the commencement of inflammation in the colon. This deficiency does not exist in UC, and thus appears to be a CD and colitis-specific deficiency. Recently, it was shown that this defect may be genetically determined. Indeed, patients with CD-colitis have a low HD2 gene copy number as compared to healthy controls, patients with UC, or more importantly, CD patients with predominant small bowel involvement [43]. The functional consequence of this HD2 deficiency was proven in recent studies, where supernatants from mucosal cultures obtained for CD patients showed decreased antibacterial activity against microorganisms of the commensal flora. Taken together, these studies indicate that deficiencies in defensin secretion may be related to the breakdown of the antimicrobial barrier in patients with IBD, and especially in CD [44].

Card15. The identification of *nod2/card15* as the first susceptibility gene for CD has revolutionized our way of thinking about the pathogenesis of the disease [45, 46]. Its greatest impact was that it drew attention to the dominant role that innate immunity may play in CD. We know now that mutations in this gene are present in one third of CD patients and confer an increase in the disease risk that varies from two- to fourfold (heterozygotes) to 15–40-fold (compound heterozygotes and homozygotes). The protein encoded by *card15* is a cytosolic pattern recognition molecule. It binds to muramyl dipeptide (MDP), which is a product of peptidoglycan, a component of the wall of almost all bacteria [47]. Binding of CARD15 to MDP generates intracellular signals that lead to activation of NFκB, upregulation of proinflammatory pathways, and, ultimately, to clearance of the invading pathogen. The functional consequences of *card15* mutations in CD patients have not yet been fully clarified [48]. If the mutation led to the loss of function, one would expect diminished activation of NFκB and weakened inflammatory responses in the intestinal mucosa. This concept is in disagreement with the pro-inflammatory mucosal immunophenotype that is characteristic of CD. Recent studies have tried to explain this apparent paradox. The underlying abnormality may occur at different or even multiple levels; this largely depends on the cellular source of the deficiency. One theory considers antigen-presenting cells (APCs) as the primary affected cell type. The main function of CARD 15 in APCs may in fact be counter-inflammatory through the suppression of peptidoglycan TLR2-mediated activation of NFκB and secretion of IL-12 [49]. It follows that patients with mutations in

card15 are unable to mount this anti-inflammatory response and are prone to chronic bacterial-triggered inflammation [50]. Along the same line, it was reported that dendritic cells from patients with *card15* mutations show defective IL-10 secretion upon stimulation with MDP, further pointing to the presence of defective regulatory pathways [51]. The end result of this APC-driven defect would then be a pro-inflammatory state at the mucosa. According to a different theory, the major functional consequence of the *card15* mutation is compromised antibacterial function at the level of the epithelial cell. CARD15 was shown to act as an antibacterial factor in epithelial cells, a function that may be lost for the mutated protein [52]. More importantly, CARD15 is expressed on Paneth cells at the intestinal crypts of the small bowel [53]. Recent research in both experimental and clinical intestinal inflammation has shown that the CD-related mutations lead to significantly compromised expression of α-defensins [54, 55]. This in turn results in a diminished antimicrobial activity in the small intestinal mucosal, rendering it susceptible to invasion by luminal bacteria. Once again that could explain the predominance of pro-inflammatory pathways during CD.

Autophagy. Autophagy is another antimicrobial pathway that may be relevant to the pathogenesis of CD. It is a mechanism for intracellular processing and elimination of various molecules, including bacterial products [56]. It helps sequestered bacteria through the formation of cytosolic vesicles (autophagosomes) and delivers them to lysosomes for final degradation. Therefore, autophagy participates in microbial clearance and elimination of invading microorganisms. Recent studies have strongly indicated that defective autophagy pathways may be implicated in IBD pathogenesis [57, 58]. The possibility of defective autophagy in CD was initially raised by the identification of a variant of the autophagy-related gene *atg16l1*, which is associated with susceptibility to CD [59, 60]. Subsequent studies in mice harboring this CD-related mutation have shown that the variant protein induces a defect in Paneth cells that results in compromised exocytosis, and reduced secretion of lysozymes in the intestinal lumen [61]. The end product is deficient intracellular processing and removal of bacteria [62]. In addition, pro-inflammatory molecules are upregulated. In other experiments, it was shown that mice with *atg16l1*-deficient macrophages are prone to DSS colitis and show enhanced secretion of IL-1β [63].

Clinical observations. More direct proof for a primarily defective innate immunity in IBD comes from some very important clinical observations. First, there are a number of genetically determined conditions which are characterized by primary or secondary defects in the function of cells of the innate immunity, such as neutrophils, monocytes, or macrophages. These conditions display reduced phagocytic activity and deficient microbial clearance, and include among others, chronic granulomatous disease, glycogen storage disease type 1b, and Chediak–Higashi syndrome, Hermansky–Pudlak syndrome, leukocyte adhesion deficiency, and cyclic neutropenias. One of the more interesting findings is that patients with these conditions show an increased incidence of IBD-like lesions in the intestine [64–67]. These associations indicate in a straightforward manner in which defective innate immune responses lead to intestinal inflammation [68]. Second, in an elegant clinical study of the acute inflammatory response following endoscopically inflicted

injury in the intestinal mucosa, it was clearly shown that CD patients had significantly reduced responses to injury compared to healthy controls or UC patients [69]. This impairment may be the result of defective secretion of neutrophil-specific chemokines [69]. It is therefore implied that, in CD patients, the inability of the innate immune system to confine an acute inflammatory event may lead subsequently to the establishment of chronic inflammation.

Defective Immunoregulation

The acquired immune system in the gut mucosa is characterized by exceptional features that are crucial for countering the unique immune challenges that exist within the intestinal environment. These features allow for the effective elimination of pathogenic microorganisms, on the one hand, and the peaceful coexistence with the commensal flora on the other [70, 71]. One integral component of this dual functionality is the tendency of the mucosal immune system to generate suppressive/regulatory responses when it encounters flora-derived, harmful bacterial antigens [72]. At the same time, when pro-inflammatory responses are necessary (i.e., for elimination of potentially pathogenic invaders), these responses are rapidly confined by the induction of apoptosis in the effector lymphocytes.

During IBD, these regulatory mechanisms are defective. The result is that pro-inflammatory responses are generated but not terminated in the intestinal mucosa, as indicated by the heavy infiltration of the mucosa with lymphocytes that have an activated phenotype and secrete large quantities of cytokines. One of the major concepts in IBD pathogenesis has traditionally been that CD and UC represent terminally polarized conditions in terms of the immunophenotype of their infiltrating mucosal lymphocytes [73]. In particular, CD has been considered a prototypic Th1 condition, dependent upon the IL-12/IFN-γ/TNF-α axis [74]. In contrast, UC was considered an atypical Th2 condition based on the finding of increased IL-13 production, most probably by nonclassical NK-T cells of the mucosa [75, 76]. This Th1/Th2 paradigm is also rapidly changing as novel mechanisms come into play. It is now clear that the notion of highly polarized immunophenotypes is too simplistic and not supported by recent studies, the most dramatic example being the highly beneficial effect of anti-TNF-α treatment in UC. Instead, it is becoming increasingly understood that during chronic intestinal inflammation there is a redundancy of immunological pathways that act in synergy to create the final tissue injury [38, 77].

Th17 pathway. The Th17 pathway has arisen in recent years as the first significant modification of the traditional Th1/Th2 model of effector immune responses [78]. The hallmark of Th17 lymphocytes is the expression and secretion of the cytokine IL-17A. The polarization of naïve CD4+ T cells toward the Th17 phenotype is a multistep process. It requires an environment rich in TGF-β1, IL-1β and IL-6 which are important during the initial Th17 differentiation process. The stabilization and expansion of the Th17 phenotype is critically dependent upon the presence of IL-23, which acts via the IL-23R that is upregulated on the T-cell surface. The transcription factor RORγt is the master nuclear factor for Th17

polarization. Besides IL-17, the end products of the Th17 pathway include several pro-inflammatory cytokines, such as IL-21, IL-22, IL-26, and TNF-α. Recent studies have highlighted the importance of the IL-23/IL-17 axis for the pathogenesis of intestinal inflammation [79, 80]. First, many of the molecules that are associated with the Th17 pathway show increased expression in the inflamed intestinal mucosa of patients with IBD [81–83]. Second, several genetic associations that have been proposed for IBD represent mutations in genes whose products participate in the Th17 pathway. In fact, of the top 30 CD-associated gene regions, four are directly involved in IL-23 signaling (*il-23r*, *il-12a*, *stat3*, and *jak2*) [84]. In particular, mutations in the *il-23r* gene show the strongest association with IBD [85]. Interestingly, some mutations have a protective effect, whereas others increase susceptibility for IBD. Third, the IL-23/Th17 pathway was shown to be central in the pathogenesis of murine colitis. Blockade of this pathway leads to amelioration of colitis in several models of experimental IBD [86, 87]. Finally, the possibility exists that several of the functions that used to be attributed to IL-12 (hence considered Th1 related) may in fact be mediated by IL-23. The reason for this is that IL-12 and IL-23 share one common chain (p40). Many of the anti-IL-12 antibodies, including the one that was used in a recent clinical trial of CD, are directed against p40 [88]. Therefore, it may be that the beneficial effects of p40 blockade were due to the neutralization of IL-23 rather than the intended IL-12 [88, 89].

TL1A/DR3/DcR3. Members of the tumor necrosis factor (TNF) and tumor necrosis factor receptor (TNFR) superfamilies of proteins (TNFSF and TNFRSF, respectively) play pivotal roles in the function of the immune system [90]. Several of these molecules were found to participate in the pathogenesis of experimental and clinical IBD. The most convincing evidence originates from the efficacy of anti-TNF-α regimens (i.e., infliximab, adalimumab, and certolizumab pegol) for the treatment of both UC and CD [91]. Recently, a mutation in the *tnfsf15* (TL1A) gene was shown to be strongly associated with susceptibility to CD. This association was confirmed in subsequent studies in various ethnic groups [92, 93]. TL1A can bind to two receptors with opposing functions: DR3 is a death-domain receptor that represents the functional receptor, whereas DcR3 is a decoy receptor that competes with DR3 and inhibits TL1A-driven signaling [94]. Interestingly, an association between mutations in the *tnfrsf6b* gene (DcR3) and pediatric IBD was reported recently. Recent studies have advanced our understanding of the function of the TL1A/DR3/DcR3 system in IBD. First, all three molecules are upregulated in the inflamed bowel during IBD [95, 96]. Second, TL1A acts as a significant co-stimulator for memory T cells and induces proliferation and cytokine production in association with TCR or cytokine-mediated signals [97–99]. Third, TL1A appears to be involved in both Th1 and Th17 type responses, both of which are relevant for the pathogenesis of IBD [100]. Fourth, association of TL1A with its two receptors may be involved in the mechanisms leading to defective apoptosis that characterizes IBD. Finally, the functional effects of the mutations in *tnfsf15* and *tnfrsf6b* are being revealed, and it was shown that the existing mutations directly affect protein expression of the relevant molecules [101].

Diversity in IBD

The abundance of incoming recent information regarding the pathogenesis of IBD has made it difficult to include all data into a single pathogenic model. For this problem to be solved, we need to understand that IBD may not be a single condition, but rather represent a common name for a number of clinically related but etiologically diverse disorders. Accumulating evidence shows that this may actually be the case (Fig. 4.2).

At the clinical level, it has been long recognized that IBD comprises a wide spectrum of different manifestations. The Montreal classification has clearly pointed out the different phenotypes that exist and are of importance within each entity [102]. For example, UC may present as isolated proctitis, but also as fulminant and potentially lethal pancolitis. Similarly, CD may affect the ileum or the colon and may present as inflammatory enteritis or show fibrostenotic or perforating behavior. Additionally, both diseases may display a variety of extra-intestinal manifestations.

There is now strong evidence to support the notion that additional diversity exists on the immunogenetic level. We now recognize that *card15*-mutation-related CD is a distinct entity that is associated with ileal localization, young age of presentation, and fibrostenotic behavior. The genetic associations with *tnfsf15* and *il-23r* mutations may soon define additional groups of IBD with a particular phenotype. Similarly, patients with serum reactivity against multiple bacterial antigens (ASCA, anti-OmpC, anti-I2, anti-flagellin) are a CD subgroup with aggressive

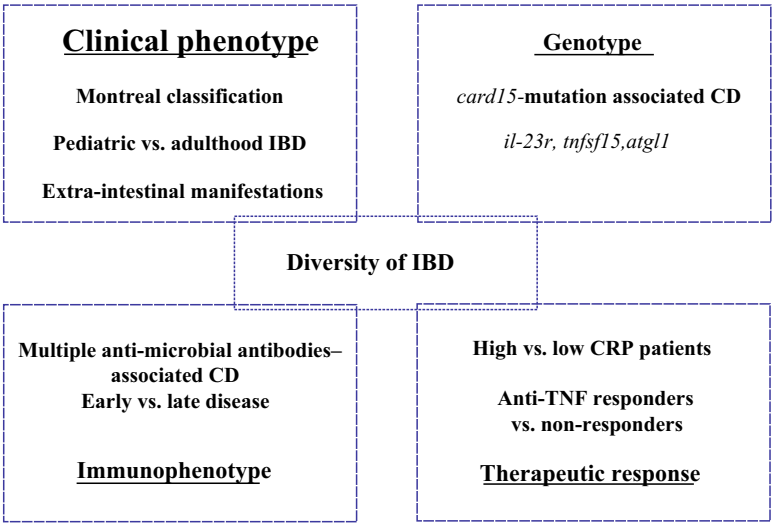

Fig. 4.2 IBD comprises several subgroups of patients with distinct clinical, genetic, immunological, or therapy-related characteristics. These subgroups are separate from each other and may require individualized approaches to management

disease course [103, 104]. This may also have therapeutic implications as these patients appear to respond more to treatment with antimicrobial agents.

Another additional point relates to the diverse immunological mechanisms that may predominate in different phases of the disease, even in the same individual. For example, in mice it has been clearly shown that the initial induction of inflammation is immunologically distinct from the late, long-standing chronic inflammatory phase [77]. Recent studies indicate that the same may hold true in the human condition as well [105]. In light of these findings, the study of pediatric IBD and the exploration of differences between early and late onset disease may be critical for the understanding of the different immunological pathways involved in induction versus established phases of intestinal inflammation [106].

Finally, therapeutic studies have also highlighted the high level of heterogeneity in IBD. First, patients with high serum CRP levels respond better to treatment with biologic agents. A possible explanation may be that the increased inflammatory activity in this subgroup may allow them to be more responsive to immune modulation. Second, one third of CD patients and more than 50% of UC patients do not respond to anti-TNF-α treatment, indicating that alternative, non-TNF-α-dependent mechanisms may prevail in these subsets [107]. It is clear that the clarification of genetic and immunological abnormalities that underlie each subgroup eventually leads to more focused and effective treatments.

Conclusions

The field of IBD research is one of the most rapidly expanding areas in gastroenterology. The constantly increasing number of animal models of intestinal inflammation, as well as the accumulating genetic data, has led to significant progress in our understanding of IBD pathogenesis. With these new insights comes the realization that there is need for a change to the traditional conceptual framework for IBD pathogenesis, which must evolve to incorporate new lines of evidence on the role of the bacterial flora and innate immunity. Undoubtedly, the most important new development has been the paradigmatic shift in focus from acquired to innate immunity as the primary defective pathway in IBD. The old paradigm considered IBD as the result of an overly reactive mucosal immune system toward bacterial antigens of the flora. Nowadays, it appears more possible that IBD, particularly CD, represents a state of immunodeficiency, where the primary abnormality is defective clearance of intestinal bacteria by the innate immune system. Another important evolution of our knowledge is that nonimmune cells may be equally important and may explain more peripheral areas of IBD pathogenesis. For example, endothelial cell abnormalities may explain the thrombophilic state as well as the neo-angiogenesis that is observed in IBD. Similarly, myofibroblasts are at the center of the fibrotic process that is apparent in a substantial percentage of CD patients and a cause of therapeutic refractoriness and frequent surgical interventions. Finally, neuromodulation is a rapidly evolving area and greatly

relevant mechanism that may explain the effect of smoking and stress in exacerbations of IBD. It is certain that elucidation of these pathways offers unique management opportunities for these debilitating conditions.

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Chapter 5
State of the Art Medical Treatment of the Adult Patient with IBD: The Mesalamine-Based Therapies

L. Campbell Levy and Corey A. Siegel

Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Mesalamine • 5-ASA • Sulfasalazine • Balsalazide • Olsalazine • Meta-analysis • Compliance • Chemoprophylaxis

Key Points

- Mesalamine-based therapies have been used for Crohn's disease and ulcerative colitis for over six decades with a long track record of safety.
- Despite multiple studies over years that demonstrated some efficacy of aminosalicylates in Crohn's disease, a more critical review of the literature reveals little if any benefit.
- Effective for the induction and maintenance of remission for ulcerative colitis, oral aminosalicylates are the drugs of choice for mild to moderate extensive UC.
- There is no evidence that a single aminosalicylate formulation is clearly superior to the others. However, convenient dosing regimens enabled by the newer formulations may have an impact on adherence to therapy.
- Current data suggest that 5-aminosalicylic acids (5-ASA) may have a chemoprotective effect against colorectal cancer though further study is needed.

Introduction

It has been over 65 years since the initial report of the use of sulfasalazine for ulcerative colitis (UC) in patients initially given the compound for rheumatic polyarthritis [1]. This serendipitous discovery began an era of treating patients with the

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inflammatory bowel diseases (IBD) with sulfasalazine. When it was revealed approximately 35 years ago that the therapeutically active moiety of the compound was 5-aminosalicylic acid (5-ASA) and that the sulfapyridine moiety acted as a carrier [2], new efforts to deliver 5-ASA to the gut began.

Owing to the relative safety of aminosalicylates, vast amounts of research and resources have been directed at evaluating their efficacy for the treatment of both Crohn's disease (CD) and UC. Multiple newer 5-ASA agents have been developed in an effort to improve efficacy and reduce side effects from sulfasalazine. Not only has 5-ASA been used for the treatment of IBD, but it is also believed to have chemoprotective properties reducing the risk of developing colorectal cancer. We review the data supporting the efficacy of aminosalicylates for IBD; address potential advantages of newer 5-ASA agents; and also review the most current evidence for the utility of 5-ASA as a chemoprotective agent.

Metabolism and Mechanism of Action

Sulfasalazine is absorbed in the small intestine and excreted into the bile. It undergoes metabolism within the colonic lumen where the active compound, 5-ASA, and the therapeutically inactive carrier, sulfapyridine, are formed from the reductive cleavage of the azo bond by bacterial azoreductase [3]. Sulfapyridine is reabsorbed in the colon, acetylated in the liver, and excreted in the urine. The 5-ASA moiety is acetylated by *N*-acetyltransferase-1 to its inactive metabolite *N*-Ac-5-ASA in epithelial cells of the intestine, liver, and kidney. Absorbed 5-ASA and *N*-Ac-ASA are excreted in urine while approximately 50% of the 5-ASA is excreted in feces [4]. Studies of the pharmacokinetic profiles of different oral mesalamine formulations and prodrugs have reported varied results. However, a systematic review evaluating the fecal excretion and urinary excretion of total 5-ASA described no major differences between available mesalamine agents or between delayed release formulations [5, 6].

It has been known since the 1970s that the therapeutic benefit of 5-ASA compounds is mediated by a local, topical effect on the mucosa, but the precise mechanism of action remains elusive [2]. Theorized mechanisms are various and involve many of the pathways of the inflammatory cascade that have been implicated in the pathogenesis of IBD. For example, it has been suggested that mesalamine modulates specific humoral inflammatory responses such as blocking the production of leukotrienes and prostaglandins [7]. Other proffered theories include the inhibition of leukocyte chemotaxis and scavenging of oxygen-derived radicals [8, 9]. Mesalamine inhibits, at least to a small degree, a major inflammatory signal, tumor necrosis factor (TNF)-dependent nuclear factor kappaB (NF-κB) [10, 11]. Other more recent experiments involving animal models of colitis have shown that 5-ASA promotes peroxisome proliferation activated receptor-γ, thereby interfering with the NF-κB pathway [12].

Different formulations and preparations release mesalamine at different sites within the gastrointestinal tract making one formulation of 5-ASA perhaps more suitable than another depending on the site on inflammation. These differences in drug delivery may also be one factor accounting for the variability in efficacy between different mesalamine agents [13]. Currently, there are eight oral mesalamine formulations or prodrugs available in the USA and two rectally administered topical formulations. Controlled-release capsules include Pentasa® (Shire US Inc, Wayne, PA), which releases 5-ASA continuously through micropellets coated in a semipermeable membrane so that 20–30% of drug is released proximal to the colon [14]; Asacol® and Asacol HD® (Warner Chilcott, Rockaway, NJ) incorporate a pH-dependent resin, Eudragit-S, that is thought to dissolve in the ileum and colon where the pH ≥7 [15]. Lialda® (Shire US Inc; also marketed outside the USA as Mezavant®) has a pH-dependent Eudragit-S coating and a multimatrix (MMX®) core system of wax, stearic acid, and cellulose that also targets the drug to the distal ileum and colon [16]. Apriso™ (Salix Pharmaceuticals Inc, Morrisville, NC; marketed outside of the USA as Salofalk®), contains granulated mesalamine with a Eudragit-L coating (dissolves at a pH ≥6, presumably in the small bowel) as well as an extended release polymer matrix core (Intellicor™) designed to release the mesalamine over an extended period of time.

Prodrugs which take advantage of bacterial azoreduction to release 5-ASA in the colon include sulfasalazine (Azulfidine®; Pfizer, New York, NY and generics) and olsalazine (Dipentum®; Pfizer, Inc), which consists of two 5-ASA molecules linked by an azo bond, and balsalazide (Colazal®; Salix Pharmaceuticals Inc, Morrisville, NC and generics) which is a 5-ASA molecule linked to an inert carrier 4-aminobenzoyl-β-alanine [17]. Mesalamine is also administered via rectal suppository (Canasa®; Axcan Pharma, Inc, Birmingham, AL) and enema (Rowasa®; Alaven Pharmaceutical LLC, Marietta, GA and generics) in the USA and also as foam in Europe.

Adverse Effects and Safety

Aminosalicylates have had an excellent overall long-term safety profile with few serious adverse events [18]. Due to a dose-dependent effect of the sulfapyridine moiety in sulfasalazine, adverse effects occur in as many as 50% of patients [19]. Most of these manifestations include dyspepsia, diarrhea, fever, rash, and headache [20]. Rare serious adverse reactions to sulfasalazine have included hepatitis, pancreatitis, leukopenia, hemolytic anemia, neurotoxicity, and pulmonary fibrosis. As expected, up to 90% of patients who discontinue sulfasalazine due to adverse side effects tolerate mesalamine without difficulty [4]. Though clinical trials of mesalamine are powered to evaluate efficacy and not safety as a primary endpoint, they have shown that doses of up to 4.8 g/day of mesalamine are well tolerated by subjects [21]. Moreover, systematic analysis of multiple clinical trials demonstrates that the proportion of patients taking aminosalicylates who experience adverse

effects or withdraw from trials due to adverse events is similar to, if not smaller than, that proportion of patients taking placebo [22]. As with sulfasalazine, serious adverse effects have been reported with mesalamine, including blood dyscrasias, pancreatitis, and nephrotoxicity. While analysis of administrative data has caused some to theorize that pancreatitis and interstitial nephritis may be more commonly associated with mesalamine than with sulfasalazine, causality is difficult to determine [23]. Most importantly, these serious adverse events are idiosyncratic and exceptional. The rate of treatment-related nephrotoxicity has been estimated as low as 0.26% per patient-year making it difficult to recommend meaningful monitoring routine practices for this rare event [24].

Aminosalicylates also have a reassuring track record of safety in pregnancy, and lactation. Except for a rare association with diarrhea occurring in infants who are breastfed by mothers taking mesalamine [25], 5-ASA is safe to continue during both pregnancy and lactation [26]. All of the aminosalicylates are a pregnancy category "B" except for olsalazine which is category "C." Sulfasalazine's antifolate effect should be countered with at least 2 mg of daily folate supplementation during prenatal stages and pregnancy. There is little evidence to suggest that aminosalicylates alter fertility significantly, but reversible azoospermia has been reported in young and middle-aged men taking sulfasalazine [27].

Aminosalicylates for the Treatment of Crohn's Disease

The 5-ASAs have been a mainstay for the treatment of Crohn's disease since the publication of the National Cooperative Crohn's Disease Study (NCCDS) [28]. The long history, early results, and safety of 5-ASAs left the position of this class of medications in the Crohn's treatment algorithm unchallenged for many years. However, based on recent closer inspection of the data, the "state of the art" for the use of 5-ASAs may be not to use them at all.

Early Lessons on 5-ASAs in Crohn's Disease

The NCCDS showed that 5-ASAs are effective, but only in a select population. In the 569 patient, randomized controlled 17-week induction trial, 43% of patients taking sulfasalazine (1 g/15 kg daily – mean dose 4.7 g daily) entered remission compared to 30% of patients taking placebo. This difference was not statistically significant ($p=0.08$) except for the subgroups of patients with colonic disease or ileocolonic disease ($p=0.006$; $p=0.027$, respectively). In addition, sulfasalazine was ineffective for patients who had received corticosteroids, most likely indicating that this drug only works in patients with mild disease. In the 24-month maintenance portion of NCCDS, sulfasalazine (at a mean dose of 2.5 g daily) was no more effective than placebo in maintaining remission.

Recent Data with Newer Agents

Due to its ethylcellulose coating facilitating time-dependent drug release, conceptually Pentasa® might be superior for Crohn's disease with increased drug delivery to the distal small bowel and proximal colon. In a randomized controlled trial from 1993 [29], 310 patients were studied using varying doses of Pentasa® as compared to placebo. Forty-three percent of patients taking Pentasa® 4 g daily entered remission, compared to 18% of patients taking placebo ($p<0.01$), with reductions in Crohn's disease activity index (CDAI) being 72 points and 21 points, respectively ($p<0.01$). Those with isolated ileal disease had the largest improvement with a drop in CDAI of 93 points (compared to a 2-point improvement in the placebo group).

In 1994, the Mayo Clinic studied the efficacy of Asacol® for the treatment of Crohn's disease [30]. Among 38 enrolled patients, 60% of those randomized to 3.2 g Asacol® daily achieved partial or complete remission. Compared to placebo (22% response rate), this difference was statistically significant ($p=0.04$). The validity of these results (and those from the above Singleton study) has been questioned, specifically pointing toward the large drop-out in both studies.

More Critical Review of the 5-ASA and Crohn's Literature

Based on the uncertainty of the efficacy of 5-ASAs for Crohn's disease, three meta-analyses have been performed. The first, in 1997, was an analysis of 15 randomized controlled studies that evaluated the efficacy of 5-ASAs for the maintenance of Crohn's disease remission [31]. This study included over 2,000 patients, and found that 5-ASAs were effective in maintaining remission, however, only in the group who were in a postsurgical (as opposed to medically induced) remission. This finding is contrary to what was seen in two more recent randomized controlled trials evaluating 5-ASAs for postoperative prophylaxis, where 5-ASAs were not more effective than placebo [32, 33].

A meta-analysis of three trials utilizing Pentasa® for the induction of remission in mild–moderate Crohn's disease was published in 2004 [34]. This study incorporated the "positive" Singleton article above, but interestingly also included two previously unpublished "negative" randomized controlled trials. All three studies were 16 weeks and compared the efficacy of Pentasa® 4 g daily to placebo. In their intention to treat analysis, the improvement in CDAI was 63 points, as compared to 45 points in those treated with placebo. Although this difference was statistically significant ($p=0.04$), the clinical significance of an 18 point difference in CDAI (where 70–100 points is typically considered clinically meaningful) is suspect.

Finally, a Cochrane analysis published in 2005 evaluated the effectiveness of 5-ASAs for the maintenance of remission for Crohn's disease [35]. In this analysis of six randomized controlled trials of 5-ASA versus placebo, where patients were followed for up to 12 months, the odds ratio was 1.0 (95% CI 0.80–1.24). This led

the authors to conclude that there is no evidence that 5-ASAs are superior to placebo for the maintenance of Crohn's disease remission, and furthermore, they suggested that additional randomized controlled trials of this regimen are not justified.

Conclusions About 5-ASAs for Crohn's Disease

In 2001, practice guidelines from the American College of Gastroenterology included 5-ASAs as the treatment of choice for mild to moderate Crohn's disease [36]. Since, guidelines for academic societies and expert consensus statements have progressively excluded aminosalicylates for Crohn's disease treatment algorithms [37, 38]. Most recently, an expert consensus from 2007 recommended budesonide for the treatment of mild–moderate ileocolonic Crohn's disease, and included sulfasalazine for the treatment of left-sided Crohn's colitis [39]. This evidence-based algorithm completely excluded 5-ASAs (including sulfasalazine) for maintenance therapy. We generally agree with these most recent guidelines, and consider 5-ASAs in Crohn's disease only for patients with mildly active Crohn's colitis. Sulfasalazine at doses between 3 and 6 g are typically required, and, if not tolerated, a brief trial (4–8 weeks) of a mesalamine-based product with good colonic delivery is reasonable. We have a low threshold to start immunomodulators for Crohn's disease at our institution, and more typically use antibiotics (as opposed to 5-ASAs) in the first 3–4 months while awaiting these agents to take effect. The state of the art of 5-ASAs for the treatment of Crohn's disease has evolved dramatically over the past decade, and based on the best available evidence, in contrast to ulcerative colitis, do not appear to have much of a role.

Aminosalicylates for Ulcerative Colitis

Efficacy for Induction and Maintenance of Remission

Due to favorable efficacy and safety profiles, oral aminosalicylates remain the standard treatment for mild to moderate extensive ulcerative colitis. For the remission of active ulcerative colitis, aminosalicylates were evaluated in a 2006 Cochrane meta-analysis of 21 studies (9 placebo-controlled) incorporating over 2,100 patients [40]. Aminosalicylates proved better than placebo (OR for failing to induce clinical improvement or remission was 0.40; 945% CI 0.30–0.53) at all dose levels. A statistically insignificant trend for superiority of mesalamine over sulfasalazine for endoscopic and clinical improvement was observed. A significantly higher withdrawal rate for sulfasalazine was noted. Despite indications that sulfasalazine may be somewhat less effective for the induction of remission and that it is likely not as well tolerated as its mesalamine counterparts, the increased cost of these newer

formulations should also be taken into account. Thus, any of the oral aminosalicylate formulations may be a reasonable choice for the initial treatment of mild to moderate extensive colitis.

For left-sided disease, including sigmoiditis and proctitis, rectally administered treatments have had the most success in inducing remission. Randomized clinical trials have shown local topical treatments with foams, enemas, or suppositories are more effective than oral medications at inducing and maintaining remission, and a combination of oral medications and local therapy is more effective than oral therapy alone [41]. More recently, even patients with extensive ulcerative colitis were shown to have increased benefit when a local therapy was added to an oral regimen [42].

Like that done for the induction of remission, a Cochrane analysis completed in 2006 evaluated aminosalicylates for the maintenance of remission. Again, aminosalicylates were found to be more effective than placebo (OR for failure to maintain clinical or endoscopic remission was 0.47; 95% CI 0.36–0.62) [18]. Sulfasalazine showed a slight but statistically significant benefit over mesalamine in maintaining remission. While there was no difference in adverse effects or withdrawal due to side effects, many of the analyzed trials excluded patients intolerant to sulfasalazine, thereby incorporating an inherent bias. Noncompliant patients in the analysis were at higher risk of relapse. In summary, for mild to moderate extensive ulcerative colitis, aminosalicylates are effective for both induction and maintenance of remission. There appears to be little, if any, proven difference in clinical efficacy between sulfasalazine and other mesalamine agents.

Optimal Dosing

Dosing of mesalamine has varied between 1.2 and 4.8 g/day (or the equimolar dose of prodrugs) for the treatment of active colitis and for maintenance [21, 43]. Sulfasalazine doses between 2 and 4 g have been recommended for active and quiescent disease though dose-dependent side effects are more common at doses higher than 2 g/day [20]. Higher dosing for more active disease is conceptually more appealing because presumably higher mucosal concentrations of drug are more effective given the improved outcomes observed with the addition of local therapies to oral regimens. Moreover, Cochrane analyses have indicated a trend toward a dose–response relationship [40]. However, evidence for higher doses to achieve or maintain remission has been inconsistent and the question of whether mesalamine doses above 4 g/day might benefit certain subgroups remains unanswered.

Data from ASCEND I and II trials, which compared a standard dose of mesalamine (2.4 g/day) to a higher dose (4.8 g/day) after 6 weeks, showed that the overall improvement rates were significantly better (59% vs. 72%, respectively; $p < 0.05$) among patients with moderately active but not in patients with mild disease [21]. Interestingly, this result was not confirmed in the ASCEND III trial which included only patients with moderately active disease again comparing 2.4–4.8 g/day of

5-ASA (66% vs. 70%, respectively; p=NS) [44]. Despite some evidence of improved dose-related outcomes when partial response or clinical improvement is used as an endpoint, multiple clinical trials have shown no benefit to doses of mesalamine above 2.4 g/day (or the appropriate equivalent dose for prodrugs) when complete remission is used as an endpoint [43]. However, data from subgroup analyses of patients with more refractory disease indicate a possible added benefit with higher doses. Among patients in ASCEND III who had previously been on at least two other medications (including oral 5-ASA, rectal therapies, steroids, or immunomodulators), the higher dose was more efficacious (69.6% vs. 58.1%, p=0.011). Similar patients (had prior oral or intravenous steroid treatments) from ASCEND I and II also had a greater benefit with the 4.8 g/day dose compared to 2.4 g/day (79% with clinical improvement vs. 52%, p<0.01) [45]. Therefore, there may be a steroid sparing role for higher doses of mesalamine, though this hypothesis has yet to be tested. It is difficult to know whether there is an upper dose limit of therapeutic 5-ASA levels or whether the limiting step in aminosalicylate therapy is the ability of the drug delivery system to treat the appropriate sites of disease. While 5-ASAs have proved relatively safe, higher doses are associated with increase systemic absorption, and therefore further study needs to investigate which subgroups of patients might benefit from a higher dose and how that drug is delivered.

Differences Between Mesalamine Formulations

Differences in chemistry and bioavailability between agents are compounded by strong marketing forces, which make it difficult for physicians to decipher meaningful clinical differences between delivery systems of 5-ASAs without head-to-head clinical trials. Unfortunately, owing to the variability of end points and definitions of response and remission used in clinical trials, using the available literature for direct comparison of the efficacy of different formulations of aminosalicylates is problematic [46]. This methodologic variability can produce widely differing results depending on which definitions and end points are used.

However, one clear difference between formulations is the required dosing schedule and pill burden. The newest formulations boast once-a-day dosing. The MMX mesalamine (Lialda®) contains 1.2 g of 5-ASA per tablet and has been studied with single daily dose regimens. While studies have not been designed to determine if the multimatrix release system is superior to other mesalamine formulations in ulcerative colitis, it appears to be at least equivalent. In a double-blinded, placebo-controlled 8-week study of Lialda® (2.4 and 4.8 g), both doses of Lialda® were superior to placebo in achieving clinical and endoscopic remission (40.5% at 2.4 g, p=0.01; 41.2% at 4.8 g, p=0.007; placebo 22.1%). A reference arm of patients taking Asacol® 2.4 g/day showed a statistically insignificant benefit over placebo (32.6%, p=0.124) [47]. A once-daily dosage of granulated mesalamine (Apriso™) was shown to be effective in doses up to 3.0 g daily. Due to the more convenient regimens, there is potential for improving adherence. Like the Cochrane analysis that found that non-adherent patients were at greater risk of relapse [18], other

studies have underscored the importance of complying with a maintenance regimen. A prospective study of 99 patients with ulcerative colitis over 24 months found that those patients who did not adhere to a maintenance regimen of mesalamine had greater than a fivefold risk (HR 5.5, 95% CI 2.3–13) of clinical recurrence compared to adherent patients [48]. Recently published data from an online questionnaire by Loftus of over 44,000 patients revealed that poor adherence is a common problem in the treatment of IBD. Sixty-five percent of respondents reported missed medications, and approximately 30% reported missing medications at least once per week [49]. Heavy pill burdens and high dosing frequencies are only two of many factors that contribute to the complicated problem of non-adherence to IBD treatments, but simplifying medication regimens with these newer formulations may offer a practical strategy to help remedy the problem.

Chemoprophylaxis

An increased risk of colon cancer is a known complication of UC and Crohn's colitis, and medical societies have published guidelines endorsing cancer prevention strategies [50, 51]. Some epidemiologic data have demonstrated an increased incidence of colon cancer with a longer duration of disease [52]. The extent and severity of inflammation also are important factors contributing to the risk of cancer [53]. While the incidence of colorectal cancer among IBD patients in referral centers may be as high as 18% 30 years after diagnosis, other studies have shown significantly lower rates [54–56]. Mesalamine is believed to have a possible chemoprotective effect due to its anti-inflammatory properties and possibly other unique properties that may disrupt molecular pathways in the pathogenesis of colon cancer [57]. While multiple studies have evaluated the role of mesalamine in preventing colon cancer in UC, few have addressed its efficacy in Crohn's colitis [58]. A meta-analysis and systematic review of 9 UC studies (3 cohort studies and 6 case-controlled studies) involving over 1,900 patients showed a protective effect of 5-ASA in 5 of the 9 studies. The odds ratio for protection against colorectal cancer was 0.51 (95% CI 0.37–0.69). Despite these results, the chemoprotective effect of 5-ASAs remains largely uncertain. Large prospective, placebo-controlled studies are unlikely to be forthcoming because of sheer impracticality and large numbers of patients and follow-up required. However, further prospective study in cohorts of selected high-risk population may unveil evidence to help confirm or disprove the chemoprotective value of 5-ASAs.

Conclusion

The aminosalicylates have been the standard treatment for IBD for many years. Clearly, their role in UC is solidified, and the more recent focus has been on developing better drug delivery systems and optimizing dosing regimens. Although still

commonly used for the treatment of Crohn's disease, the data supporting the use of aminosalicylates in these patients are scant, and expert opinions have gradually excluded them from treatment algorithms. The most recent exciting developments regarding aminosalicylates have resulted in easier-to-tolerate formulations with a lower pill burden. Ideally, future research will teach us which subgroups will benefit the most from these therapies.

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Chapter 6
State of the Art Medical Treatment of the Adult Patient with IBD: Modern Use of Corticosteroids

Wojciech Blonski, David Kotlyar, and Gary R. Lichtenstein

Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Corticosteroids • Controlled ileal release • Enema • Prednisone • Prednisolone • Budesonide • Hydrocortisone • Beclomethasone dipropionate • Adrenocorticotropic hormone

Key Points

Ulcerative colitis

- Conventional corticosteroids, such as prednisone, should be used as a therapy to induce remission in patients with mild to moderately active ulcerative colitis with inadequate response or intolerance to 5-ASA, or in patients presenting with moderate to severe UC.
- Patients with ulcerative proctitis may benefit from combined treatment with rectal enema formulations of beclomethasone dipropionate and 5-ASA.
- Rectal formulations of topical budesonide might be a promising treatment in patients with left-side colitis.
- Corticosteroids are not effective in maintaining remission in ulcerative colitis.
- Intravenous corticosteroids are indicated in patients not responding to oral corticosteroids or in those with severe activity of disease.

Crohn's disease

- Controlled ileal-release formulations of topical budesonide should be used in patients with mild to moderate ileocecal Crohn's disease.
- Conventional corticosteroids are recommended in patients with moderate to severe CD regardless of disease location or in those with ileocecal CD with no response to budesonide.

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- Corticosteroids are not recommended in patients presenting with perianal fistulas.
- Systemic corticosteroids are not effective as maintenance therapy of CD.
- Budesonide 6 mg daily is effective and safe in maintaining medically induced remission in CD but the duration of remission is limited only up to 6 months while on therapy.
- Intravenous corticosteroids are indicated in patients not responding to oral corticosteroids or in those with severe activity of disease.

Introduction

Corticosteroids (CS), the earliest discovered successful therapy for inflammatory bowel disease (IBD), were suggested by Truelove and Witts more than 50 years ago [1]. Interestingly, the same medications are still of great use and have helped countless patients.

Since the initial studies on their use, tremendous strides have been made in the field of IBD research, and CS have found a more focused role in the treatment of IBD. We now know that while CS have great benefits, there are also significant adverse effects, especially when such medications are given systemically for long periods of time. In addition, new formulations of CS have been able to target specific parts of the GI tract, thereby sparing the patient from unwanted systemic side effects, while maximizing the action and effectiveness of the medication.

In this chapter, the authors discuss the efficacy of both topical and systemic forms of CS for both induction of remission in ulcerative colitis (UC) as well as maintenance therapy. The next section discusses the usage of both topical and systemic agents in the induction of remission of Crohn's disease and maintenance therapy for the illness. The last section discusses the adverse effects of these CS preparations. While great advances are being developed in therapy for IBD, CS remain a crucial instrument in the gastroenterologist's toolbox.

Corticosteroids in Ulcerative Colitis

Current American Gastroenterological Association guidelines recommend that conventional CS, such as prednisone, should be used in patients with mild to moderately active ulcerative colitis who do not respond adequately or are intolerant to first-line therapy with 5-aminosalicylic acid (5-ASA) formulations or in patients presenting with moderate to severe UC [2]. Induction of remission can be effectively achieved with prednisone administered at doses 40–60 mg/day (or 1 mg/kg/day) with an average of 7–14 days [2]. Once remission is achieved, the administered dose of prednisone should be tapered by 5 mg/week to a dose of 20 mg [2]. After that, the dose should be tapered 2.5–5 mg/week below 20 mg [2]. Patients failing to respond to oral CS or presenting with severe UC may benefit from parenteral CS (40–60 mg/day of methylprednisolone or 200–300 mg/day of hydrocortisone) [2].

CS are considered not effective as maintenance therapy of UC [2].

Topical Corticosteroids

Induction of Remission

Therapy with topical agents, such hydrocortisone or budesonide, administered rectally is recommended for UC located in the distal part of colon (ulcerative proctitis or left side UC) [2]. A meta-analysis of 2 controlled trials [3, 4] demonstrated that conventional rectal CS were shown to be more efficacious than placebo in inducing remission with pooled odds ratios of 0.07 (95% CI 0.02–0.29) and 0.34 (95% CI 0.10–1.20) for symptomatic and endoscopic remission, respectively [5]. On the other hand, conventional rectal CS were found less efficacious than rectal 5-ASA in inducing symptomatic (pooled OR = 2.42, 95% CI 1.72–3.41), endoscopic (pooled OR = 1.89, 95% CI 1.29–2.76), and histological (pooled OR = 2.03, 95% CI 1.28–3.20) [5] remission in distal UC based on pooled data from 7 controlled trials [6–12]. An analysis of controlled trials demonstrated that remission rates ranged from 60 to 70% in patients receiving 5-ASA enemas at doses 1–4 g/day and from 30 to 40% in those receiving CS enemas after 4 weeks of treatment [13]. A multicenter, double-blind, and controlled trial observed that 4-week combination therapy of topical 5-ASA and topical beclomethasone dipropionate (BDP) given as retention enemas were superior to monotherapy with either agent in achieving clinical (100% [BDP/5-ASA] vs. 70% [BDP] and 76% [5-ASA]), endoscopic (100% [BDP/5-ASA] vs. 75% [BDP] and 71% [5-ASA]), and histological improvement (95% [BDP/5-ASA] vs. 50% [BDP] and 48% [5-ASA] in active ulcerative proctitis [14].

Newer generation topical CS, such as budesonide given rectally at doses between 2 and 2.5 mg, were shown to be equally effective as conventional CS given at doses between 100 and 125 mg of hydrocortisone equivalent and administered rectally in inducing symptomatic (pooled OR 2.08, 95% CI: 0.84–5.14), endoscopic (pooled OR 1.40), and histological (pooled OR 1.23, 95% CI: 0.80–1.91) remission [5]. Of note, rectal budesonide produced significantly less endogenous cortisol suppression than rectal conventional CS with the weighted mean difference between pooled treatment arms of 119.1 nmol/L (95% CI: 70.3–167.9) [5]. However, this formulation of budesonide is not available in the USA.

Maintenance Therapy

The use of topical CS for maintaining remission in UC has not been evaluated.

Systemic Corticosteroids

Induction of Remission

Several studies analyzed the efficacy of oral systemic CS in the treatment of patients with active UC. In a group of 210 patients with mild to severe UC who were treated with oral cortisone at the dose of 100 mg daily ($n = 109$) or placebo ($n = 101$) for a

period of 6 weeks, Truelove and Witts observed significantly higher efficacy of systemic CS in inducing remission when compared to placebo (41.3% vs. 15.8%, $p<0.001$) [15, 16]. Two-week combined therapy with CS given orally (prednisolone 20 mg daily) and in enema forms (hydrocortisone 100 mg) were found to be more efficacious than sulfasalazine (8 g daily for the first week followed by 4 g daily for the second week) in inducing remission of active UC (76% vs. 52%, $p<0.05$) [17]. A population-based inception cohort study from Olmsted County, Minnesota observed that among 63 of 185 patients with active UC (34%) who were treated with oral prednisone (40–60 mg daily) or intravenous CS with tapering over 3–6 months, 34 patients (54%; 95% CI, 41–67%) were in complete remission, 19 (30%; 95% CI, 19–43%) were in partial remission, and 10 (16%; 95% CI, 8–27%) did not respond to the treatment over the first 30 days [1]. After 1 year of the first use of CS, 49% of patients achieved prolonged response, 22% of them were CS-dependent, and 29% of patients underwent surgery [1]. An open-label study of three doses of prednisone given at three different daily doses (20, 40, or 60 mg) demonstrated that those given the lowest dose had significantly ($p<0.01$), threefold lower remission rates when compared with doses of 40 or 60 mg daily [18].

One randomized double-blind, controlled trial compared the efficacy and safety of oral controlled-release formulation of budesonide (10 mg daily) ($n=34$) vs. oral prednisolone (40 mg daily) ($n=38$) given for 9 weeks in patients with extensive or left-sided, mild to moderately active UC [19]. Although both agents equally decreased the overall mean endoscopic score (mean decrease: budesonide 1.20 vs. prednisolone 1.36, $p=0.12$) at week 9, segmental analysis showed significant superiority of prednisolone over budesonide in sigmoid colon (mean decrease: budesonide 0.96 vs. prednisolone 1.40, $p=0.04$) after 4 weeks [19]. Prednisolone was more efficacious ($p=0.022$) than budesonide in decreasing an overall histopathological score, but segmental analysis at week 4 demonstrated that this significant superiority over budesonide was limited only to descending and sigmoid colon [19]. Oral budesonide was shown to have no effect on a morning plasma cortisol level, whereas oral prednisolone significantly depressed it after 2 ($p=0.001$) and 4 ($p=0.01$) weeks of treatment [19].

It is recommended that patients presenting with severe UC who do not respond to orally administered high-dose prednisone given for 7–14 days should be treated with intravenous CS, such as methylprednisolone (40–60 mg daily) or hydrocortisone (200–300 mg daily) [2, 20]. The response rates observed in studies which evaluated 5–14 day treatment with intravenous CS ranged from 45 to 80% [21–24]; however, neither placebo-controlled studies nor studies comparing different parenteral CS were performed.

Maintenance Treatment

It has been demonstrated that therapy with CS is not efficacious in maintaining CS-induced remission of UC [25, 26]. Relapse rates were similar between patients receiving maintenance therapy with oral prednisone given at dose of 50 mg/day

($n=37$) and those receiving placebo ($n=31$) (48.6% vs. 41.9%, $p>0.005$) [25]. Similar results were obtained by Lennard-Jones et al. who evaluated the efficacy of oral prednisone administered at the dose of 15 mg daily for 6 months [26]. Remission (37.5% vs. 40%) and relapse (56.2% vs. 56.7%) rates were almost the same regardless of the treatment with prednisone or placebo, respectively [26]. Although one double-blind crossover trial observed superiority of oral prednisolone given at dose 40 mg over placebo (relapse rates: 0% vs. 46%, $p<0.01$) in maintaining remission during 3-month therapy, the rates of CS-related adverse events were higher than in placebo group [27]. In light of the aforementioned findings, therapy with CS is not recommended as maintenance treatment in UC.

Corticosteroids in Crohn's Disease

Current American Gastroenterological Association guidelines recommend that controlled ileal release (CIR) formulations of the topical corticosteroid budesonide should be used in patients with mild to moderate ileocecal Crohn's disease (CD) [2]. The recommended initial dose of budesonide in inducing remission is 9 mg which should be subsequently tapered to the dose of 6 mg and then to the dose of 3 mg [2]. Short-term therapy for up to 3 months with budesonide is safe and effective in maintaining remission [2].

Conventional CS (prednisone) are recommended in patients with moderate to severe CD regardless of disease localization or in those with ileocecal CD with no response to previous therapy with budesonide [2]. Induction of remission can be effectively achieved with prednisone administered at doses 40–60 mg/day (or 1 mg/kg/day) within average of 7–14 days [2]. Once remission is achieved, the administered dose of prednisone should be tapered by 5 mg/week to a dose of 20 mg [2]. After that the dose should be tapered 2.5–5 mg week below 20 mg [2]. Conventional CS are not effective in maintaining remission in patients with CD [2].

Patients presenting with severe CD or those who fail to respond to therapy with oral CS may benefit from admission to the hospital and therapy with parenteral CS (40–60 mg/day of methylprednisolone or 200–300 mg/day of hydrocortisone) as an inpatient [2]. CS are not recommended in patients presenting with perianal fistulas [2].

Topical Corticosteroids

Induction of Remission

The results of several randomized-controlled trials comparing the efficacy of oral treatment with CIR budesonide to placebo [28, 29], mesalamine [30], or systemic CS [31–35] for inducing remission in active mild to moderate active CD suggest that this agent might be a useful alternative to systemic CS for inducing remission in ileocecal CD.

A recent meta-analysis of two randomized-controlled trials [28, 29] demonstrated that CIR budesonide given at the dose of 9 mg daily was superior to placebo at 8 weeks in inducing remission with the pooled odds ratio of 2.85 (95% CI 1.67–4.87) and number needed to treat of 5 to achieve remission [36]. The International Budesonide–Mesalamine Study Group observed that CIR budesonide administered at the dose 9 mg daily was superior to mesalamine at the dose of 4 g daily in inducing remission at 8 weeks (69% vs. 45%, $p = 0.001$) [30] with a number needed to treat of 4 to achieve remission [36]. A meta-analysis of five randomized-controlled trials which compared the efficacy of CIR budesonide to systemic CS (prednisolone or prednisone) for inducing remission in patients with [31–35] observed that CIR budesonide was significantly inferior to systemic CS (prednisone or prednisolone) with pooled odds ratio of 0.69 (95% CI 0.51–0.95) and number needed to treat of 12 [36]. However, a systematic review of five trials comparing CIR budesonide vs. prednisolone [31–34, 37] observed that patients with low disease activity (Crohn's Disease Activity Index score: 200–300) had similar likelihood of inducing remission regardless of agent used (RR = 0.91, 95% CI: 0.77–1.07) [38]. The efficacy of budesonide compared to prednisone depended on the location of disease and was comparable to that of prednisone when the disease was confined to the either terminal ileum, and/or cecum and/ or ascending colon, (response: 55.6% vs. 50%), and was lower when the disease was confined to the distal colon and rectum (response: 47% vs. 62.5%) or to the colon, (response: 20% vs. 58.8%) [34].

Treatment with CIR budesonide for 8–10 weeks was associated with a similar or lower proportion of CS-related adverse events than the treatment with placebo (pooled OR = 0.98, 95% CI 0.58–1.67) [28, 29] or systemic CS (pooled OR = 0.38, 95% CI 0.28–0.53) [31–35], respectively [36]. These trials, [31, 33, 35] which evaluated plasma cortisol levels, observed that patients treated with CIR budesonide were more likely than those receiving systemic CS to have normal plasma cortisol levels (pooled OR = 0.28, 95% CI 0.18–0.43) [36].

Maintenance Treatment

Several randomized-controlled trials evaluated the efficacy of CIR or pH-modified release budesonide in maintaining CS-induced remission of CD and also among patients with CS-dependent inactive CD.

A predetermined pooled analysis of four randomized placebo-controlled trials [39–42], including 380 patients with medically induced remission CD and who received 12-month treatment with oral CIR budesonide (3 or 6 mg) or placebo observed that budesonide given at a higher daily dose significantly reduced relapse rates after 3 and 6 months ($p < 0.001$ and $p < 0.05$, respectively) but not after 9 and 12 months when compared to placebo. Although 1-year relapse rates were not different between a higher dose of budesonide and placebo, therapy with a higher dose of budesonide significantly increased the median time to relapse when compared to placebo (268 vs. 154 days, $p = 0.0024$) [43].

CIR budesonide given in doses 6–9 mg daily was also found efficacious in treating CS-dependent patients with quiescent CD. A randomized-controlled trial observed that CIR budesonide given at 6 mg daily for up to 1 year significantly reduced the 1-year relapse rate when compared to oral mesalamine (3 g daily) (55% vs. 82%, $p=0.045$) and maintained remission for a longer period of time (241 vs. 147 days, $p=0.003$) [44]. Moreover, prednisolone-dependent patients with inactive ileocecal CD who switched their therapy from prednisolone to CIR budesonide 6 mg daily had significantly lower relapse rates that those who switched to placebo after 1 week (17% vs. 41%, $p=0.004$) and 13 weeks (32% vs. 65%, $p<0.001$) without prednisolone [45].

Oral therapy with low dose (3 mg daily) of pH-modified release budesonide was not found more effective than placebo for maintaining CS-induced remission of CD after 12 months of therapy with relapse rates of 67 and 65%, respectively [46]. Recently, a large double-blind controlled trial from the Netherlands and Germany ($n=160$) did not observe any difference in low, 1-year relapse rates (24% vs. 19%, $p=0.43$) nor time to relapse ($p=0.46$) between daily doses of 6 or 9 mg of pH-modified release budesonide [47]. It has been suggested that low 1-year relapse rates in that trial were most likely caused by the inclusion of patients with a relatively mild course of CD [48].

Current data indicate that treatment with budesonide at a dose of 6 mg daily is safe and effective in maintaining a medically induced remission in CD, although the duration of remission may be limited to 6 months while on therapy.

Two European double-blind and placebo-controlled trials which evaluated the efficacy of CIR [49] or pH-modified release [50] budesonide administered in daily doses of 6 or 3 mg in maintaining surgically induced remission in CD for a period of 12 months did not find any superiority of either form of budesonide over placebo in preventing endoscopic recurrence [49, 50]. However, a subgroup of patients who underwent surgery due to disease activity took CIR budesonide, and when compared to placebo showed significant reductions in endoscopic recurrence rates after 12 months of treatment (32% vs. 65%; $p=0.047$) and showed a trend toward lower recurrence rates after 3 months of treatment (21% vs. 47%; $p=0.11$) [49].

Systemic Corticosteroids

Induction of Remission

Several studies analyzed the efficacy of oral systemic CS in the treatment of patients with moderate to severe active CD. A recent meta-analysis of two randomized-controlled trials [51, 52] demonstrated that systemic CS were significantly superior over placebo in inducing remission in CD (pooled RR 1.99; 95% CI 1.51–2.64; $p<0.00001$) with a number needed to treat of 3 to induce remission [53]. Therapy with CS, such as oral prednisone, given at dose 0.5–0.75 mg/kg daily

with tapering over 17 weeks [51] or oral methylprednisolone given at a dose of 48 mg daily with tapering by 8 mg/week over 18 weeks [52] resulted in absolute risk reduction by 30% (95% CI 20–41%) [53]. CS were also found to be nearly twofold more efficacious than 5-ASA agents in inducing late remission (>15 weeks after the onset of treatment) of CD (pooled RR 1.65; 95% CI 1.33–2.03; $p<0.00001$), with absolute risk reduction of 27% (95% CI 17–37%) and a number needed to treat of 3.7 to induce remission [51–54].

A population-based inception cohort study from Olmsted County, Minnesota observed that among 74 of 173 patients with active CD (43%) who were treated with oral prednisone (40–60 mg daily) or intravenous CS with tapering over 3–6 months, 43 patients (58%; 95% CI, 46–69%) were in complete remission, 19 (26%; 95% CI, 16–37%) were in partial remission, and 12 (16%; 95% CI, 9–27%) did not respond to the treatment after 30 days from the initiation of therapy [1]. After 1 year of the first use of CS, 32% of patients achieved prolonged response, 28% of them were CS-dependent, and 38% of patients underwent surgery [1]. Similar results were also found by a population-based study from Denmark in which among 109 of 196 patients with active CD (56%) who were treated with oral prednisolone at the dose of 1 mg/kg daily with subsequent taper within weeks to a maintenance dose of 10–15 mg daily for 3–5 months, 48% were in complete remission, 32% in partial remission, and 20% did not respond within 30 days of treatment initiation [55]. Among all the patients treated with CS, 44% remained in prolonged remission beyond first 30 days of treatment, 36% experienced relapse of 30 days after discontinuation or dose reduction and 20% were CS-resistant [55].

The use of intravenous CS in moderate to severe active CD was evaluated in one double-blind, controlled study in which 88 patients were randomly assigned to continuous intravenous treatment with either hydrocortisone ($n=44$) (300 mg daily) or adrenocorticotropic hormone (ACTH) (120 U/day) ($n=44$) [56]. Both intravenous hydrocortisone and ACTH were found equally effective with full response rates of 93% (CI 84–99%) and 82% (CI 67–2%) after 10 days of treatment, respectively [56]. In addition, one retrospective study observed that 5-day therapy with intravenous CS resulted in immediate remission in 76% of patients hospitalized due to severe CD [57].

Maintenance Treatment

The efficacy of systemic CS in maintaining medically or surgically induced remission in patients was evaluated in a pooled meta-analysis [58] of three double-blind placebo-controlled trials [51, 52, 59]. It was observed that therapy with systemic CS given at daily dose of 0.25 mg/kg, 7, or 8 mg were no more effective than placebo in reducing the risk of relapse during 2-year follow-up with the pooled odds ratio for the relapse of 0.71 (95% CI: 0.39–1.31), 0.82 (95% CI: 0.47–1.43), and 0.72 (95% CI 0.38–1.35) at 6, 12, and 24 months, respectively [58].

Based on the data from clinical trials, it is clear that low-doses of systemic CS are not effective in maintaining the remission of CD. They are not recommended

as maintenance therapy. Due to increased risk of significant side effects, high doses of CS have not been evaluated as a potential maintenance treatment of CD.

Adverse Effects of Corticosteroid Therapy

While CS therapy has proven to be a boon for patients, there remain several possibly serious adverse effects of therapy, particularly if therapy is systemic and/or prolonged. The use of CS, in general, has been shown to increase the risk of striae, risk of infection, osteonecrosis and osteoporosis, increase in the level of triglycerides, weight, cataracts, hypokalemia, proximal myopathy and of the limb girdle, acne, mood alterations, increase in the risk of hyperglycemia and diabetes, hypertension, and lower extremity edema [60, 61]. One large study of 86 patients which compared budesonide vs. prednisolone for Crohn's Disease showed that prednisolone had a panoply of side effects, of which moon face (36%), acne (23%), and lower extremity edema (12%) were most prominent [31]. A study using data from the TREAT registry showed that patients on CS had elevated the risk of death with an odds ratio of 2.10 (CI 1.15–3.83) and an elevated risk of serious infection with an OR of 2.21 (CI 1.46–3.34) [62].

CS may also cause CS dependence, wherein withdrawal of CS may cause a worsening of the patient's clinical condition. One definition of dependence in the literature has stated that if a patient relapses within 30 days of their discontinuation of the CS medication, or relapses due to lowering of dose such that it prevents the patient from discontinuing CS for more than 1 year, they have the condition [55]. Several studies have shown that from 22 to 38% of patients who suffer from IBD may suffer from CS dependence [1, 55, 63].

Several large randomized-controlled trials have also examined the risk of adverse effects with conventional systemic CS therapy for Crohn's Disease. In the National Cooperative Crohn's Disease Study of 1979, 32% of patients experienced an adverse event on CS vs. 7% of those on placebo [51, 64, 65]. In a similar trial in Europe, the European Cooperative Crohn's Disease Study (1984), 2/45 (4.4%) had adverse events which required discontinuation of the drug [52]. A pooled analysis by the Cochrane collaboration of five randomized trials showed that patients taking CS for Crohn's Disease had a relative risk of an adverse event of about 2 (RR 2.38; 95% CI 1.34–4.25; $p=0.003$) when compared with patients taking low-dose ASA [53].

Fortunately, alternative formulations of CS, in particular budesonide, seem to have significantly lowered the adverse effect profiles. In one major European study of 120 patients, efficacy using CIR budesonide was comparable to using systemic CS, and the rate of adverse effects decreased 50% [45]. Another study showed that the most prevalent side effect seen was gastrointestinal symptoms, followed by an increased risk of moon face and acne in patients on budesonide for Crohn's Disease [43]. See Table 6.1 for a list of studies examining the adverse effects of CS. More studies are helpful in delineating the precise risk of adverse effects when using these useful targeted formulations.

Table 6.1 Adverse effects of corticosteroids

					Corticosteroid-related side effects				
Type of IBD	*n*	Interventions tested	Time	Overall AEs	Overall	Moon face	Acne	Hirsutism	Psychosis/ mood swings
CD (ileocecal)	67	Bud 3 mg daily	8 weeks	81%	15%	Bud, 7%; placebo, 2% ($p=0.001$)	ND	ND	NR
	61	Bud 9 mg daily		90%	26%				
	64	Bud 15 mg daily		88%	38%				
	66	Placebo		76% (all NS)	26% (all NS compared with placebo)				
CD (ileocecal)	80 79 41	Bud 9 mg daily Bud 4.5 mg BID Placebo	8 weeks	ND for overall AEs (93, 91, 94%, respectively) Early termination due to AEs: Bud 9 mg daily, 6/80; Bud 4.5 mg BID, 8/79; placebo, 3/41 (NS)	ND (specific data not provided)	NR	NR	NR	NR
CD (ileocecal)	91 89	Budesonide 9 mg daily Mesalamine 2 g BID	16 weeks	63% SAEs, 13%; 72% SAEs, 25%a ($p=0.04$)	NR	NR	NR	NR	NR

CD (ileocecal)	88	Bud 9 mg daily	8 weeks		Bud, 29/88 (33%)	Bud, 15/88	Bud, 5/88	Bud, 2/88	NR
	88	Pred 40 mg daily then tapered			Pred, 48/88 (55%) ($p=0.003$)	Pred, 31/88	Pred, 20/88	Pred, 2/88	
CD (ileocecal)	58	Bud 9 mg daily	8 weeks	Bud 9 mg, 78%	Weight gain: Bud 9 mg, 1 kg	Higher in Pred group (specific numbers NR)	NR	NR	NR
	61	Bud 4.5 mg BID		Bud 4.5 mg BID, 90%	Bud 4.5 mg BID, 0				
	58	Pred 40 mg daily then tapered		Pred, 90%	Pred, 2.1 kg ($p<0.0001$)				
CD (ileocecal)	35	Bud 3 mg TID	8 weeks	Bud, 11/35 (31.4%)	Bud, 10/35 (28.6%)	Bud, 5/35 (14%)	Bud, 5/35 (14%)	Bud, 5/35 (14%)	Bud, 7/35 (20%)
	33	Pred 48 mg daily then tapered		Pred, 24/33 (72.7%)	Pred, 23/33 (69.7%) ($p=0.0015$)	Pred, 16/33 (48%) Dermatologic side effects	Pred, 16/33 (48%) Dermatologic side effects	Pred, 16/33 (48%) Dermatologic side effects	Pred, 10/33 (30%)
CD (ileocecal)	100	Bud 3 mg TID	8 weeks	ND	Bud, 14%	Bud, 16/100	Bud, 19/100	Bud, 2/100	Bud, 10/100
	101	Prednisone 40 mg daily then tapered			Prednisone, 30% ($p=0.006$)	Prednisone, 33/101 ($p<0.05$)	Prednisone, 29/101 ($p<0.05$)	Prednisone, 8/101 ($p<0.05$)	Prednisone, 16/101 ($p<0.05$)
CD (ileocecal)	427	Bud 9 mg/day	8 weeks	NR	NR	11%	15%	5%	NR
	145	Pred 40 mg/day				37%[a]	23%[a]	3%	
	107	Placebo				4%	13%	2% (p=NS)	
CD (ileocecal)	138	Bud 6.8 mg/day (mean)	2 years	96% (SAEs, 35%)	51%	9%	15%	7%	17%
	134	Pred 14.9 mg/day (mean)		98% (SAEs, 29%)	71% ($p<0.001$)	33%[a] ($p<0.0001$)	26%[a] ($p=0.026$)	13% (NS)	25% (NS)

(continued)

Table 6.1 (continued)

					Corticosteroid-related side effects				
Type of IBD	*n*	Interventions tested	Time	Overall AEs	Overall	Moon face	Acne	Hirsutism	Psychosis/ mood swings
CD (active)	85	Prednisone 0.5–0.75 mg/kg/ day	17 weeks	Prednisone, 27/85 (32%)	NR	Prednisone, 47%	Prednisone, 30%	Prednisone, 7%	Prednisone, 2%
	77	Placebo		Placebo, 5/77 (6%)		Placebo, 3%	Placebo, 7%	Placebo, 1%	Placebo
	59	AZA 2.5 mg/kg		AZA, 19/59 (32%)		AZA, 3%	AZA, 18%	AZA, 0%	
	74	Sulfa 1 g/15 kg		Sulfa, 10/74 (14%) (moderate-severe AEs)		Sulfa, 8% ($p<0.05$ for prednisone)	Sulfa, 8% ($p<0.05$ for prednisone or AZA)	Sulfa, 0% ($p<0.05$ for prednisone)	
CD (maintenance)	89	Prednisone 0.25 mg/kg/day	2 years	Prednisone, 16/61 (26%)	NR	Prednisone, 25%	Prednisone, 19%	Prednisone, 8%	Prednisone, 3%
	121	Placebo		Placebo, 8/101 (8%)		Placebo, 3%	Placebo, 21%	Placebo, 1%	Placebo, 0%
	73	AZA 1 mg/kg		AZA, 11/54 (20%)		AZA, 2%	AZA, 8%	AZA, 0%	AZA, 0%
	77	Sulfa 0.5 g/15 kg		Sulfa, 7/58 (12%) (moderate-severe AE's)		Sulfa, 7% ($p<0.05$ for prednisone)	Sulfa, 9% ($p<0.05$ for sulfa/AZA compared with placebo)	Sulfa, 0% ($p<0.05$ for prednisone)	Sulfa, 2% (p=NS)

Corticosteroid-related side effects									
Hypertension	Cataracts	Striae	Respiratory infection/ sepsis	Ankle edema	Petechial bleeding	Easy bruising	Buffalo hump	Adrenocortical axis	References
NR	NR	NR	ND	ND	NR	NR	ND	Cosyntropin stimulation abnormal in 50% of those treated with 9 mg/day compared with 19% for placebo ($p=0.006$) Cortisol levels decreased for 9-mg dose and 15-mg dose; no change for 3-mg dose and placebo	Greenberg et al. [19]
NR	NR	NR	NR	NR	NR	NR	NR	Normal adrenal function: Bud (both), 53%; placebo, 83% ($p<0.01$)	Tremaine et al. [313]
NR	NR	NR	NR	NR	NR	NR	NR	Abnormal cosyntropin stimulation in 10% of Bud-treated patients and none of mesalamine-treated patients ($p=0.02$)	Thomsen et al. [20]
NR	NR	Bud, 0/88 Pred, 0/88	NR	Bud, 2/88 Pred, 10/88	NR	Bud, 2/88 Pred, 6/88	Bud, 1/88 Pred, 3/88	Cortisol suppression greater with Pred (week 8) ($p=0.02$)	Rutgeerts et al. [21]

(continued)

Table 6.1 (continued)

Corticosteroid-related side effects									
Hypertension	Cataracts	Striae	Respiratory infection/ sepsis	Ankle edema	Petechial bleeding	Easy bruising	Buffalo hump	Adrenocortical axis	References
NR	NR	NR	NR	NR	NR	NR	NR	Cortisol suppression greater with Pred ($p=0.0035$)	Campieri et al. [23]
NR	NR	NR	NR	NR	NR	NR	NR	NR	Gross et al. [22]
NR	NR	Bud, 3/100 Prednisone, 2/101 ($p=$NS)	NR	Bud, 6/100 Prednisone, 6/101 ($p=$NS)	NR	Bud, 0/100 Prednisone, 2/101 ($p=$NS)	Bud, 2/100 Prednisone, 10/101 ($p<0.05$)	NR	Bar-Meir et al. [13]
NR	NR	1%	11%	7%		15%	1%		Entocort EC package insert [314]
		0%	14%	9%		9%	3%		
		2% ($p=$NS)	7%	6%		11%	2%		
NR	NR	1%	NR	8%	NR	12%	1%	Abnormal cosyntropin stimulation test results found in corticosteroid-dependent patients on Pred compared with Bud ($p=0.038$); ND between Bud and Pred in other groups	Schoon et al. [80]
		3% (NS)		13% (NS)		23%[a] ($p=0.012$)	2% (NS)		

Prednisone, 13%	NR	Prednisone, 6%	Prednisone, 27%	NR	Prednisone, 6%	Prednisone, 17%	NR	NR	Summers et al. (NCCDS), [36, 73]
Placebo, 0%		Placebo, 0%	Placebo, 10%		Placebo, 0%	Placebo, 3%			
AZA, 0%		AZA, 0%	AZA, 5%		AZA, 0%	AZA, 5%			
Sulfa, 3% ($p<0.05$ for prednisone)		Sulfa, 3% ($p<0.05$ for prednisone)	Sulfa, 10% ($p<0.05$ for prednisone)		Sulfa, 3% ($p<0.05$ for prednisone)	Sulfa, 5% ($p<0.05$ for prednisone)			
Prednisone, 13%	NR	Prednisone, 7%	Prednisone, 8%	NR	Prednisone, 6%	Prednisone, 16%	NR	NR	Summers et al. (NCCDS), [36, 73]
Placebo, 9%		Placebo, 0%	Placebo, 19%		Placebo, 0%	Placebo, 7%			
AZA, 4%		AZA, 2%	AZA, 17%		AZA, 0%	AZA, 6%			
Sulfa, 3% (p=NS)		Sulfa, 3% ($p<0.05$ for prednisone)	Sulfa, 17% (p=NS)		Sulfa, 3% (p=NS)	Sulfa, 3% ($p<0.05$ for prednisone)			

(continued)

Table 6.1 (continued)

		Corticosteroid-related side effects							
Hypertension	Cataracts	Striae	Respiratory infection/ sepsis	Ankle edema	Petechial bleeding	Easy bruising	Buffalo hump	Adrenocortical axis	References
	Total (sum of part 1/ phase 2) +part 2								
CD	113	Methylprednisolone 8 mg/day (from 48 mg/day)	2 years	Patients withdrawing due to AEs	NR	Higher in Pred; incidence 1.9–2.5/100 patient months vs. 0.49 for placebo	ND	ND	ND
	117			Pred, 5/113					
	112	Sulfa 3 g/day		Sulfa, 5/117					
	110	Methylprednisolone +3 g/day Sulfasalazine		Combination, 6/112					
				Placebo 3/110					
UC	N	Corticotropin (ACTH) 120 U/day	10 days	NR	Similar in both groups (specifics not provided)	NR	NR	NR	NR
	66	Hydrocortisone 300 mg/day IV							

Studies included provided toxicity data Reprinted from [20]. Copyright Elsevier

AE adverse event; *Bud* budesonide; *ND* no difference; *NR* not reported; *BID* twice daily; *Pred* prednisolone; *SAE* serious adverse event; *TID* 3 times daily; *Sulfa* sulfasalazine

[a]Significant

The reference numbers in the Table are not numbers of the references in the chapter

Conclusion

Traditional CS still have a role in the treatment of both ulcerative colitis that is resistant to 5-ASA and that is moderate to severe, but does not have a role in the prevention of relapse. Topical formulations may be helpful in UC for sigmoidal or rectal disease and intravenous formulations are helpful for severe UC or UC not responsive to oral medication. For Crohn's Disease, the first-line therapy for mild to moderate CD would be budesonide due to its favorable safety profile as compared with standard formulations, and in addition budesonide has a role in preventing relapse for up to 6 months, whereas standard CS are not useful for this indication. More severe or refractory CD may require standard CS, but those with perianal fistulas should not be given CS. In sum, CS remain vital for the treatment of both UC and CD and help supplement the new and exciting therapies on the horizon for IBD.

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Chapter 7
State-of-the-Art Medical Therapy of the Adult Patient with IBD: The Immunomodulators

Dana Moffatt and Charles N. Bernstein

Keywords Immunomodulator • Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Azathioprine • 6-Mercaptopurine • Methotrexte • Cyclosporine • Tacrolimus • Mycophenolate mofetil • Thalidomide

Key Points

- AZA/6-MP are the most well-studied immunomodulators effective at reducing steroid use, inducing and maintaining remission in CD and UC.
- TPMT phenotype (genotype if phenotype not available) should be checked in all patients before initiating therapy with AZA or 6-MP, to avoid profound bone marrow toxicity and to facilitate more complete dosing earlier.
- Methotrexate is an effective alternative to AZA/6-MP in Crohn's disease and possibly in UC if given parenterally at doses >15 mg/week.
- Cycosporine A is effective at inducing remission in severe UC, and may lead to a reduced rate of colectomy if used as a bridge to long-term AZA or 6-MP therapy.
- Tacrolimus, mycophenolate mofetil, and thalidomide may have a role as third line immunomodulators in complicated or fistulizing CD.
- 6-Thioguanine should not be used as a therapy for active IBD due to frequent hepatotoxicity and occurrence of nodular regenerative hyperplasia.

Introduction

Patients with inflammatory bowel disease (IBD) tend to suffer from multiple relapses unless therapies intended to maintain remission are instituted. The backbone of medical therapy for patients with IBD consists of immunomodulator

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therapy with azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX), which now have evidence for the induction and maintenance of remission in Crohn's disease (CD) with lesser degrees of evidence for ulcerative colitis (UC) Table 7.1. Other immunomodulators, such as cyclosporine A (CYA), tacrolimus, mycophenolate mofetil (MMF), thalidomide, and the specific thiopurine metabolite 6-thioguanine (6-TG), are also discussed in this review of immunomodulator therapy in IBD.

Azathioprine/6-Mercaptopurine

Mechanism of Action and Metabolism

AZA and 6-MP are purine analogs with multiple effects on the immune system, including inhibition of DNA and RNA synthesis which inhibits cell mediated immunity by reducing natural killer (NK) T cells over weeks to months. They also induce T cell apoptosis by interfering with the enzyme Rac1, and activation of target genes, such as mitogen-activated protein kinase, nuclear factor-κB, and the induction of mitochondrial mediated apoptosis [1]. The net effect is down regulation of the cell-mediated immune response.

There is a well-defined pathway by which AZA is rapidly metabolized into 6-MP and then onward via three separate but intertwined enzymatic pathways (Fig. 7.1). Two pathways convert 6-MP into the inactive metabolites 6-methylmercaptopurine (6-MMP) and 6-thioinosine monophosphate (6-TU). The final pathway involves the conversion of 6-MP into the immunologically active metabolite 6-TG and is mediated by the enzyme hypoxanthine phosphoribosyltransferase [2, 3]. The ability to measure these metabolites has been harnessed to help understand clinical response to these agents. The data from AZA and 6-MP are often discussed interchangeably as AZA is metabolized to 6-MP and the approximate dose equivalence is 2:1 (AZA:6-MP), without any evidence that one agent is more effective than the other.

AZA/6-MP for Treatment of CD

Induction and Maintenance Therapy

The first large-scale study to assess the role of AZA in CD was the National Cooperative Crohn's Disease Study. In this study, AZA at a dose of 2.5 mg/kg over 17 weeks did not induce remission at a significantly different rate ($p < 0.05$) than placebo. However, the trend was in favor of a benefit, and over time we have

Table 7.1 Randomized-controlled trials and large retrospective trials evaluating thiopurines and methotrexate in inflammatory bowel disease

Study	Study design	IBD	*N*	Drug/dose	Outcome
Present et al. [5]	RCT – induction of remission	CD	83	6-MP – 1.35 mg/kg/day	67% vs. 8% remission
Ewe et al. [85]	RCT – induction of remission	CD	42	AZA – 2.5 mg/kg/day	76% vs. 38% remission
Candy et al. [6]	RCT – induction and maintenance of remission	CD	63	AZA – 2.5 mg/kg/day	76% vs. 67% remission 42% vs. 7% maintenance at 15 months
Markowitz et al. [7]	RCT – induction and maintenance of remission	CD	55	6-MP – 1.5 mg/kg/day	89% vs. 89% remission 9% vs. 47% relapse at 18 months
O'Donoghue et al. [9]	RCT – Maintenance of remission	CD	51	AZA 2 mg/kg/day	5% vs. 41% relapse at 1 year
Kirk and Lennard-Jones [15]	RCT – induction of remission	UC	44	AZA 2-2.5 mg/kg/day	$p<0.001$
Fraser et al. [17]	Retrospective review – induction of remission	UC	346	AZA – variable	58% induced remission
Hawthorne et at. [86]	RCT – maintenance of remission	UC	79	AZA – variable	36% vs. 59% relapse rate
Ardizzone et al. [21]	Retrospective – maintenance of remission	UC	56	AZA – 2 mg/kg/day	64–69% remission at 1–3 years 75% reduction in relapse
Fernandez-Banares et al. [19]	Case series – maintenance of remission	UC	13	AZA 2–2.5 mg/kg/day	10% relapse after mean 16 months
Feagan et al. [41]	RCT – induction of remission	CD	141	MTX – IM 25 mg/day	39.4% vs. 19.1% remission ($p=0.025$)
Oren et al. [42]	RCT – induction of remission	CD	84	MTX – Oral 12.5 mg/week	38% vs. 46% ($p=$NS)
Arora et al. [43]	RCT – induction of remission	CD	76	MTX – Oral 15 mg/week	54% vs. 20% remission, $p=$NS
Feagan et al. [46]	RCT – maintenance of remission	CD	76	MTX – IM 15 mg/week	65% vs. 39% remission ($p=0.004$)
Mate-Jimenez et al. [49]	RCT – induction of remission	UC and CD	72	MTX – IM 15 mg/week	Remission at 30 weeks: 78.6% vs. 25% (5-ASA group)$p<0.005$

AZA azathioprine, *MTX* methotrexate, *RCT* randomized-controlled trial, *CD* Crohn's disease, *UC* ulcerative colitis

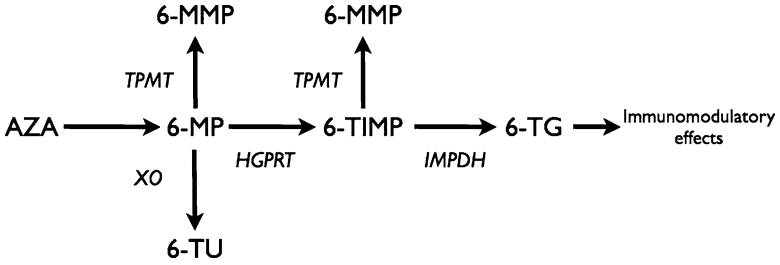

Fig. 7.1 Azathioprine pathway of metabolism. 6-*MMP* 6-methyl mercaptopurine; *6-TG* 6-thioguanine; *6-TIMP* 6-thioinosine monophosphate; *6-TU* 6-thioruic acid; *HGPRT* hypoxanthine guanine phosphoribosyltransferase; *IMPDH* inosine monophosphate dehydrogenase; *TPMT* thiopurine methyl transferase; *XO* xanthine oxidase

learned that the level of dosing and duration of follow-up was not optimal for many patients with CD [4]. The first study to show the effect of AZA/6-MP on active CD was the landmark trial by Present et al., published in 1980. It was a placebo-controlled trial of 83 CD patients randomized to 6-MP at 1.35 mg/kg/day or placebo for 2 years. Crossover data showed improvement in 26/39 on 6-MP (67%) compared with 3/39 placebo (8%) ($p<0.001$). The study also demonstrated the improvement in fistulizing disease (31% 6-MP vs. 6% placebo), and a significant reduction in steroid use in the active arm (75% 6-MP vs. 36% placebo. $p<0.001$) [5].

In 1995, a second randomized-control trial demonstrated similar effects, with 76% of steroid-dependent CD patients responding to AZA over a 12-week period [6]. A landmark study in 2000, randomized 55 children with newly diagnosed active CD and steroid dependent to 1.5 mg/kg/day 6-MP vs. placebo, and initiated a steroid taper in both groups. Although remission rates in both groups were 89% at the end of the study period, the 6-MP-treated patients had used significantly less steroid, with only 3% requiring a second tapering course compared to 31% in the placebo group ($p<0.0001$) [7] showing a powerful steroid sparing effect of 6-MP. This was in essence the first "top down" study approach for proving the value of instituting immunomodulator therapy early just after diagnosis. The steroid sparing effects of this study were especially germane in the pediatric population where steroid side effects can be detrimental.

A meta-analysis assessing the effect of AZA/6-MP on active CD showed a significant effect on the induction of remission OR 3.09 (95% confidence interval, CI 2.45–3.91). The meta-analysis also showed a significant steroid-sparing effect of AZA/6-MP, OR 3.69 (95% CI, 2.12–6.42), and a beneficial effect on fistulae closure OR 4.44 (95% CI, 1.50–13.20) [8].

AZA/6-MP can maintain remission when compared to placebo, which has emerged as a principle indication for these agents [4–6]. An older study from 1978 showed a very low relapse rate of 5% at 1 year when treated with AZA,

compared to placebo [9]. More recently, Candy et al., showed that 42% patients vs. 7% of CD patients were still in remission at 15 months when treated with AZA or placebo, respectively [6]. Markowitz et al., showed that 91% vs. 53% of patients were free of relapse at 18 months when treated with AZA vs. placebo [7]. Finally, a Cochrane systematic review showed that the overall OR for AZA maintaining remission of CD was 2.16 (95% CI 1.35–3.47), with an overall number-needed-to-treat (NNT) of 7. This review also showed a steroid-sparing effect for AZA over the long term, OR 5.22 (95% CI 1.06–25.68) with an overall NNT of 3 [10].

While there is ample evidence that AZA/6-MP have an effect on maintaining remission of CD, it is unclear how long patients in remission should remain on therapy. Two studies have examined this question specifically. The first study involved patients with CD in long-term remission (>6 months) on AZA 2 mg/kg/day. In 157 patients that continued to take the therapy over the long term, relapse rates were 11 and 32% at 1 and 5 years, respectively. In 42 patients who discontinued therapy, relapse occurred in 38 and 75% at 1 and 5 years ($p<0.001$) [11]. More recently, in 2005, the same group of investigators reexamined the same question, showing that in long-term remission (>42 months on AZA 2 mg/kg/day) discontinuation of medication led to relapse in 21% of patients compared to 8% in those continued on the medication over the next 18 months ($p<0.05$). The authors concluded that therapy from 3 to 5 years is significantly more effective than withdrawal of medication [12]. Despite that the balance of data suggests that purine analogs are very beneficial, a report from these same investigators (the GETAID group) revealed that in an era and jurisdiction with frequent use of purine analogs in CD there was no decrement in surgery rates over a 25-year period [13]. Hence, there are no data to date that the use of these agents changes the natural history of disease, including phenotype evolution [14].

In summary, AZA/6-MP have been shown to be effective for the induction of remission in active CD, to have a strong steroid sparing effect, to maintain remission, and may also have a beneficial effect on fistulizing disease.

AZA and Ulcerative Colitis

Although there are fewer controlled studies examining the role of AZA/6-MP in UC, and the ones that exist are small, the evidence suggests that these are effective agents for inducing and maintaining remission of disease that does not respond to 5-aminosalicylates or is steroid dependent. A placebo-controlled trial published in 1982, showed a significant reduction in disease activity with 2–2.5 mg/kg/day AZA, in 44 steroid-dependent UC patients ($p<0.001$) [15]. More recently, 72 patients with steroid-dependent UC on more than 10 mg/day of prednisone for 6 months were randomized to either AZA 2 mg/kg/day or 5-ASA at 3.2 g/day. The primary endpoint was complete endoscopic and clinical remission with discontinuation of steroids. At the end of 6 months, 19/36 (53%) AZA patients were in remission,

compared with 7/36 (21%) of 5-ASA patients with a calculated OR of 4.78 (95% CI, 1.57–14.5, $p<0.005$). This study also documented a statistically significant decrease in physician global assessment, Powell-Tuck index and Baron index in the AZA group at 3 and 6 months when compared to placebo [16]. Other larger, uncontrolled studies have also documented a benefit of AZA for the induction of remission and maintenance of remission when compared to placebo or no therapy [17–19]. Finally, a recent Cochrane review meta-analysis showed that based on the available data, AZA/6-MP were valuable agents for maintaining remission in UC, with a relative risk reduction (RRR) of 0.41 (95% CI 0.24–0.7) and an NNT of 5 [20].

Postoperative Therapy with AZA/6-MP in Crohn's Disease

An unblinded study of 142 CD patients randomized to AZA 2 mg/kg/day or mesalamine 3 g/day postsurgical resection showed a nonsignificant reduction in clinical relapse at 24 months (17.4% AZA vs. 28.2% mesalamine), with an OR of 2.04 (95% CI 0.89–4.67). However, subgroup analysis showed that AZA was more effective in patients who had undergone prior surgical remissions, 12.8% vs. 35.9% relapse, OR 4.83 (95% CI, 1.47–15.8, $p=0.03$) [21]. A multicenter trial showed that the use of 6-MP 50 mg/day was superior to mesalamine 3 g/day and to placebo, in a group of 131 CD patients followed in the postoperative setting. Clinical recurrence at 24 months occurred in 50, 58, and 77% in patients treated with 6-MP, mesalamine and placebo, respectively ($p<0.05$). However, endoscopic recurrence occurred in only 43, 63, and 64%, which is not only lower than expected but surprisingly also lower than clinical recurrence rates, leading to criticism of this study as being biologically implausible [22]. Despite the lack of clear evidence for using AZA in the postoperative setting, we recommend that patients considered high risk for recurrence because of aggressive disease, previous surgical resections or ongoing smoking should be given the option to be treated with AZA or 6-MP in the postoperative setting to prevent disease recurrence.

TPMT Genotype and Monitoring Metabolite Levels

Although it has been known since the early 1990s that AZA and 6-MP had variable rates of absorption and effectiveness in different individuals, it has only been in the last decade that the complete pathway of metabolism and pharmacogenomic expression has been completely understood (Fig. 7.1). It is recommended to identify the thiopurine methyl transferase (TPMT) phenotype of every patient prior to starting therapy with a thiopurine. The phenotypes or enzyme levels correlate well with genotypes. One in 300 (0.3%) of western populations have low to absent enzyme activity of TPMT (homozygous TPMT-L), 11% have intermediate TPMT action (TPMT-H/TPMT-L heterozygous), and 89% have normal to high levels of activity (homozygous

wild type TPMT-H) [23, 24]. While any genotype can be associated with dangerous leucopenia, this can happen earlier and more profoundly in those with lower enzyme levels [25]. Hence, those with very low TPMT levels (or homozygous TPMT-L if genotype is measured) should likely not receive these agents. Those with low to intermediate levels (or genotypically heterozygotes) should be initiated with low doses and have WBCs followed closely. Those with normal to elevated levels (homozygous wild type TPMT-H) can be started at full doses to potentially achieve a clinical effect sooner, while WBC should still be monitored monthly.

The role of measuring metabolite levels is still in debate, with some studies showing an ability to alter management and predict hepatotoxicity as well as bone marrow toxicity [26, 27], while others finding little clinical utility, other than documenting noncompliance or metabolism favoring a nontherapeutically active metabolite (6-MMP) in nonresponders [28–30]. In subjects who achieve either remission or leucopenia with AZA/6-MP metabolite measurement is likely unnecessary. In subjects using high doses of AZA/6-MP (2.5 mg/kg) without achieving remission or leucopenia, metabolite measurements can be instructive. Further prospective studies further elucidating the optimal therapeutic levels are needed.

Adverse Events with AZA/6-MP

Different studies have shown wide ranges (15–30%) of adverse events in patients taking AZA or 6-MP. The most common events are gastrointestinal, dermatologic, and musculoskeletal complaints although these are usually not severe enough to discontinue medication. Life-threatening adverse events include bone marrow toxicity, pancreatitis, and hepatotoxicity, which may be severe enough to warrant discontinuation of medication in 8.9% of patients [31]. Profound bone marrow toxicity should be avoidable in modern practice with the availability of TMPT phenotyping prior to the initiation of therapy as discussed above. However, some patients may still have significant bone marrow toxicity despite normal TMPT phenotyping. These events may be due to promoter mutations, drug interactions, or environmental factors [32].

Significant hepatotoxicity is a rare at (<1% of patients). Elevated transaminases are the clue and stopping the drug typically facilitates reversal of hepatotoxicity. Veno-occlusive disease can occur in purine analog users. Acute pancreatitis is considered an idiosyncratic reaction that occurs in approximately 3% of patients within the first 4 weeks of therapy. It is not recommended to rechallenge patients with thiopurines if this reaction has occurred, as there is virtually a 100% chance of recurrence of pancreatitis [31]. There may be a role in rechallenging patients with 6-MP who have discontinued AZA secondary to malaise, gastrointestinal upset, or rash, as a recent retrospective review showed that 61% of those with GI upset tolerated the medication and 100% of patients with rash did not recur with 6-MP [31].

The use of long-term AZA/6-MP may be associated with a risk of developing future lymphomas. Case-series and cohort studies, from around the world, have yielded conflicting results as to the level of risk, with a wide range with standard

incidence ratios (SIR) ranging from 0 to 37.5 [33, 34]. A meta-analysis was performed utilizing data from 6 of the largest cohort studies performed to date, encompassing a total of 3,891 patients exposed to thiopurines. The authors found a total of 11 cases of lymphoma where 2.63 should have been expected, giving an SIR of 4.18 (95% CI 2.07–7.51) [35]. However, the difficulty in interpreting any of these data lies in the fact that IBD itself may to be a weak risk factor for lymphoma, which has been shown in case-series and cohort studies [36, 37]. One author used a Markov decision analysis to quantify the risks and benefits of using AZA in CD patients with chronically active disease and showed that the risk of lymphoma would have to be increased tenfold in order to offset the increase in quality-adjusted life years gained by therapy [38].

Methotrexate

Methotrexate in Crohn's Disease

Methotrexate (MTX) is the most commonly used immunomodulator in rheumatoid arthritis, psoriatic arthritis, and psoriasis, and also has been shown to be effective in CD and UC. MTX is a folate antagonist, which binds to dihydrofolate reductase and inhibits folate synthesis. MTX has several other mechanisms of action that lend it immunomodulatory effects, including inhibiting interleukins 1, 2, 6, and 8, inducing adenosine, and inhibiting purine synthesis. The net result is to reduce cellular and humoral immune responses [39, 40]. MTX is incompletely absorbed when taken orally which is why intramuscular or subcutaneous administration is more reliably effective. MTX is primarily eliminated via the kidneys [40].

Although MTX has become the most commonly used alternative immunomodulator to AZA/6-MP in CD, there is still a paucity of randomized control trial data showing consistent benefit, and much of the support for its use comes from retrospective data. In 1995, Feagan et al. published the first randomized control trial using MTX to induce remission in CD. Steroid-dependent CD patients were randomized to 25 mg IM MTX weekly vs. placebo. At the end of 16 weeks, 39% of patients in the MTX group were off prednisone and in remission compared to 19% in the placebo group. The likelihood ratio for the induction of remission was 1.95 (95% CI 1.09–3.48) for patients on <20 mg prednisone per day prior to enrollment and 3.88 (95% CI 1.6–9.43) for those on >20 mg prednisone per day. [41]. Two other randomized-controlled trials have been performed, both using 15 mg of oral MTX/day. Both studies showed a nonsignificant improvement in disease activity when compared to placebo [42, 43]. This is likely due to the variable absorption of MTX, the relatively low dose used in these two studies and the likelihood that they were underpowered to show benefit.

Another randomized-controlled trial compared MTX 25 mg/week for 12 weeks then 12.5 mg/week orally, to AZA 2 mg/kg/day for the induction of remission of

steroid- dependent CD. This study showed similar rates of response to therapy and discontinuation of medication at 3 months, with 12/27 (44%) of MTX treated vs. 9/27 (33%) of AZA group meeting the primary endpoints of discontinuation of steroids [44] At 6 months, both groups continued to improve, with 56% of those on MTX in remission compared to 63% in the AZA group. The general weakness in this study is the lack of a placebo group; however, the rates of remission are higher than that would be expected from any placebo response [44]. Finally, a Cochrane systematic review and meta-analysis recently concluded that despite the lack of available data, and heterogeneity of included studies, MTX is effective therapy for steroid- dependent CD as long as it is given parenterally and at a dose of >15 mg/week [45].

MTX has also been shown to be effective for the maintenance of remission in CD. A second phase of Feagen et al.'s study on the induction of remission, randomized patients who had responded to MTX with 25 mg/week intramuscular MTX to either 15 mg/week or placebo. At 40 weeks, 65% of those on MTX were still in remission compared to 39% who had been switched to placebo ($p < 0.04$), with an absolute risk reduction of relapse of 26%. This study also showed that patients on MTX had a less frequent need for prednisone (28% vs. 58% on placebo) and that if relapse occurred off MTX, restarting a dose of 25 mg/week was effective at inducing remission the majority of the time (55%) by the end of the study [46]. Several retrospective studies have also shown an impact of MTX on maintenance of remission, including a review of 70 patients with IBD (48 CD, 22 UC) using mostly oral therapy. Remission occurred in 34/55 patients within 3 months. The rates of maintenance of remission at 1, 2, and 4 years were 90, 86, and 78%, respectively. If the MTX was stopped after remission occurred, rates of persistent remission were 42, 21, and 16% at 1, 2, and 4 years, respectively [47]. The authors also commented that the induction and maintenance of remission were more common in those on doses higher than 15 mg/week of MTX.

Methotrexate in UC

Randomized-controlled trials have shown inconsistent results when using MTX to induce remission in UC, but they have been mostly underpowered to show an effect. Oren et al. Randomized 67 patients with refractory UC to oral MTX 15 mg/week or placebo, the rates of remission at 4 months were 46.7 and 44.4% for MTX and placebo, respectively. No difference was observed in time to remission or in rate of relapse after remission [48]. In a trial comparing MTX 15 mg/week intramuscular to 1.5 mg/kg/day 6-MP and 3 g/day 5-ASA in steroid-dependent IBD, data can be extracted from the 38 patients with UC. It showed that at 30 weeks remission had occurred in 78.6% of MTX-treated patients compared to 58 and 25% of AZA and 5-ASA-treated patients, respectively ($p < 0.05$ for MTX vs. 5-ASA groups) [49]. Two older small case series also have shown that MTX intramuscular can be effective at inducing remission in chronically active UC in approximately

60–80% of patients, and at the very least may lead to decreasing the dose of prednisone by 50% or more [50, 51]. Retrospective data are available from several centers showing a statistically significant benefit in inducing and maintaining remission in active UC [47]. Finally, a Cochrane systematic review of the use of MTX in UC has suggested that although there appears to be some benefit in some patients, it cannot be recommended until further studies are done [52]. Despite the inconclusive evidence available in the literature to date and the recommendations from the Cochrane review, we routinely use MTX in patients with UC who cannot tolerate AZA or 6-MP but are still requiring steroids and are not candidates or do not tolerate biologic therapies.

Adverse events in MTX

Mild adverse events, including stomatitis, nausea, vomiting, and malaise occur frequently in patients on MTX therapy, but it is uncommon for them to be treatment limiting. Data from rheumatology has shown that administration of 1 mg/day of folic or folinic acid can attenuate these GI side effects, and as such we recommend their use in all patients on MTX [53]. More serious adverse events are rare at the doses used to treat IBD, though they include pulmonary fibrosis, renal failure due to MTX crystal nephropathy, bone marrow toxicity, and hepatotoxicity. An increase in transaminases is common and hence routine liver enzyme monitoring is warranted. Occasionally, transaminases rise beyond threefold from baseline and at that point discontinuing therapy is prudent. Percutaneous liver biopsy is considered after a cumulative dose of 1.5 g, much like in psoriasis. It is unknown as to whether or not this practice is wholly necessary in IBD. Finally, any woman who is a candidate for MTX therapy needs to be counseled on the teratogenic effects of MTX on fetal tissue [54].If MTX therapy is instituted in a fertile woman, we recommend two methods of reliable birth control at all times.

Cyclosporine A in IBD

CYA is a lipophilic cyclic peptide calcineurin inhibitor that inhibits the production of interleukin-2 and blocks activation of T-lymphocytes by interleukin-2, resulting in downregulation of the cellular immune response [55]. CYA has traditionally been used as an antirejection drug for solid organ transplantation, but has an off-label use in rheumatoid arthritis and IBD. The role of CYA in CD is very limited at the present time. The drug has been studied in patients refractory to steroid and thiopurine therapy, or in CD patients with active fistulization refractory to other therapies, where two small case series have shown that 80–90% of fistulas have decreased drainage and symptoms [56, 57]. Four randomized-controlled studies failed to show a benefit of CYA at maintaining remission in CD. On the basis of

these latter data, the high frequency of side effects and the availability of more efficacious therapies (including biologics) CYA is rarely used in CD today.

In UC, CYA has been shown to be effective at decreasing or delaying the need for colectomy in severe disease that is refractory to steroid therapy. In a study of patients with severe UC not responding to >7 days of IV steroids, subjects were randomized to IV CYA 4 mg/kg/day or placebo. At the end of the study 9/11 patients (82%) in the CYA arm had responded to therapy and did not require colectomy, compared to 0/9 of those on placebo ($p<0.001$) [58]. Mean disease activity index decreased by 50% in the treatment arm as well, allowing all patients to be discharged from hospital. However, a follow-up study by the same authors showed that over the following 6 months, 44% of those patients that had responded to CYA went on to require colectomy [59]. D'Haens et al. subsequently showed that IV CYA can be used instead of IV steroids in acute severe UC flares. The authors randomized 29 patients with acute severe UC to either IV methylprednisolone (40 mg/day) or IV CYA 4 mg/kg/day. Nine of fourteen (63%) CYA treated patients vs. 8/15 (53%) IV steroid patients responded to therapy ($p>0.05$). Over the following 1 year, five patients in each group went on to require colectomy, and the incidence of adverse events was equal in both groups. This data indicates that IV CYA may be an effective monotherapy for acute severe UC, and decreases the total amount of steroid patients will be exposed to [60]. A more recent study showed that during acute severe UC flares, IV CYA may be equally as efficacious at either 2 or 4 mg/kg/day, and the lower dose resulted in a 60% reduction in hypertension, as well as more modest decreases in renal and neurotoxicity [61].

Despite the short-term efficacy ascribed to CYA therapy in acute UC, routine use of CYA is limited due to high rates of colectomy in long-term follow-up. Interestingly, several uncontrolled longitudinal studies have shown fairly good long-term response rates when using IV CYA and switching to oral CYA once stabilized. Colectomy rates at 4–5 years are as high as 54% but as low as 10% [62–65]. Also, there appears to be value in switching patients who have responded to IV CYA to oral immunomodulators, such as AZA. Fernandez-Banares et al. showed that the addition of oral AZA 2 mg/kg/day to IV CYA-induced remission of severe UC reduced the need for colectomy from 60 to 26% at a mean of 16 months [19]. Our practice is to use CYA as a bridge to AZA and to assure the patients know that the CYA is discontinued by 6 months. Typically, we aim to get the steroid dose tapered below 20 mg/day before initiating AZA so that patients are not on all of high-dose steroids, CYA and AZA all at once. Currently, the major dilemma in acute severe UC when the patient wants to avoid surgery is to decide between CYA and anti-TNF therapy.

Aside from uncertainty over long-term benefit, CYA is also difficult to use in IBD, due to a relatively high rate of adverse events. The most common nonlife threatening adverse events attributable to CYA are reversible paresthesias, hypomagnesemia, headache, hypertrichosis and are reported to occur in 51, 42, 27, and 23%, respectively. More serious adverse events include nonreversible nephrotoxicity, seizure, and serious infections (including *pneumocystis carinii* pneumonia, community acquired pneumonia, and disseminated viral infections) which may occur in 5, 3.5, and 6%, respectively [66].

In summary, CYA has been shown to be effective at inducing remission in acute severe UC. It has the ability to delay colectomy by 6–12 months in patients that initially respond to IV therapy, and in a smaller subset may act as a bridge to other effective immunomodulator therapy, such as AZA/6-MP. This combination approach to CYA therapy may lead to a decreased rate of colectomy over time.

Other Immunomodulators in IBD

Tacrolimus

Tacrolimus is a highly potent calcineurin inhibitor which blocks binding with cyclophilin and FK-binding protein 12, down-regulating activated T cells and IL-2 expression. Tacrolimus has a similar side effect profile to cyclosporine, including nephrotoxicity, electrolyte abnormalities, nausea, diarrhea, headache, tremors, paresthesias, insomnia, alopecia, hirsutism, and gingival hyperplasia. Only one randomized-controlled trial has been performed, evaluating the effect of tacrolimus on active CD, although it was designed to specifically assess fistulizing disease. The investigators randomized patients to placebo or oral tacrolimus 0.2 mg/kg/day, for 10 weeks. At conclusion of the study, 9/21 (46%) tacrolimus-treated patients vs. 2/25 (8%) placebo-treated patients had significant fistula improvement ($p < 0.001$). However, there was no difference found in the rate of fistula remission, or in CDAI [67]. Retrospective data have shown a more promising picture in active CD with long-term response rates from 55 to 91%, remissions from 11 to 25%, and significant steroid-sparing effects [68–70]. Also, topical tacrolimus has been shown in two small studies to have beneficial effects on perianal disease, and at the very least, appears to be an alternative to topical steroids [71, 72]. Tacrolimus has not been rigorously studied in UC, although retrospective case series seem to show beneficial effects in steroid-dependent disease and acute severe UC. The largest retrospective series, to date, showed that out of 40 patients with severe UC treated with steroids and tacrolimus, 77.5% had a response to therapy, and 40% had a complete remission. At the time of publishing, this effect extended out to 45 months, and only 9/40 (22.3%) patients had undergone colectomy. These data are promising, although clearly, larger prospective-controlled trials are required before tacrolimus can be recommended outside of either clinical trials, or in patients who are intolerant to all other immunomodulators.

Mycophenolate Mofetil

MMF is an immunomodulator that inhibits inosine monophosphate dehydrogenase (IMPDH) which inhibits de novo guanosine nucleotide synthesis and exhibits a

cytostatic effect on T and B lymphocytes [73]. MMF is quickly becoming one of the most commonly prescribed drugs in solid organ transplantation, due to its lack of nephrotoxicity, and favorable side effect profile. Unfortunately, data in IBD are very limited and conflicting. One open label control trial followed patients with active CD, randomized to either 2.5 mg/kg/day AZA and prednisone, or 15 mg/kg/day MMF and prednisone and followed them for 12 months. Rates of remission at 3 and 6 months were similar in both groups, although MMF may have been more effective in the most severely active CD patients [74]. Unfortunately, two other small prospective studies have not been able to show a similar effect [75, 76]. Recently, a single center review of 70 patients with IBD, who had been treated with MMF after failing other immunomodulators was published. This study showed that 17/70 (24%) of patients responded to MMF and were maintained in remission over an average of 5 years. Unfortunately, the majority of patients either failed therapy (51%), requiring additional medications or surgical intervention, or were intolerant to the drug (27%) [77]. Also, there have been several reports of MMF inducing a graft vs. host disease-like enteritis or IBD-like colitis [78], and therefore it is not recommended to use MMF in active IBD until further prospective randomized trials are performed.

6-Thioguanine

Another potential immunomodulator for the therapy of IBD is 6-TG, the active metabolite of AZA and 6-MP. Initial studies appeared promising even in patients who were intolerant or allergic to AZA, reporting steroid free remission rates of 49 and 76% at 6 and 12 months [79]. Unfortunately, in another study in 2003, significant liver enzyme abnormalities were found among a large number of patients receiving the medication, and liver biopsy found nodular regenerative hyperplasia in several patients [80]. A more recent study published in 2007, followed 26 patients treated with 6-TG for a median of 36 months. During treatment, 6/26 developed nodular regenerative hyperplasia and associated portal hypertension. The portal hypertension was shown to regress with discontinuation of the medication, but it is unclear if the damage from nodular regenerative hyperplasia was permanent or not [81]. As a result, 6-TG is no longer recommended for therapy in IBD.

Thalidomide

Thalidomide is an orally administered immunomodulator with anti-TNF alpha activity. Its original use was as a sedative and antiemetic. Despite its dark history as a teratogen and neurotoxin, it has found new life as a therapy for cutaneous lupus, graft vs. host disease and seronegative arthritis [82]. Data in using

thalidomide to treat IBD are limited to case reports and three open label studies. These studies have uniformly had promising results with response rates in luminal disease from 75 to 90%, improvement in fistulas from 40 to 82% with fistulas remitting in 20–40% [82–84]. Unfortunately, side effects consisting of drowsiness and sedation occur commonly and may lead to discontinuation in up to one third of patients. The other major problem is the significant teratogenicity that can occur with fetal exposure to thalidomide. Although these findings are promising, prospective placebo-controlled trials are still lacking. As a result, we recommend that thalidomide therapy only be prescribed to female patients of childbearing age by experienced IBD physicians, and along with two effective forms of birth control.

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Chapter 8
State-of-the-Art Medical Treatment of the Adult Patient with IBD: The Biological Therapies

Stephen B. Hanauer

Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Biological • Tumor necrosis factor • Infliximab • Adalimumab • Certolizumab pegol • Natalizumab • Azathioprine • Corticosteroids • Immunogenicity

Key Points

- Three biological therapies targeting TNFα are currently marketed with similar efficacies and risks for the treatment of Crohn's disease.
- To date, only infliximab is approved for the treatment of ulcerative colitis.
- Natalizumab, a humanized antialpha4 integrin is effective for the treatment of Crohn's disease but compromised by a risk of progressive multifocal encephalopathy.
- Induction and regularly scheduled maintenance therapy optimizes clinical results for all biological agents.
- Immunogenicity is an important factor for all biologicals and can be reduced by high-dose induction and regularly scheduled maintenance therapy.
- Concomitant immunosuppression reduces immunogenicity but does not improve efficacy for patients with refractory disease *but* may improve therapeutic efficacy for patients who are immunosuppressive naive.
- Infectious complications are increased in patients on concomitant corticosteroids and/or immunosuppressants.
- Dose modification is needed in many patients to maintain remissions.
- Switching between anti-TNF agents is effective for patients who develop immunogenicity but is less effective for patients who lose response in the presence of circulating biological concentrations.

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- The ultimate positioning of biological agents will be determined by future studies assessing comparative effectiveness of different therapeutic strategies in both Crohn's disease and ulcerative colitis.

Introduction

The era of biological therapy for inflammatory bowel disease (IBD) began over a decade ago with the introduction of infliximab for the treatment of Crohn's disease. Since that time, we have garnered a great deal of information and experience with biological agents for the treatment of IBD and other chronic immune-mediated inflammatory disorders, including rheumatoid and other inflammatory arthritides, psoriasis that respond to anti-TNF therapies, multiple sclerosis, and Crohn's disease that respond to monoclonal antibodies targeting adhesion molecules.

Several basic principles apply to the treatment of chronic immune-mediated inflammatory disorders (including IBD) with biological therapies. The first is the definition of biological agents which, in contrast to drugs that are chemically synthesized, are molecules derived from living sources, such as humans, animals, and microorganisms, including native biological preparations and isolates, recombinant peptides or proteins (including cytokines), antibody-based therapies, nucleic acid-based therapies (antisense oligonucleotides), and somatic gene therapies that are agents targeted against specific mechanisms of disease [1]. At present, the only biological agents to have achieved regulatory approval for the treatment of IBD are monoclonal antibodies, or antibody fragments, that target tumor necrosis factor (TNF) alpha or alpha-4 integrins.

The second principle is that all biological agents developed, to date, are immunogenic. They are antigenic by virtue of the ability to be recognized by a preexisting T-cell receptor (TCR) or a B-cell receptor (antibody). While the same antigen can induce different responses depending upon factors, such as the mode of administration and uptake by and costimulation of antigen presenting cells (APCs), immunogenicity of a biologic varies by: features of the drug and its route, dose and timing of administration, intrinsic patient factors, and concomitant use of immunosuppressives [1]. In contrast, "humanness," as pertains to "chimeric," "humanized," or "fully human," refers to how a biologic was produced and does not reflect the final protein sequences or posttranslational glycolization that determines immunogenicity. Hence, functional "humanness," or the degree to which a compound may potentially induce an immune response, relates to the degree of homology that an agent shares with some human proteins such that a fully human antibody can be more immunogenic than a chimeric antibody.

There are two functional consequences of immunogenicity: immune-related reactions and reduced circulating and/or tissue concentrations of the biological agent. While both effects occur simultaneously, the ultimate impact is decreasing the effectiveness of the agent associated with lowered serum (and tissue) concentrations [1]. The practical solutions to minimize immunogenicity include: "high-dose"

induction followed by regularly scheduled maintenance therapy (in contrast to episodic dosing), concomitant use of immunosuppressives, or pretreatment with corticosteroids [2, 3]. Once immunogenicity has developed, higher doses or reduced intervals between doses can transiently overcome the neutralization of biologics, but this typically becomes impractical because of incremental dosing requisites and progressive infusion/injection-site reactions.

Biological Therapy for Crohn's Disease

Biological therapies for Crohn's disease include agents that target TNF-α (infliximab, adalimumab, and certolizumab pegol) and alpha-4 adhesion molecules (natalizumab) [4].

Infliximab, a chimeric monoclonal antibody targeting TNFα [5] has been the most extensively evaluated and "set the stage" for the development programs of other biologicals. Initially approved for marketing in the USA in 1998 based on clinical trials demonstrating short-term efficacy infliximab was approved for the treatment with a single infusion for active luminal disease [6] and as a series of three infusions for fistulizing disease [7] in patients who were not responding to conventional agents (aminosalicylates, antibiotics, corticosteroids, or immunosuppressives). However, it soon became apparent that the short-term benefits gradually waned, but could be recouped with subsequent dosing [8] that, when administered on an "episodic" or prn basis led to increasing risks of acute or delayed infusion reactions and/or eventual loss of response [9].

Eventually, maintenance studies were performed with patients who responded, initially, to infliximab that led to regulatory approval for maintenance therapy. The ACCENT I trial demonstrated that patients who responded to an initial induction regimen of infliximab (5 mg/kg initially followed by dosing at 2- and 6-weeks) were more likely to maintain their clinical responses and clinical remissions with regularly scheduled dosing of 5 mg/kg every 8-weeks up to 1 year [10]. Patients randomized to maintenance infliximab were also more likely to wean from corticosteroids, maintain an improved quality of life and had less hospitalizations and surgeries [11] than patients who initially responded but were randomized to placebo maintenance. Similar results were identified for patients with draining fistulas who were followed in the ACCENT II trial [12, 13]. In both trials, there was no significant difference between maintenance therapy with 5 mg/kg compared to 10 mg/kg although patients who lost response to 5 mg/kg were able to regain their response to an increased dose to 10 mg/kg and maintenance dosing was superior to episodic dosing [14, 15]. In addition, patient receiving induction and maintenance dosing had less formation of antibodies to infliximab (previously human antichimeric antibodies, HACA), independent of whether they were receiving concomitant immunosuppressives [16]. Furthermore, concomitant immunosuppression, while reducing immunogenicity to infliximab, did not alter response rates to maintenance therapy in these patients who were refractory to the treatment with corticosteroids and immunosuppressives.

Based on the results of the ACCENT I and ACCENT II trials recommendations for treatment with infliximab included the use of concomitant immunosuppressives and regularly scheduled maintenance therapy to reduce immunogenicity [17, 18]. However, concerns regarding the risk of hepatocellular T-cell lymphomas and the finding that there were no significant differences in long-term outcomes for patients treated with induction and maintenance infliximab, with or without concomitant immunosuppressives, led to recommendations for monotherapy in patients who were refractory to immunosuppressive therapy [19].

Subsequently, three trials have prospectively addressed the question of monotherapy with infliximab vs. concomitant therapy with an immunosuppressive. What is known as the "step-up, top-down" trial by D'Haens et al. [20] randomized patients who were *steroid-naive* to induction therapy with corticosteroids or a combination of infliximab induction (5 mg/kg at weeks 0, 2, and 6) with azathioprine maintenance. Patients induced with steroids then had the steroids tapered and were retreated with steroids if their symptoms flared. If they could not taper steroids after two courses, they were treated with azathioprine and, if they continued to be symptomatic, with episodic infliximab. Patients randomized, initially, to infliximab and azathioprine that developed symptoms were "rescued" with episodic infliximab. The endpoint of the trial was a steroid-free remission and, while there were no significant differences in clinical activity of Crohn's disease between the groups, those randomized from the outset to infliximab had reduced exposure to corticosteroids and significantly better endoscopic outcomes with the absence of mucosal ulcerations compared to patients who were randomized to corticosteroid-induction.

A second trial (COMMIT) evaluated *immunosuppressive-naive* patients with chronic, active Crohn's disease who were induced into a clinical remission with corticosteroids and then randomized to receive infliximab monotherapy or combination therapy with infliximab and methotrexate [21]. After a regimented steroid, taper the endpoints of the study were steroid-free clinical remissions at 14-weeks and 1 year. In this trial, there were no differences in steroid-free remissions with or without concomitant methotrexate suggesting that combined induction therapy with steroids and infliximab was sufficient to transition patients to mono-maintenance therapy with infliximab. However, the results could have been influence by the study design, whereby all infliximab infusions were done in the setting intravenous hydrocortisone (200 mg), which may have prevented the formation of neutralizing antidrug antibodies.

The third trial (SONIC) also enrolled *immunosuppressive-naive* patients with chronic, active Crohn's disease, many of whom were also steroid refractory, to induction and maintenance monotherapy with infliximab or azathioprine, or, combination therapy with infliximab and azathioprine [22]. Again, the endpoint was a steroid-free remission which, in contrast to prior studies, demonstrated a benefit for patients who received combination therapy compared to monotherapy with infliximab or azathioprine. In none of these trials were there more adverse events (infections or neoplasia) during the duration with mono- or combination therapy.

The reconciliation of these studies suggests that for patients who are refractory to an immunosuppressive, concomitant therapy, while reducing immunogenicity, does not have a greater than 5–10% benefit for maintaining infliximab-induced responses.

However, for patients who are corticosteroid-naive or immunosuppressive-naive combination therapy with corticosteroid-induction and infliximab maintenance, or combination of infliximab and an immunosuppressive (thiopurine or methotrexate) offer improved short-term and long-term (i.e., 1-year) benefits.

The question as to how to maintain benefits longer than 1 year with infliximab has been less rigorously explored. Van Assche and colleagues studied a group of patients who were in clinical remissions on combination infliximab and azathioprine therapy for at least 1 year who were randomized to continue or discontinue azathioprine [23]. The endpoint of the study was a need for adjustments in the infliximab maintenance regimen.

While there were no differences between the groups who had been maintained on combination therapy for at least 1 year according to the need for adjustments in infliximab maintenance over the subsequent 2 years, there was a gradual decline in trough infliximab levels suggesting the potential for an eventual loss of response. Louis et al. also monitored a group of patients who had been in a stable remission on concomitant infliximab and azathioprine for at least 6 months (mean duration of combination therapy was over 2 years) in whom infliximab was discontinued [24]. Of the patients who discontinued infliximab, approximately 50% were maintained with azathioprine monotherapy. Predictors of a persistent remission on azathioprine were a low CRP and no mucosal ulcerations at the time infliximab was withdrawn. Furthermore, all patients who relapsed after infliximab discontinuation (all of whom had received at least 6-month combination maintenance therapy) tolerated reinfusions of infliximab to reestablish remission.

Adalimumab is a fully human monoclonal antibody targeting TNFα [5] that, in contrast to infliximab, is self-administered subcutaneously. At doses of 160 mg followed by 80 mg 2 weeks later, and then 40 mg every other week adalimumab has been effective at inducing [25] and maintaining [26] clinical remissions for patients with refractory active Crohn's disease despite therapy with aminosalicylates, steroids, and immunosuppressives. Adalimumab has also been effective for treating patients who had lost response or developed allergy or intolerance to infliximab [27]. Similar to infliximab, high-dose induction followed by regularly scheduled maintenance therapy is more effective than interrupted therapy at improving clinical outcomes, including the improved quality of life, reducing hospitalizations and surgeries [28] and "closing" perianal fistulae [29].

Certolizumab Pegol is a Fab' antibody fragment linked to polyethylene glycol that also targets TNFα and is administered subcutaneously. In contrast to infliximab and adalimumab, certolizumab pegol does not appear to directly induce apoptosis of cells bearing TNF on their membrane [5]. Certolizumab pegol has also been demonstrated to be effective at improving and maintaining clinical response for patients who have been refractory to conventional agents at a dose of 400 mg administered initially and then after 2 weeks and, subsequently, on a monthly basis [30, 31]. Certolizumab pegol has also been effective for patients who were intolerant or lost response to infliximab [30, 32] and improves the quality of life [33].

Natalizumab is a humanized IgG4 monoclonal antibody that targets alpha 4 integrins that are ubiquitous along the vasculature and are the binding sites for mononuclear cell egress from the vasculature into tissues [34]. Based on a series of

randomized controlled trials in patients with refractory Crohn's disease with an inadequate response to conventional agents or anti-TNF therapy natalizumab has been efficacious for both induction and maintenance therapy of Crohn's disease [35, 36]. Unfortunately, due to the risk of progressive multifocal encephalopathy [37], despite its rare occurrence, natalizumab has been delegated to a secondary role for the treatment of Crohn's disease for patients who have failed therapy with conventional agents and an anti-TNF biologic. Furthermore, combination therapy with immunosuppressants has been proscribed by the FDA [38].

Biological Therapies for Ulcerative Colitis

Infliximab is the only currently approved biological therapy for the treatment of ulcerative colitis. Based on two large clinical trials that enrolled patients with refractory disease despite aminosalicylates, corticosteroids, or immunosuppressives infliximab were shown to induce and maintain clinical remissions, allow steroid-tapering, and induce mucosal healing at the same 5 mg/kg dose that is used for induction and maintenance therapy for Crohn's disease [39].

Risks of Biological Therapies

Anti-TNF and anti-adhesion molecule therapies are immunosuppressive with documented risks of infectious complications and, possibly, neoplasia. While the risk of pneumonias [40] serious infections is relatively small, they are increased in patients on both anti-TNF and anti-adhesion molecule therapy [41–43]. The risk of infections is increased according to the number and (likely) duration of concomitant therapy with corticosteroids and immunosuppressives [44–47]. In particular, opportunistic infections with intracellular organisms, such as tuberculosis and histoplasmosis are increased with anti-TNF therapy, whereas progressive multifocal leukoencephalopathy is a reactivation of the polyomavirus that has been associated with natalizumab.

It is less clear whether anti-TNF therapy is, independently, related to the risk of neoplasia in IBD patients as most reports of malignant complications have been associated with concomitant therapy with immunosuppressants [41, 47, 48].

In addition to potential infectious and neoplastic complications, biological therapies, as foreign proteins, have the potential for allergic or immunogenic complications [49, 50]. Infliximab has been associated with both acute and delayed hypersensitivity reactions [3] that can be minimized by completing an induction regimen and continuing regularly scheduled maintenance dosing or with the addition of a concomitant immunosuppressive or high-dose corticosteroids [3, 16]. There has been an increasingly recognized association with cutaneous pustular psoriasiform eruptions [51, 52] and inhibition of TNF also leads to the development

of antinuclear and anti-DNA antibodies that can, rarely, induce a reversible drug-induced lupus syndrome [52, 53]. Biological therapies targeting TNF are also contra-indicated in patients with severe congestive heart failure [4].

Controversies Regarding Biological Therapies for IBD

While the past decade has brought forth significant advances in the treatment of Crohn's disease and ulcerative colitis, in particular for patients with chronically active disease or steroid-dependence [4], there remain a substantial number of un answered questions regarding the positioning and optimization of these approaches.

A first issue pertains to positioning of these agents that were all initially evaluated for patients with chronically active disease and have regulatory and international guideline [54, 55] recommendations for patients failing to respond to conventional agents. Furthermore, the anti-TNF agents share more similarities than differences in their efficacy and tolerability [41]. However, from clinical trials with all of the anti-TNF agents in Crohn's disease, there is evidence that the absolute clinical response is superior for patients with short duration of disease. Hence, there is increasing consideration for a "top-down" or early aggressive approach to introduce anti-TNF therapy earlier to avoid corticosteroid therapy [4, 56]. Identification of populations of patients who are more likely to require and respond to specific biologics would be a substantial advantage, in particular with future trends toward regulatory evaluation of comparative effectiveness.

Another component of positioning therapy relates to patients who lose response to a first biologic agent. It appears from data in Crohn's disease and rheumatoid arthritis, that patients who lose response due to immunogenicity respond to an alternative anti-TNF agent [56–58] although these individuals may be more likely to develop immunogenicity to the subsequent biological agent [58]. In contrast, patients who lose response, while in the presence of circulating concentrations of biologicals, more likely need to switch to a different mechanistic class [50, 56]. An important aspect of evaluating the loss of response pertains to dose-adjustments that may be required for individual patients. The recommended doses are based on clinical trial results, but experience from many experienced centers suggests that increasing doses are likely to be required by over one-third of patients with any of the anti-TNF biologicals [57, 59].

A second issue remains the use of concomitant immunosuppressive therapy. Results from phase III clinical trials leading to regulatory approval of infliximab [10], adalimumab [26], and certolizumab pegol [31] did not identify a statistically significant benefit for combination therapy *in patients who were already refractory to immunosuppressives.* However, the recently reported SONIC study [22] and the benefits of concomitant immunosuppressives at reducing the immunogenicity [50] and increasing circulating concentrations of biological agents suggest that there may be a role for immunosuppressive naive patients that require additional clinical trial substantiation and evaluation of the risk/benefit ratio.

Finally, the issue of whether these agents are required life-long remains to be established. Recent data suggest that some patients may be able to be induced into remission with biologics and then transitioned (bridged) to an alternative immunosuppressive but the risks and benefits of these alternative approaches need to be more comprehensively evaluated.

Future Biological Therapies

As the pathogenesis of IBDs become unraveled, one can anticipate subsequent developments pertaining to biological therapies [4, 60]. Already novel anti-TNF-directed therapies are coming to market [5, 61] as are therapies directed at alternative cytokines, including IL-12/23 [62]. The effectiveness of natalizumab for Crohn's disease is also leading to the development of alternative inhibitors of adhesion molecules directed at gut-specific alpha4 beta7 integrins that, potentially, reduce the risk of progressive multifocal leukoencephalopathy [34]. It is clear that, as each new agent is introduced, similar debates regarding relative efficacy, safety, and ultimate position of these novel agents continues to surface until ultimate causation and potential cure/prevention for these chronic immune-mediated disorders have been established.

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Chapter 9
Prebiotics, Probiotics, Antibiotics, and Nutritional Therapies in IBD

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Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Probiotics • Prebiotics • Antibiotics • Pouchitis • Nutritional therapies • Total parenteral nutrition (TPN) • Enteral nutrition inflammation

What's New and Exciting

- Prebiotics have yielded emerging, promising results in the induction of CD and UC, the most notable of which is germinated barley foodstuffs.
- Although level 1 evidence is available for the use of probiotics in the induction and maintenance of remission in UC with promising results in pouchitis, it remains unclear why some probiotic strains are effective and others are not.
- Adjunctive antibiotic therapy is effective at inducing remission in UC, while there are promising results in CD. The effectiveness of this therapy diminishes over time for unknown reasons making it unsuitable for maintenance purposes.
- Although inferior to corticosteroid therapy for inducing remission, the new diet formulations with increased mucosal healing indicate that nutritional therapies in conjunction with conventional therapies may be a suitable option for certain patients with either CD or UC.

Introduction

Inflammatory bowel disease (IBD) refers to a group of diseases of which Crohn's disease (CD), ulcerative colitis (UC), and pouchitis are the most common. The etiology of each is unknown, but all involve the interaction between genetic, immunologic,

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and environmental factors. Although our understanding of the diseases is incomplete, abundant evidence implicates the intestinal microflora as a critical component. The areas of the gastrointestinal tract with the most abundant flora, the terminal ileum and colon, are also the areas where intestinal lesions are most likely to occur in IBD patients. Intestinal inflammation has been ameliorated through modifications that affect the gut's biome, including antibiotic treatment, diversion of the fecal flow, and therapy that alters the bacterial species composition and available nutrients. Although there is primarily circumstantial evidence implicating the role of microflora in human IBD, compelling direct evidence has been derived from animal models of IBD in which intestinal inflammation fails to develop in germ-free conditions (e.g., IL-10 knockout mice, and human leukocyte antigen-B27 transgenic rats) [1, 2].

The bacterial species normally inhabiting the human intestine do not initiate an immune response in a healthy host. The systemic immune system does not actively maintain a tolerance to commensals, but rather appears to be ignorant of these bacteria. This systemic ignorance of the intestinal microflora is lost in patients with IBD, as evidenced by the presence of cell-mediated and humoral immune responses to these bacteria [3]. Furthermore, adherent and mucosa-associated bacteria, particularly *Bacteroides* and *Escherichia coli* species, are more abundant in patients with CD than in control subjects [4]. This dysbiosis also extends to a decrease in bifidobacteria species [5].

The identification of a link between intestinal microflora and IBD has led to an abundance of studies investigating the therapeutic potential of modification of the luminal microbiota environment through the use of antimicrobial substances, host-directed nutritional therapy, and the ingestion of probiotic microbes and prebiotics, defined as dietary substances that stimulate the growth of endogenous protective intestinal bacteria.

Summarized below are the human clinical trials using these agents in IBD. In addition, Tables 9.1–9.8 provide peer-reviewed details of clinical trials published between January 2003 and March 2008, while Table 9.9 summarizes the findings of recent meta-analyses.

Abbreviations for Tables 9.1–9.8

BIO-THREE	2 mg *Streptococcus faecalis* T-110, 10 mg *Clostridium butyricum* TO-A, and 10 mg *Bacillus mesentericus* TO-A
C	Controlled trial
CFU	Colony forming units
CI	Confidence interval
DB	Double-blind
EPIC	Epanova Program in Crohn's – Study 1 [EPIC-1] and Study 2 [EPIC-2]
IL1-α	Interleukin 1-alpha
IPAA	Ileo-pouch anal anastomosis
L. salivarius	*Lactobacillus salivarius subsp. Salivarius* UCC118 strain
LGG	*Lactobacillus rhamnosus* GG
NNT	Number needed to treat
NSD	No significant difference

Table 9.1 Summary of studies investigating the effect of prebiotic treatment on the induction or maintenance of remission in inflammatory bowel diseases (IBD) 2003–2008

References	Design and duration	Group (dose/day)		Concomitant therapy	Results
		Prebiotic and probiotic	Comparator		
Crohn's disease – induction of remission					
Lindsay et al. [11]	O 4 Weeks	Fructo-oligosaccharides (15 g) in weeks 2–4; $n=10$	None	Stable doses of azathioprine, methotrexate, oral steroids, aminosalicylate	Reduced Harvey Bradshaw index from 9.8 to 6.9 ($P<0.01$). Fecal bifidobacteria increased by 9.4% ($P<0.001$). Expression of TLR4 by dendritic cells increased ($P<0.001$)
Ulcerative colitis – induction of remission					
Casellas et al. [16]	R, C 2 Weeks	Oligofructose-enriched inulin (12 g); $n=10$	Placebo (maltodextrin, 12 g); $n=9$	Mesalazine (3 g/day)	Rachmilewitz index scores for both groups significantly decreased during the 14 days. Only the treatment arm had a significant decrease in fecal calprotectin concentration at days 7 and 14 *vs.* day 0 ($P<0.05$)
Hanai et al. [15]	R, C 1 year	Germinated barley foodstuff (20 g); $n=22$	Placebo; $n=37$	Aminosalicylate, corticosteroids	Clinical activity index was significantly lower in the treatment vs. the control arms at 3, 6, and 12 months ($P<0.05$ for each). Remission failure was lower in the treatment arm (4/22) vs. the control (17/37; $P<0.05$)
Kanauchi et al. [14]	O 24 Weeks	Germinated barley foodstuff (20–30 g); $n=21$	None	Aminosalicylate, corticosteroids	Reduced clinical activity index ($P<0.05$)

Table 9.2 Summary of studies investigating the effect of probiotic treatment on the induction or maintenance of remission in Crohn's disease 2003–2008

Reference	Design Duration	Group (dose/day) Probiotic	Comparator	Concomitant therapy	Results
Induction of remission					
Fujimori et al. [22]S	O 13 ±4.5 Months	*Bifidobacterium breve* (3×10^{10} CFU), *Lactobacillus casei* (3×10^{10} CFU), *Bifidobacterium longum* (1.5×10^{10} CFU), Psyllium (9.9 g); $n=10$	None	Aminosalicylate, prednisolone, home enteral nutrition	Improved CDAI and IOIBD scores compared with baseline (255–136, $P=0.009$ and 3.5–2.1, $P=0.03$, respectively). 60% (6/10) achieved remission
Schultz et al. [21]	DB, R, C 6 Months	LGG (2×10^{9} CFU); $n=5$	Placebo $n=6$	Ciprofloxacin, metronidazole, corticosteroids	NSD
Maintenance of remission					
Chermesh et al. [12]S	DB, R, C 2 Year	Synbiotic 2000 (1×10^{10} CFU); $n=20$	Placebo $n=10$	Not indicated	NSD regarding postoperative recurrence of symptoms High drop-out rate ($n=21$)
Van Gossum et al. [85]	DB, R, C 12 Week	*L. johnsonii* LA1, Nestle (1×10^{10} CFU); $n=27$	Placebo $n=22$	None	NSD for endoscopic score High drop-out rate ($n=21$)
Marteau et al. [86]	DB, R, C 6 Months	*L. johnsonii* LA1, Nestle (2×10^{9} CFU); $n=43$	Placebo $n=47$	Loperamide, cholestyramine, tapered corticosteroids	NSD for endoscopic scores Drop-out rate ($n=8$)
Bousvaros et al. [87]	DB, R, C 2 Year	LGG (4×10^{10} CFU); $n=39$	Placebo $n=36$	Aminosalicylates, 6-mercaptopurine, azathioprine, corticosteroids	NSD for time to relapse

Table 9.3 Summary of studies investigating the effect of probiotic treatment on the induction and maintenance of remission in ulcerative colitis 2003–2008

Reference	Design	Group (dose/day)		Concomitant therapy	Results
		Probiotic	Comparator		
Induction of remission					
Tsuda et al. [30]	O 4 Week	BIO-THREE (9 tablets); $n=20$	None	Mesalamine, 6-mercaptopurine	For 11/20 patients who achieved remission, their mean UCDAI scores decreased from 5.18 to 1.91 ($P=0.0054$)
Matthes et al. [88]	DB, R, C 4 Weeks	*E. coli* Nissle 1917 ($>10^8$ CFU/ml) as 10, 20, or 40 ml (enema); $n=20$	Placebo $n=20$	None	Remission induced in 18.2% (placebo), and varied by dose in the treatment group: 27.3% (10 ml); 44.4% (20 ml), and 52.9% (40 ml)
Bibiloni et al. [25]	O 6 Weeks	VSL#3 (3.6×10^9 CFU); $n=32$	None	Mesalamine, corticosteroids, 6-mercaptopurine/ azathioprine	77% remission or response rate
Furrie et al. [17]S	DB, R, C 4 Weeks	*B. longum* (4×10^{11}) and Synergy 1 (12 g prebiotic fructo-oligosaccharide/ inulin mix); $n=8$	Placebo $n=8$	Corticosteroids, immunosuppressors, aminosalicylates	TNF-α and IL1-α were reduced in the treatment arm vs. placebo at 4 weeks ($P=0.018$ and $P=0.023$, respectively). The trend indicated that the treatment arm had greater improvements in both sigmoidoscopy and histology scores, but these were not statistically significant
Kato et al. [27]	DB, R, C 12 Weeks	*Bifidobacterium*-fermented milk (100 ml); $n=10$	Placebo $n=10$	Sulfasalazine and mesalamine	Reduced UCDAI ($P<0.05$)

(continued)

Table 9.3 (continued)

Reference	Design	Group (dose/day)		Concomitant therapy	Results
		Probiotic	Comparator		
Tursi et al. [29]	R, O 8 Weeks	Balsalazide (2.25 g) and VSL#3 (1×10^{11} CFU); $n=30$	Balsalazide (4.5 g); $n=30$ Mesalamine (2.4 g); $n=28$	None	Balsalazide and VSL#3 outperformed the two comparator groups (symptoms assessment, endoscopic appearance, and histological evaluation)
Guslandi et al. [26]	O 4 Weeks	*Saccharomyces boulardii* (750 mg); $n=25$	None	Mesalamine	Reduction in UCDAI scores
Maintenance of remission					
Zocco et al. [89]	O 1 Year	*Lactobacillus* GG (1.8×10^{10} CFU); $n=65$	Mesalamine (2.4 g); $n=60$ Mesalamine + LGG; $n=62$	None	NSD in relapse rates at 12 months; LGG more effective than mesalamine for prolonging duration of remission ($P<0.05$)
Cui et al. [32]	DB, C 8 Months	BIFICO (1×10^{7} CFU); $n=15$	Placebo $n=15$	None	$P<0.01$ where 93% of placebo relapsed vs. 20% of active treatment group
Kruis et al. [34]	DB, R, C 1 Year	*E. coli* Nissle 1917 ($2.5–25\times10^{9}$ CFU); $n=162$	Mesalamine (1.5 g) $n=165$	None	As effective as mesalamine at maintaining remission (significant equivalence, $P=0.003$)
Ishikawa et al. [33]	R, C 1 Year	*Lactobacillus* and *Bifidobacterium*-fermented milk (100 ml); $n=11$	Placebo $n=10$	Salazosulfapyridine, mesalazine, steroids	Reduced exacerbation of symptoms ($P<0.01$)

Table 9.4 Summary of studies investigating the effect of probiotic treatment in pouchitis 2003–2008

Reference	Design	Group (dose/day)		Concomitant therapy	Results
		Probiotic	Comparator		
Induction of remission					
Laake et al. [90]	O 4 Weeks	*L. acidophilus* and *Bifidobacterium lactis*-fermented milk (500 ml); $n=67$ of which 51 had UC	None	Loperamide	Significant decrease in the mean endoscopic score portion of PDAI (4.5–3.0) after 4 weeks ($P=0.0001$)
Laake et al. [39]	O 4 Weeks	*L. acidophilus* and *B. lactis*-fermented milk (500 ml); $n=51$	None	Loperamide	Improved PDAI; no difference in histology
Kuisma et al. [38]	DB, R, C 3 Months	*Lactobacillus* GG (1×10^{10} CFU); $n=10$	Placebo $n=10$	Not indicated	No difference in PDAI
Maintenance of remission					
Kuhbacher et al. [91]	DB, R, C 2 Months	VSL#3 (6 g); $n=10$	Placebo $n=5$	Not indicated	The probiotic group achieved 100% remission vs. 0% in the control group
Gosselink et al. [92]	R, C 3 Year	*L. rhamnosus* GG (CFU $>10^{10}$); $n=78$	Placebo $n=39$	Not indicated	Increased duration of remission ($P=0.011$)
Mimura et al. [43]	DB, R, C 1 Year	VSL#3 (6 g); $n=20$	Placebo $n=16$	Not indicated	Increased duration of remission ($P<0.0001$)
Gionchetti et al. [41]	DB, R, C1 Year	VSL#3 (1×10^{11} CFU); $n=20$	Placebo $n=20$	None	Increased duration of remission ($P<0.05$)

Table 9.5 Summary of studies investigating the effect of antibiotic treatment on the induction and maintenance of remission in Crohn's disease 2003–2008

Reference	Design	Group (dose/day)		Concomitant therapy	Results
		Antibiotic	Comparator		
Induction of remission					
Selby et al. [56]	R, DB, C 16 Weeks	Clarithromycin (750 mg), rifabutin (450 mg), clofazimine (50 mg); $n=102$	Placebo $n=111$	16-Week tapering of oral prednisolone (40–0 mg), azathioprine or 6-mercaptopurine, aminosalicylate	Remission achieved by 66% of the treatment arm vs. 50% of the placebo ($P<0.02$)
Prantera et al. [52]	R, C 12 Weeks	Rifaximin (800 mg o.d.) $n=25$ Rifaximin (400 mg b.d.) $n=29$	Placebo $n=29$	Mesalamine	NSD, however, reduced disease exacerbation in the antibiotic group
West et al. [93]	R, C 18 Weeks	Ciprofloxacin (500 mg b.d.), $n=11$	Placebo $n=13$	Infliximab, azathioprine, methotrexate, corticosteroids	Improvement was seen in 73% of the treatment arm vs. 38% of the control arm
Maintenance of remission					
Selby et al. [56]	R, DB, C 2 Year	Clarithromycin (750 mg), rifabutin (450 mg), and clofazimine (50 mg); $n=67$	Placebo $n=55$	Azathioprine or 6-mercaptopurine, aminosalicylate	NSD regarding duration of remission or time to relapse
Rutgeerts et al. [55] 2005	DB, R, C 1 Year	Ornidazole, $n=38$	Placebo $n=40$	Corticosteroids (1 months)	Reduced clinical recurrence ($P=0.046$) after 1 year. NSD at 2 and 3 years

Table 9.6 Summary of studies investigating the effect of antibiotic treatment on induction and maintenance of remission in ulcerative colitis 2003–2008

Reference	Design	Group (dose/day)		Concomitant therapy	Results
		Antibiotic	Comparator		
Induction of remission					
Guslandi et al. [94]	O 4 Weeks	Rifaximin (800 mg) $N=30$	None	Mesalamine (2.4 g)	Remission in 77%; decreased disease activity in 20%
Ohkusa et al. [95]	R, C 2 Weeks	Amoxicillin (500 mg t.d.), tetracycline (500 mg t.d.), or metronidazole (250 mg t.d.); $n=10$	Placebo $n=10$	Corticosteroids, aminosalicylates	Treatment group (9/10) had a higher rate of remission than the control group (5/10; $P=0.037$)

Table 9.7 Summary of studies investigating the effect of antibiotic treatment in pouchitis 2003–2008

Reference	Design	Group (dose/day)		Concomitant therapy	Results
		Antibiotic	Comparator		
Isaacs et al. [48]	DB, R, C	Rifaximin (400 mg t.d.)	Placebo	None	NSD
	4 Weeks	$n=8$	$n=9$		
Abdelrazeq et al. [66]	O 2 Weeks	Ciprofloxacin (2 g)+rifaximin (1 g); $n=8$	None	None	Remission in 68% and response in 25%

MHR Multivariate hazard ratio
O Open-label
OR Odds ratio
PDAI Pouchitis disease activity index
PEN Partial enteral nutrition
R Randomized
RCT Randomized controlled trial
RR Relative risk
S Synbiotic therapy Synbiotic 2000, commercial product containing 1×10^{10} CFU each of *Pediacoccus pentoseceus, L. raffinolactis, L. paracasei* subsp. Paracasei 19, *L. plantarum* 2362, and fermentable fibers (prebiotic component) consisting of 2.5 g of each of β-glucans, inulin, pectin, resistant starch

Table 9.8 Summary of studies investigating the effect of nutritional therapy on the induction and maintenance of remission in Crohn's disease 2003–2008

Reference	Design	Group (dose/day) Nutritional intervention	Comparator	Concomitant therapy	Results
Induction of remission					
Berni Canani et al. [74]	C 8 Weeks Pediatric	Polymeric, $n=12$ Semielemental, $n=13$ Elemental, $n=12$	Corticosteroids; $n=10$	None	NSD regarding clinical remission NSD between nutritional therapies Reduced mucosal inflammation seen in 26/37 in the nutrition arm vs. 4/10 in control arm ($P<0.05$)
Borrelli et al. [73]	O, R, C 10 Weeks Pediatric	Polymeric, $n=19$	Oral corticosteroids; $n=18$	None	NSD regarding remission rates, although mucosal healing was higher in the polymeric treatment arm (14/19, 74% vs. 6/18, 33%; 95%CI 16–57%, $P<0.05$) Endoscopic and histologic scores were decreased in the polymeric arm ($P<0.001$)
Johnson et al. [96]	R, C 6 Weeks Pediatric	TEN (elemental), not allowed to eat, $n=25$	PEN (50%) and unrestricted diet; $n=25$	None	Remission rate was higher in the TEN group vs. PEN (42% vs. 15%, $P=0.035$) CDAI and diarrhea reduction were greater in the TEN group vs. PEN ($P=0.005$ and $P=0.02$, respectively)
Afzal et al. [76]	O 8 Weeks Pediatric	Polymeric: Colonic disease, $n=14$; Ileal disease, $n=12$; Ileocolonic disease, $n=39$	None	Aminosalicylate	Ileal and ileocolonic groups had greater remission rates (91.7 and 82.1%, respectively) vs. the colonic group (50%, $P=0.021$). PCDAI improved for all groups ($P<0.03$)
Di Sabatino et al. [77]	O 8 Weeks	Butyrate in enteric-coated tablets (4 g), $n=12$	None	None	Remission achieved in 7/12 (58%). Endoscopical and histological scores improved at ileocecal level ($P<0.05$). Mucosal NF-kappaB and IL-1beta decreased after treatment vs. baseline ($P<0.05$)

Knight et al. [68]	O 6 Weeks Pediatric	Enteral nutrition, $n=44$	None		None	Remission achieved in 40/44 (90%)
Ockenga et al. [75]	R 1 Week	TPN and 0.3 g/kg L-alanine-L-glutamine; $n=12$	TPN, $n=12$		None	NSD
Maintenance of remission						
Feagan et al. [81]	R, C 58 Weeks	Omega-3 free fatty acids (4 g) EPIC-1: $n=188$ EPIC-2: $n=189$		Placebo EPIC-1: $n=186$ EPIC-2: $n=190$	None	EPIC-1: NSD EPIC-2: NSD
Yamamoto et al. [79]	R, C 1 Year	Elemental diet infusion (night) Low-fat diet (day), $n=20$		No dietary restrictions, $n=20$	None (surgically induced remission at time of entry)	Treatment group had 1 (5%) fail remission vs. 7 (35%) in the control group ($P<0.05$). Endoscopic scores were higher in the control group at 1 year ($P=0.04$) and cytokine levels were significantly higher
Takagi et al. [97]	R, C 1 Year	Partial elemental nutrition 50% (night); $n=26$		Free diet; $n=25$	None	The PEN group had fewer relapses (34.6% vs. 64.0%), MHR 0.40 (95% CI: 0.16–0.98)
Esaki et al. [98]	O 1 Year	TEN (>1,200 kcal) $n=24$		PEN (<1,200 kcal); $n=16$	Aminosalicylate	Remission relapses occurred less in the total vs. partial enteral nutrition arms (46% vs. 75%, $P=0.017$)
Knight et al. [68]	O 6 Year Pediatric	Enteral nutrition $n=40$		None	Corticosteroids as needed	Relapse rate was 25/40 (62%) at a median of 54.5 weeks. Corticosteroid use was delayed for a median of 68 weeks in 21 patients
Romano et al. [80]	R,C 1 Year Pediatric	Omega-3 fatty acids (3 g) $n=18$		Placebo; $n=20$	Aminosalicylate (50 mg/kg)	The treatment arm had 11 relapses vs. 19 in the control arm at 1 year ($P<0.001$)

Table 9.9 Summary of meta-analyses investigating the effect of probiotics, antibiotics, or nutritional therapy on the induction and maintenance of remission in IBD 2003–2008[a]

IBD	Therapy	References	Studies included	Outcomes
Induction of remission				
CD	Antibiotic	Rahimi et al. [46]	10 RCT $n=530$	Pooled analyses yielded an OR of 2.14 (95% CI 1.678–3.036, $P<0.001$) in preference of antibiotic therapy vs. placebo for the induction of remission in CD patients
CD	Nutrition (enteral, pediatrics)	Dziechciarz et al. [71]	11 RCT $n=394$	NSD for remission rates between corticosteroid and enteral nutrition treatment arms (RR 0.97, 95% CI 0.7–1.4, random effect model) based upon pooled data from 4 RCTs ($n=144$). Pooling of data was restricted due to different experimental measures
CD	Nutrition (enteral)	Zachos et al. [69]	10 RCT $n=334$	NSD for the efficacy of elemental vs. nonelemental formulas (OR 1.10, 95% CI 0.69–1.75). In subgroup analyses, NSD was found for diets varying in protein compositions (elemental, semielemental, or polymeric), fat content, or type of fat. Another subgroup analyses (8 RCT, $n=352$) favored corticosteroid therapy over enteral nutrition (OR 0.33, 95% CI 0.21–0.53) for induction purposes
UC	Probiotics	Mallon et al. [99]	4 RCT $n=244$	Pooling of data was not possible. Available evidence does not support the use of probiotics for the induction of remission in UC
UC	Antibiotic (broad-range)	Rahimi et al. [58]	6 RCT $n=804$	Pooled analyses provided an OR of 2.257 (95% CI 1.48-3.09, $P<0.0001$) in preference of adjunctive antibiotic therapy over placebo for the induction of remission in UC patients. Subgroup analyses of short-term trials (5–14 days) found a higher rate of clinical remission in UC patients receiving antibiotic therapy (OR 2.02, 95% CI 1.36–3.00)
Maintenance of remission				
CD	Probiotics	Rahimi et al. [24]	8 RCT $n=320$	Pooling of 7 RCTs ($n=253$) showed NSD for clinical relapse between the treatment and control groups (OR 0.92, 95% CI 0.52–1.62, $P=0.8853$). Pooling of 3 RCTs ($n=177$) examining endoscopic relapse showed NSD between the treatment and control groups (OR 0.97, 95% CI 0.54–1.78, $P=0.93$). Authors conclude that probiotics are ineffective for maintenance of clinical or endoscopic remission in CD

CD	Probiotics	Rolfe et al. [23]	7 RCT $n=248$	It was not possible to pool the data due to deferent experimental designs. Subgroup analysis by probiotic strains showed no beneficial therapeutic effect of probiotics vs. controls
CD	Nutrition (enteral)	Akobeng et al. [78]	2 RCT $n=84$	Data pooling was not possible. Authors conclude that enteral nutrition supplementation could be considered as either an adjunct to maintenance drug therapy or an alternative in CD, although additional large-scale trials are required
CD	Nutrition (omega-3 fatty acids)	Turner et al. [82]	4 RCT $n=301$	NSD was found between the treatment and control groups regarding relapse rates (RR 0.64; 95%CI 0.4–1.03; $P=0.07$). Subgroup analyses of 3 RCTs ($n=166$) showed that enteric-coated capsules were beneficial for extending the duration of remission (RR 0.49; 95% CI 0.35–0.69; RD 0.31; 95% CI 0.19–0.43) and the NNT to prevent relapse in 1 year was three patients (95% CI 2–5; I(2) = 19%). However, authors conclude that there is insufficient data to recommend the daily oral intake of enteric-coated capsules containing omega-3 fatty acids
UC	Nutrition (omega-3 fatty acids)	Turner et al. [84]	3 RCT $n=138$	Pooled analysis showed NSD in relapse rates between the omega-3 fatty acid supplementation groups and controls (RR 1.02; 95% CI 0.51–2.03; $P=0.96$). Although each study used different formulations and doses, there were no differences regarding various subgroup and sensitivity analyses or statistical heterogeneity ($P=0.93$, I(2) = 0%). Authors conclude that there is no evidence to support the use of omega-3 fatty acids for the maintenance of remission in UC
Pouchitis	Probiotics	Elahi et al. [45]	5 RCT $n=258$	Pooled analyses showed that the probiotics treatment group had fewer incidences of pouchitis vs. the placebo group (OR 0.04, 95% CI 0.01–0.14, $P<0.0001$). Authors conclude that probiotic therapy following IPAA is beneficial to prevent pouchitis

[a]No meta-analyses have been published during 2003–2008 regarding the use of prebiotics in IBD

TEN Total enteral nutrition
TNF-α Tumor necrosis factor-alpha
TPN Total parenteral nutrition
UCDAI Ulcerative colitis disease activity index VSL#3, commercial mixture containing *Bifidobacterium longum, B. infantis, B. breve*. *Lactobacillus acidophilus, L. casei, L. delbrueckii* subsp *bulgaricus, L. plantarum,* and *Streptococcus salivarius* subsp *thermophilus*

Prebiotics in the Treatment of Inflammatory Bowel Disease

Prebiotics, such as lactosucrose, fructo-oligosaccharides, inulin, bran, pysllium (*Plantago ovata*), and germinated barley extracts [6, 7], are dietary additives that are preferentially fermented by *Lactobacillus* and *Bifidobacterium* to produce short chain fatty acids (e.g., butyrate and acetate) [8]. Prebiotic supplementation increases the intestinal population of protective commensal bacteria, while their byproducts improve epithelial barrier and dendritic cell functions by inhibiting mucosal inflammation [8–10]. Augmenting the dietary intake with prebiotics is an indirect method to positively rebalance the gut's biome and potentially alleviate symptoms of IBD as opposed to the direct method of ingesting probiotic organisms. Balanced against this potential beneficial effect of prebiotics is the real threat of also upregulating the growth of the existing luminal, and potentially disease-inducing, bacteria. Unique prebiotics that utilize probiotic-selective nutrient transport systems are currently being designed to mitigate this possibility.

To date, there have been very few studies examining the therapeutic benefits of prebiotics for IBD patients. More recently, a few investigators have conducted human trials which administered a combination of prebiotics and probiotics that has been termed synbiotics (see Table 9.2, entries marked "S").

Crohn's Disease (CD) (Table 9.1)

To date, only a single open-label study has explored the effect of prebiotic therapy in CD. Lindsay et al. found that oral supplementation with fructo-oligosaccharides reduced the Harvey Bradshaw index from 9.8 to 6.9 ($P<0.01$); this effect was associated with a 9.4% increase in fecal bifidobacteria ($P<0.001$) with the corollary being that the intestinal population was also increased [11]. In addition, the mucosal immune system responded with a 3.4% increase in expression of TLR2, TLR4, and IL-10 by dendritic cells ($P<0.001$). A small randomized placebo-controlled trial in 30 CD patients using Synbiotic 2000, a mixture of prebiotics and probiotics, including 4 lactic acid bacterial strains (10^{10} *Pediococcus pentosaceus*, 10^{10} *L. raffinolactis*, 10^{10} *L. paracasei* subsp paracasei 19, 10^{10} *L. plantarum* 2362) plus 4 different fermentable fibers (2.5 g β-glucans, 2.5 g inulin, 2.5 g pectin, and

2.5 g resistant starch), failed to prevent postoperative endoscopic disease recurrence compared to placebo [12], although this study was likely underpowered.

Ulcerative Colitis (UC) (Table 9.1)

Induction and Maintenance of Remission

In 1998, Mitsuyama and colleagues conducted a small trial in which patients with active UC were fed germinated barley foodstuffs for 4 weeks [13]. The significant reductions in both the clinical activity and endoscopic index scores ($P<0.05$ and $P<0.0001$, respectively) were associated with significantly increased stool butyrate concentrations ($P<0.05$). In 2003, the same group conducted a larger ($n=21$) trial for 24 weeks with UC patients who had mild-to-moderate disease activity [14]. At the conclusion, the intervention cohort had a significant reduction in their clinical activity index score relative to the baseline ($P<0.05$). In 2004, a randomized control trial (RCT) was conducted for 12 months with UC patients in clinical remission [15]. The intervention cohort consumed 20 g germinated barley foodstuffs per day and had improved clinical activity index scores at 3, 6, and 12 months vs. the control cohort ($P<0.05$). Remission failure was lower in the intervention group in spite of steroid tapering. Germinated barley foodstuffs are well-tolerated and evidence from one research group indicated that they provide some therapeutic benefits for UC patients when administered in conjunction with conventional therapy. However, additional evidence is required from placebo-controlled trials conducted by other research groups.

A small, placebo-controlled (1:1) pilot study performed by Casellas et al. reported the adjunct effect of 2-week oligofructose-enriched inulin in 19 patients with mild-to-moderately active UC who also received mesalamine (3 g/day) [16]. Calprotectin is a marker of the amount of luminal inflammatory cells (neutrophils) and has been used as an objective and quantitative marker of intestinal inflammation. Quantification of human DNA excretion in feces is a marker of leucocyte and epithelial cell desquamation. This study reported a significant reduction of fecal inflammatory marker calprotectin in prebiotic-treated patients after 1 week in the treatment groups compared to the placebo group, suggesting that these prebiotics were able to reduce intestinal inflammation. However, no difference in human DNA excretion in feces was observed.

Furrie et al. performed a double-blind, randomized controlled study using synbiotics in 18 UC patients. Patients were fed a combination of *B. longum*, isolated from healthy rectal mucosa, combined with oligofructose-enriched inulin (1:1) for 1 month. Rectal biopsies were collected before and at the end of treatment and epithelium-related mucosal immune markers were measured. Synbiotic treatment reduced endoscopic and microscopic colonic inflammation vs. controls, concomitant with a decrease of sigmoidoscopy scores. Colonic β-defensins mRNA, TNF-α, and IL-1α were significantly reduced in patients [17].

Pouchitis

In 2002, Welters and colleagues performed a small ($n = 19$) randomized, double-blind, placebo-controlled trial examining the physiological effect of the prebiotic inulin (24 g/day) [18]. Of the 16 patients who had surgical intervention due to UC, none had ever experienced pouchitis. This, in combination with the short trial duration, did not make for an effective study using inulin for maintaining remission in pouchitis.

Probiotics in the Treatment of Inflammatory Bowel Disease

In a strain-specific manner, probiotics have been shown to modulate mucosal immunity in a number of ways including enhancement of immunoglobulin production, stimulation of dendritic cell and T cell hypo-responsiveness leading to a decrease in NFκB pathway activation, and induction of immune cell apoptosis. Probiotics have been shown to induce intestinal production of anti-inflammatory cytokines (e.g., IL-10, TGFβ), while reducing production of proinflammatory cytokines (e.g., TNF-α, IL-8) [19]. Probiotic bacteria can also exhibit biological effects that enhance epithelial barrier function such as normalizing the barrier function in IL-10-deficient mice and enhancing epithelial resistance in the T84 human epithelial cell line [20]. These in vitro and in vivo probiotic characteristics suggest that some probiotic bacterial species may be efficacious in the treatment of IBD. Summarized below are the results of human clinical trials with probiotics in IBD. While there is a strong suggestion and even scattered level 1 evidence that some, but not all, probiotics can be effective in IBD, the entire field is plagued by small and underpowered trials. For probiotics to successfully enter the mainstream of disease therapy, adequately powered randomized controlled clinical trials will be needed.

Crohn's Disease (Table 9.2)

Induction of Remission

There is a paucity of data on the treatment of active CD with probiotics. Between 2002 and 2007, only two small scale trials ($n < 11$) were conducted. The 6-month randomized, controlled trial did not find a significant difference regarding the rates of remission induction between the treatment arms *Lactobacillus GG* and placebo [21]. Conversely, the open-label study reported a remission rate of 6/10, but the results were confounded by the combination of probiotic–prebiotic therapy and home enteral nutrition [22].

Maintenance of Remission

Since 1997, there have been six randomized controlled trials reported examining the efficacy of probiotic therapy to maintain remission. Although there is considerable variation in the probiotics and concomitant therapy, the evidence with respect to trial size, duration, and results strongly suggests that probiotic therapy has negligible impact on the duration of maintenance for patients with CD, irrespective of whether the remission is medically or surgically induced. Two recent meta-analyses by independent groups also arrived at the same conclusion [23, 24].

Ulcerative Colitis (Table 9.3)

Induction of Remission

Unlike CD, ulcerative colitis disease activity appears to respond to probiotic therapy. An initial probiotic trial in 1999 provided evidence that *Escherichia coli* Nissle 1917 (1×10^{11} CFU q.d.) was as effective as mesalamine at inducing remission. Since then, every major trial has provided additional evidence associating probiotic therapy with achieving remission in patients with active UC [25–29]. Interestingly, a range of probiotic species has been investigated, either as a single species, or in combination, and all were found similarly effective relative to the comparator [28, 30]. A systematic review of all randomized controlled trials up to 2006 concluded that probiotic therapy, used as an adjunct to conventional treatments, modestly reduced disease activity in patients with mild-to-moderately severe UC [31].

Maintenance of Remission

In extension to their apparent effectiveness for induction of remission, probiotics have also been found to be effective in maintaining remission of UC. Since 1999, four trials have provided evidence that a range of probiotics, or combinations thereof, confer sustained benefits to patients such as prolonging the duration of remission, reducing exacerbation of transient symptoms, or being equally effective as mesalamine [32–35]. In contrast, the studies that examined *Lactobacillus* GG or *L. salivarius* as single strains to maintain UC remission were not effective [36, 37]. Further studies are required to explore the long-term value of probiotic therapies in excess of 1 year to better understand how they may best be used.

Pouchitis (Table 9.4)

Induction of Remission

Treating active pouchitis with probiotics has not yielded overly encouraging results. Kuisma et al. using *Lactobacillus* GG (1×10^{10} CFU q.d.) demonstrated no therapeutic effect on acute pouchitis when administered for 3 months [38]. Similarly, Laake et al. treated 51 acute pouchitis patients for 4 weeks with a fermented dairy product containing *L. acidophilus* and *B. lactis* (500 ml q.d.) and found an improvement in PDAI scores, but not in histology [39]. However, recently, Gionchetti has suggested, in an open-label trial, that double-dose VSL#3 can induce remission of active pouchitis [40]. This study will need to be replicated.

Maintenance of Remission

Although there is little evidence to support the use of probiotics for the induction of remission, level 1 evidence exists for the use of VSL#3 during maintenance of pouchitis remission. In 2000, Gionchetti et al. found that a commercial mixture (VSL#3) of eight probiotic strains significantly extended the duration of remission vs. placebo in patients who previously had pouchitis that was placed into remission with antibiotics. Since this pivotal finding, three other studies have provided similar evidence for the use of VSL#3 in the maintenance of remission following antibiotic-induced healing of pouchitis [41–43]. Probiotics also appear to have benefit in preventing pouchitis after surgical formation of the pouch. Gionchetti showed significant benefit for VSL#3 vs. placebo in a small ($n = 40$) trial ($P < 0.05$), while Gosselink and colleagues ($n = 117$) showed benefit for *L. rhamnosus GG* vs. historical controls ($P = 0.011$) [44]. A meta-analysis of five randomized controlled trials showed that probiotic treatment groups had a significantly reduced odds ratio (OR) 0.04 (95% CI 0.01–0.14, $P < 0.0001$) than the control groups, supporting the use of probiotic therapy following ileal-pouch anal anastomosis (IPAA) [45].

Antibiotics in the Treatment of Inflammatory Bowel Disease

The first controlled trial investigating the efficacy of antibiotic therapy dates back to 1978 [46, 47] Antibiotic therapy has been commonly used for treating IBD along the same lines of rationale as probiotic and prebiotic therapies [48–52], following the concept that bacterial organisms play an important role in the initiation and perpetuation of IBD.

Crohn's Disease (Table 9.5)

Induction of Remission

Antibiotics are often used to treat CD, yet this practice is not well-supported by strong evidence from randomized trials [53]. A meta-analysis of six randomized, placebo-controlled trials yielded an odds ratio of 2.257 (95% CI, 1.678–3.036; $P<0.001$) in favor of antimicrobial therapy, yet the authors conclude that further trials are required [46]. The efficacy of antibiotics, specifically metronidazole (1 g) and ciprofloxacin (1 g), was found to be similar to that of methylprednisone (0.7–1 mg/kg) in a small ($n=41$) randomized trial, although other studies are required to fully explore this steroid-sparing induction option [54]. In a study that examined induction of remission using budesonide with or without metronidazole and ciprofloxacin, subgroup analysis suggested that antibiotics provided beneficial effects in CD patients in which colonic involvement was present [53].

Maintenance of Remission

The efficacy of ornidazole given to patients postoperatively in preventing disease recurrence is modest and seems to be limited to the duration of antibiotic administration: in that this preventative effect seems to be lost once the antibiotic is stopped [55, 56]. At present, it is unclear as to why the protective effect of antibiotic therapy wanes over time [57]. Selby et al. conducted a randomized, double-blind, placebo-controlled trial using triple therapy (clarithromycin, rifabutin, and clofazimine) designed to treat *Mycobacterium avium* subspecies paratuberculosis as an infective agent in CD [56]. This study did not find a sustained maintenance of remission benefit.

Ulcerative Colitis (Table 9.6)

Induction of Remission

A meta-analysis of six randomized controlled trials (antibiotic treatment 5–14 days) indicated that patients receiving antibiotics in addition to conventional therapy achieved a higher rate of clinical remission than those receiving placebo and conventional therapy (OR, 2.02; 95% CI, 1.36–3) [58]. Although the use of antibiotics for inducing remission appears beneficial, it is important to note that the trial sizes have been modest ($n<90$), results have been conflicting, and that three of the trials originated from the same research team [59–62]. The only recent studies have been open-label or small ($n=10$) in the active treatment group.

Maintenance of Remission

Only two randomized, placebo-controlled trials have explored the use of antibiotics for maintaining remission, both of which concluded that no significant difference (NSD) was found between the treatment and control arms [63, 64]. There are no comparison studies of antibiotics vs. mesalamine treatment.

Pouchitis (Table 9.7)

Induction and Maintenance of Remission

Most patients are given oral metronidazole or ciprofloxacin; however, controlled trials are lacking. Treatment seems to be most effective in acute episodes and is likely less effective in chronic disease. One early double-blind crossover trial randomly assigned patients with chronic unremitting pouchitis to metronidazole (400 mg t.i.d. for 7 days) or placebo [65]. Metronidazole was associated with a significant reduction in stool frequency by three movements per day (vs. an increase of one per day with placebo), but there was no change in the endoscopic or histologic grade of inflammation. Most antibiotic studies in pouchitis represent small numbers of patients and have not been powered to confirm statistical significance [48, 50, 66, 67]. A recent pilot trial did not demonstrate efficacy with the nonabsorbable antibiotic rifaximin [48], but combining rifaximin with ciprofloxacin appeared effective in an open-label trial [66].

Nutritional Therapies in the Treatment of Inflammatory Bowel Disease

Nutritional therapies are attractive to both patients and physicians as conventional drugs such as corticosteroids, biologics, and immunosuppressants are associated with a wide range of undesirable side effects or are not well-tolerated by patients. Clinical trials of nutritional therapies often involve pediatric patients in the hope that they will avoid exposure to drugs that may interfere with their growth or are unsuitable for a lifetime of dependency [68]. Various formula designs have been developed, yet enteral and parenteral nutrition is primarily used in Western countries as adjunctive therapy in IBD patients with malnutrition [69]. Conversely, Japanese medical guidelines consider total enteral nutrition as primary therapy for pediatric cases of CD [70].

Crohn's Disease (Table 9.8)

Induction of Remission

The most recent meta-analysis provides additional support that corticosteroid therapy is superior to enteral nutrition for the induction of remission (8 trials, $n = 352$) [69]. Nevertheless, physicians, particularly in the pediatric population, balance risks and often choose enteral therapy because of the significant growth-associated adverse events of corticosteroids. Interestingly, a recent pediatric meta-analysis (4 RCTs, $n = 144$) found NSD regarding induction of remission between the enteral nutrition and the corticosteroid treatment groups [71]. In a seminal study of the induction of remission in CD, Greenberg et al. confirmed that the benefit of nutrition was associated with the increased caloric intake and much less with the bowel rest [72].

An open-label, randomized trial with 37 pediatric patients found no difference in remission rates, but that 74% of the polymeric group showed evidence of mucosal healing after 10 weeks of therapy vs. 33% of those receiving oral corticosteroids ($P < 0.05$) [73]. Similar mucosal healing results were reported in an 8-week pediatric trial, indicating that further investigations are required that will explore the effectiveness of combined enteral nutrition and corticosteroid therapy. NSDs between the different enteral diet formulations (elemental, free amino acids; semielemental, oligopeptides; or polymeric, whole protein) and remission rates have been identified [69, 74, 75]. Additional evidence is required in order to determine if there is an association between the location of disease activity and the efficacy of enteral nutrition [76]. Administration of butyrate, a prebiotic, in an 8-week, open-label trial mimicked the results of probiotic therapy [77]. Larger, well-designed studies are needed to corroborate this finding and compare the results with conventional therapies.

Maintenance of Remission

A recent Cochrane Collaboration systematic review of enteral therapy in the maintenance of remission of CD concluded that although enteral nutrition appears to convey therapeutic benefits to these patients when used alone or in conjunction with conventional therapy, the data are both weak and limited; further randomized controlled studies are required [78]. A subsequent trial compared the remission relapse rates between patients who received a nighttime elemental infusion and a daytime low-fat diet ($n = 20$) vs. patients with no dietary restrictions ($n = 20$) [79]. After 1 year, the control group had more clinical remission failures (35% vs. 5%, $P < 0.048$) and more endoscopic recurrences (70% vs. 30%, $P = 0.027$). Although enteral nutrition is undesirable for many, for those who have the fortitude this may

represent a promising therapy for maintaining remission. While early small trials using nutritional supplementation with omega-3 fatty acids led to a significant improvement in remission rates ($P<0.001$) at 1 year [80], a recent multinational randomized placebo-controlled study did not demonstrate sustained remission with omega-3 free fatty acids [81]. A meta-analysis concluded that more data are required to support the preliminary beneficial therapeutic effects of enteric-coated capsules containing omega-3 fatty acids for CD patients in remission [82].

Ulcerative Colitis

Induction and Maintenance of Remission

Although omega-3 fatty acid supplementation has been found to ameliorate certain chronic inflammatory diseases [80], a randomized controlled trial with UC patients found NSD regarding the maintenance of remission between the treatment and control arms after 1 year [83]. A meta-analysis of three randomized controlled trials ($n=138$) concluded that there was no evidence to support the use of omega-3 fatty acids (fish oil) during periods of remission to prevent relapse for UC patients [84]. From 2003 to March 2008, no randomized controlled trials or large-scale, open-label studies have been conducted on this topic.

Pouchitis

Induction and Maintenance of Remission

There are no studies investigating the use of nutritional therapy to achieve or maintain remission in pouchitis.

Conclusion

The essential role of microbes in the pathogenesis of chronic IBDs has been established. Attempts to alter intestinal microbial constituency with prebiotics, probiotics, and antibiotics and thus use these agents as therapeutic modalities have seen varied successes. As yet, more studies are required to investigate the preliminary findings with respect to the therapeutic benefit of prebiotics in CD and UC. While there is level 1 and 2 evidence for the efficacy of some probiotics in the induction and maintenance of remission of UC and pouchitis, it is by no means clear why some probiotic strains are effective, whereas others are not. In contrast, current studies have not shown consistent efficacy for probiotics in the induction and maintenance

of remission of CD. The efficacy profile of antibiotics in IBD is similar to that of probiotics. There is increasing amounts of quality evidence that suggest some antibiotics, but not all, may be synergistic to conventional therapy during disease that involves the colon or pouch. Nutritional therapy trials are producing interesting results regarding mucosal healing that merit further investigation regarding the induction and maintenance of remission in CD and to a lesser extent in UC. Nutritional (enteral) therapy, for the most part, will likely remain a therapeutic option in some pediatric age groups, where avoidance of corticosteroids and immunosuppressives may be deemed a priority.

Regardless of the results obtained from the prebiotic, probiotic, antibiotic, and nutritional therapy trials, the largest collective problem is that they are underpowered and often designed as open-label studies. For any new therapy to be accepted into routine clinical practice, well-designed randomized trials comparing these agents against conventional therapies or placebo are essential. As our understanding of these diseases increases, the complexity of study designs must also incorporate an expanding array of experimental tests such as quality of life, tissue healing, and treatment protocol adherence. By extrapolation, the population density and species variation within the host gut's biome in addition to the host genetic make-up suggest that IBD encompasses an incredible range of pathogenic differences between patients that have been grossly grouped together. As such, it is not surprising that patients respond differently to the same treatment. However, until such etiology is identified and well-understood, it is imperative that subsequent clinical trials obtain as much information about each treatment as possible to create "designer" therapies appropriate to the needs and expectations of each patient.

Tables 9.1–9.8 contain summaries of moderate-to-good quality, peer-reviewed studies published in journals from 2003 through to March 2008 retrieved from PubMed, Medline, EMBASE, and the Cochrane Library.

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Chapter 10
State-of-the-Art Management of the Pediatric IBD Patient

Marla Dubinsky

Keywords Crohn's disease • Ulcerative colitis • Inflammatory bowel disease • Epidemiology • Etiopathogenesis • Children • Corticosteroids • Growth failure • Bone mass • Dual energy X-ray adsorptiometry • Quality of life • Transition of care • Quantitative computed tomography

Key Points

- Approximately 20% of inflammatory bowel disease (IBD) cases present in the pediatric or adolescent age group.
- Genetics and specific serum immune markers may identify children with more aggressive Crohn's disease.
- Both upper and lower endoscopies with biopsies should be performed in pediatric patients suspected of having IBD.
- Earlier appropriate use of thiopurines, and subsequently biologics, should be considered in patients sick enough to require corticosteroids.
- Growth failure and defective bone mass accrual are risks specific for this population that are multifactorial in nature and must be correctly identified, quantitated, and treated, when possible.
- Adherence to prescribed medication regimens is low in the pediatric and adolescent population, especially among children with dysfunctional families or with poor coping strategies.

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Introduction

Inflammatory bowel disease (IBD) first presents in childhood and adolescence in approximately 20% of all cases. The pediatric age group has emerged as the fastest growing incident population for IBD. Recent advances in diagnostics technologies and therapeutics have improved the care provided to these children. There are specific distinguishing features that differentiate early (pediatric)-onset IBD from later (adult)-onset IBD. Physical and psychosocial development remains a critical focus for pediatric gastroenterologists when providing comprehensive management to the pediatric IBD patient. Children are not just little adults and consideration must be given to the stages of development and how these stages impact disease presentation and management. This chapter will highlight the many unique facets involved in the presentation, diagnosis, treatment, and psychosocial well-being of the child with IBD.

Epidemiology

A European study reported that in the entire IBD population (children and adults) the incidence of Crohn's disease (CD) increased significantly (+23%), while the incidence of ulcerative colitis (UC) decreased (−17%) [1]. A North American study reported an incidence of IBD in Wisconsin children to be 7.05 per 100,000. The incidence of Crohn's disease was 4.56, which was more than twice the rate of ulcerative colitis (2.14). Of interest, in this population-based study, an equal IBD incidence occurred among all ethnic groups, and children from sparsely and densely populated counties were equally affected and the majority (89%) of new IBD diagnoses were nonfamilial [2]. There were very few Jewish patients in this study which could explain the lack of familial inheritance. Like most studies of pediatric IBD, the median age of onset was 12 years and there appears to be a slight male predominance in the younger age group. Given the rise in incidence and the onset of disease coinciding with growth and development, it is very important to highlight the considerations that should be taken into account when managing childhood-onset IBD.

Etiopathogenesis

The underlying pathogenesis of IBD in children appears to be similar to that in adult-onset such that IBD results from a complex interaction of environmental, genetic, and immune factors. Genetics, however, may play an even greater role in disease onset and susceptibility in patients who present earlier in life. To date, however, a gene specific to pediatric-onset disease has not been identified.

The most well-known genes, NOD2 in particular, are similarly present in both 30–35% of adult and pediatric CD patients. Although the true pathogenic role of NOD2 in CD remains unknown, it is an important gene involved in innate immunity which lends support to the notion that genetically determined defects in innate and likely adaptive immunity alter the way our mucosal immune system interacts with our resident bacterial flora [3] Despite similar clinical characteristics, significantly lower frequencies of CARD15 mutations have been seen in African–American and Hispanic children with CD compared with Caucasian children with CD [4]. A study from Israel suggested that G908R (SNP12) allele-variant of the NOD2/CARD15 gene is closely related to the appearance of CD at a young age in Jewish Ashkenazi patients [5]. Research is ongoing to further examine the influence of ethnicity on disease susceptibility and disease modification in both children and adult-IBD patients. A pediatric genome-wide association study identified [6] early-onset genes unique to children. Initial genotype–phenotype correlation studies in children demonstrated that NOD2 is associated with fibrostenosing CD and more rapid progression to surgery [7]. It appears that genetics is only part of the story when it comes to understanding the influences or risk factors at predicting the natural history of disease in pediatric patients. Initial work suggested that there are specific immune markers present in the serum of children with IBD [8]. These markers were initially used to help differentiate CD from UC and to aid in the distinction between functional GI symptoms and those due to underlying IBD, CD in particular. The concept that seroreactivity to specific microbial antigens seen in a subgroup of patients with IBD likely represents a surrogate measure of an individual's (mal) adaptive immune response has led to an influx of research focused on understanding the role of these markers in IBD etiopathogenesis. CD-specific antigens for which immune reactivity can be measured include ASCA (anti-*Saccharomyces cerevisiae* antibody), the *Pseudomonas fluorescens*-related protein (I2), *Escherichia coli* outer membrane-porin (OmpC), and CBir1 flagellin (CBir1) [9–11]. The evolution of serum immune response from diagnostic markers to markers of disease behavior and predictors of prognosis has resulted in studies that have shown that the presence and magnitude of immune responses in a given child is associated with more aggressive disease phenotypes and more rapid disease progression to complication and surgery [12, 13].

Diagnosis

The diagnostic approach to IBD in children is a two-tiered approach. The first diagnostic question is whether the presenting symptoms are compatible with a diagnosis of IBD. In the face of classic alarm symptoms, the differentiation between IBD and diseases that mimic the symptoms of IBD can be relatively simple. Diarrhea and abdominal pain are the most common symptoms in both CD and UC with rectal bleeding more commonly seen in UC and weight loss and anorexia more characteristic of CD. Perianal disease, like in adults, remains characteristic of CD

and can be present in up to 30% of pediatric patients at presentation or soon thereafter. Growth failure, however, is a clinical presentation that certainly distinguishes pediatric-onset IBD from their adult counterparts. This is more commonly in CD then UC patients. Not unlike the standard approach to any patient regardless of age group, routine labs looking for signs of inflammation (ESR, CRP, platelet count) complete blood count with a focus on the hemoglobin for anemia and other labs such as iron panel and albumin to look at nutritional/absorptive state are performed along with stools studies to rule out infection especially in the presence of a travel history or recent antibiotic use. Endoscopic evaluation and histopathological diagnosis remains the gold standard [14]. It is recommended that all children undergo both an upper endoscopy and colonoscopy at the time of initial investigation. The findings on upper endoscopy, although often nonspecific, may provide additional information in a patient with indeterminate disease of the colon, especially if granulomas are found. A recent study found upper gastrointestinal inflammation in 29 of 54 children (22 CD; 7 UC); however. overall the proportion of pediatric patients with upper tract disease is likely closer to 25–30% depending on what the definition of upper tract disease is [15]. In this small study, epigastric and abdominal pain, nausea and vomiting, weight loss, and pan-ileocolitis were predictive of upper gastrointestinal involvement. Perhaps of even more interest is that, 31% of the children with upper gastrointestinal involvement were asymptomatic at presentation. Thus, absence of specific upper gastrointestinal symptoms does not preclude presence of upper gastrointestinal inflammation. Small bowel radiography is also part of the initial diagnostic evaluation of pediatric IBD patients especially in CD patients. This is especially so for patients in whom ileal intubation was not successful at the time of the colonoscopy or diagnosis is indeterminate. It has been suggested that a normal small bowel radiography alone should not be used to rule out pediatric IBD when the symptoms suggest it. Colonoscopy with terminal ileal intubation is feasible and safe; it should be attempted in all children with symptoms consistent with IBD [16]. Radiographic evaluation of the small bowel has evolved to include MRI enterography (MRE) and CT enterography (CTE) [17]. Not all centers have a dedicated radiologist who is trained to interpret MRE and this may limit its use. CTE that can assess both the small and large bowel and evaluate for any extraintestinal changes has virtually replaced small bowel fluoroscopy in some IBD Centers. The radiation is somewhat greater than a standard CT scan, but is less than a small bowel follow-through with prolonged fluoroscopy [18]. Positron emission tomography (PET) using fluorine-18-fluoro-deoxyglucose to identify metabolically active tissues was evaluated as a simple noninvasive alternative to conventional studies in identification and localization of active intestinal inflammation in children with IBD [19]. The authors concluded that PET, which may be cost-prohibitive, will likely not replace conventional studies; however, it may be useful when conventional studies cannot be performed or fail to be completed. White cell scans have also been proposed as a noninvasive way of evaluating active inflammation; however, there can be many false negative and false positive readings and advances in technology such as the video capsule endoscopy (VCE) provides a way of evaluating the small bowel mucosa with increased sensitivity and specificity [20].

VCE may be helpful in patients with persistent small bowel symptoms, plus or minus laboratory abnormalities, despite what has been reported as a normal small bowel X-ray particularly in those children with persistent growth failure. VCE may be very helpful in patients with IBD unspecified (IBDU) to distinguish UC from CD particularly before colectomy [21].

In the face of diagnostic uncertainty, such as in children presenting with symptoms compatible but not diagnostic of IBD, the pediatric approach tends to be less invasive then the approach to an adult patient presenting with similar symptoms. In this setting, pediatricians tend to use noninvasive testing first to gather information that may increase the probability of disease and hence lead to more evidence to support invasive diagnostic testing. Other than routine laboratory tests as noted above, there are fecal markers, such as calprotectin and lactoferrin, and serological markers, such as ASCA and pANCA, that may aid in the differential diagnosis. Earlier reports demonstrated that fecal calprotectin correlated closely with the best invasive measures of colonic and small bowel inflammation in childhood IBD and lends itself particularly to the monitoring and assessment of therapeutic interventions in children with IBD [22]. Novel technologies have led to the development of a diagnostic algorithm to evaluate the sensitivity and specificity of serological immune markers as predictors of IBD vs. non-IBD. Historically, these tests were accurate in differentiating IBD from non-IBD in 2/3 of cases [23]. Further validation studies in pediatric patients are needed to determine if indeed these tests will help pediatric gastroenterologist increase the likelihood of diagnosing IBD in the face of positive markers and whether this leads to change in diagnostic approach in the face of a positive or negative test.

The next tier in the diagnostic process of IBD is the differentiation between CD and UC. In the face of a classic CD presentation which includes small bowel localization, presence of granulomas, typical endoscopic and histological findings, the differentiation is simple. However, there are some features of pediatric-onset IBD that may pose more of a diagnostic dilemma when disease is confined to the colon. Despite the classic teachings of UC always involving the rectum, there are reports of rectal sparing in pediatric patients carrying a diagnosis of UC. The group from Boston reported that a significant proportion of children with new-onset UC had patchiness of microscopic features of chronicity (21% of patients), relative (23%) or absolute (3%) rectal sparing, and had little or no crypt architectural distortion in their rectal biopsies (8%). Of interest, these features were not observed in adult patients with UC. In addition, a higher proportion of children with UC initially presented with subtotal or pancolitis compared with the adults [24]. Another study demonstrated that children <10 years of age had significantly less crypt branching, plasma cells in the lamina propria, cryptitis, crypt abscesses, and epithelial injury than adults. Endoscopic rectal sparing was also seen in another study in 23% of children with newly diagnosed, untreated UC, and this feature did not correlate with presenting symptoms. However, the presence of rectal sparing may indicate more aggressive disease that is less responsive to medical treatment [25]. These studies must be interpreted with caution as these patients likely have what has

become known as UC-like CD, and although clinically present with UC symptoms, there are endoscopic and histological features more characteristic of CD. In these cases, a more accurate evaluation of the small bowel with VCE may be warranted and perhaps serological immune responses will be helpful in differentiating between CD and UC. Studies have shown that pANCA is more commonly seen in patients with ulcerative colitis and ASCA, anti-CBir1, and anti-OmpC are more prevalent in CD patients [11]. There is, however, a subgroup of pANCA+/CBir1+ CD patients who appear to have a unique phenotype which manifests itself more so after an ileal-pouch anal anastomosis (IPAA) is performed [26].

Treatment

Modern approaches to IBD therapy call upon the need for disease-modifying targets with the goal of mucosal healing. It is hypothesized that mucosal healing could reduce disease-related complications and alter the natural history of disease. This would certainly be a welcome strategy in children given the longer duration of disease and the potential long-term consequences of early-onset aggressive disease presentations. Currently, there are few therapies approved for children with IBD; however, pediatric GI physicians have been using therapies off label for years and extrapolating data from adult studies which may not be applicable to a child. The treatment objectives for children remain similar to those for adults with IBD with the exception of focus on growth:

- Maximizing efficacy
- Maximize adherence
- Minimize toxicity
- Maximize quality of life
- Maintain physical growth
- Prevention of disease complications

The current treatment approach is based on disease severity. In other words, the traditional "step up" approach is applied in most cases. This approach also takes into account medication safety as the more milder/less toxic medications are often employed first letting patients declare themselves failures necessitating navigating up the pyramid to more aggressive anti-inflammatory agents. Pediatric gastroenterologists are limited in their ability to interpret whether this is the correct strategy given few studies have been done in children to support use of these medications, especially the mesalamine-based therapies. Given the potential growth and development implications of persistent inflammation and corticosteroid dependency, efforts are made to maximize both anti-inflammatory and steroid-sparing strategies. Aside from the potential growth effects, the esthetic changes associated with corticosteroid use can be devastating to a child. Sole nutritional therapy can be a very important strategy to maximize growth and development; however, compliance can be an obstacle to administration. A recent prospective, 10-week open-label trial in

children with active naive CD randomized children to orally polymeric formula alone or oral corticosteroids. In this small study, children with active and recently diagnosed CD, a short course of polymeric diet was more effective than corticosteroids in inducing healing of gut inflammatory lesions [27]. Further large-scaled studies are needed to further evaluate the short- and long-term benefits of this treatment strategy. In the USA, enteral nutrition is typically used more so as supplemental nutrition in the face of malnutrition and growth failure. There are some pediatric IBD centers that have an excellent program in place and have been successful in implementing sole nutritional therapy in children and avoiding steroids.

There continues to be discussion surrounding the notion of turning the therapeutic pyramid upside down, aka "top-down therapy." In other words, in patients who are candidates for corticosteroids, more potent biological therapies, such as antitumor necrosis factor-α (anti-TNFα) therapies, may be considered as alternatives early on in the course of disease [28]. However, the strategy of short-term corticosteroids with 6-MP as bridge therapy may be a safer and equally effective strategy in this patient population. Markowitz et al. [29] demonstrated that a significant proportion of children were off steroids and in remission 600 days after the combination therapy was initiated. If, however, the desired outcome of a steroid-free remission is not achieved in the expected time frame (4–6 months) of this combination, then at that time the introduction of a biological therapy should be considered. This early appropriate intervention strategy needs to be implemented in both pediatric- and adult-IBD patients associated with biologics. The hesitation to go directly to a biologic stems from the fact that the thiopurines work well in children and the serious safety concerns, more specifically infectious and malignancy complications. There are definitely safety concerns associated with thiopurines as well; however, TPMT screening and metabolite monitoring enable clinicians to identify at-risk patients and dose adjust so to minimize toxicity and dose escalate safely in patients with subtherapeutic levels and not responding to their current dose [30].

The REACH trial was the first of its kind in pediatrics to evaluate in a multicenter fashion the efficacy and safety of infliximab in 113 patients [31]. The study was not powered for efficacy, but the results do support its use in children with the response rate at 10th week close to 90% and a remission rate at 54th week of approximately 50%, which includes children off corticosteroids when receiving drug every 8th week as opposed to every 12th week. The safety may have been more favorable among patients receiving the every 12-week infusions; however, the efficacy benefit of every 8th week may outweigh its safety risks. The data lead to the approval of infliximab for children with luminal Crohn's disease. Clinical trials are underway to evaluate the efficacy and safety of infliximab in children with ulcerative colitis as well adalimumab for pediatric CD.

Weighing the risks and benefits of each therapy must be considered and should be communicated to the child and the family. New safety information has emerged which has already started to alter the approach to patients receiving infliximab. There have been 20 confirmed cases of hepato-splenic T cell lymphoma (HSTCL) reported in patients receiving combination thiopurines and anti-TNFα therapy [32]. Although rare, the majority of cases are fatal which has forced pediatricians to

rethink their approach to this patient population. This calls into question the concomitant immunomodulation for the purpose of immunogenicity and perhaps improvement in response rates and how it relates to safety. In the REACH trial, all children had to be on concomitant therapy to be eligible, so it is not known whether monotherapy would have been as effective. In the adult ACCENT-1 trial, only one third of patients were on concomitant thiopurine or methotrexate, and at the end of 1 year, the remission rate off corticosteroids was only 24% [33]. Another distinguishing factor noted between the two trials was the median duration of disease at the time of a patient's first infliximab exposure, which was much lower in REACH as compared to ACCENT 1. There has been significant interest in the advantage of early use (within 1–2 years from diagnosis) as compared to later use and its impact on efficacy of anti-TNFα. A significant proportion of children are being removed from thiopurines and continuing the infliximab and some clinicians are extrapolating data from the rheumatoid arthritis literature that suggests that low-dose methotrexate (7.5 mg po weekly) is associated with increased trough infliximab levels and decreased levels of antibodies to infliximab [34]. There is no data among pediatric patients and further research is needed to validate this strategy as well as to see the final results of the adult trials that are looking at infliximab and methotrexate in combination. Methotrexate in any form of administration has not been common place in pediatrics. There was always the notion that injections are traumatizing to children and that the oral form may be associated with treatment limiting nausea and the bioavailability was inferior to that when given subcutaneously or intramuscularly. A more recent report, however, showed that the bioavailability of methotrexate in patients with IBD is no different from that observed in other disease states [35].

Perhaps the key to deciding the best strategy for an individual patient will be in identifying the at-risk patient up front whose risk of untreated progressive disease outweighs the risk of the medications. A recent study reported that imunomodulators are used in approximately 60% of children with CD within 1 year of diagnosis and suggested that lower serum albumin levels and hematocrit, and elevated erythrocyte sedimentation rate at diagnosis may predict the need for immunomodulators earlier in the disease course [36]. Future research will help to stratify patients based on risk of disease progression, which will in turn help to individualize treatment strategies so that risk of disease progression outweighs risk of therapies.

Special Considerations

Bones and Growth

Puberty is the most dynamic phase of growth in childhood. Maintaining adequate nutrition, minimizing inflammation, and maximizing treatment off corticosteroids remains an integral part of managing the potential growth stunting effects of active IBD, most specifically small bowel CD. Growth failure has been reported in up to

40% of children with CD and <10% of UC. On occasion, growth and pubertal delay is the only presenting sign of IBD and can precede any GI symptoms [37]. The cause of growth failure is multifactorial and results from decreased intake contributing significantly to malnutrition as well as increased GI losses, malabsorption, psychosocial factors and medication effects which can certainly impact an individual's nutritional state. Ongoing inflammation with release of specific cytokines that suppress growth factors is also very important determinants of growth failure. Evidence suggests that IL-6 mediates growth failure in children with Crohn's disease [38]. Nutritional supplementation and need for "catch-up" growth should be an important part of the evaluation of a pediatric IBD patient. It is very uncommon, in the face of adequate caloric intake and control of inflammation, that patients are in need of growth hormone therapy. Administration of growth hormone was examined in a pilot study (7 patients) and did not demonstrate any effect on growth [39]. However, the combination of growth hormone with nutritional supplementation in IBD patients would likely yield positive results given the importance of adequate caloric intake in patients with ongoing inflammation.

Defective bone mass accrual is another complication of chronic inflammatory disease in children and growth failure is one of the major causative factors. There are, however, other variables, such as physical activity, altered body composition, and disordered calcium and vitamin D metabolism, which certainly play a role in maintaining bone mass. Like with growth failure, persistent inflammation in the face of IBD can also impact the maintenance of bone mass. The method for assessment of bone mass in children is very important and what is currently used in adults does not apply to the pediatric age group. Bone mineral density (BMD) *T*-scores are appropriate for individuals who have reached skeletal maturity, but they should not be used in pediatric DEXA reports [40]. Instead, a *Z*-score should be calculated by subtracting the measured BMD from the expected BMD for individuals of the same age and sex and dividing the result by the standard deviation. Additional adjustments may be needed in small or physically immature children (e.g., using height age or bone age instead of chronological age for *Z*-score calculation). It is important to note that a diagnosis of osteoporosis should not be made in children based on DEXA results alone. Experts in the field suggest that a *Z*-score of <−2.0 in children should be reported descriptively as "reduced bone mineral mass for age" [41]. Because of these limitations, total body bone mineral content may be clinically more useful than BMD in children, especially when studying patients over a longitudinal time frame. Quantitative computed tomography (QCT) is an alternative to measure BMD in both adults and children [42]. QCT offers the advantage of providing a true volumetric BMD, and it can distinguish the individual contributions of cortical and trabecular bone. QCT can be performed in conventional CT scanners, usually in the lumbar vertebrae. It involves a higher radiation dose than DEXA. CT devices are available that measure BMD in the peripheral skeleton, with minimal radiation exposure, but the clinical significance of these measurements in children and adults with IBD is not known. Other experts in the field have shown that the apparent prevalence of osteopenia in children with IBD differs according to the method of data

analysis used. Failure to account for bone age led to a label of moderate-or-severe osteopenia in 65% of cases. After adjustment for bone age, the proportion of children with osteopenia fell to 22%. Data suggest that children with IBD often have small bones for age because they have growth retardation. When DEXA data are interpreted with adjustment for bone size, most children are found to have adequate bone mass. Correct interpretation of DEXA is important for identifying children who may be at a real risk of osteoporosis [43].

Quality of Life and Psychosocial Functioning

In order to assess the psychosocial burden of IBD on children, the IMPACT questionnaire, a disease-specific measure of health-related quality of life (HRQOL), was developed and validated for use in children and adolescents with IBD ages 10–18 years inclusive [44, 45]. One study reported that the majority of patients perceived an improvement in HRQOL within 1 year of diagnosis and this improvement was in keeping with the overall improvement in disease severity [46]. Loonen et al. [47] asked whether it may prove helpful to ask significant others or caregivers besides the patients themselves when evaluating health and the perception of health of patients. This study reported that parents and children with IBD show high agreement when reporting observable aspects of the child's HRQOL. On the other hand, agreement was lower when it concerns more subjective aspects of HRQOL, such as social functioning and emotions. When comparing self-reported psychosocial functioning (behavioral/emotional functioning, social competence, self-esteem, stress coping strategies, and social support) of children with IBD to that of healthy children, it appears that most children with mild IBD report normal psychosocial functioning that is similar to that of healthy children [48]. Psychosocial functioning, among other factors, may certainly impact medication adherence. Adherence rates among children with chronic disease are typically reported to be approximately 50% with adherence being the lowest in adolescence and when maintenance medications are used even when the disease is in remission [49]. Parents are often responsible for ensuring their children take their medication, so when evaluating adherence, both the patient and parent must be considered. One study examined the reports of adherence to oral medications, parent–child concordance in reports of adherence, and factors associated with poor adherence in adolescents with IBD. Mean parent and child-reported adherence scores fell between the "most of the time" and "always" categories, although perfect adherence was low. Among IBD-specific medications, <50% of children and <40% of parents reported being always adherent to all medications and parent–child concordance was high. Family dysfunction and poor child-coping strategies were associated with worse adherence and there appeared to be a trend between more behavioral/emotional problems and lower adherence [50].

Transition of Care

The transition from pediatric to adult medical care of patients with IBD can be difficult for the child and caregivers. Clinicians must be sensitive to this transition and the barriers it may present. It has been recommended that the child be approached from the commonly accepted developmental stages, roughly defined chronology by ages 11–13, 14–16, 17–19, and 20–23 [51]. Communication is critical in order for the child and caregiver to anticipate the new roles each member will play in this transition. The process of transition should be gradual and if the process is delayed the transition may be less successful as the time to prepare and anticipate change has been limited. It is not unusual for the process to be more difficult on the family/primary caregivers than the child themselves. Family members need to relinquish responsibility and the weaning process should begin fairly early in adolescence so that when the time comes to meet with an adult gastroenterologist the patient and caregiver are prepared. In preparation for the transition from pediatric-oriented care to that of an internist, patients may want to put a notebook/file together whereby key documents can be brought to their visit to minimize duplication of history taking and perhaps procedures and tests. Key documents for transfer include medical summaries, procedure reports, surgical reports, medication history, recent laboratory results, and health insurance information.

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Chapter 11
Innovations in the Surgical Treatment of Inflammatory Bowel Disease

Roger Hurst

Keywords Surgery • Laparoscopic surgery • Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Strictureplasty • Heineke-Mikulicz strictureplasty • Michelassi strictureplasty • Finney strictureplasty • Continent ileostomy • Ileoanal anastomosis

Key Points

- Intestinal resections in Crohn's disease should remove the gross margins of disease with a 2-cm margin of normal bowel; extended resection of microscopic disease does not affect recurrence rate.
- Bowel-sparing strictureplasties are important advances in the surgical management of small bowel Crohn's disease, particularly in patients requiring resection of multiple segments or in preventing short bowel syndrome.
- A laparoscopic approach to certain surgeries may speed the recovery and lessen complications in IBD patients.
- The potential advantages of laparoscopic IBD surgery are not sufficient to warrant a strategy of earlier surgical intervention.
- Multiple factors determine the choice of surgery in patients with ulcerative colitis, including patient frailty, continence, and procedure-related expertise and complications.
- The presence of colon cancer or dysplasia in a patient with ulcerative colitis may impact the choice of surgical technique and increase the need for endoscopic surveillance of the ileoanal pouch.

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Introduction

Despite the advances in the medical treatment of inflammatory bowel disease surgery is still required for many patients with Crohn's disease and ulcerative colitis. The basic concepts of surgery are simple in that disease tissue is removed, obstruction relieved, fistulas are closed, and abscesses are drained. Most innovations in the surgical treatment of inflammatory bowel disease focus on measures to achieve these goals while minimizing complications and consequences to the patient. This chapter entails a concise review of the current status for the surgical treatment of Crohn's disease and ulcerative colitis.

Crohn's Disease

The most common procedures performed for intestinal Crohn's disease include resection, strictureplasty, intestinal bypass procedures, and drainage of abscesses. Of these procedures, drainage of abscesses are now often performed by interventional radiologists and open surgical drainage of abscesses is required only for those cases where segments of intestine or other vital structures obscure a clear path to the abscess. Intestinal bypass procedures are also rarely employed and are for the most part limited to the treatment of severe stricturing disease of the duodenum.

Intestinal Resection

Resection with primary anastomosis is the most common surgical strategy utilized for patients with Crohn's disease. Typically this entails removal of the ileum and proximal colon with an ileocecectomy for classic terminal ileal disease. Segmental resections of the small intestine or the colon can also be required, depending upon the pattern of disease. Over the last few decades, the basic techniques of resection and anastomosis have remained relatively unchanged. Anastomosis can be constructed with hand suture techniques or with stapling devices. Both approaches have equivalent short-term and long-term results. Several studies have been undertaken to determine the ideal configuration of the anastomosis (end to end, vs. end to side, vs. side-to-side, etc.). The results of these studies are conflicting with no one type having a clear advantage over the other.

Division of the thickened mesentery is often the most challenging technical aspect of small bowel resection for Crohn's disease. New tissue sealing instruments such as the Ligasure® or EnSeal® devices have provided greater ease for this task over the standard clamping and suture ligation of the mesenteric vessels. Both of these devices entail the principals of bipolar electrocautery in a manner that is capable of sealing blood vessels of substantial size.

Recurrence of disease is probably the most significant concern associated with resection for Crohn's disease. Recurrences most commonly occur in the intestinal

segment just proximal to the anastomosis. Variations in surgical techniques have been employed in hopes of reducing the risk of preanastomotic recurrence. These strategies include varying the extent of resection and altering the configuration of anastomosis. Early retrospective data have suggested that wider resections involving 10–30 cm of normal bowel proximal and distal to the area of gross disease can result in lowered recurrences of disease [1]. However, a well designed randomized control trial by Fazio et al., failed to show any difference in the recurrence rates when resection margins were 2 cm in length or 12 cm [2]. Additionally, the presence of microscopic disease at the resection margin did not appear to affect the rate of recurrence. Thus, the current practice is to resect the normal gross margins with a small, 2 cm margin of normal bowel. Frozen sections to assess the margins for microscopic disease are not necessary.

Strictureplasty

Most patients requiring surgery for the treatment of small bowel Crohn's disease have relatively short segment involvement and thus can be managed with a limited resection. Other patients, however, may have extensive disease that would require lengthy resections and loss of significant portions of their small intestine in order to remove the disease. This is particularly true for patients with extensive Crohn's disease involving the jejunum and ileum. In order to avoid the severe consequences of lengthy small bowel resection, bowel preserving techniques such as intestinal strictureplasty have been advanced.

Although many different surgical techniques for intestinal strictureplasty have been described three specific approaches; the Heineke-Mikulicz, the Finney, and the Michelassi strictureplasty have the broadest application.

With the Heineke-Mikulicz strictureplasty a longitudinal incision is made over the area of the stricture. This longitudinal enterotomy is then closed in a transverse fashion to provide extra length to the circumference at the point of stricture. With a Finney strictureplasty, the loop of involved intestine is folded onto itself and an antiperistaltic side-to-side anastomosis is created. The Michelassi strictureplasty is performed by dividing the strictured segment of intestine and then drawing the two ends onto themselves and creating a long isoperistaltic side-to-side anastomosis [3]. The Heineke-Mikulicz strictureplasty is best performed for short strictures less than 5 cm in length. The Finney strictureplasty can be applied to strictures between 5 and 12 cm in length. The Michelassi strictureplasty has the advantage in that it can be used for much longer strictures or for long segment disease that contains multiple strictures grouped closely together. This procedure can be technically demanding. It is not unusual to require the placement of over 300–400 sutures in order to construct this type of strictureplasty. By its nature this procedure has been limited to specialized centers. In spite of the special expertise required, the Michelassi strictureplasty provides significant benefit to the appropriately selected patients, as the safety record for this procedure is very good and the long-term results are excellent [4].

Indications for Strictureplasty

Stricturoplasties are best performed as in those cases where strictureplasty would obviate the need for lengthy resections [5]. This, for example, would include patients with diffuse small bowel disease with symptomatic strictures, especially single or multiple short fibrotic strictures. This would also include patients who have undergone multiple prior resections who now have recurrent stricturing disease and therefore require aggressive measures to preserve as much intestinal length as possible. The appropriate use of strictureplasties is limited to cases involving uncomplicated stricturing disease. Specifically strictureplasty is not appropriate for segments of intestine that contain fistulas abscesses or deep sinuses. Additionally, if the bowel wall is extremely thickened, rigid, and unyielding, standards strictureplasty techniques are not feasible. Strictureplasty is also contraindicated in the presence of peritoneal sepsis and peritonitis. With all these considerations approximately 15% of patients undergoing surgical treatment for small bowel Crohn's disease are appropriate candidates for one or more of the strictureplasty techniques.

Potential Complications

Unlike resections where diseased tissue is removed to grossly normal margins and anastomotic suture are placed in healthy tissues, sutre lines of stricturoplasties are typically placed within scarred and diseased tissue. This has led to concerns for their risk of dehiscence of these suture lines. Fortunately, with experience, perioperative morbidity with strictureplasty has proven to be low [6]. The most common complication directly attributed to stricturoplasties is intraluminal suture line hemorrhage at the site of the strictureplasty and suture line dehiscence. Some degree of suture line hemorrhage occurs in up to 9% of cases with half of these resulting in the need for transfusions in excess of three units [7]. Bleeding severe enough to require reoperation is however very uncommon and occurs in less than 1% of the cases. Poor healing with suture line leakage is a more serious, but less frequent complication and occurs in 1–2% of strictureplasty cases. When a suture line dehiscence occurs at a strictureplasty, open laparotomy with resection of the strictureplasty and establishment of a temporary ileostomy is often required.

Because the diseased tissue remains after strictureplasty, the possibility of progression of this disease has been a concern. While there are no controlled studies comparing intestinal resection to strictureplasty, follow-up studies indicate that recurrence of disease severe enough to require reoperation after strictureplasty is similar to that seen with resection and primary anastomosis. Reported recurrence rates from large series of patients undergoing strictureplasty are similar to reported recurrence rates for all patients undergoing surgical treatment of small bowel Crohn's disease and few now question the opinion that strictureplasty provides effective and long-term palliation of Crohn's disease symptoms [6, 8–10].

Controversies and Long-term Results

Since with strictureplasty disease segments are left behind, there has been concern that this could increase at risk for the development of adenocarcinoma. While epidemiologic studies have shown an increased risk for small bowel adenocarcinoma in Crohn's disease patients, it is not yet known if strictureplasties have any effect on this risk. It is at least possible that the continued presence of active inflammation may increase the risk for malignancy. On the other hand repeated observations have indicated that the activity of disease is actually lessened by the strictureplasty procedure. That is to say, that the inflammatory process itself is altered by the mechanical reconfiguration of the strictureplasty. Upon reoperation of patients who have had a previous strictureplasty, the recurrence is typically located away from the site of the previous strictureplasty and the strictureplasty site itself often demonstrates little or no evidence of ongoing information by either inspection or palpation [8, 9]. Additionally, Poggoli reported on a small series of patients undergoing an antiperistaltic side-to-side anastomosis between diseased terminal ileum and the ascending colon [11]. Colonoscopy performed at 6 months postoperatively demonstrated surprising improvement in the signs of grossly apparent inflammation of the terminal ileum. Whether stricturoplasties actually alter the course of the inflammatory process and whether such an effect would alter the risk of cancer is not entirely unclear. To date, there have been three reported cases of an adenocarcinoma developing at the site of a previous small bowel strictureplasty and the long-term risk of malignancy remains an open issue [12, 13].

Despite some remaining controversy there is little doubt that for complex stricturing disease these techniques have been demonstrated to be safe and effective. As such intestinal stricutureplasty represents a significant advance in the surgical treatment of Crohn's disease affecting multiple segments or for patients at risk for the short bowel syndrome.

Laparoscopic Surgery for Crohn's Disease

Laparoscopic surgery for Crohn's disease is an area of exciting innovation. The objective of laparoscopic surgery is to minimize the impact of resection by shortening recovery and minimizing the scarring. The overall strategies of laparoscopic surgery are the same as open procedures in that, segments of affected intestine are removed and an anastomosis is performed. Hence, the indications for surgery and the surgical strategies for laparoscopic surgery are identical to the open approach. While the advantages of shortened length of stay, less narcotic use, faster recovery, and better cosmetic results for laparoscopic bowel resection are becoming more apparent, these advantages are not so dramatic that the indications for surgical referral should differ. Specifically the advantages of laparoscopic surgery are not sufficient to warrant a strategy of earlier surgical intervention. Contra-indications

to laparoscopic surgery include severe COPD or hemodynamic instability in patients who would not tolerate the carbon dioxide insufflation due to risk of hypotension or hypercarbia. Reasons for converting to an open procedure are often related to difficultly identifying the anatomy and most often occur in patients with adhesions, obesity, complex fistulizing disease, or patients with altered anatomy due to previous surgeries.

The most commonly performed laparoscopic procedure for Crohn's disease is the laparoscopic ileocolectomy. With this approach the ileum cecum and right colon are mobilized laparoscopically to allow for delivery of the intestine through a small laparotomy incision. Once delivered through this incision the bowel is divided, the mesentery is transected, and the anastomosis is performed. Randomized controlled studies of patients undergoing ileocolonic resection for Crohn's disease have shown similar times to return of bowel function and use of pain medication. Length of stay is shortened with the laparoscopic approach and minor complications are fewer with laparoscopic ileocolectomy [14, 15].

Ulcerative Colitis

Standard surgical treatment of ulcerative colitis requires complete removal of the colon and rectum. This can be established by a total proctocolectomy in which the colon, rectum, and anus are removed and a permanent ileostomy is established. It can also be accomplished with an ileoanal procedure where the colon and rectum are removed, the anal sphincters are preserved, and an ileal reservoir is anastomosed to the anal canal.

Total Proctocolectomy

Total proctocolectomy involves complete removal of the colon, rectum, and anal sphincters with establishment of a permanent ileostomy. This procedure is typically performed through an abdominal incision for the colectomy portion of the procedure, and a perineal incision is made to remove the rectum. This procedure has the advantage in that it can be completed in a single operation. Also, patients undergoing this procedure do not have to deal with the risk of incontinence or pouchitis that can occur after the ileoanal procedure. They, of course, do have to live with the burden of a permanent ileostomy.

While the total proctocolectomy is considered to be obsolete for most patients with ulcerative colitis, the procedure is still utilized in those cases where the ileoanal procedure would not be appropriate. This would include elderly frail patients and patients who have anal incontinence.

Total proctocolectomy has seen some innovation particularly in the area of laparoscopic techniques. Total proctocolectomy can be performed laparopscopically

utilizing only small abdominal port site incisions and a perineal incision. Almost all other laparoscopic bowel resection procedures require an abdominal incision, albeit small, for removal of the specimen and creation of the anastomosis. This is not the case for laparoscopic total proctocolectomy where the colon and rectum can be extracted through the perineal incision, and no abdominal incision is needed. This is a very new approach and current experience with laparoscopic total proctocolectomy is very limited. Further data is required to confirm the value of this innovative procedure [16, 17].

Continent Ileostomy

One of the refinements of the total proctocolectomy procedure has been the creation of the continent ileostomy. With this approach an intraabdominal ileal reservoir is created with an internal nipple valve. Intestinal contents accumulate within the reservoir which is then emptied at the patient's convenience by placing an evacuation tube into a surface stoma and through the valve. This procedure eliminates the need for an appliance and allows for a small flat stoma rather than a larger protruding Brooke ileostomy. The continent ileostomy procedures, however, have been burdened with significant limitations. Firstly, an overwhelming majority of patient's with ulcerative colitis are candidates for the preferred ileoanal procedure and secondly, those patients who are not good candidates for the ileoanal procedure are often poor candidates for the continent ileostomy. Additionally, the continent ileostomy procedure has been plagued with high complication rates, prolonged recovery times, and frequent need for revisional surgery. A well functioning continent ileostomy, however, does provide substantial advantage over a standard end ileostomy and if the technical difficuties could be overcome, then this procedure would likely have a resurgence. Several investigators are working to this end, and significant improvements in the continent ileostomy procedure may be forthcoming.

Ileoanal Anastomosis

The ileal pouch procedure has been the mainstay of surgical treatment of ulcerative colitis for 30 years. Many thousands of patients have benefited from this procedure and it has withstood the test of time. Over the last three decades the procedure has undergone multiple refinements. Initially the procedure was performed as a true pull-through operation where the rectum was transacted at the level of the midrectum, the retained distal rectum was then denuded of its mucosa by an extensive mucusectomy, and the ileal pouch was delivered through the denuded rectal stump and anastomosed to the anal canal. This approach was thought to be necessary to allow for appropriate defecatory function. The old pull-through procedure was

plagued by infections developing between the ileal pouch and the rectal wall; so-called cuff abscess. With the current ileoanal procedure the rectum is transected at the top of the anal canal and the ileal pouch is anastomosed to the anus without being pulled through any remnant of the rectum.

Additional modifications of the procedure include the stapled ileoanal anastomosis. With the modification the anastomosis is created with a stapling device at the top of the anal canal rather than at the dentate line with the older hand suture technique. The stapled technique allows for better overall function and in most cases is preferred over the hand sutured technique.

A concern regarding stapled technique is that the procedure leaves behind the anal transition zone and some amount of rectal mucosa that may be at risk for ongoing inflammation. Normally this ongoing information does not create symptoms nor does it significantly alter pouch function. There is concern, however, that this small amount of inflamed rectal mucosa may be at risk for developing a cancer in the long-term. Ulcerative colitis patients are known to be at increased risk for the development of cancer of the colon and rectum. The risk of colorectal cancer in ulcerative colitis patients increases linearly over time beginning at 10 years after diagnosis at a rate of between 1 and 2% per year [18]. Surgical removal of all but 1–3 cm of columnar epithelium is likely to greatly diminish this risk, but to what degree is not clear. Fortunately, however, the available data has been encouraging. Remzi et al. followed 289 patients with double-stapled ileoanal procedures for a mean of 130 months (range 120–157 months) [19]. Routine surveillance biopsies of the retained columnar epithelium demonstrated dysplasia in only eight patients (4.5% incidence of dysplasia at 10 years with a 95% confidence interval of 2–8.8%). The risk for dysplasia in the anal transition zone was associated with a history of cancer or dysplasia in the proctocolectomy specimen removed prior to the ileoanal procedure. Two of the patients with dysplasia were treated with complete mucosectomy with pouch advancement. The other six patients with dysplasia were followed with repeated examination and biopsy, and in each case subsequent sampling failed to notice a persistence of the dysplasia. None of the patients within the study developed invasive cancer. Other studies have also failed to demonstrate the risk of developing dysplasia as a significant problem, at least within the initial years after ileal pouch anal anastomosis [20–25].

To date, there are only four reported cases of adenocarcinoma developing from the area of the anal transition zone or retained rectal mucosa after double-stapled ileal pouch anal anastomosis in ulcerative colitis patients [26–29]. In these four cases, cancer was diagnosed at 16, 24, 60, and 84 months after ileal pouch anal anastomosis. Three of the four cases had either cancer (two patients) or high-grade dysplasia (one patient) in their resected colon and rectum. In the fourth case, the patient had no prior history of dysplasia or cancer until 7 years after a stapled ileoanal anastomosis when an adenocarcinoma of the anal transition zone was diagnosed.

Most of the documented cases of dysplasia or cancer in the retained columnar epithelium after stapled ileoanal anastomosis have occurred in ulcerative colitis patients who had cancer or dysplasia in the original proctocolectomy specimen.

For this reason, most surgeons recommend a complete mucusectomy with hand sutured ileoanal anastomosis instead of a stapled anastomosis for ulcerative colitis patients known to have high-grade dysplasia or invasive colorectal cancer. This recommendation, however, is not universally accepted as a required standard.

Recommendations regarding the need and frequency of surveillance biopsy of the anal transition zone vary. Most surgeons, however, recommend anoscopy with biopsy every 3–5 years [30].

Laparoscopic Ileal Pouch Anal Anastomosis

Laparoscopic restorative proctocolectomy with ileopouch anal anastomosis is an emerging innovation in the surgical treatment of ulcerative colitis. With this approach the abdominal colectomy and the rectal dissection are performed with laparoscopic instruments and the suprapubic Pfannenstiel incision is made to extract the colon and rectum. Through this incision the pouch is also constructed and the anastomosis is fashioned. Modifications include the use of a "hand-assisted" approach where the surgeon's hand is placed through the Pfannenstiel incision to assist with the colectomy dissection. It is a somewhat disappointing observation that the difference in recovery times for laparoscopic vs. open bowel resections are not as dramatic as with other laparoscopic procedures such as cholecystectomy; and such is the case with laparoscopic ileoanal procedure. Time to recovery of gastrointestinal function is less with a laparoscopic ileoanal procedure but lengths of hospital stays are only slightly diminished [31]. Operative times for the laparoscopic approach are longer and upfront costs are higher. On the other hand, complication rates, long-term functional results, and quality of life with laparoscopic surgery are at least equivalent and may be superior to the open procedure [32]. Some of the clear benefits of laparoscopic ileoanal procedure include better cosmesis and a lower risk for incisional hernias [33]. Additionally because laparoscopic surgery in general is known to produce fewer intraabdominal adhesions, it is believed that the laparoscopic approach may lessen the long-term risk for adhesive postoperative bowel obstructions, although the necessary long-term follow-up data to support this theory is yet to be reported. Currently, there is also no available data on whether the laparoscopic approach would have an effect on the risk for infertility in women undergoing the ileoanal procedure.

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Chapter 12
Clinical Utility of Serological Markers and Thiopurine Drug Monitoring in IBD: An Evidence-Based Review

Raja Tamaz and Ernest G. Seidman

Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Indeterminate colitis • Serological markers • Anti-*Saccharomyces cereviciae* antibodies • Outer membrane porin of *E. coli* • *Pseudomonas fluorescens*-related sequence I2 antigen • Antibodies to bacterial flagellin • Antineutrophil cytoplasmic antibodies • Thiopurine *S* methyltransferase

Serological Markers in IBD: Facts and Perspective

Key Points

Potential roles of serology testing in IBD

- Differentiate ulcerative colitis (UC) from Crohn's disease (CD).
  - Help classify indeterminate colitis or IBD of undetermined type.
  - Assist in diagnosis prior to deciding surgical approach (colectomy ± pouch).
- Adjunctive test for the initial diagnosis of IBD (when biopsy evidence is lacking).
- Identify patients at risk for aggressive disease (prognosis).
- Predict risk of pouchitis after restorative proctocolectomy.
- Predict response to therapy (potential role).

Serological markers have long been used in clinical practice to assist in the identification of specific immune-mediated disorders, as well as biomarkers of disease severity. Numerous studies have evaluated the clinical utility of various

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serological tests against microbial and self-antigens in the context of inflammatory bowel disease (IBD). Nevertheless, their clinical value in diagnosing, stratifying, and predicting specific IBD phenotypes remains controversial [1]. The aim of this review is to provide an overview of recent advances in serological markers in IBD, to evaluate their potential roles, performance, and pitfalls in managing patients.

Serology as Adjunctive Tests for the Diagnosis of Suspected IBD

The discovery of the first serological markers for IBD two decades ago was the fortuitous result of research aimed at searching for autoantibodies or antibodies to various dietary and bacterial antigens that might be implicated in the pathogenesis of ulcerative colitis (UC) or Crohn's disease [2, 3]. The first, and arguably still the most important, among these consists of IgA or IgG antibodies directed against a sequence of mannose residues expressed in cell wall mannan of *Saccharomyces cereviciae* (ASCA), known as bakers' and brewers' yeast [4]. Crohn's disease-associated *NOD2* mutations have consistently correlated with an increased seroreactivity to microbial antigens, including ASCA, outer membrane porin of *E. coli* (OmpC), the *Pseudomonas fluorescens*-related sequence I2 antigen, and the flagellin antigen CBir1 [5]. *C. albicans* has also been described as a potential immunogen for ASCA [6]. Despite the utility of antibodies to microbial antigens as biomarkers with high specificity for Crohn's disease [1, 4, 7], their potential role in the pathogenesis of IBD, if any, remains unclear. Antineutrophil cytoplasmic antibodies (ANCA) were first described in primary vasculitis and Wegener's granulomatosis. Subsequently, a distinct perinuclear pattern in ANCA was found to be associated with UC, as opposed to the cytoplasmic granular (cANCA) or speckled (sANCA) pattern seen in vasculitis and other diseases [3].

The clinical presentation of IBD is customarily straightforward, leading to a rapid and definitive diagnosis in most cases. However, patients may present with nonspecific symptoms, delaying diagnosis. Vague symptoms can be difficult to distinguish from those associated with functional gastrointestinal disorders (IBS), a highly prevalent problem in the same population. Although the clinical presentation of celiac disease can also mimic IBS, screening with antitissue transglutaminase antibodies is a highly effective, inexpensive strategy. In contrast, in order to exclude IBD in this situation, more expensive and invasive investigations such as ileo-colonoscopy, radiological imaging, or even capsule endoscopy of the small bowel have traditionally been needed. The availability of accurate, noninvasive serological tests would be useful in such cases.

In the pediatric age group, nonspecific presentations of Crohn's disease are not uncommon. These include intermittent vague abdominal pain, fever of unknown origin, arthritis, growth failure, and pubertal delay. Given that endoscopic procedures are considered even more invasive in young patients, efforts have particularly been focused on the search for accurate markers that would help us distinguish

between IBD and IBS in this age group. We conducted the first prospective study that analyzed the clinical utility of serologic testing in a cohort of pediatric patients referred to eliminate IBD in a clinical setting highly suggestive of IBS [8]. Patients were eligible if they presented with recurrent abdominal pain and/or diarrhea in at least 3 months duration. Exclusion criteria included overt symptoms or signs of "alarm" highly suggestive of IBD, such as bloody diarrhea, fever, arthralgias or arthritis, an abdominal mass, perianal lesions, clubbing, etc. In this study, serological testing using enzyme-linked immunosorbent assays (ELISA) for pANCA, ASCA, and anti-OmpC was found to be useful in screening for IBD in children and adolescents referred for symptoms suggestive of a functional bowel disorder. The positive predictive value (PPV) of serological testing was 90%, although the negative predictive value (NPV) was 80% [8]. In a subsequent economic impact analysis, this use of serology to evaluate a pediatric patient suspected of having IBD in the absence of "alarm" symptoms was found to be a cost-effective strategy [9].

The presence of antibodies to bacterial flagellin (anti-CBir1) has been shown to identify a subset of patients with Crohn's disease not identified by other serum markers [10]. Almost half of ASCA(−) patients were reported to have anti-CBir1 antibodies. A recent study [11] involving over 700 recently diagnosed children with CD showed that anti-CBir1 antibodies were more often detected than ASCA in very young children. The addition of anti-CBir1 test reduced the proportion of seronegative Crohn's patients below age 8 from 70% to less than 30%.

Data on the accuracy of these serological tests from prospective studies in adult patients are generally lacking. In a small study, ASCA and pANCA had an accuracy of 78% for detecting Crohn's disease and 75% for detecting UC, respectively [12]. A meta-analysis of the diagnostic precision of ASCA and pANCA was analyzed using data from 60 studies (44 prospective nonrandomized, 16 retrospective, 12 pediatric) in over 11,600 subjects with IBD and controls [13]. When used to distinguish between IBD and non-IBD, positive ASCA results (either IgG or IgA) had a sensitivity and specificity of 40% and 93%, respectively. Positive pANCA alone was also found to be weakly sensitive, but highly specific for IBD (32% and 97% respectively). Sensitivity increased to 63% when both serological markers were combined and either test was positive. Given the limited sensitivity of serological assays, the authors concluded that negative ASCA and pANCA tests do not rule out IBD [13]. It should be recognized that such a meta-analysis introduces a negative bias to the validity of the serology tests as there is substantial heterogeneity in cutoff levels and the variability in accuracy of ELISA kits used in different laboratories [14]. Another limitation of interpreting serological results from various studies relates to the uneven prevalence of the disease in the populations tested. When the prevalence of IBD is low, a greater number of positive test results will turn out to be false, leading to a lower PPV. Conversely, when the prevalence of IBD is high, the PPV of the test will also be high. An analysis of four studies where the prevalence of IBD ranged from 42% to 68% yielded a PPV of 90%–96% for ASCA and pANCA testing [15]. At the same time, when the pretest probability of IBD is in this moderate range, the NPV ranges from 50% to 80%, in effect meaning that up to half of subjects with a negative test still have IBD [15].

It is thus important for clinicians to consider the pretest probability of IBD on the basis of the history, physical exam, and standard laboratory tests in order to interpret serological test results. It is furthermore important to emphasize that a positive serological test is considered supportive, but insufficient alone for a diagnosis of IBD. Serological results must be confirmed by a complete diagnostic investigation, including endoscopy, histology, and/or radiological imaging.

More recently, a novel serology panel has been examined, comprised of seven components, including IgA and IgG ASCA (1, 2), OmpC (3), pANCA (3 components, 4–6) and anti_cBIR (by ELISA and two independent immunofluoresence assays), as well as anti-CBir1 [16]. An alternative method to determine test results has been proposed that disregards traditional cutoff values in favor of analyzing these 7 titers using complex pattern recognition software and an algorithm technology. In order to validate the performance of this novel test, we carried out a prospective study in 123 pediatric patients referred for evaluation of suspected IBD [17]. Serum was obtained prior to standard diagnostic evaluation using the usual endoscopic and imaging studies. The overall prevalence of IBD in this population was found to be 53%. The seven test IBD serology panel had a higher sensitivity (86%) compared to the previous technology based on cutoff values, described above. The specificity was 76% for IBD, with PPV and NPV of 80% and 83%, respectively. Further studies are needed to validate the clinical utility of this panel and methodology.

A very recent study analyzed the utility of various anticarbohydrate antibody tests in IBD [18]. The diagnostic accuracy of antichitobioside carbohydrate antibody testing (ACCA), antilaminaribioside carbohydrate antibodies (ALCA), and antimannobioside carbohydrate antibodies (AMCA) was compared with ASCA in a cohort of 272 adult subjects (43% Crohn's disease, 31% UC, 26% controls). ASCA had the highest sensitivity (67%) for Crohn's disease, followed by AMCA (31%), ACCA (27%), and ALCA (25%). Positivity of at least one of the four assays increased the overall sensitivity of antibody testing in Crohn's disease to 85.5%. ASCA levels were significantly higher in CD patients who were younger at diagnosis and had longer disease duration before blood sampling ($p<0.001$) [18].

Distinguishing IBD Subtypes: Ulcerative Colitis and Crohn's Disease

Despite adequate clinical, radiologic, endoscopic, and histopathologic assessment, differentiation between CD and UC can be problematic. Approximately 10% of adult cases are classified as "indeterminate colitis" or IBD undefined (IBDU) [19, 20]. This is an even more common problem in pediatric patients [21]. Accurate serologic markers would be of great value in such patients, especially when faced with potential surgical decisions.

Although studies have found positive pANCA to be more often associated with UC [13], there is a well-defined overlap in pANCA+ UC-like Crohn's colitis [22]. Furthermore, although ASCA has a high specificity for CD, it is generally associated with small bowel involvement. Thus, these markers do not yield a high enough PPV

to be clinically useful in discriminating between these two disorders. Similarly, although recently described anticarbohydrate markers increased the sensitivity for Crohn's disease [18, 23], none of the anticarbohydrate assays was predictive of colonic Crohn's disease in patients in whom the distinction between Crohn's and UC is not obvious [18].

Few studies have focused on the validity of serologic tests in patients with "indeterminate colitis" or IBDU. In a pediatric series [8], one of nine cases that initially tested pANCA+ was later reclassified as UC, while the only child with positive ASCA titers was later confirmed to have CD. In a large Belgian cohort study ($n=582$) assessing the diagnostic value of serologic markers in IBD, 28 were classified as IBDU [24]. After 17-month follow-up, a definitive diagnosis was achieved in 7/28. All three UC patients were pANCA+. However, one of the Crohn's disease patients with UC-like features also tested positive for pANCA.

An important prospective multicenter study by Joossens et al. [25] specifically evaluated the diagnostic accuracy of ASCA and pANCA in 97 IBDU patients from three European centers. Testing for pANCA and ASCA was carried out and patients were followed prospectively for up to 6 years. A definitive diagnosis was reached in 32% of the cases. Of these, 80% of the ASCA+/pANCA− patients were ultimately diagnosed with Crohn's disease, and 64% of the ASCA−/pANCA+ patients were diagnosed with UC. However, nearly half of the cohort remained seronegative for both ASCA and pANCA, and in most, the diagnosis of IBDU could not be further defined.

Other potential candidate markers include IgA anti-OmpC, directed against outer membrane porin C of *E. coli,* and anti-I2, directed against *P. fluorescens*, each found in approximately 50% of CD patients [26]. Joosens et al. assessed the value of these markers in the cohort of IBDU described above [27]. The prevalence of anti-I2 in the IBDU cohort, healthy controls, and inflammatory controls was 41.9% (39/93), 17.2% (16/93), and 31.3% (20/64), respectively. Consequently, the respective sensitivity, specificity, PPV, and NPV of anti-I2 in the IBDU cohort were 41.9, 76.4, 48.1, and 71.6%. The prevalence of anti-OmpC in the IBDU cohort, healthy controls, and inflammatory controls was 17.2% (16/93), 2.2% (2/93), and 25% (16/64), respectively. Respective sensitivity, specificity, PPV, and NPV of anti-OmpC in patients with IBDU were 17.2%, 88.5%, 47.1%, and 64.4% [27]. The low prevalence of anti-I2 and anti-OmpC in this study cohort was not unexpected, as both markers are associated with ileal Crohn's disease. Moreover, a large proportion of inflammatory controls had positive titers of anti-OmpC and anti-I2 antibodies. The authors concluded that the predictive capacity of serological tests in IBDU only increased marginally and specificity dropped significantly with the addition of anti-OmpC and anti-I2 tests.

In summary, the most specific serologic test to distinguish Crohn's disease from UC is the combination of ASCA and pANCA. The Crohn's disease-associated serologic pattern is ASCA+/pANCA−, whereas the UC-associated pattern is pANCA+/ASCA−. Reviewing three large retrospective studies, the specificity of these markers to distinguish CD from UC was 92%–98% [28]. However, the sensitivities were only 44%–57%. Therefore, half of patients cannot be classified by this strategy, which significantly limits its clinical utility. Clearly, other markers are needed to help distinguish such cases.

A test that has shown more promise in this regard is based on the flagellin CBir1 antigen, initially identified as playing a role in the aberrant immune response in a strain of mice which spontaneously develops human IBD-like colitis. About half of patients with Crohn's disease were reported to have anti-CBir1 antibodies [29]. The discriminative ability of anti-CBir1 was examined in a subset 50 IBD patients, all of whom were pANCA positive. The CBir1 test was positive in only 1 of 25 cases of UC, compared to 44% of those with Crohn's disease [29]. These results suggest that CBir1 testing may add to an accurate prediction of Crohn's disease in UC-like, pANCA+ Crohn's disease. However, the data were obtained in retrospective studies where the clinical diagnosis was the gold standard. No prospective data have been reported to validate this serological strategy. This would be clinically useful to determine the appropriateness of restorative proctocolectomy in patients with a clinical diagnosis of UC.

A study employing a nested, case-control design to predict a change in diagnosis from UC to Crohn's disease was recently reported [30]. At initial colonoscopy, cases were more likely to have extensive colonic involvement than UC controls ($p<0.008$). Multivariate regression identified nonbloody diarrhea at initial presentation ($p<0.01$) and weight loss >10% at presentation ($p<0.007$) as independent predictors of diagnostic change. Serologic markers (ASCA, I2, OmpC, CBir1, and pANCA) did not add to the contribution of these two clinical factors in predicting a change in diagnosis from UC to Crohn's disease. Diagnostic change was observed in six of six (100%) patients with both predictors, compared with 8 of 50 (16%) with neither of these factors ($p<0.0001$) [30].

One small, retrospective study evaluating serologic markers and the development of perianal fistulas following IPAA in patients with ulcerative or indeterminate colitis revealed that patients who were pANCA−/ASCA+ were at increased risk for the development of fistulas postoperatively compared to patients who were pANCA+/ASCA− (44 vs. 0%) [31]. Another intriguing study evaluated factors which might predict a change in diagnosis of UC or IBDU to Crohn's disease in 238 consecutive patients after a restorative proctocolectomy with a pouch [32]. Crohn's disease was defined by small bowel inflammation proximal to the ileal pouch or a perianal fistula identified at least 3 months after ileostomy closure. Sixteen patients (7%) were diagnosed with Crohn's disease after a median of 19 (range, 1–41 months). Significant factors for postoperative Crohn's disease after ileal pouch-anal anastomosis included a family history of Crohn's (hazard ratio, 8.4; 95% confidence interval, 2.96–24.1; $p<0.0001$) and IgA ASCA seropositivity (hazard ratio, 3.14; 95% confidence interval, 1.1–9.81; $p=0.04$). Crohn's disease developed in only 8 of 198 patients (4%) without these predictors vs. 8 of 40 patients (20%) in those with at least one of these factors ($p=0.002$). The cumulative risk of Crohn's disease among patients with two risk factors (67%) was higher than in patients with either risk factor (18%) or neither risk factor (4%, $p<0.001$). The authors thus concluded that patients with ulcerative or indeterminate colitis with a family history of Crohn's disease or preoperative ASCA seropositivity are more likely to be diagnosed with Crohn's disease after ileal pouch-anal anastomosis [32]. As has been oft

said, nothing brings out Crohn's in a patient like a restorative proctocolectomy with an IPAA.

Serological Markers to Predict Natural History and Response to Therapy

Although the majority (74%) of patients with Crohn's disease present with uncomplicated mucosal disease at diagnosis, that number falls to 52% and 31% after 5 and 10 years, respectively [33]. The disease behavior changes in the other cases towards more aggressive phenotypes, such as fibrostenosing or fistulizing Crohn's disease [20]. There is thus considerable clinical interest in biomarkers which could accurately predict those patients who will suffer unfavorable outcomes that are associated with increased morbidity, hospitalizations, surgery, and higher healthcare costs. An increasing body of evidence has established a correlation between serologic markers and disease phenotype in Crohn's disease. ASCA has been associated with younger age at onset, rapid disease progression, ileal or ileocolonic involvement, fibrostenosing or penetrating/fistulizing disease, and higher rate of early surgery [8, 18, 34–39]. Similar findings were also obtained with the more recent IBD-associated antibodies, such as OmpC [40, 41] and anti-CBir1 [29, 41], and anticarbohydrate antibodies [18, 42]. Based on the accumulating evidence, we believe that the results of serological testing can be clinically useful in predicting which patients with benign-appearing ileitis or ileocolitis at diagnosis will have an unfavorable disease course and therefore should be considered as candidates for more aggressive treatment early on (Table 12.1).

Table 12.1 Association between antibody responses, *NOD2* Genotype, and IBD outcomes

Biomarker[#]	Small bowel involvement	Complicated CD phenotype*	Small bowel surgery	UC-like CD	Pouchitis
NOD2	↑	↑		↓	
ASCA	↑	↑	↑	↓	
Anti-CBir 1	↑	↑		↓	↑
Anti-l2		↑	↑		
Anti-OmpC		↑			
pANCA	↓	↓	↓	↑	↑

[#]NOD2- Mutation of NOD2/CARD15 gene on chromosome 16; ASCA- IgA or IgG anti Saccharomyces cerevisiae antibodies; Anti-Cbir1-anti-flagellin antibodies; Anti-l2- Pseudomonas fluorescens; Anti-OmpC- anti-E. coli; pANCA- perinuclear anti-neutrophil antibodies.
*Complicated CD phenotype includes fibrostenosing or internal-penetrating disease.
↑ Significant positive association; ↓ Significant negative association

Another area where serological biomarkers can be predictive of outcomes relates to the risk of pouchitis after restorative proctocolectomy. Higher titers of pANCA [43–45], and more recently, the presence of anti-CBir flagellin [46] were associated with pouchitis in UC and IBDU (Table 12.1). Chronic pouchitis was seen in 29% of cases with high serum pANCA levels (>100 EU/mL) vs. 11% of those with low-level pANCA titers [46].

Response to therapy varies widely among IBD patients and it would be of enormous clinical benefit if the likelihood of response might also be determined by the presence or absence of IBD markers. Patients with ANCA+ left-sided ulcerative colitis were shown to be more refractory to medical treatment, than those ANCA– (90% vs. 62%) [47]. However, these findings have not been confirmed in prospective trials using the more specific pANCA assay. In a large Belgian cohort of 279 patients with Crohn's disease, Esters et al. [48] identified a trend towards poor response to infliximab in a small subgroup of patients who tested pANCA+/ASCA–. Their response rate of 50% was much lower than those who were pANCA–/ASCA+ or pANCA–/ASCA– (~80%, $p = 0.067$).

Other Antibodies and Future Directions

Efforts are ongoing in the search of novel biomarkers that may serve as valuable complementary tools to those existing in differentiating Crohn's disease and UC from each other and with other non-IBD functional bowel disorders. Newer serological biomarkers include five new antiglycan antibodies such as antichitobioside IgA (ACCA), antilaminaribioside IgG (ALCA), and antimanobioside IgG (AMCA) [18, 23]. Other new serum/plasma IBD biomarkers that show some promise include ubiquitination factor E4A (UBE4A), CXCL16 (a chemokine), resistin, and apolipoprotein A-IV [18]. Others have focused on the potential use of genomic methods to uncover a molecular profile that may differentiate IBD from IBS [49]. Further studies in larger series are needed to confirm whether serological or other biomarkers could predict a subgroup of IBD patients with a poor response to anti-TNF or other therapeutic agents.

TPMT Testing and 6-MP Metabolite Monitoring

Key Points

Knowledge of TPMT genotype or phenotype

- Reduces risk of potentially life-threatening myelotoxicity.
- Allows accelerated dosing ("full throttle" therapy).
- Reduces delay to achieve therapeutic drug levels.
- Cost benefits, with reduced risk of morbidity/mortality.

Potential benefits of 6-MP metabolite measurement

- Provides an explanation for cause of nonresponse.
- Enhances response rate by achieving target metabolite level.
- Detects nonadherence or poor compliance.
- Identifies therapeutic failures (despite achieving therapeutic metabolite level).
- Ascertain cause of nonidiosyncratic adverse events.

The clinical indications for the use of thiopurine drugs [50] and their efficacy in Crohn's disease [51, 52] and ulcerative colitis [53] have been discussed extensively (Chap. 5). This section reviews the evidence-based foundation behind screening for deficiency of thiopurine S methyltransferase (TPMT) activity prior to initiating treatment. We also review the evidence that the measurement of thiopurine metabolite levels permits clinicians to individualize and optimize therapeutic outcomes.

Thiopurine Metabolism: TPMT – the Key Enzymatic Pathway

The metabolic pathways of thiopurine drugs [54] are summarized in Fig. 12.1. Azathioprine (AZA) is a prodrug rapidly converted to 6-mercaptopurine (6-MP) and an imidazole derivative by a nonenzymatic reaction. The subsequent metabolism of 6-MP occurs via three enzymatic pathways. Xanthine oxidase is responsible for first-pass metabolism, converting 6-MP into the inactive 6-thiouric acid. Two competing intracellular pathways then metabolize the remaining 6-MP, namely TPMT and hypoxantine guanine phosphoribosyltransferase (HPRT). The latter pathway leads to

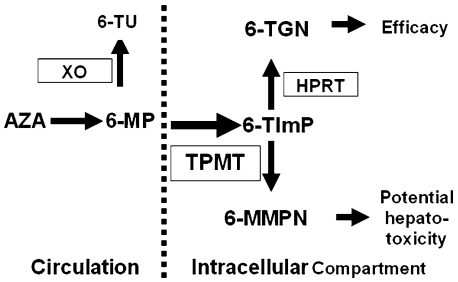

Fig. 12.1 Enzymatic pathways in the metabolism of azathioprine (AZA) and 6-mercaptopurine (6MP). Oral AZA is rapidly converted to 6-MP by a nonenzymatic process (approximately 2:1 ratio). Initial 6-MP transformations occur along competing catabolic (*XO* xanthine oxidase; *TPMT* thiopurine methyltransferase) and anabolic (*HPRT* hypoxanthine phosphoribosyltransferase) enzymatic pathways. The latter intracellular enzyme transforms the drug into 6-thioguanine nucleotides (6-TGN), which have been shown to be the key parameter associated with efficacy. TPMT methylates 6MP, yielding 6-methyl-mercaptopurine ribonucleotides (6-MMP). Patients heterozygous for a mutant allele of TPMT will convert a higher proportion of the drug into 6-TG. This translates into a higher success rate, but with an increased risk of myelosuppression. Homozygous TPMT deficiency will result in life-threatening bone marrow suppression in effectively every case

the formation of an intermediate metabolite, 6-TIMP, and finally to 6-thioguanine nucleotides (6-TGN), the active immunosuppressive metabolites. TGN metabolites are inserted randomly into DNA and act as purine antagonists, capable of inducing cytotoxicity and immunosuppression. In the competing pathway, 6-MP and 6-TIMP are methylated by TPMT to an inactive metabolite, 6-methyl-mercaptopurine (6-MMP).

It has been well established for over two decades that relatively common genetic polymorphisms of TMPT exist, which result in lower enzyme activity and potentially cause myelotoxicity due to excessive 6-TGN levels [55, 56]. As a result of deficient TPMT activity, 6-MP is preferentially metabolized by HPRT, leading to toxic levels of 6-TGN and bone marrow suppression. Determining genetic variations and deficient TPMT activity can reduce associated severe adverse outcomes. This approach has been endorsed by the Food and Drug Administration (FDA) and by the American Gastroenterological Association (AGA) guidelines, released in 2006 [50]. Moreover, in addition to preventing mortality and morbidity, the cost-effectiveness of TMPT screening prior to initiating therapy has been demonstrated [57, 58].

TPMT Screening: Genotype vs. Phenotype

Approximately 0.3% of individuals have severe homozygous TPMT deficiency, while 11% are heterozygous, with intermediary enzyme activity [59, 60]. The frequency of mutations is independent of race or the presence of various clinical disorders. Two methods may be employed to screen for reduced TPMT activity (Fig. 12.2). Historically, the first method used was to detect genetic polymorphisms by polymerase chain reaction (PCR). Although more than 20 variant alleles have been associated with reduced TPMT activity, most are attributed to three common mutations (Fig. 12.2). The TMPT*3A allele mutation is the most widespread variant among Caucasians, whereas TPMT*3C is more frequently

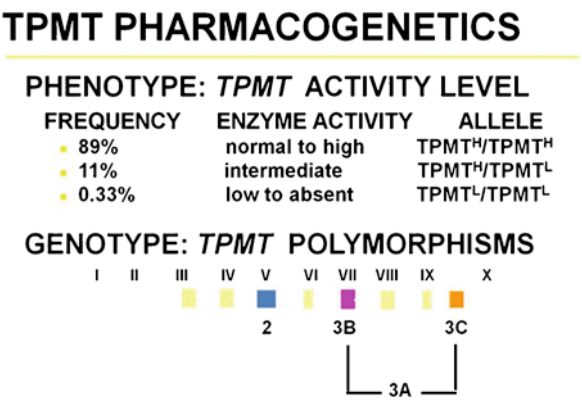

Fig. 12.2 Genotype–phenotype comparisons associated with common polymorphisms of thiopurine methyltransferase (TPMT) gene

reported in Africans and Asians [61, 62]. The genotyping commercially available is estimated to detect 97% of polymorphisms among most populations. However, genotyping will miss other mutations in people of Asian or aboriginal origin and should thus not be used in this population.

The alternative, generally superior strategy is to assay TPMT activity in vitro [62]. This test employs the patient's erythrocytes and hence cannot be relied upon within 90 days of receiving transfusions. TPMT phenotype can be classified into three categories: normal, intermediate, or low activity. Approximately 89% of the population have wild-type alleles with normal-to-high TPMT activity, and are at low risk of drug-induced myelotoxicity. However, this risk increases significantly in subjects with intermediate enzyme activities that are heterozygous for TMPT polymorphisms. Individuals with homozygous mutations have very low-to-absent enzyme activity and will uniformly present with life-threatening myelotoxicity within a month of daily exposure to AZA or 6-MP, irrespective of the dose used [63, 64]. Pharmacogenetic detection of severe TPMT deficiency can prevent severe morbidity and mortality [65].

More recently, it has become established that phenotypic analysis of TPMT enzyme activity is the preferred method [61] (Fig. 12.3). Occasional patients with markedly reduced TPMT activity were not found to have mutations by standard genotyping methods. This may be due to rare TMPT mutant alleles that are not detected by conventional genotyping. This is particularly problematic in people of Asian, First Nation American, or aboriginal populations [62, 66]. In addition to being more accurate, assaying TPMT activity is less expensive and provides quantitative results. Factors which can affect enzyme activity include drugs, promoter polymorphisms, and environmental factors (e.g., foods, uremia, and transfusions). TPMT activity should be measured prior to introduction of thiopurines drug administration, as these substrates upregulate TPMT gene expression as well as induce enzyme activity. It has been shown that 5-ASA containing drug formulations reversibly inhibit TPMT activity [67, 68]. The ingestion of liquid milk (but not other dairy products) reduces the bioavailability of thiopurines due to the presence of xanthine oxidase activity, increasing first-pass metabolism (Fig. 12.1).

In a study from the GETAID group in France [63], 41 thiopurine-treated IBD patients who developed leukopenic events were identified and TMPT mutations were detected by PCR. In the cases with homozygous mutant alleles, the delay

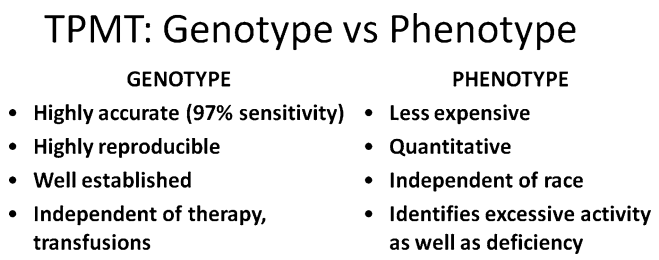

Fig. 12.3 Comparison of strategies to assess an individual's thiopurine methytransferase (TPMT) status

between administration of the drug and occurrence of bone marrow toxicity was uniformly less than 6 weeks. In all these cases, myelotoxicity was severe and required hospitalization. Among patients with heterozygous deficiency, there was a highly variable but generally much longer delay in onset of myelotoxicity. Another (environmental) factor was implicated in the 73% of patients with leukopenic events that had no TPMT mutation identified. Therefore, clinicians should be aware that although TPMT testing preempts life-threatening myelotoxicity, the majority of less severe leukopenic episodes are not related to TPMT mutations. Thus, regular monitoring of blood counts is needed to detect potential myelosuppression while on therapy, particularly in febrile patients. Recommendations for a sliding scale to guide dosing when initiating thiopurine therapy based on TPMT activity are illustrated in Fig. 12.4 [69].

6-MP Metabolite Monitoring

Levels of 6-TGN, the active metabolite of AZA and 6-MP, correlate highly with response to therapy. The frequency of therapeutic response was reported [70] to increase when 6-TGN levels were above 230 pmol/8×10^8 erythrocytes, reaching approximately a 65% remission rate off steroids (OR > 5). Conversely, there was no correlation between 6-MMP levels and clinical response. Leucopenia was also significantly associated with excessively high 6-TGN levels, beginning at levels

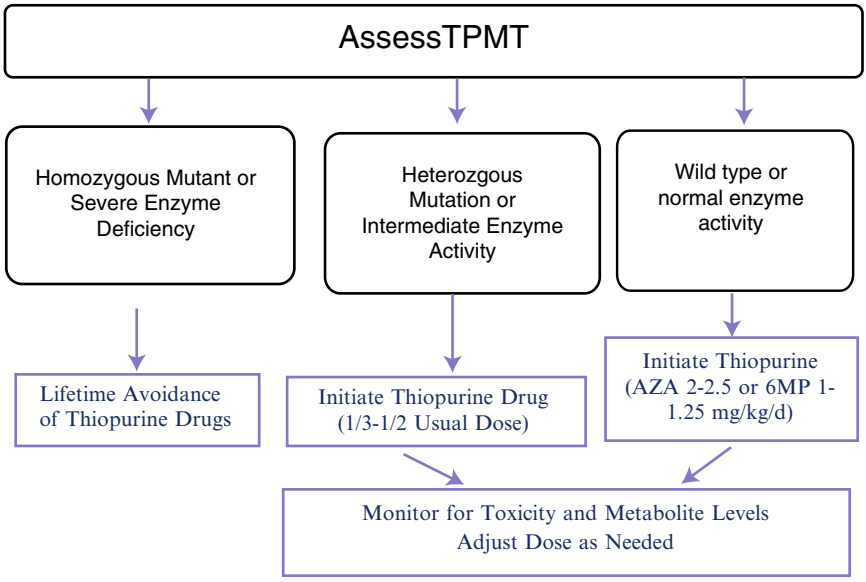

Fig. 12.4 Therapeutic algorithm to individualize thiopurine drug dosing according to thiopurine methyltransferase status. *TPMT* thiopurine methyltransferase; *AZA* azathioprine; *6MP* 6 mercaptopurine

>450 pmol/8 × 10^8 [70]. Patients with 6-TGN levels below the 230 "cutoff" may achieve clinical response, but are statistically less likely to do so [70]. In a study by Cuffari et al. [71], 81.8% of patients not responding to therapy with 6-TGN levels <230 achieved therapeutic success by titrating the dose to achieve adequate 6-TGN values (~300 pmol/8 × 10^8 erythrocytes). A recent meta-analysis [72] of studies showed that measurement of 6-MP metabolite levels is helpful and can be used to determine the adequacy of a thiopurine dose, without the risk of inducing leucopenia. The pooled odds ratio for remission with 6-TGN levels >230 was 3.3 (95% CI: 1.7–6.3 $p < 0.001$). Roblin et al. recently showed [73] that nonresponders will not benefit from excessive 6-TGN levels exceeding 400 pmol/8 × 10^8 erythrocytes.

Figure 12.5 illustrates how thiopurine metabolite levels can explain the reason for therapeutic failure in most cases. The most common cause is insufficient dosing, with inadequate 6-TGN levels [54]. Other causes revealed by metabolite levels include nonadherence or poor compliance, as well as preferential metabolism via the TPMT pathway. In noncompliant individuals, metabolite levels are barely, if at all, detectable. In cases where adherence to therapy is partial, prescribing higher doses is typically not reflected by higher subsequent 6-TGN or 6-MMP levels. Metabolite testing in patients in whom excessive TPMT activity is the cause of treatment failure will reveal excessive 6-MMP levels without reaching adequate 6-TGN levels [74].

Expression of metabolite levels as 6-MMP/6-TGN ratios provides a simple and clinically useful reflection of TPMT activity, explaining therapeutic outcomes

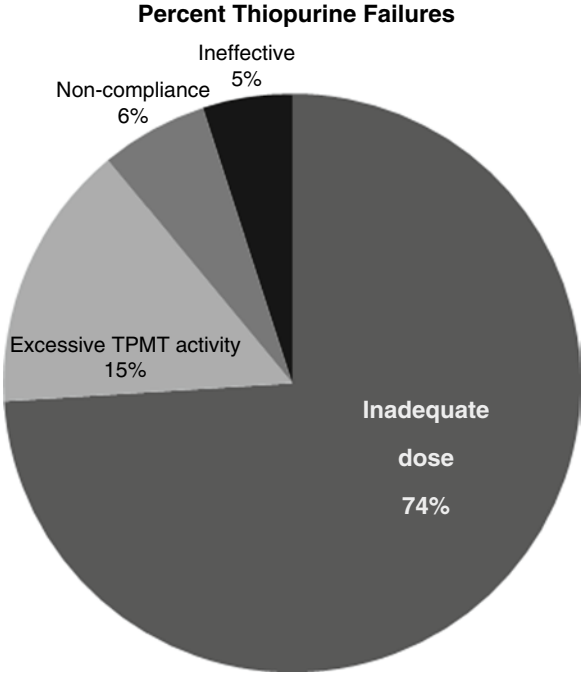

Fig. 12.5 Reasons for thiopurine treatment failures in IBD according to measurements of 6MP metabolite levels. Adapted from [54]

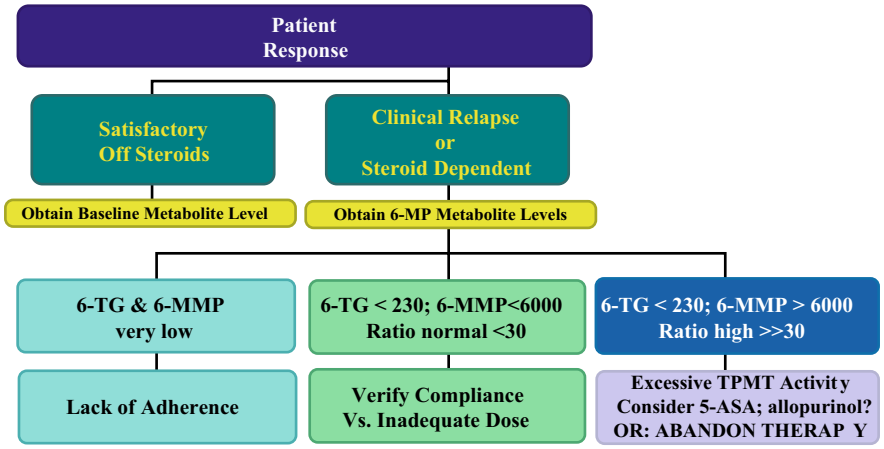

Fig. 12.6 Algorithm to interpret outcomes to thiopurine treatment of IBD using 6MP metabolite levels in concert with 6MMP/6TGN ratios

(Fig. 12.6). Patients with normal ratios (between 4 and 35) generally have a high likelihood of response to thiopurines, reflecting normal TMPT status. Individuals with very low ratios (<4) have abnormally reduced TPMT activity, usually due to a heterozygous mutation. Such cases are most likely to respond to therapy, as they generate higher 6-TGN levels, requiring lower drug doses (Fig. 12.4). 6-MMP/6-TGN ratios >35 reflect high TPMT activity, generating excessive 6-MMP and low levels of 6-TGN, despite drug dose escalation. When the 6-TGN level is low (<230) but near target (>185), and the 6-MMP/6-TGN is moderately high [35–60], fractionating the dose of thiopurine and adding a 5-ASA may resolve the problem. However, when 6-TGN levels are very low (<150) and 6-MMP/6-TGN ratio very high, an alternative therapeutic plan should be sought. In that situation, patients are considered drug-resistant due to excessive metabolism via TPMT [54, 74]. A switch "out of class" to a biologic or to methotrexate should be considered. Alternatively, this metabolic problem can be overcome by coadministering allopurinol [75, 76], a xanthine oxidase inhibitor. Oxypurinol, a metabolite of allopurinol, competes with 6-MP for TPMT, favoring the conversion of 6-MP to 6-TGN [77]. It is critical to reduce the dose of AZA or 6-MP to 25%–33% of the initial dose, in order to avoid excessive 6-TGN levels and myelotoxicity.

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Chapter 13
Caring for Women with Inflammatory Bowel Disease

Sunanda Kane and Rebecca Kowalczyk

Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Gender • Pregnancy • Menstrual cycle • Pap smears • Fertility • Contraception • Sperm • Breastfeeding • Menopause

Key Points

- The menstrual cycle can affect IBD symptoms.
- Women with IBD are more likely to develop abnormal cervical cytology.
- Fertility is not affected in UC, but can be in active CD.
- There is no increase in adverse pregnancy outcomes in quiescent IBD.
- Active disease at conception increases the risk for adverse outcomes during pregnancy.
- The majority of medications for IBD are safe in pregnancy and breastfeeding – active disease is more deleterious than active therapy.

Background

The incidence of Crohn's disease (CD) in women has been increasing over the past few decades [1]. It is not clear whether this is due to improved diagnostic techniques, an increase in smoking habits by young women (patients with CD tend to

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be smokers compared to people without CD [2]), or other factors not yet identified. However, the consequence of this trend is a growing population of patients with gender specific needs and concerns related to their medical care. Every component of the reproductive cycle can potentially affect disease course or symptomatology. Because the diagnosis of CD or ulcerative colitis (UC) is often done in the childbearing years, fertility and pregnancy are important issues that previously have been handled exclusively by gynecologists. Gastroenterologists caring for women with inflammatory bowel disease (IBD) should be aware of these issues and their appropriate management. The aim of this chapter is to review some clinically relevant gender specific issues in IBD.

Self-Image Issues

Maunder and colleagues reported consistently higher levels of symptom severity and rating of IBD patient concerns in women than men [3]. Patient concerns that differed by gender included attractiveness, intimacy, and sexual performance. Women also had stronger concerns about self-image, feeling alone, and fearful of having children.

Active disease can lead to fatigue and loss of libido, in addition to the embarrassment of fecal incontinence. Corticosteroids to treat active disease leads to Cushingoid features along with weight gain and mood swings. As inflammatory bowel disease is a chronic disease, patients with IBD suffer from the same psychiatric conditions that other patients with chronic disease suffer. The unpredictability of disease symptoms including fecal incontinence adds to the psychological and emotional toll [4].

Perineal involvement in CD can be physically deforming, as well as resulting in dyspareunia and self-consciousness. The presence of an ostomy or other surgical scars can also lead to a lower self-esteem [5].

The Menstrual Cycle

For girls diagnosed with IBD before or during puberty, the onset of menses can be delayed. This can be secondary to chronic inflammation or a poor nutritional status that directly affects steroid hormone production. Menarche usually occurs once active disease is treated appropriately.

Disease activity can also affect the menstrual cycle after the onset of menarche. This can be manifested by irregular or skipped periods, or an increase in disease symptoms during the premenstrual or menstrual phase. A study performed by our group Kane et al. confirmed that patient's with IBD had more cyclical symptoms than the general population [6]. These cyclical symptoms included diarrhea, abdominal pain, and constipation. Some women consider these "mini-flares."

In reality, this is a cyclic, predictable phenomenon which is neither random or "all in the head." Rather than treating these symptoms as active IBD, conservative treatment to alleviate symptoms is more appropriate, as symptoms will tend to resolve in a few days' time during the postmenopausal phase [7].

Some women have such debilitating symptoms that the elimination of menses is the only way to provide relief. This can be achieved with short-term injectable contraceptives (Depo-Provera®) or hormones (Lupron®). At this time a hysterectomy is not recommended for this indication, but those women who undergo this procedure for other gynecologic reasons find their IBD symptoms improve [8].

Pap Smears

It is known that immunosuppression results in a higher incidence of cervical dysplasia secondary to reduced immunity and ability to clear HPV infection. We have previously found that the incidence of abnormal cervical cytology was 42.5%, vs. 7% in women with IBD and normal controls [9]. Women with IBD were also more likely to have high grade lesions when compared to controls. This is likely related to medication-induced immunosuppression but there is evidence that women with IBD have a higher risk of an abnormal pap smear irrespective of immunosuppressive medications or type of IBD [10]. Women with IBD, especially those who use immunomodulators, should be considered at high risk and undergo annual pap smears with rigorous follow-up of any abnormal cytology. The current recommendations for HPV vaccine from the American College of Obstetrics and Gynecology include women age 9–26. It is unclear at this time whether women older than 26 would receive benefit and trials are currently underway to study this clinical scenario.

Fertility

Overall, the fertility rates for women with IBD are essentially the same as those of the normal population [11]. Early studies suggested lower fertility rates had not taken into account an increased voluntary childlessness rate in women with IBD.

Active CD, however, can reduce fertility in several ways, depending upon the location of inflammation. Active inflammation in the colon [12] and terminal ileal disease [13] can decrease fertility. Active ileal inflammation can cause inflammation or scarring of the fallopian tubes or ovaries. Women who have had any surgical resection are at risk for adhesions, which can also impair tubal function. One retrospective from Scotland revealed that women who had surgery for IBD had decreased fertility with infertility rates of 25% compared to 7% of the population [14]. A limitation to this study however, was that there was no control for voluntary childlessness. Another mechanism for increased rate of infertility is having undergone an

ileoanal anastomosis procedure. A recent metaanalysis demonstrated a threefold increased risk for infertility resulting from this procedure [15]. One way to avoid this complication is perform an ileorectal anastomosis to preserve fertility [16].

None of the medications used to treat IBD has an effect on female fertility, but it is important to remember that sulfasalazine therapy reduces sperm motility and count in males [17]. Aside from the effects of sulfasalazine therapy, men with IBD do not have a reduced reproductive capacity but men with CD tend to have small families [18]. While there is no minimum required time period for quiescent disease prior to a planned conception, at least 3 months is recommended. Open discussions between patient and physician are the best way to ensure the best outcome of a pregnancy. If a woman is doing well and in remission, the risk of disease activity if she remains on her maintenance medications is minimal. If active disease is present, it is likely to continue through pregnancy and will place the pregnancy at greater risk for a complication [19]. This risk appears to be higher in CD than in UC.

The main priority is to establish and maintain remission before the patient conceives. One of the problems in CD is the accurate definition of remission. In CD, a patient may feel fine even though she has an elevated C-reactive protein (CRP), an abnormal colonoscopy, and/or X-ray.

Some women remain childless for fear of disease transmission to their offspring. Current data suggests that this risk is low; 7% if one parent has CD and less if one parent has UC [20]. However, the risk of IBD increases as high as 37% if both parents have the disease. The risk of inheriting IBD is higher in Jewish (7.8%) than in non-Jewish (5.8%) families [21]. It is important to remember that IBD is not a genetic disorder in a true Mendelian fashion. Even with genetic predisposition, that other factors are necessary to produce expression of either disease.

Contraception

The management of contraception in those women with IBD who do not wish to become pregnant differs from that for healthy women. The most important goal still remains the selection of the most reliable method of birth control. Barrier methods of contraception are acceptable but are not as effective as alternatives. The use of intrauterine devices is not usually recommended, as any complaint of abdominal pain could potentially delay the correct diagnosis of active IBD vs. pelvic inflammatory disease. However, it is important to remember that most oral contraceptives are absorbed from the small bowel and this absorption is key for the contraceptive efficacy. Increased transit time, ileostomy, and impaired ileal absorption secondary to inflammation may lead to contraceptive failure [22].

The data regarding the safety of oral contraceptives (OCs) in IBD are conflicting. Early studies suggested an increased risk for the development of CD and UC, but did not account for tobacco use [6, 23–25]. However, two case controlled studies failed to find an association [26, 27]. Reports from Europe, where contraceptives contain a higher estrogen content, continue to show modest increases in risk for the development of CD after adjusting for cigarette use (Odds ratios 1.2–2.0) [28, 29].

Other data suggest that OC use may exacerbate disease activity [30, 31]. Two small prospective studies have found an increased risk of disease recurrence after induction of remission in CD with OC use. No information is available for a possible similar risk in UC.

At this time, no standard guidelines exist for OC use, as there are many preparations available. The variable amounts of progesterone and estrogen are the factors that determine the side effect profile. The choice of OC use has to be individualized, taking into consideration other factors including patient history, parity, and personal preferences. It does appear prudent to try a formulation that contains the lowest amount of estrogen possible, given the additional risk factors of smoking and predilection towards thromboembolic events in patients with CD.

Effect of IBD on Pregnancy

Women with inactive IBD appear no more likely to experience spontaneous abortion, still birth, or children born with a congenital abnormality. Some work has suggested that babies born to women with IBD, regardless of disease activity, are of smaller birth weight [32]. This appears to be particularly true in those women with CD. Women with active disease run a greater risk for premature birth especially those with high disease activity [33].

The presence of IBD does not appear to have an impact on maternal complications related to pregnancy, including hypertension, or proteinuria [34]. However, perianal disease may worsen or develop after a vaginal delivery. One retrospective, a study of women with CD demonstrated 18% of those without previous perianal disease developed such disease after delivery, usually involving an extensive episiotomy [35]. In the absence of perianal disease, the diagnosis of IBD alone does not have a significant impact on the method of delivery, nor is it an indication for Cesarean section. Despite this fact women with IBD are 1.5 times more likely to undergo Cesarean section [36]. It is important to note that in one study, even patients with a history of perianal CD had no relapses of perianal disease in 1 year follow-up after vaginal delivery [35].

Effect of Pregnancy on IBD

For women with quiescent UC, the rate of relapse is approximately the same in pregnant vs. nonpregnant patients [19]. This is in contrast to the presence of active disease at the time of conception, which is associated with continued or worsening disease activity in approximately 70% of women. Comparable observations are seen in CD. The older literature suggested a trend for disease to flare in the first trimester, but this was documented prior to the accepted practice of maintenance therapy, continued even during pregnancy.

It is important to remember that hemoglobin and albumin levels decrease and ESR increase during pregnancy. Because of these normal physiologic changes, disease assessment during pregnancy should rely more on clinical symptoms than laboratory parameters. Ultrasound exams are clearly safe, and there is no evidence that if indicated, that a sigmoidoscopy will induce premature labor [37]. Full colonoscopy should only be performed when extent and severity of disease specifically need to be ascertained.

There are data that suggest that a history of child bearing changes the natural history of CD [38]. Women having been pregnant had fewer resections or longer intervals between resections as compared to women who had not had children but otherwise similar disease. One theory proposed by the authors is the inhibition of macrophage function by relaxin. Relaxin is a hormone produced exclusively during pregnancy which may result in less fibrosis and stricture formation by this inhibition of macrophages. A more recent study found that patients with IBD who became pregnant during their disease course did not have changes in surgery rates, stenosis formation, or disease phenotype but did have decreased relapse rates in the years following pregnancy [39].

Treatment of IBD During Pregnancy

The key principle to management is to remember that the greatest risk to pregnancy is active disease, not active therapy [40]. Since there are limited definitive data available on the safety of IBD medications in pregnancy, the focus therefore should be on establishing remission before conception and maintaining remission during pregnancy.

Sulfasalazine readily crosses the placenta but has not been definitively associated with any fetal abnormalities. The FDA rates this therapy as low risk, although this drug is not used as frequently as in the past given the sulfa-free alternatives. Those patients taking sulfasalazine should be supplemented with folic acid before conceiving to decrease the risk of neural tube defects. A folic acid dose of one milligram twice daily would be appropriate.

The safety of mesalamine during pregnancy has been demonstrated in a number of trials despite the fact that it and its metabolite acetyl-5-aminoslicyclic acid are found in fetal plasma [41, 42]. In two separate studies, women taking 2–3 g/day had no increased incidence of fetal abnormalities than that in normal healthy women.

The data regarding immunomodulator therapy (azathioprine, 6-MP) are more conflicting. There are no large prospective studies on the use of these medications during pregnancy in women with IBD. To date, the largest amount of information comes from the transplantation literature [43] but more recently from retrospective series in IBD [44, 45]. Azathioprine metabolites have been found to cross the placenta, at levels approximately 40% of that of maternal serum [46]. With potential dose reduction to maintain remission, fetal exposure can be minimized [46]. It is generally believed by most experienced IBD clinicians that immunosuppressives

such as 6-MP, azathioprine, and cyclosporine can be used safely during pregnancy if the mother's health mandates therapy. However, there has been recent evidence from a recent Danish study that women taking these medications have an increased risk of preterm birth after adjusting for cofounders, so it is important to weigh the risks and benefits of the medication [47]. Methotrexate, another immunomodulatory medication, is contraindicated in pregnancy due to its abortogenic effect. It is also advisable to avoid its use in men who wish to father children as it is toxic to sperm. Thalidomide, a therapy that has orphan drug status to treat CD, is also contraindicated in pregnancy because of very specific birth defects that occur secondary to its mechanism of action, namely antineoangiogenesis.

Biologics are now commonly used for more aggressive disease. Mahadevan et al. examined the pregnancy outcomes of ten women intentionally treated with infliximab for active disease CD during pregnancy [48]. All ten pregnancies resulted in live births, with no congenital malformations. Infliximab is detected in the offspring of women treated with infliximab throughout pregnancy but to date the long-term effect of this placental transfer is unknown [49]. Therefore, it is important for the physician to discuss with each patient the risk to benefit ratio of biologic therapy to control disease. Similar case reports with adalimumab demonstrate its relative safety during pregnancy [50, 51]. No published data yet are available regarding certolizumab pegol, the Fab fragment just recently approved for CD. Natalizumab, the IgG4 monoclonal antibody to alpha 1 integrin, also has recently received FDA approval. It is available only through a registration program and yet pregnancy outcomes with this agent are to be known.

Corticosteroids have not been associated with teratogenicity in humans and can be used as required to control disease activity. Prednisolone crosses the placenta less efficiently than other steroid formulations such as betamethasone, dexamethasone, and even budesonide. Only limited data are available regarding the safety of antibiotics as the treatment for CD. Currently, ampicillin, cephalosporins, and erythromycin are believed safe, as well as ciprofloxacin. Metronidazole has been used to treat vaginitis in women during the first trimester of pregnancy but no controlled trials have definitively shown its safety [52]. Table 13.1 summarizes the safety of commonly used medications in IBD.

Table 13.1 Safety of IBD medications during pregnancy

Safe to use when indicated	Limited data but benefit outweighs risk	Contraindicated
Oral, topical Mesalamine	Olsalazine	Methotrexate
Balsalazide	Azathioprine	Thalidomide
Sulfasalazine	6-MP	Diphenoxylate
Corticosteroids (including budesonide)	Cyclosporine	
	Biologics	
	Metronidazole	

Breastfeeding

The medications known to be safe for breastfeeding include sulfasalazine, mesalamine, and steroids. Mothers planning on nursing should discontinue the use of cyclosporine, metronidazole, and ciprofloxacin. The antidiarrheals loperamide and diphenoxylate should also be discontinued. Preliminary data regarding the thiopurines suggests minimal secretion into breast milk and continued use should be discussed on a case by case basis. Infliximab has not been detected in milk [49]. Table 13.2 summarizes the safety data regarding medications and their use during breastfeeding.

Surgery During Pregnancy

The indications for surgery during pregnancy are identical to that of nonpregnant patients. These include obstruction, perforation, abscess, and severe refractory disease. It is not clear whether surgery has to be performed when dysplasia or cancer are detected during pregnancy, and individual circumstances are what mandate decision-making. Pregnancy has not been shown to complicate stoma function. Women may experience some prolapse due to abdominal pressure, but no increased risk to the pregnancy is encountered.

For those women who have had ileoanal pull-through procedures, an increase in the number of bowel movements during pregnancy has been reported, but no increased risk for pouchitis or delivery complications [53]. Several studies have found that there is an increased rate of Cesarean section after restorative proctocolectomy despite the fact that there have been no significant differences in pouch function following vaginal delivery [54, 55]. The mode of delivery should be determined by obstetrical considerations and not solely by the presence of an ileoanal pouch.

Table 13.2 Safety of IBD medications during breastfeeding

Safe to use when indicated	No data	Contraindicated
Oral, topical Mesalamine	Olsalazine	Methotrexate
Balsalazide	Azathioprine	Thalidomide
Sulfasalazine	6-MP	Cyclosporine
Corticosteroids	Adalimumab, certolizumab pegol, natalizumab	Ciprofloxacin
		Tacrolimus
Infliximab		Metronidazole
		Loperamide
		Diphenoxylate

Gender Specific Surgical Outcomes

There has been a varying incidence of dyspareunia following pelvic surgery, ranging from 0 to 26% [56–59]. This variation may be due to the heterogeneous nature of surgeries or underreporting of symptoms to physicians After ileoanal pull-through, one report found 15% incidence of dyspareunia, and an increase in menstrual problems [4]. In contrast, other studies have shown a decrease in dyspareunia and an increased frequency of intercourse, secondary to improvements in overall health [58].

Menopause

Menopause, whether natural or surgical, leads to many physiologic changes in a woman's body. Just as OCs can help with controlling symptoms, there are data to suggest that some of the gastrointestinal symptoms associated with IBD decrease in women who have experienced menopause.

Women with UC are at no greater risk for an early menopause than women without IBD. There are some data to suggest that women with CD may enter menopause earlier than otherwise healthy women, but a mechanism has yet to be established for this finding [8].

A recent study by our group revealed that postmenopausal women with IBD are just as likely to have a flare as women that are premenopausal [60]. This retrospective study demonstrated that HRT had a protective effect on disease activity and that this effect appeared to be dose-dependent. More research on the relationship between exogenous hormones and IBD needs to be done before HRT can be recommended for all women undergoing menopause.

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Chapter 14
Novel Radiographic Techniques in IBD Patients

V. Anik Sahni and Koenraad J. Mortele

Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Computerized axial tomography • Magnetic resonance imaging • Multidetector-row CT • Endoanal ultrasound • Anal endosonography • Transcutaneous perianal ultrasound • Positron emission tomography • PET–CT • CT enterography • MR enterography • Examination under anesthesia • Endoscopic retrograde cholangiopancreatography • MR cholangiopancreatography

Key Points

- Traditional contrast-based radiographs of the bowel have now been replaced by more modern techniques based upon computerized tomography, magnetic resonance, positron emission, and ultrasound-based imaging.
- Modern radiographic techniques have extended beyond solely diagnostic purposes to monitoring of disease activity, progression, and response to therapeutic interventions.
- The absence of ionizing radiation in MR imaging has been particularly attractive given the young population affected by inflammatory bowel disease.
- MRI and endoanal ultrasound have increasingly replaced examination under anesthesia in the evaluation of perianal Crohn's disease, as well as monitoring therapeutic response to therapy.
- Noninvasive magnetic resonance cholangiography has replaced endoscopic cholangiography to diagnose primary sclerosing cholangitis and its complications.
- Evolving future techniques include MR colonography and positron emission tomography–CT (PET–CT).

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Introduction

Evaluating the small bowel in patients with inflammatory bowel disease has been a significant challenge in the past. Its poor access via endoscopy has led to a significant reliance on radiology to diagnose and monitor disease progression. Traditionally, the radiological investigation of inflammatory bowel disease has been limited to gastrointestinal fluoroscopic contrast studies such as small bowel follow through and enteroclysis. The traditional planar views obtained by these luminal radiographic techniques are limited in the useful mural and extramural information that they provide. In addition, the inherent length of the small bowel with multiple overlapping loops is a major obstacle for a purely projectional technique. Over the past decade, however, there have been several technical advances in radiology that have revolutionized the evaluation of the small bowel. There has been a shift in the emphasis of investigations to not only those that document anatomical information but also those that provide functional information regarding disease activity and response to therapy. These developments have been primarily in the domain of the cross-sectional imaging modalities: computerized axial tomography (CAT or CT) and magnetic resonance imaging (MRI). The advent of multidetector-row CT (MDCT) has allowed the rapid acquisition of thinly collimated studies, which allow multiplanar reconstruction. Newer MR sequences now allow breath-hold acquisitions of the abdomen improving temporal resolution. Spatial resolution has been optimized with the continued development of multichannel phased array body coils. The absence of ionizing radiation in MR imaging has been particularly attractive given the young population affected by inflammatory bowel disease. CT and MR enterography are now widely available and becoming the mainstay of small bowel evaluation.

Perianal inflammatory disease is another significant problem in Crohn's disease. Accurate mapping of fistulas is crucial to prevent recurrence and sphincter damage. MRI and endoanal ultrasound have replaced examination under anesthesia (EUA) as the gold standard. Radiology is now not only involved in the diagnosis of perianal disease but also being used to monitor therapy with new disease-modifying drugs such as infliximab.

The use of radiology in inflammatory bowel disease is not restricted only to the bowel. Diagnostic imaging is being increasingly used to evaluate several of the extraintestinal manifestations. Primary sclerosing cholangitis (PSC) has been traditionally evaluated with invasive cholangiography, usually endoscopically. Magnetic resonance cholangiography provides a noninvasive evaluation of the biliary system without the inherent risks of endoscopic cholangiography. MRI also provides the capability to assess for complications such as cholangitis and cholangiocarcinoma.

Recent technological advances, however, have not been limited to radiology. Investigations such as wireless capsule endoscopy and double balloon enteroscopy are tools that have been recently added to the gastroenterologist's armamentarium. Radiology must continue to evolve to compete with these tests. Evolving techniques include MR colonography and positron emission tomography–CT (PET–CT).

The former technique allows assessment of large bowel inflammatory activity without the use of ionizing radiation and the inherent risks associated with colonoscopy. Although limited data currently exist on its performance, potential for wide spread application exists especially if minimal bowel preparation regimes can be developed. PET–CT provides noninvasive assessment of disease activity with the complementary anatomical information provided by CT.

This chapter hopes to familiarize the reader with the current state-of-the-art radiological investigations available for the investigation of inflammatory bowel disease. The techniques, findings, performances, and limitations of the imaging modalities will be reviewed in order to provide a complete understanding.

Evaluation of Small Bowel Disease

CT Enterography

CT imaging of the abdomen and pelvis is a well-established technique in the radiological evaluation of the extraenteric complications of Crohn's disease [1–3]. Fistulas, sinus tracks, and abscesses are visualized and CT can guide treatment. Crohn's disease, however, is a transmural inflammatory process and requires an imaging modality that can diagnose disease involvement from the mucosa out to the mesentery. Routine abdominopelvic CT is inherently limited in the evaluation of the mucosal and mural involvement.

CT enterography is a relatively new technique that optimizes the evaluation of both the luminal and extraluminal components of Crohn's disease. Recent technical advances, primarily the advent of MDCT, have allowed this technique to flourish. MDCT allows rapid thin collimation imaging of the abdomen and pelvis within a breath-hold, thereby minimizing artifact from both respiration and bowel peristalsis. A volume of data is acquired, which can be reconstructed and displayed in multiple planes. The second major technological progression has been the development of neutral contrast agents. These agents are of lower density as compared to conventional positive CT contrast agents, such as barium sulfate and gastrografin, and therefore do not obscure visualization of the contrast-enhanced bowel wall. Water can be used as a neutral agent; however, it is absorbed by the gastrointestinal tract resulting in suboptimal distension of the distal small bowel [4]. VoLumen (E-Z-EM, Lake Success, NY), a barium sulfate-based solution with a concentration of 0.1% w/v, is a newly developed oral contrast agent. It has a Hounsfield Unit density of between 10 and 30. It has been shown to distend the duodenum, jejunum, and ileum significantly better than both water with methylcellulose or regular 2% barium sulfate suspension [5, 6]. In addition, wall visualization with VoLumen is superior when compared with higher attenuation contrast medium [6].

In common with all radiological investigations, an optimal technique is the key to accurate diagnosis. Several factors specific to CT enterography require close attention. These include adequate luminal distension throughout all segments of the

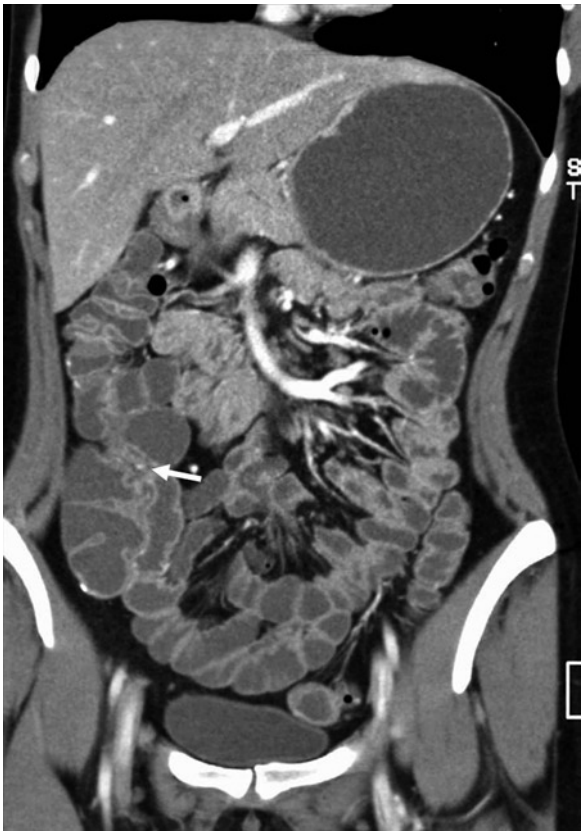

Fig. 14.1 Coronal CT enterography image at the level of the ileocecal valve (*arrow*) with enteric VoLumen and intravenous contrast. Normal small bowel fold pattern and enhancement are demonstrated

small bowel, optimal phase of intravenous contrast enhancement, and thin section collimation with multiplanar reformats (Fig. 14.1). CT enterography requires larger volumes of oral contrast as compared to routine abdominopelvic CT. The key to adequate distension is to avoid collapsed loops, which may mimic wall thickening or abnormal enhancement [7]. Multiple regimes for oral preparation exist [6, 8–10], which involve drinking up to 1,800 ml of contrast. Administration of contrast via a nasojejunal tube was initially thought to be mandatory to achieve adequate distension of the bowel. Equivalent distension and detection of active disease however can be achieved via peroral administration [11]. Partial small bowel obstruction is one indication where nasojejunal intubation provides superior diagnostic information [12, 13]. Our current technique involves the ingestion of 1,350 ml of VoLumen starting 45 min prior to the scan with 450 ml drunk every 15 min.

Abnormal mural enhancement is one of the most important signs that is evaluated on CT enterography. As a result, optimizing the timing of the imaging

acquisition with respect to the intravenous contrast injection is imperative. Single phase scanning is considered adequate for the assessment of inflammatory bowel disease especially since many of these patients are young and the radiation dose should be kept to a minimum. There is a statistically significant difference in small bowel wall enhancement between the arterial phase (30 s) and the portovenous phase (60 s) [4]. This is not thought to be clinically important. Other studies have corroborated this by determining that no additional information is obtained by using dual phase imaging in Crohn's disease [11, 14]. The portovenous phase provides superior imaging of the upper abdominal organs and is therefore the preferred phase. We currently acquire images at 70 s after intravenous administration of 100 ml of nonionic iodinated contrast material.

Reconstruction of the axial images at 3 mm or less is recommended. Further thinner slices are reconstructed to produce coronal and sagittal reformats. The images are preferentially reviewed on a computer workstation due to the large amount of images available and the tubular nature of the bowel. At our institution, we reconstruct the axial data at a thickness of 3 mm with a 3-mm interval. A second set is reconstructed at a 0.625-mm thickness with a 0.5-mm interval. This latter set is reformatted in the coronal and sagittal planes with a reconstruction thickness of 3 mm at 3 mm intervals.

The primary role of CT enterography is to identify active Crohn's disease. Multiple imaging features are associated with active disease and can aid in the diagnosis. It is important to appreciate that the mucosal changes of early active Crohn's disease are not well appreciated on CT enterography. These are still better demonstrated on traditional fluoroscopic small bowel studies. Wireless capsule endoscopy may even see earlier changes [15]. Mucosal/mural hyperenhancement is described as segmental hyperattenuation of small bowel loops relative to nearby normal appearing bowel [16] (Figs. 14.2 and 14.3). Good distension of the bowel is necessary as attenuation can be overestimated in bowel loops that are collapsed. The upper limit of normal for bowel wall thickness is 3 mm [17]. Again, adequate distension is required to evaluate this appropriately. Mural stratification indicates a laminated appearance to the bowel wall secondary to infiltration of the bowel wall. In the acute phase, this may be due to water or inflammatory changes. In chronic inflammation, fat can be deposited (Fig. 14.3). The attenuation of the bowel wall depends on the process involved. In the perienteric fat, stranding and engorgement of the vasa recta indicate active disease. The prominence of the vessels results in the well-recognized "comb" sign. Fibrofatty proliferation can also occur, typically on the mesenteric aspect of the bowel [16]. This is usually a sign of chronic disease (Fig. 14.2). Strictures are also a chronic manifestation of Crohn's disease. They are secondary to fibrotic changes of the submucosa and smooth muscle [18] and demonstrate only moderate enhancement after intravenous contrast due to the fibrotic changes [15]. Strictures can manifest as small bowel obstruction and are usually associated with signs of active disease. With the increased use of wireless capsule endoscopy, the detection of stricturing disease is paramount to prevent obstruction and capsule retention. Like routine abdominopelvic CT, CT enterography can also be used to detect extraenteric complications of Crohn's disease.

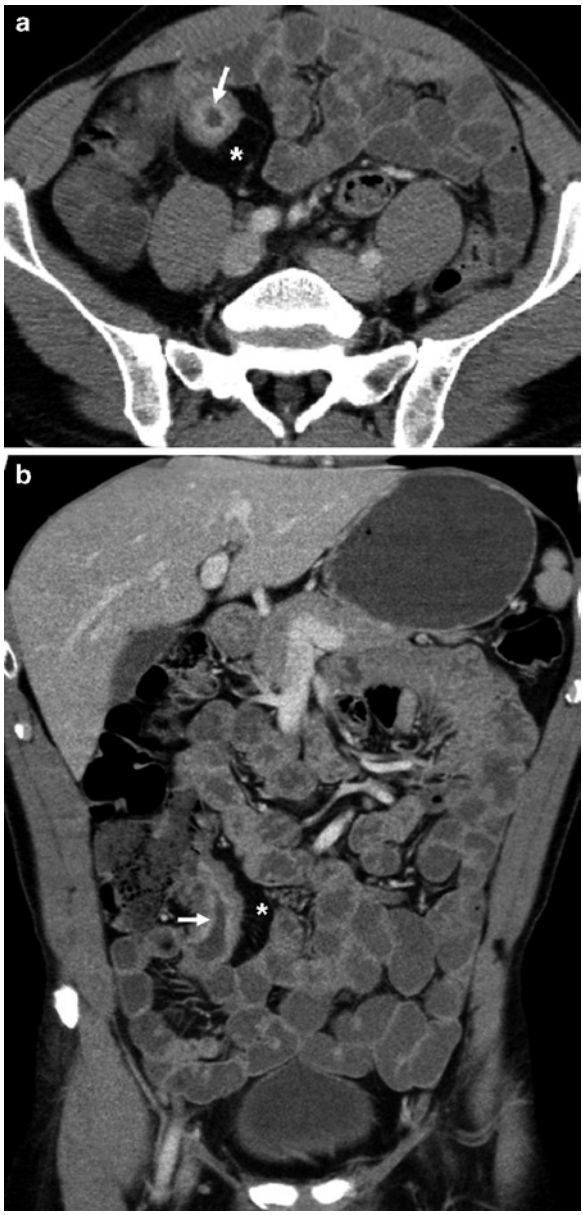

Fig. 14.2 Axial (**a**) and coronal (**b**) CT enterography images with enteric VoLumen and intravenous contrast demonstrate mucosal hyperenhancement consistent with acute inflammation (*white arrows*). Fibrofatty proliferation (*asterisks*) is present in keeping with chronic inflammation

Transmural inflammation of the bowel wall can result in localized perforation leading to fistula, sinus track, and abscess formation. The location and extent of these complications are well demonstrated on CT enterography. Finally, extraintestinal manifestations of inflammatory bowel disease can, in addition, be reviewed on CT enterography. These include biliary, renal, and musculoskeletal manifestations.

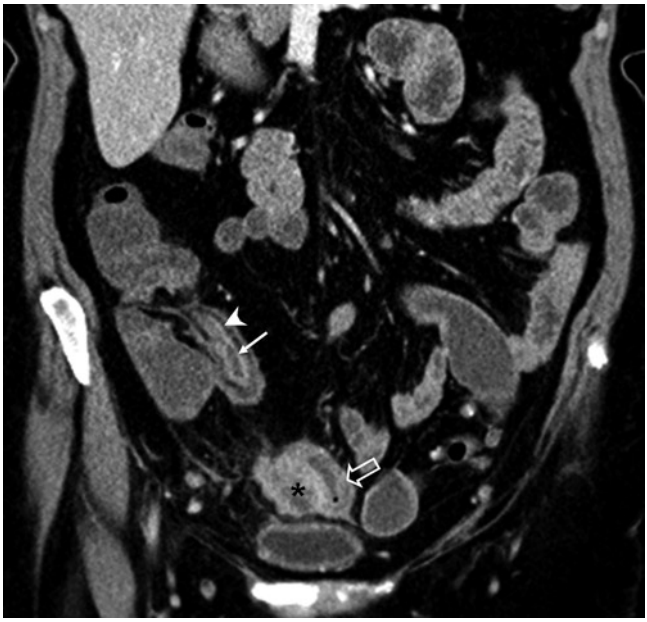

Fig. 14.3 Coronal CT enterography image with enteric VoLumen and intravenous contrast demonstrates mucosal hyperenhancement consistent with acute inflammation (*white arrow*). An abscess is noted in the pelvis (*asterisk*) next to an inflamed bowel loop (*open arrow*). Submucosal fat deposition is present in the terminal ileum in keeping with chronic inflammation (*arrowhead*)

There are two main indications for CT enterography. These include the initial diagnosis of Crohn's disease and the follow up of patients with established disease looking in particular for disease activity and complications. Research has therefore focused on evaluating CT enterography as a primary diagnostic tool and on whether findings correlate with disease activity.

Many early studies evaluating the use of CT against endoscopy in the diagnosis of Crohn's disease used CT enteroclysis (nasojejunal intubation) [19, 20] or positive oral contrast agents [21], so the results for these studies are difficult to extrapolate to current techniques available. Nonetheless, sensitivities are variable. For detecting active Crohn's disease, Wold et al. [11] demonstrated a sensitivity and specificity for CT enterography of 78 and 83%, respectively. These results were not significantly different to those of CT enteroclysis or SBFT. The CT examinations were more sensitive, however, in the detection of extraenteric complications. Recent trials have compared CT enterography, capsule endoscopy, SBFT, and ileoscopy [10, 22]. Hara et al. [10] showed that Crohn's disease was depicted by capsule endoscopy in 71%, ileoscopy in 65%, CT enterography in 53%, and SBFT in 24%. Of note however, out of the 17 patients investigated, ileoscopy was incomplete in four patients and capsule endoscopy in two patients. Solem et al. [22] demonstrated no significant difference in sensitivity between CT enterography and

capsule endoscopy (82% vs. 83%). The specificity of CT, however, was significantly higher (89% vs. 53%). Although capsule endoscopy may detect early mucosal changes that are radiographically occult [15, 23], it has several limitations. In patients where strictures are present it can result in capsule retention and bowel obstruction [24]. In addition, findings are less specific with abnormalities being detected in up to 14% of asymptomatic adults [25].

Two recent studies have tried to correlate imaging evidence of active disease with clinical, endoscopic, or histopathological evidence [8, 9]. Colombel et al. [9] retrospectively reviewed 143 CT enterography studies and found endoscopic severity was significantly correlated with bowel enhancement, engorgement of the vasa recta, and fat density. Histopathological inflammation had the strongest correlation with bowel enhancement. Interestingly, the CRP correlated with perienteric inflammation but not inflammation limited to the small bowel wall. Bodily et al. [8] compared CT enterography data from 96 patients who underwent ileoscopy. Terminal ileal mural attenuation and wall thickness correlated significantly with active disease. The importance of these two studies is that imaging has the possibility of justifying, guiding, and monitoring therapy. Reproducible measurements of wall attenuation and thickness would allow CT enterography to become an objective tool in the management of patients with Crohn's disease [26].

MR Enterography

One major drawback of CT enterography is the use of ionizing radiation. The median age of diagnosis of Crohn's disease is approximately 30 years [27]. In addition, the disease has a relapsing and remitting course. As a result, patients undergo multiple radiological investigations during their lifetime. MR examination of the small bowel permits evaluation without the use of ionizing radiation. The superior contrast resolution as compared to CT and the direct multiplanar image acquisition are other significant advantages [28]. Dynamic evaluation of the small bowel is also possible with dedicated sequences [29]. This allows the evaluation of peristalsis and the differentiation of strictures from spasm by repeated scanning of a defined area. This facility is not possible with CT as the high radiation dose is prohibitive.

Consensus on the optimal imaging technique has still to be decided as multiple variables exist: enterography vs. enteroclysis, pulse sequences used, type of enteric contrast agent, and timing of image acquisition. Enteroclysis requires intubation of the duodenum or proximal jejunum through which the contrast is infused, ideally as a continuous infusion, whereas enterography requires the subject to drink large quantities of fluid. Conflicting limited data exist [11, 30–32], on which is the best approach. Although studies have shown that distension is better with enteroclysis, this does not necessarily translate into improved diagnostic accuracy [30, 32]. Conventional enteroclysis has been shown to be the investigation of choice in diagnosing Crohn's disease [33], but there are distinct disadvantages associated with

nasojejunal tube placement. The nasojejunal tube requires fluoroscopic guidance to place which negates in part the radiation-free advantage conferred by MRI. In addition, placement of the tube is widely recognized as being an uncomfortable procedure [34].

The pulse sequences used in MR enterography are primarily a combination of T1-weighted and T2-weighted imaging in multiple orthogonal planes. The T1-weighted imaging can be performed with or without fat suppression and are the sequences of choice to assess enhancement postintravenous injection of gadolinium. The T2-weighted sequences are highly sensitive to fluid and, therefore, to the inflammatory change within the bowel wall and the perienteric fat. The development of fast breath-hold sequences has allowed MR enterography to become a possibility, but bowel peristalsis can still cause artifact. This can be minimized by using antispasmodic agents such as glucagon [35].

A variety of enteric contrast agents exist for use in MR enterography. These have variable appearances depending on the pulse sequence used. Negative agents are of low signal intensity on the T1- and T2-weighted imaging. These allow good visualization of enhancement postcontrast on the T1-weighted sequences and provide maximal contrast between the bowel and the surrounding inflammation on the T2-weighted imaging. Positive contrast agents are of high signal on all sequences. They demonstrate wall thickening, but appreciation of enhancement on T1-weighted scans is limited by the high luminal signal [36]. Biphasic agents vary their signal intensity depending on the acquisition sequence. This is usually low on T1-weighted and high on T2-weighted imaging. Water would give this appearance but is rapidly absorbed by the proximal small bowel [37]. VoLumen acts as a biphasic agent and as demonstrated by CT enterography provides good luminal distension [5]. Currently, no trials exist to validate its use in MR enterography.

The optimal timing of image acquisition after drinking oral contrast is variable and dependant on multiple factors. These include the ability of the patient to drink, presence of disease including strictures, the type of oral contrast being administered, and the patient's inherent transit time [38]. Early initial scanning has been advocated at 20 min postcontrast ingestion and then further image acquisition dependant on where the majority of the contrast bolus is located [38]. As in CT enterography, there is also still debate regarding the optimal timing of image acquisition postintravenous contrast. Repeated scanning during multiple phases and time points is perceived as less of an issue with MR compared to CT due to the absence of ionizing radiation. Multiple acquisitions can as a consequence be obtained without a radiation penalty.

The acute findings in Crohn's disease on MRI are similar to those reported on CT, namely mucosal/mural hyperenhancement and stratification, engorgement of the vasa recta, and perienteric stranding (Fig. 14.4). Complications such as fistulas, sinus tracks, and abscesses can also be assessed. Much of the data regarding the performance of MRI compared to conventional barium studies has evaluated MR enteroclysis. This has been shown to be superior to conventional enteroclysis [31, 39, 40] with added advantage of being able to assess the extraluminal manifestations of Crohn's disease.

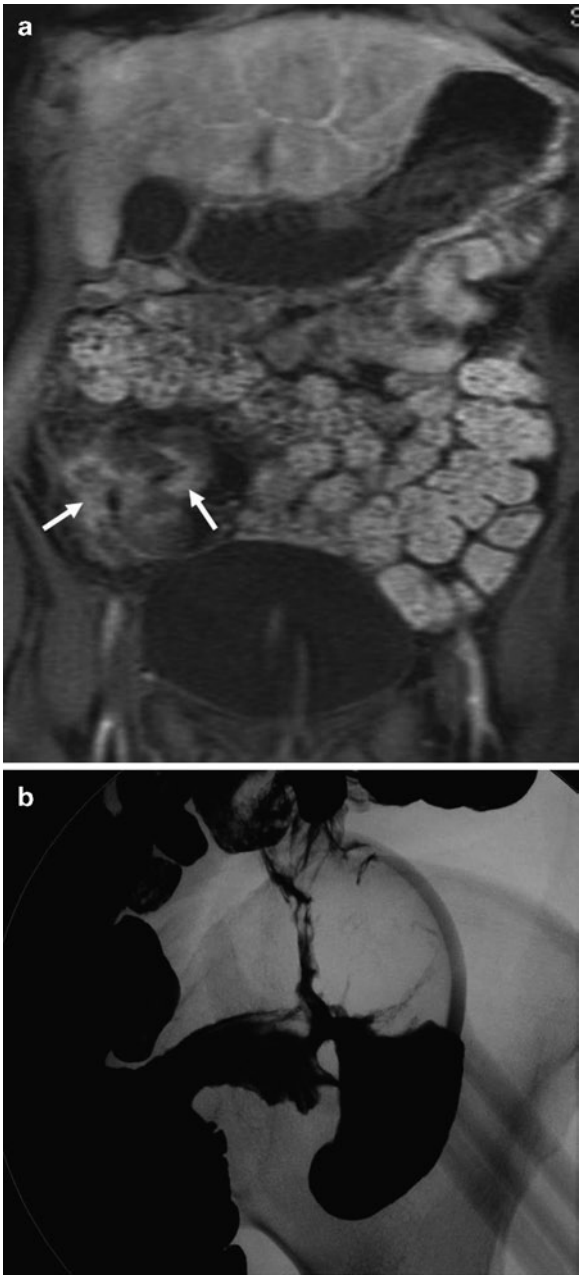

Fig. 14.4 (**a**) Contrast-enhanced T1-weighted fat suppressed coronal MR enterography image with positive oral contrast demonstrates terminal ileal mucosal hyperenhancement and mural thickening consistent with acute inflammation (*short white arrows*). (**b**) Single view from a single contrast small bowel series of the same patient shows active inflammation of the terminal ileum

Wireless endoscopy has been shown to be more sensitive than MRI in the detection of inflammatory mucosal lesions [41, 42]. As mentioned before, the technique is contraindicated in patients with strictures and limited in the diagnosis of extraenteric involvement. In keeping with CT, there is correlation between disease

activity and imaging findings. Multiple markers of disease activity have been correlated with MRI findings. These include endoscopic findings [43–45], acute phase reactants [46], surgery [44], and clinical disease activity indices such as the Crohn's Disease Activity Index [47]. Features such as wall thickness, mural enhancement, increased mesenteric vascularity, wall T2 signal, and fibrofatty proliferation T2 signal have been found useful in identifying and predicting disease activity [43–47].

Although MR evaluation of the small bowel holds great promise, it is not without its short comings. When compared with CT, there is inferior spatial resolution and examinations are lengthy despite faster breath-hold sequences. This compounded with the limited availability of MR scanners makes accessibility for all patients an issue. MRI may serve well a selective cohort of patients, such as the young, who would benefit maximally from the lack of ionizing radiation.

Evaluation of Perianal Disease

Perianal Crohn's disease encompasses a wide range of conditions including skin tags, ulceration, fissures, abscesses, and fistulas. Perianal fistulas occur in up to 36% of cases, [48] with almost 100% incidence when there is rectal Crohn's involvement [49]. Fistulas associated with Crohn's disease tend to be complex with secondary extensions and abscesses and, as a result, their diagnosis and treatment can be particularly challenging. Accurate anatomical mapping and the identification of abscesses are imperative as they determine the outcome of both medical and surgical treatment [50]. Failure to appreciate the complexity of fistulas may be responsible for the high rate of recurrence [51].

Historically, contrast fistulography has been used to delineate fistula anatomy. The external opening is cannulated and injected with water soluble contrast medium under fluoroscopic control. The study is limited in that complex fistulas and abscesses may be underdiagnosed if they fail to fill with contrast. In addition, the relationship between the sphincter complex and levator plate cannot be assessed. An accuracy of only 16% has been shown using this technique [52]. CT also has major limitations in the evaluation of perianal Crohn's disease. It lacks the adequate contrast resolution to accurately differentiate fistulas from the sphincter complex unless the fistulas contain air or contrast [53]. A role, however, exists for CT in the guidance of drainage of deep pelvic abscesses.

High soft-tissue contrast resolution, true multiplanar capability, wide field of view, and the lack of ionizing radiation all make MRI a well-suited examination for the diagnosis of perianal Crohn's disease. The use of MRI in pelvic Crohn's disease has been described as far back as 1989 [48] with subsequent technological advances in both hardware and dedicated sequences making this a powerful tool. Most protocols use a combination of T1 and T2-weighted sequences in the axial and coronal planes with and without fat suppression. Imaging can be supplemented with dynamic intravenous gadolinium-enhanced sequences and by MR fistulography. Image acquisition is performed with either a phased array body coil

or an endoanal coil. Endoanal coils provide high-resolution imaging of the sphincter complex and the internal openings of the fistulas [54]. They have, however, several disadvantages, which include small field of view, poor patient tolerance in the setting of perianal disease, and high signal flare adjacent to the coil, which may obscure the internal fistula opening [55]. If extensive disease is suspected, examination with a phased array coil is mandatory. It provides a wider field of view and, therefore, defines the full extent of the disease and adequately visualizes the supralevator space [56].

T1-weighted images provide anatomical information of the sphincter complex and demonstrate active fistulas as low signal with enhancement postgadolinium. The active fistula track is of high signal on T2-weighting (Fig. 14.5). Fistula conspicuity is accentuated by using fat suppression, which eliminates the high signal from fat in the pelvis thus maximizing tissue contrast. Inactive fistulas have low signal on T2-weighted images. Fistulas can be classified according to the Parks' classification [57], a surgical-based classification, to provide the surgeon with a road map, which should minimize both operative trauma to the anal sphincters and subsequent recurrence. Fistulas can also be classified according to the St James's University Hospital classification [58], which is an MR imaging-based classification.

Anal endosonography (AES) involves the use of a high-frequency (between 10 and 16 MHz) endoanal rotating probe, which provides 360° cross-sectional images of the anal sphincter. The internal sphincter appears as a hypoechoic ring while the external sphincter is of mixed echogenicity. Active fistulas are visualized as hypoechoic tracks secondary to fluid content. Foci of hyperechogenicity within the tracks represent air. If the track is inactive, then the hypoechogenicity is less pronounced and there is no air present [59]. The use of contrast agents, such as hydrogen peroxide and Levovist (Schering Pty. Ltd., Alexandria, Australia), have improved accuracy [60–63]. The external orifice of the fistula track is cannulated and contrast injected. Small air bubbles form within the track giving a hyperechoic appearance and improving conspicuity.

Recent developments have occurred in the field of AES. Three-dimensional (3D) AES allows a 3D volume to be reconstructed from multiple parallel transaxial images. The data are displayed as a cube, which can be rotated and viewed at different angles [64]. Multiplanar reformats in coronal, sagittal, and oblique planes can also be obtained. Accuracy of diagnosis has also been improved by using computer-assisted evaluation of the ultrasound images. Quantitative and objective assessment of the images by dedicated image-analysis software has raised the diagnostic performance of the technique to values comparable to MRI [59]. AES allows rapid evaluation in real time with no use of ionizing radiation and provides high-resolution images of the sphincter complex. It is relatively cheap and can be performed in an ambulatory setting. Its primary limitation is the limited field of view it provides, which results in suboptimal visualization of the ischiorectal fossa and the supralevator area. This can lead to abscesses and fistulas being missed, and as a consequence, a high rate of recurrence [65]. In addition, the endoanal probe cannot be tolerated in a proportion of patients with perianal inflammation due to anal stenosis or pain.

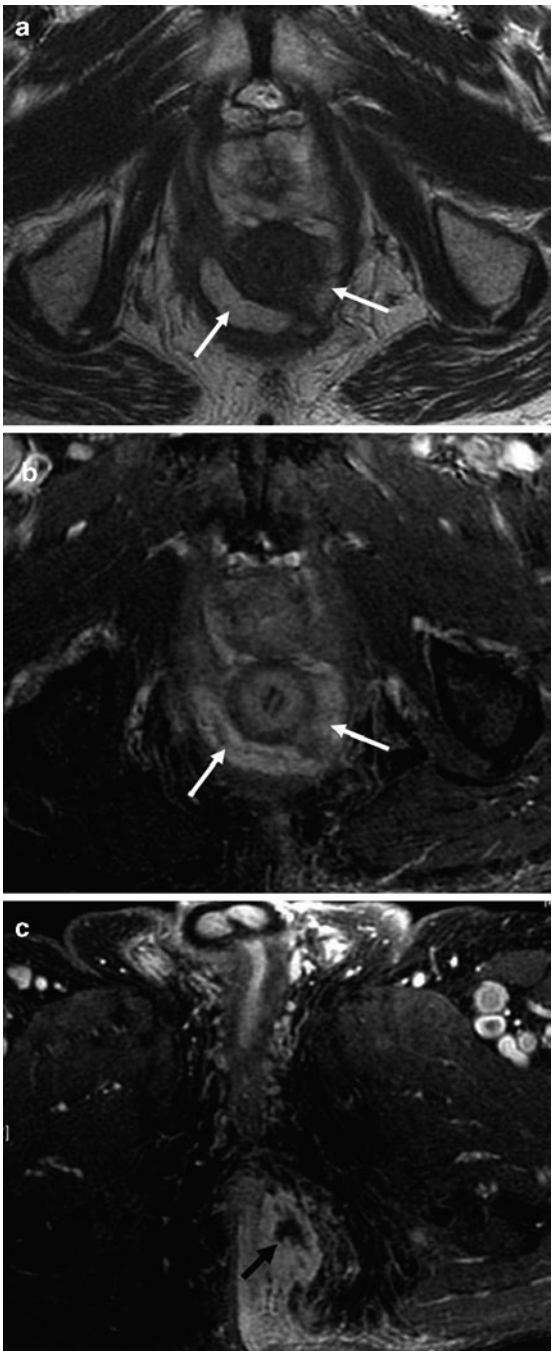

Fig. 14.5 T2-weighted axial MR image (**a**) and contrast-enhanced T1-weighted fat suppressed axial MR images (**b**, **c**) demonstrate an enhancing horseshoe fistula in the intersphincteric space (*white arrows*, **a**, **b**). A peripherally enhancing abscess is noted in the left ischioanal fossa (*black arrow*, **c**)

Transcutaneous perianal ultrasound (PAUS) is an additional technique that can be used to assess perianal sepsis. Unlike MRI or AES, it does not require specialized hardware and can be performed with widely available high-resolution linear ultrasound transducers. PAUS can be used in patients who cannot tolerate an endoanal probe or where MRI is contraindicated. It allows a cheap, quick real-time assessment of the perianal region. In conjunction with transvaginal scanning, it can also provide a large field of view [66]. Studies have shown that it is accurate in detecting and classifying perianal fistulas and/or abscesses in Crohn's disease [67] with sensitivity comparable to MRI [68]. Limitations, however, include poor visualization of the internal sphincter and a relatively steep learning curve to become proficient [66, 68].

Recently, there has been a shift in emphasis in the use of radiology in perianal Crohn's disease. Traditionally, its indication was confined to the diagnosis and mapping of disease preoperatively. The development, however, of the drug, infliximab, has resulted in a role for radiology in monitoring response to therapy. Infliximab is an antitumor necrosis factor antibody that is the only drug that has been shown to result in fistula closure [69]. It is administered initially as a three dose induction course with further maintenance treatments at 8 week intervals. Several trials [50, 70, 71] have assessed the clinical and radiological healing of the fistulas post treatment. A combination of MRI [50, 70] and PAUS [71] was used for follow up. These studies have consistently shown that despite the presence of fistula healing clinically, fistulas may persist radiologically. The significance of this is that if infliximab therapy is terminated prematurely prior to radiological healing, early relapse may occur [71]. As the use of infliximab increases, radiology will be crucial in guiding therapy.

The preferred investigation for perianal disease depends in part on local expertise, facilities available, and patient tolerance. Two prospective studies, however, have compared these techniques with surgical EUA in patients with Crohn's disease [72, 73]. Schwartz et al. [72] found that all three techniques had an accuracy of over 85%. By combining any two procedures, the accuracy improved to 100%. By contrast, Orsoni et al. [73] found AES to be the most sensitive modality. The agreement of ultrasound and MRI with EUA was 82 and 50%, respectively. The low agreement of MRI with EUA in the study by Orsoni et al. [73] may be due to the fact that a whole body coil was used rather than a phased array coil, which provides thinner slices and better spatial resolution. Another major difference was that Orsoni at al. used EUA as the gold standard whereas Schwartz et al. [72] used a consensus opinion of all three techniques to establish the gold standard. A further study [74] evaluated all three methods against a reference standard that comprised consensus between the three examinations and clinical follow up. Only 8 out of the 108 patients had Crohn's disease. There was a significant linear trend in the proportion of fistula tracks correctly classified: EUA (61%), AES (81%), and MRI (90%). Systematic evidence-based review has demonstrated that MRI is the investigation of choice in accurately classifying perianal fistulas [75].

Evaluation of Biliary Disease

Extraintestinal manifestations occur in approximately 25% of patients with inflammatory bowel disease [76]. One of the most significant conditions is PSC. This occurs in up to 7.5% of patients with ulcerative colitis and 3.4% of patients with Crohn's disease [77]. Seventy to eighty percent of patients with PSC have ulcerative colitis [78].

Cholangiography, usually endoscopic retrograde cholangiopancreatography (ERCP), is considered the gold standard for diagnosis of PSC [79]. It is however invasive with associated complications, such as infection and pancreatitis [80]. These are thought to occur more frequently in patients with PSC rather than those without [81]. In addition, it involves ionizing radiation. MR cholangiopancreatography (MRCP) provides an alternative without the aforementioned problems. MR imaging also allows assessment of ducts proximal to obstruction and in combination with routine liver MR sequences can evaluate the duct walls and hepatic parenchyma [82]. Complications of PSC, such as cholangitis and cholangiocarcinoma, can therefore be diagnosed.

MRCP images are obtained by using heavily T2-weighted sequences that return a high signal from the slow moving bile. The background is conversely of low signal thus optimizing visualization of the pancreaticobiliary system. Sequences are obtained during breath-hold and without intravenous contrast. Thick and thin collimation oblique coronal slabs are obtained. Thick slabs provide an overview of the entire ductal system producing images similar to conventional cholangiography. The thin slab images provide increased detail, which can identify small filling defects that may be missed on the thick images [83]. Imaging is usually supplemented with a routine MR liver protocol including T1 and T2-weighted sequences and dynamic postgadolinium acquisitions to identify duct wall and liver parenchymal abnormalities [84].

The classical appearance of PSC on MRCP images is of multiple diffuse short (1–2 mm) strictures that alternate with normal or slightly dilated segments [85] (Fig. 14.6). This can affect both the intra and extrahepatic biliary system producing a beaded appearance. Peripheral duct side branches become obliterated as the disease progresses resulting in "pruning." Other abnormalities identified are webs, diverticula, and stones [82]. Conventional liver protocol MRI may demonstrate further abnormalities. These include peripheral wedge-shaped areas of T2 hyperintensity and peripheral areas of increased enhancement on the contrast-enhanced arterial phase [86]; both may be caused by acute cholangitis or confluent hepatic fibrosis. Morphological hepatic changes include atrophy of the right and left lobes with caudate lobe hypertrophy [87]. Periportal and portacaval lymphadenopathy can also be seen and is not necessarily associated with malignancy [86].

Cholangiocarcinoma is the most feared complication of PSC and occurs in 10–15% of patients with PSC [80]. Features that suggest the diagnosis include high-grade ductal narrowing, rapid progression of strictures, long strictures, marked ductal dilatation distal to strictures, and polypoid lesions [88]. Tumors are usually

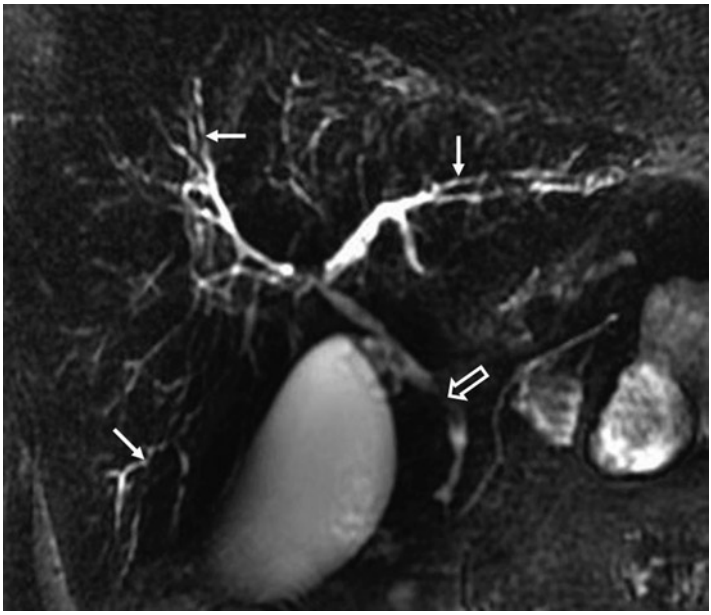

Fig. 14.6 Oblique coronal, thick slab MRCP image demonstrates multiple short intrahepatic (*white arrows*) and extrahepatic (*open arrow*) biliary strictures alternating with areas of mild dilatation in keeping with primary sclerosing cholangitis

hypointense on T1 and hyperintense on T2-weighted images. Enhancement is variable but can demonstrate progressive enhancement on delayed imaging due to the tumors fibrous composition [82]. MR is important not only in diagnosis but also in determining respectability.

Debate persists whether MRCP can match ERCP in its ability to diagnose PSC. ERCP has superior spatial resolution and may be more sensitive for the early signs of PSC such as wall irregularity [89]. Multiple studies [90–93] have compared the diagnostic capabilities of each test and demonstrated comparable diagnostic accuracy. MRCP may even depict more strictures of the peripheral intrahepatic ducts [94]. However, results thus far, using MR imaging to predict clinical severity and prognosis, have been disappointing [95, 96].

Future Techniques

MR Colonography

MR colonography is a relatively new technique that utilizes the excellent soft-tissue contrast of MR to evaluate the colon without ionizing radiation. Its evolution has been primarily driven by the need to develop noninvasive tools to diagnose

colorectal polyps, the noncancerous precursor to colorectal cancer. Several trials, however, also exist of its use in inflammatory bowel disease [97–100]. Unlike CT and MR enterography, which are essentially used to diagnose and assess Crohn's disease, MR colonography evaluates both ulcerative colitis and colonic Crohn's disease.

Prior to the examination, full cathartic bowel preparation is required. Immediately before the procedure, the colon is filled with fluid via a rectal catheter to produce adequate distension. The fluid instilled can result in either a bright or a dark signal lumen on T1-weighted imaging. A gadolinium-DTPA/water mixture results in high signal while water alone results in low signal [101]. To maximize the contrast between the lumen and the enhancing wall postintravenous gadolinium, a dark lumen technique is preferred [102]. Imaging should be performed using a combination of fast T1- and T2-weighted sequences in the coronal and axial plane with intravenous gadolinium and an antispasmodic to reduce bowel peristalsis. Virtual endoscopy is of limited value in the setting of inflammatory bowel disease [103] and has not found to add clinical information [98]. The predominant findings of colonic wall thickening and enhancement can be well appreciated on the axial and coronal images.

MR colonography is still in its relative infancy and is yet to be fully validated in its performance against the gold standard colonoscopy. Colonoscopy, however, is an invasive procedure with associated risks. In order for MR colonography to be a viable alternative to colonoscopy, it must be able to accurately diagnose and quantify inflammatory activity. Evidence at present [97, 98] is inconclusive. Comparison of individual colonic segments on MR colonography against a colonoscopic or histopathological reference has yielded sensitivities ranging from 31.6 to 87% [97, 98]. Specificity performs better ranging from 91.4 to 100%. One area where MR colonography may hold an advantage is if the test could be performed without bowel preparation. Bowel preparation has been recognized to be the least favored part of colonic examinations [104]. Results to date in unprepared studies have also been disappointing with sensitivities ranging from 30.2 to 70.2% [99, 100]. The current use of MR colonography in inflammatory bowel disease is limited. As technology advances and techniques are refined, its position as a complimentary test to optical colonoscopy will certainly become established [105].

PET/CT

Oncological indications are the primary use of PET–CT scanning, where it is used to detect, stage, and monitor tumors. PET imaging is most commonly obtained by using a positron emitting isotope, such as 18-fluorodeoxyglucose (FDG). FDG is a glucose analog taken up by metabolically active tissue with high glycolytic rates such as malignancy, inflammation, and infection [106]. The degree of uptake is proportional to the metabolic activity [107]. Current technology allows CT imaging

to be obtained by the same machine at the same sitting thereby fusing the functional information from the PET with anatomical localization from the CT scan.

The advantage conferred by this method is that disease activity can be assessed and monitored by a noninvasive technique. Multiple trials have assessed PET alone in inflammatory bowel disease [108–112] with high sensitivities ranging from 80 to 100%. Several of these trials [110–112] have only looked at the pediatric population. Many traditional radiological and endoscopic investigations are invasive and may be embarrassing for the teenage population [112, 113]. PET allows painless, noninvasive assessment of both the large and small bowel, without the need for bowel preparation.

Recent studies [114, 115] have used PET–CT to assess inflammatory activity. Using endoscopy, radiological studies and disease activity indices as the gold standard sensitivities as high as 100% have been achieved [114]. Interestingly, this high sensitivity was for a subset of severe endoscopic lesions such as deep ulcers and strictures. The sensitivity, however, dropped to 72.9% when all endoscopic lesions were assessed.

Several limitations exist for the use of PET–CT. High costs, limited availability of scanners, and large radiation doses make this test prohibitive for widespread implementation. Other issues of note include the relevance of positive areas of FDG avidity with no endoscopic correlate and whether the PET changes associated with treatment mirror disease activity.

Conclusion

The radiological investigation of inflammatory bowel disease continues to evolve, enhancing the treatment of patients. Several of the new radiological investigations discussed in this chapter are now well established and have replaced traditional diagnostic tests in many centers. As a result expertise will continue to grow, and through research the true capabilities will become realized. The shift from diagnosis to monitoring disease progression and treatment is an exciting prospect that will aid the clinician in the often difficult management of patients with inflammatory bowel disease.

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Chapter 15
Novel Techniques in the Diagnosis of Inflammatory Bowel Disease

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Keywords Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Anti-*Saccharomyces cerevisiae* antibodies • Perinuclear antineutrophil cytoplasmic autoantibodies • Anti-OmpC • Anti-I2 • Anti-CBir1 • Fecal calprotectin • Fecal lactoferrin • Capsule endoscopy • Patency capsule • Double-balloon enterography • CT enterography • MR enterography • MR colonography • Magnification endoscopy • Chromoendoscopy • Confocal laser endomicroscopy • Optical coherence tomography

Key Points

- Substantial advances in the diagnosis and management of inflammatory bowel disease (IBD) have arisen from novel laboratory and radiographic tests, as well as from endoscopic luminal and mucosal imaging techniques.
- Serological markers used in combination may be helpful in differentiating between Crohn's disease and ulcerative colitis.
- Elevated levels of calprotectin or lactoferrin in the feces may be helpful in assessing disease activity and response to medical therapy in IBD patients.
- Capsule endoscopy and double-balloon enteroscopy are considered to be complementary in the evaluation of suspected small intestinal disorders.
- The Consensus Committee on Colorectal Cancer Surveillance in IBD has endorsed the incorporation of chromoendoscopy performed by trained endoscopists for CRC surveillance in patients with ulcerative colitis.
- CT enterography may be the preferred test in the initial evaluation of suspected small bowel Crohn's disease.

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Introduction

Inflammatory bowel disease (IBD) is defined as a spectrum of inflammatory disorders of the gastrointestinal tract, and includes Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC). Due to the absence of a gold standard for evaluation, the diagnosis and classification of IBD is usually established by a combination of tests (laboratory, endoscopic, and/or radiologic) in the presence of clinical symptoms. The diagnosis of this group of disorders, particularly small bowel disease, has proven considerably difficult in the past, due to a myriad of clinical presentations, and paucity of diagnostic tests to effectively evaluate the small bowel. The recent evolution in diagnostic modalities holds great promise in overcoming these limitations of the past. Novel techniques including laboratory tests (serologic and fecal markers), endoscopic modalities (capsule endoscopy and double-balloon enteroscopy), radiologic studies (CT enterography, MR enterography, CT colonography (CTC), and MR colonography (MRC)), and endoscopic mucosal imaging techniques (magnification endoscopy, chromoendoscopy, confocal laser endomicroscopy, and optical coherence tomography (OCT)) represent significant advancements both in the diagnosis and long-term management of IBD.

Laboratory Markers

Serologic Markers

The presence of antibodies in the serum of patients with IBD serves as a noninvasive adjunct for diagnosis of IBD, differentiation between UC and CD, classification of patients with IC, and determination of disease prognosis. The main serologic markers include anti-*Saccharomyces cerevisiae* antibodies (ASCA), perinuclear antineutrophil cytoplasmic autoantibodies (pANCA), antibodies to *Escherichia coli* outer membrane porin (anti-OmpC), antibodies to *Pseudomonas fluorescens* (anti-I2), and antibodies to CBir1 flagellin (anti-CBir1).

ASCA antibodies (IgA and IgG) are targeted against *S. cerevisiae*, which is also known as baker's or brewer's yeast. It is unclear whether these antibodies arise as a result of an immunologic response to antigens on *S. cerevisiae* or an unrecognized autoantigen that cross reacts with the yeast antigens. ASCA antibodies have been reported in 40–70% of patients with CD [1–3]. However, these antibodies are not specific for CD, as they have also been detected in 5–15% of patients with UC (12%) [4, 5], 40–60% of patients with celiac sprue [6, 7], and up to 4% of healthy controls [5]. In addition to serving as markers for the diagnosis of CD, ASCA antibodies may be predictive of an aggressive phenotype of CD with stricturing and penetrating disease, and a greater likelihood of surgery [8–10].

Atypical pANCA are markers for the diagnosis of UC, and may be present in the serum of 45–82% of patients with UC and 5–15% of patients with CD [2, 3]. The atypical pattern of staining with pANCA is characterized by perinuclear fluorescence with outward diffusion into the cytoplasm, described as a "snow-drift appearance" [11]. pANCA antibodies have been reported to predict the occurrence of both acute and chronic pouchitis after proctocolectomy and ileal pouch anal anastomosis, in patients with UC [12, 13]. In addition, the risk for pouchitis appears to correlate with the titer of autoantibodies prior to colectomy, with a greater likelihood of pouchitis in patients with higher titers of pANCA [14].

The combination of serologic markers (ASCA and pANCA) is of considerably more value in the differentiation between CD and UC, than either marker alone. These combinations of ASCA+/pANCA− and ASCA−/pANCA+ have a positive predictive value of 77–96% for distinguishing between these two disorders [2, 3]. The presence of ASCA and absence of pANCA have a sensitivity of 30–64% and specificity of 92–97% for CD. Likewise, the presence of pANCA and absence of ASCA have a sensitivity of 44–58% and specificity of 81–98% for UC [5, 15–17]. In terms of likelihood ratios, patients who are ASCA+/pANCA− are 16 times more likely to have CD, and patients who are pANCA+/ASCA− are 19 times more likely to have UC [18]. ASCA and pANCA may also play a role in the appropriate classification of IC. ASCA+/pANCA− is predictive of CD in 80% of patients, while ASCA−/pANCA+ is predictive of UC in 64% of patients. However, the utility of these markers in IC appears to be limited, as 48.5% of patients do not express either of these antibodies [19].

ASCA and ANCA do not appear to have much utility in predicting response to medical therapy. Esters et al. [20] evaluated the role of these serologic markers in 279 patients with CD being treated with infliximab, and found no correlation between presence of the immunologic markers and response to therapy.

Additional serologic markers have been identified in IBD, but their true role in the diagnosis and management of these disorders is not entirely clear. Antibodies to *E. coli* outer membrane porin (anti-OmpC) have been reported in 24–55% of patients with CD [21], and may be associated with an aggressive fistulizing phenotype of the disease [22]. These antibodies may also be present in about 11% of patients with UC and 5% of healthy controls [23]. The seroprevalence of I2 antibodies targeted against *P. fluorescens* is reported to be about 50% in patients with CD, 42% in patients with UC, and 36% in patients with IC [21, 24]. Similar to anti-OmpC, these antibodies may also denote the presence of internal penetrating and stricturing disease [10]. An immunologic response to flagellin CBir1 has been reported in 50% of patients with CD, 6% of patients with UC, and 8% of control patients [25, 26].

Despite their utility, one has to maintain caution in the interpretation of serologic markers in patients with a low pretest probability for IBD, due to a high false positive rate of up to 30% in both healthy controls and patients with irritable bowel syndrome [27]. Similarly, these markers may not offer any additional input in the diagnosis of patients with a high pretest probability for IBD.

Their main benefit appears to lie in the evaluation of patients with a moderate pretest probability for IBD, in conjunction with endoscopic and/or radiologic studies [28, 29].

Fecal Calprotectin

Calprotectin is a 24 kD heterodimer present in polymorphonuclear cells (PMNs), monocytes, macrophages, and epithelial cells, which is released from leucocytes after cell disruption or death. In addition, a soluble form of the protein is present in plasma, feces, urine, and saliva [30, 31]. Fecal calprotectin serves as a noninvasive biomarker of intestinal inflammation, and has been found to be useful in diagnosing IBD, assessing response to medical therapy, and in predicting clinical relapse [32–35]. Levels of fecal calprotectin have been reported to be elevated in both pediatric and adult patients with IBD, relative to healthy controls [36, 37]. In addition, the fecal concentration of the marker has been shown to correlate with endoscopic and histologic disease activity [38, 39]. Fecal calprotectin may also serve as a noninvasive test to screen for postoperative recurrence of Crohn's disease. Costa et al. [40] evaluated 12 patients who had undergone intestinal resection for CD and found elevated levels of fecal calprotectin in all 8 patients who had postoperative recurrence, while the patients without recurrence had normal levels of the protein. Several studies have evaluated the role of calprotectin in predicting relapse of IBD. A study by Tibble et al. [33] reported a sensitivity of 90% and specificity of 83% with fecal calprotectin, for detecting relapse of IBD. Based upon a separate study by Costa et al. [41] the sensitivity for detection of relapse appears to be higher for UC (90%) as compared to CD (43%). Based on small case series, fecal calprotectin also appears to be of benefit in determining an objective response to medical therapy in patients with IBD [42, 43].

Fecal Lactoferrin

Lactoferrin is a 76 kD glycoprotein, which is present in PMNs and absent in monocytes and macrophages. It is secreted by mucus membranes, and may be present in serum, milk, synovial fluid, lacrimal fluid, and feces. Infiltration of PMNs into the intestinal mucosa and their subsequent degradation leads to increased fecal lactoferrin in patients with intestinal inflammation [44]. Similar to fecal calprotectin, higher lactoferrin levels have been found in patients with IBD, as compared to controls [45]. Fecal lactoferrin has been reported to have a high sensitivity (90%) and specificity (98%) for evaluation of disease activity, and may also be useful in determining response to medical therapy [44, 46–48]. In addition, the marker may be useful in evaluating postoperative recurrence of CD, with a sensitivity of 71% and specificity of 90% [49].

Endoscopy

Capsule Endoscopy

Capsule endoscopy (CE) has revolutionized our ability to evaluate the entire small bowel mucosa. CE is currently FDA approved for use in both pediatric patients (older than 10 years) and adults [50]. The advantage of CE, over other endoscopic techniques, is its ability to allow visualization of the entire small bowel in a noninvasive manner [51]. Two SB capsule endoscopes are currently available, the PillCam SB (Given Imaging, Yoqneam, Israel; http://www.givenimaging.com) and EndoCapsule (Olympus, Tokyo, Japan; http://www.olympusamerica.com). Both systems include a wireless capsule endoscope (26×11 mm), data recorder, and computer workstation. The PillCam SB capsule includes a lens, light source, CMOS (complementary metal oxide semiconductor) imager, battery, and wireless transmitter. The Endocapsule differs from the Pillcam capsule in that it uses a CCD (charged-couple device) imager as opposed to CMOS [52].

The capsule traverses the gastrointestinal tract by peristalsis and has the capacity to take images at the rate of two images per second over an 8 h period. The main indications for CE include obscure gastrointestinal bleeding and CD. Other potential indications include celiac disease and surveillance of polyposis syndromes. The yield for CE in the evaluation of abdominal pain or diarrhea is quite low [53]. Preliminary studies in patients with obscure gastrointestinal bleed have found a similar overall yield and safety profile with both the Pillcam and Endocapsule [54–56].

SB involvement occurs in up to 70% of patients with CD, and up to 30% of these patients have isolated SB involvement [57]. Diagnosis of SB Crohn's has been difficult in the past, due to only limited evaluation of the proximal and distal small bowel by push enteroscopy (PE) and ileoscopy respectively [58]. CE not only facilitates diagnosis of CD which may be missed on conventional endoscopy but also may allow for an accurate assessment of the extent of SB disease (Fig. 15.1).

CE has been established as superior to other diagnostic modalities in the evaluation of patients with CD. A meta-analysis of 11 studies that compared CE to other diagnostic techniques (ileoscopy, PE, small bowel follow through (SBFT), enteroclysis, CT enterography, and MR enterography) showed that CE had a significantly higher diagnostic yield in CD patients overall [59]. The yield for CE vs. SBFT was 63 and 23% respectively (IY_w 40%); yield for CE vs. ileoscopy was 61 and 46% respectively (IY_w 15%); yield for CE vs. computed tomographic enterography (CTE) was 69 and 30% respectively (IY_w 38%); and yield for CE vs. PE was 46 and 8% respectively (IY_w 38%). Subanalysis of this data revealed a significantly higher yield for CE in patients with established CD, but not for suspected CD, which may have been due to a type II error.

The diagnostic yield of CE compared to other modalities in patients with suspected CD has been evaluated in multiple prospective studies. The yield of CE has been reported to range from 9 to 77%, as compared to 0–23% yield with SBFT [60–64]. The yield of CE (28–58%) has been found to be comparable to, and may be slightly

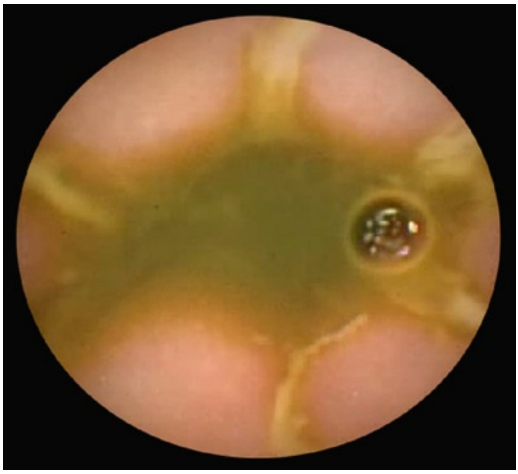

Fig. 15.1 Circumferential ulceration in distal ileum seen on video capsule endoscopy in a patient with small bowel Crohn's disease

higher in comparison to ileoscopy (21–53%) [60, 62, 64, 65]. Two studies that compared CE to PE showed a higher yield with CE (9–28% vs. 0–10% respectively) [62, 63], and two additional studies showed a higher yield of CE as compared to CTE (37.5–77% vs. 20–25%) [61, 64]. A more recent updated meta-analysis also suggests that CE may have a higher diagnostic yield than SBFT, not only for established but also for suspected CD [66].

CE has been reported to impact medical management, with resultant clinical improvement in more than 70% of patients who undergo this diagnostic test [67, 68]. According to the ICCE Consensus Committee for Inflammatory Bowel Disease, CE may alter disease management of patients with established CD, by providing information on the extent and severity of SB inflammation, and appears to have a potential role in patients with suspected CD, who have had negative radiologic and endoscopic evaluations (http://www.icce.info/en-int/Pages/consensus.aspx). However, larger prospective studies are considered necessary to confirm those observations [69].

CE may be useful in the appropriate classification of patients with indeterminate colitis. Mow et al. evaluated the role of CE in patients with indeterminate colitis, and showed that CE allowed a diagnosis of CD in 22% of the patients, with SB findings suspicious for CD in an additional 7% [67]. Based upon additional studies, CE facilitates a diagnosis of SB Crohn's in up to 40% of patients with indeterminate colitis [71–73].

An additional role for CE is the detection of postoperative recurrence of CD. Bourreille et al. compared the yield of CE and ileoscopy for the diagnosis of postoperative CD. Although ileoscopy had a higher sensitivity for the detection of SB recurrence (90% vs. 62%), CE facilitated detection of SB lesions in 67% of patients in proximal locations not accessible to ileoscopy. The overall lower yield of CE may have been related to compromised mucosal visualization in the neoterminal ileum [58].

One of the main limitations related to the use of CE in CD is the low specificity of SB findings, and thus the inability to differentiate CD from other etiologies of SB inflammation [74]. It has a lower specificity than CTE in the diagnosis of CD

(53% vs. 89%) [75]. SB erosions and ulcerations detected on CE may be related to CD, celiac disease, infection, ischemia, radiation injury, autoimmune diseases, immunodeficiency syndromes, or drugs. Erosions and mucosal breaks may also be seen on CE in up to 13% of healthy volunteers on NSAIDs. It has hence been suggested that NSAIDs be discontinued at least a month prior to performing CE [76]. A CE scoring index has recently been proposed, and may eventually improve the specificity of CE findings. This index is based on three parameters (villous edema, ulceration, and/or stenosis), and allows standardized reporting of SB inflammation and an objective measurement of SB inflammatory activity [77].

In addition, CE may be complicated by a high retention rate of 6.7–13% in patients with known CD strictures [78, 79]. This risk for capsule retention can be avoided by identifying patients with strictures, performing a radiologic imaging study, balloon-assisted enteroscopy, or using the Agile patency capsule, prior to CE [80].

Agile Patency Capsule

The Agile Patency Capsule (Given Imaging, Yoqneam, Israel; http://www.givenimaging.com) is useful in preventing capsule retention, and is FDA approved in patients with suspected small bowel strictures or obstruction [81]. The system includes a patency capsule, patency scanner, and Testag. The capsule is similar in size to a capsule endoscope, and is composed of a body with radiofrequency identification tag (RFID) covered with lactose and barium, with a timer plug on either side. The RFID patency scanner allows detection of the RFID tag. The capsule is designed to disintegrate after a period of 30 h post ingestion. Patency of the intestinal tract may be confirmed by witnessed passage of the capsule by the patient, or absence of the RFID tag at or prior to 30 h post ingestion. Fluoroscopy may be used instead of the RFID scanner for detection of the tag in patients with pacemakers, or for accurate localization of the capsule. Herrerias et al. conducted a study of 106 patients with suspected strictures or obstruction, who ingested the patency capsule. Fifty-six percent of patients who excreted the capsule intact subsequently underwent CE without any cases of capsule retention. Significant findings on CE were present in 41% of these patients [82]. A similar study by Spada et al. found that the patency capsule was excreted intact after a mean transit time of 25.6 h in 65.3% of patients with known or suspected intestinal strictures. CE was performed in all these patients without any adverse events [83].

Double-Balloon Enteroscopy

Double balloon enteroscopy (DBE) (Fujinon Inc., Wayne, NJ; http://www.fujinon-endoscopy.com) was introduced by Yamamoto in 2001 for the evaluation of SB disorders [84]. DBE allows visualization of the entire SB, usually by a combined antegrade and retrograde approach in up to 86% of patients (Fig. 15.2). It has the advantage over CE of facilitating biopsies and therapeutic interventions [85, 86]. Both CE and DBE are considered to be complementary in the evaluation of SB

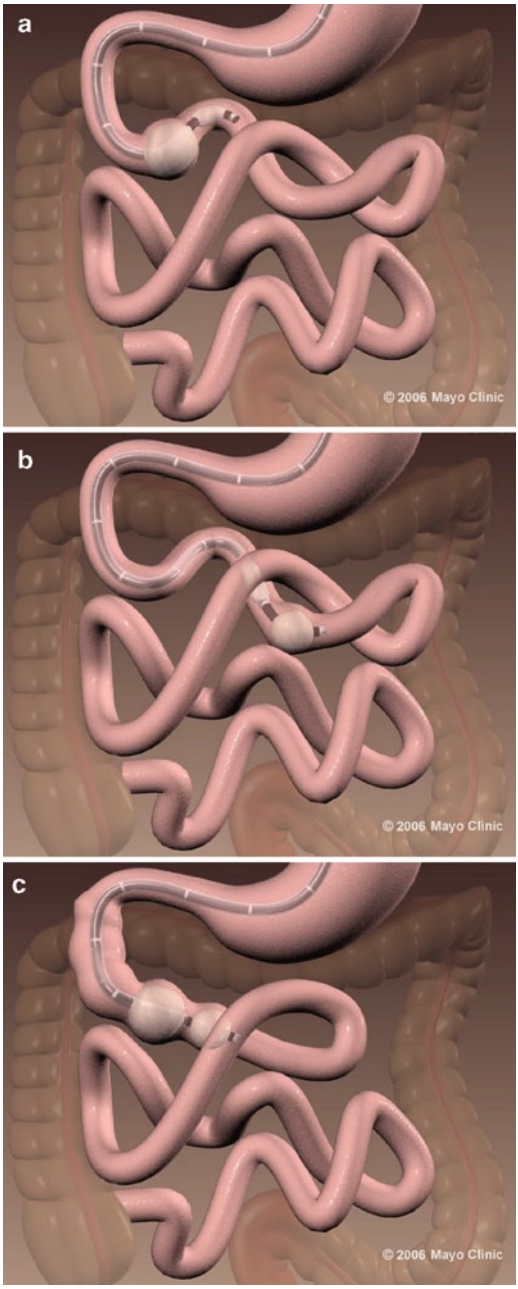

Fig. 15.2 Technique of antegrade double balloon enteroscopy (DBE). (**a**) Step 1 – Enteroscope and overtube are advanced into the small intestine and balloon on overtube is inflated. (**b**) Step 2 – Enteroscope is further advanced into small intestine and balloon on enteroscope is inflated. Step 3 – Overtube with balloon deflated is advanced over endoscope. (**c**) Step 4 – With both balloons inflated, system is withdrawn which allows telescoping of small intestine

disorders. DBE may have multiple potential roles in IBD, including diagnosis, determination of extent and severity of disease, documentation of endoscopic remission after medical therapy, performance of therapeutic interventions, and SB cancer surveillance (Fig. 15.3).

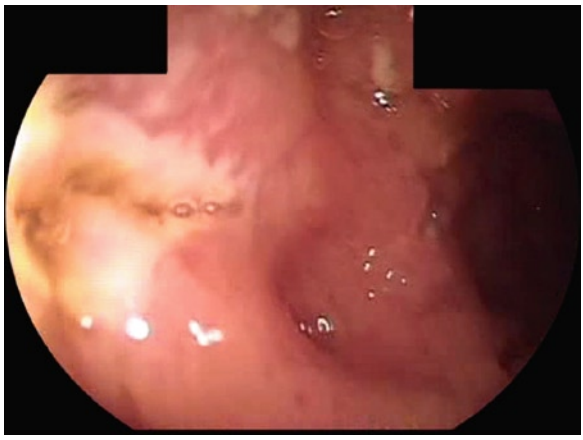

Fig. 15.3 Scattered ulcerations in distal ileum seen on retrograde DBE in a patient who presented with obscure GI bleed. Crohn's disease was confirmed on pathology

The yield of DBE for CD has been reported as 5–13% in patients undergoing DBE for suspected SB disorders, predominantly occult GI bleeding (OGIB) [85, 87]. The yield for SB disease has been found to be significantly higher in patients with established CD. Numata et al. [88] evaluated 22 patients with known IBD and suspected SB disease, of whom 96% had SB involvement confirmed on DBE. A study by Oshitani et al. compared the yield of DBE and SBFT in 40 CD patients. Sixty percent of patients had SB involvement proximal to the distal 20 cm of ileum, and hence not amenable to detection by ileoscopy [89]. The yield for mucosal erosions and ulcerations was found to be higher with DBE than SBFT. Both tests had similar yield for longitudinal and deep SB ulcerations. DBE did not facilitate detection of all ileal strictures, which may have been due to its purely endoluminal view or failure to reach the strictured areas (Figs. 15.2 and 15.3).

A meta-analysis of 11 studies that compared DBE and CE showed a comparable diagnostic yield with the two modalities, for both SB Crohn's and SB disorders overall. Hence, due to its ease of administration and relatively noninvasive quality, CE may be the preferred initial diagnostic test in suspected CD. Furthermore, CE may be useful in guiding the optimal route of DBE. DBE would then be indicated for the confirmation of diagnosis by biopsies, therapeutic interventions, and in patients with a negative CE, but high clinical suspicion for SB Crohn's [90].

In addition to diagnosis, DBE may also play an important role in the management of SB Crohn's. DBE may be useful in the evaluation of the underlying etiology of SB strictures in CD, whether inflammatory or fibrotic. It facilitates biopsies from SB strictures to rule out concomitant adenocarcinoma. DBE can also facilitate endoscopic removal of retained capsules in patients with SB strictures, hence avoiding the need for laparoscopic removal [89]. In addition, balloon dilation of CD strictures may be successfully performed with DBE, thereby obviating the need for stricturoplasty and surgical resection [91]. DBE allows therapeutic interventions for achieving hemostasis in patients with bleeding from SB ulcers.

Objective endpoints of endoscopic and histologic remission, as opposed to clinical response alone, are now considered essential to evaluate efficacy of treatment with

immunomodulator and antitumor necrosis factor therapy [92]. DBE may hence be useful in determining response to medical therapy, and necessity for surgery in patients with persistent SB inflammation, despite aggressive medical management. An additional role for DBE would be performance of SB chromoendoscopy for surveillance of dysplasia and SB adenocarcinoma, although data are limited [93]. Larger, prospective studies are necessary to determine the true utility of DBE in the management of small bowel CD.

Overall, DBE appears to be a safe procedure. The main complication of DBE in CD patients is perforation (2%), which has been described with inflation of the overtube balloon in the presence of deep linear ulcers [89, 94]. Other major complications with DBE, including ileus and pancreatitis, are rare [95, 96].

Endoscopic Mucosal Imaging Techniques

Current guidelines for colorectal cancer surveillance in patients with long standing UC include periodic performance of colonoscopies every 1–2 years, initiated after 8–10 years of disease. Due to a higher risk for CRC, earlier surveillance, preferably initiated at the time of diagnosis, is recommended for patients with concomitant PSC [97]. Due to the multifocality of dysplasia, a minimum of 33 biopsies (two to four random biopsies every 10 cm as well as targeted biopsies of all suspicious areas) throughout the colon is recommended, which has a positive predictive value of 90% for the detection of dysplasia [98]. The most important shortcoming of the current surveillance program is that it is a time-consuming process leading to both physician noncompliance and sampling error [99]. Less than 50% of gastroenterologists are reported to follow these recommendations, resulting in less than 30 biopsies per colonoscopy for up to 73% of gastroenterologists [100]. In addition, the strategy of random nontargeted colon biopsies carries the inherent risk of sampling error, with less than 1% of the colorectal mucosa adequately sampled with 32 colon biopsies [101]. Novel endoscopic mucosal imaging techniques have the potential to overcome these shortcomings, due to their ability to allow accurate identification and targeted tissue sampling of dysplastic and malignant lesions.

Magnification Endoscopy and Chromoendoscopy

Magnification endoscopy allows 100-fold magnification views of the mucosal surface, similar to stereoscopic microscopy, and therefore allows identification of mucosal details that are difficult to visualize with conventional colonoscopy [102]. Chromoendoscopy involves intravital staining of mucosal epithelium with the use of contrast or absorptive dyes. Methylene blue is an absorptive dye with a high affinity for noninflamed mucosa and low affinity for inflamed and dysplastic

mucosa, thereby enabling the detection of abnormal mucosal changes. Indigo carmine is a contrast dye that is poorly absorbed by the colonic mucosa. It coats the mucosal surface, and allows enhancement of mucosal details (pits and grooves) and detection of disruption in the normal pit-pattern [103]. The SURFACE guidelines are used in chromoendoscopy to describe selection of patients, unmasking of mucosal surface (bowel preparation), reduction of peristalsis (antispasmodic agents), full length staining of the colon (dye application), augmented detection of lesions, analysis in vivo of mucosal structure, and endoscopic targeted biopsies [104]. Kiesslich et al. randomized 165 patients to undergo either conventional colonoscopy alone or chromoendoscopy in conjunction with magnification, for CRC surveillance. Chromoendoscopy allowed differentiation of neoplastic from non-neoplastic lesions with a high sensitivity and specificity (93%), and a threefold increase in detection of dysplastic lesions, over conventional colonoscopy [105]. Rutter et al. [106] performed back to back colonoscopy (conventional and chromoendoscopy) in a group of patients with IBD, and demonstrated a 4.5-fold increase in the detection of dysplastic lesions with chromoendoscopy. The Consensus Committee on Colorectal Cancer Surveillance in IBD has endorsed the incorporation of chromoendoscopy performed by trained endoscopists for CRC surveillance in patients with UC [97].

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (Mauna Kea Technologies, Paris, France; http://www.maunakeatech.com) utilizes a confocal microscope attached to the distal end of the colonoscope, in combination with administration of a topical (acriflavine) or systemic (fluorescein) contrast agent. This mucosal imaging technique has been reported to allow accurate detection of neoplastic lesions with a sensitivity of 97% and specificity of 99% [107]. A randomized trial evaluating the utility of chromoendoscopy, in conjunction with confocal laser endomicroscopy, for CRC surveillance in patients with UC, found a 4.5-fold increase in the detection of dysplastic lesions as compared to conventional colonoscopy [108]. In addition, the combination of chromoendoscopy and confocal laser endomicroscopy can lead to a tenfold reduction in the number of biopsies [109].

Narrow-Band Imaging

Narrow-band imaging (NBI) is a new optical technique that utilizes a xenon light source and special optical filters, thereby allowing enhanced visualization of the mucosal structure and microvasculature [110]. Its main advantage over chromoendoscopy and confocal laser endomicroscopy is the preclusion of contrast dyes and

the ability to instantaneously change from NBI to conventional mode, and vice versa. In a pilot study, Machida et al. [111] showed that NBI was equivalent to chromoendoscopy and superior to conventional colonoscopy in the differentiation of neoplastic from non-neoplastic lesions. Dekker et al. conducted a randomized crossover study using both NBI and conventional colonoscopy in 42 patients with UC. Although there was a twofold increase in suspicious lesions detected by NBI, the overall detection of dysplastic and neoplastic lesions was similar for both modalities. The authors contended that the low yield with NBI may have been related to sampling error, and compromised visualization with the first generation prototype NBI endoscopic imaging system used in the study [112].

Optical Coherence Tomography

OCT provides real-time, cross-sectional, high-resolution images of the colon, based on the pattern of backscattering of infrared light, with a spatial resolution 10–25 times higher than endoscopic ultrasonography, computed tomography, and magnetic resonance imaging [113]. Based on the disrupted layered structure indicative of transmural inflammation, OCT has the potential ability to differentiate CD from UC, with a sensitivity of 90% and specificity of 83% [113]. Although preliminary data indicates its utility in the identification of dysplastic lesions, further technical improvements and research are considered necessary to confirm this observation [114].

Radiology

Computed Tomographic Enterography

CTE is a dedicated examination of the SB that allows enhanced endoluminal and transmural evaluation. The technique differs from conventional abdominal computed tomography (CT) in the use of a larger volume of oral contrast (neutral or negatively charged), intravenous contrast, and thin cut imaging with a high resolution multidetector CT scanner [115]. A quantity of 1,350 mL of dilute barium solution given over 45–60 min has been found to provide excellent SB distention for up to an hour [116]. In comparison to CTE, which involves oral ingestion of contrast, CT enteroclysis involves direct injection of contrast into the SB via a nasojejunal tube. Due to a lack of difference in diagnostic yield and accuracy between the two techniques, CTE is preferred over CT enteroclysis, due to both ease of performance and better patient tolerance [117].

Classic features of CD on CTE, include wall thickening (>3 mm) of a well-distended loop of SB, mucosal hyperenhancement, mesenteric fat stranding, prominence of vasa rectae (“comb sign”), abscesses, fistulae, and mural stratification

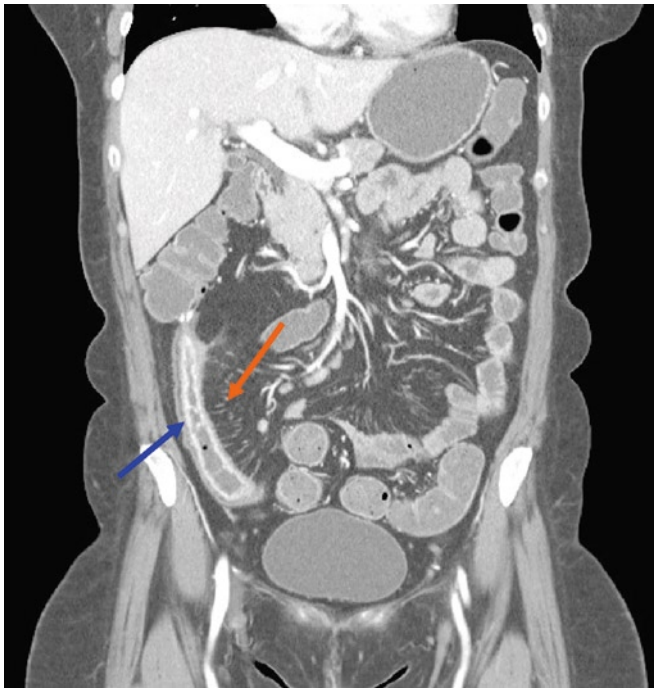

Fig. 15.4 Coronal image of CT enterography showing SB mucosal enhancement (*blue arrow*) and Comb sign (*orange arrow*) characteristic of small bowel Crohn's disease

[118, 119] (Fig. 15.4). Luminal narrowing is another finding in CD, which may be related to inflammation or fibrosis. The bowel wall displays features of mural stratification in the setting of inflammatory narrowing and homogenous enhancement with fibrotic strictures. The distinction between inflammatory and fibrotic strictures is important as it carries implications for decisions regarding medical vs. surgical management [116, 120] CTE has been reported to have an accuracy of 94% for the detection of SB CD, with a sensitivity of 86% and specificity of 100% [121]. Studies have indicated that CTE may be superior to SBFT for detection of active CD. Hara et al. [64] found a diagnostic yield of 53% with CTE as compared to 24% for SBFT in 17 patients with suspected CD. In addition, CTE may be more sensitive than SBFT for the detection of abscesses and fistulae [117].

CTE findings have been reported to correlate with both clinical and histologic activity in Crohn's disease. Bowel wall thickening and mural hyperenhancement appear to have the highest sensitivity and specificity for active CD. Active inflammation is indicated by bowel wall thickening of more than 3 mm and/or mural hyperenhancement of more than 190 Hounsefield units (HU) [122, 123]. Mural stratification is another means of determining activity of SB Crohn's, and may be bilaminar or trilaminar based on different enhancement patterns of the three enteric layers [122–124].

An accurate comparison of the diagnostic yield of CTE and CE in SB Crohn's is limited by the fact that CE can only be performed in a subset of CD patients without strictures. Voderholzer et al. prospectively evaluated 56 CD patients with CT enteroclysis, followed by CE (after exclusion of strictures/stenoses). The diagnostic yield of CE (61%) was found to be significantly higher than CT enteroclysis (29%) in the 41 patients in whom both tests could be performed. There was no difference in the two techniques for the detection of CD involving the terminal/neoterminal ileum [68]. A blinded four way comparison study of ileoscopy, CTE, CE, and SBFT showed that the sensitivities of both CE (83%) and CTE (82%) were comparable for the detection of active CD, but CTE had a higher specificity (89%) as compared to CE (53%). Hence, CTE may be the preferred test over CE in the initial diagnostic evaluation of suspected SB CD [75]. CE would be useful for the detection of subtle mucosal abnormalities that may be missed on CTE [117]. The main advantage of CTE over CE is that it can be safely and successfully performed in patients with both nonstricturing and stricturing CD. It thereby has the added benefit of allowing identification of patients at risk for capsule retention.

CTE may be inadequate for the detection of postoperative recurrence of CD. A study that compared CT enteroclysis to ileoscopy found a false negative rate of 23% with CT enteroclysis in patients who had postoperative recurrence of SB Crohn's [125].

The main limitations of CTE are related to ionizing radiation exposure in patients who undergo multiple CTEs for follow-up of CD, and its relative contraindications in pregnant women and patients with renal insufficiency.

Magnetic Resonance Enterography

Magnetic resonance enterography (MRE) is a relatively new radiologic technique that allows both transmural evaluation of the SB, as well as extramural evaluation of the soft tissues. It is similar to CTE with the added advantage of avoiding exposure to ionizing radiation [126]. The use of faster imaging techniques has led to significant improvement in motion artifact, and hence efficacy of MRE in the evaluation of SB Crohn's [127]. Characteristics of active SB inflammation include ulcerations, submucosal edema ("double halo sign"), and increased mesenteric vascularization ("comb sign") [126]. An additional advantage of MRE is its ability to evaluate extramural soft tissue, for the presence of abscesses and fistulae.

MRE has been shown to be superior to conventional enteroclysis in the detection of CD. A study that compared MRE and conventional enteroclysis in 27 patients with CD found that MRE detected additional findings (abscesses and fistulae) in 74% of patients. The sensitivities of MRE and enteroclysis were 100 and 0% for abscesses and 83 and 17% for fistulae, with surgery as the gold standard [128]. An additional study that evaluated 25 patients with CD (terminal ileitis and or/colitis) and abdominal pain showed that MRE (52%) had a higher diagnostic yield than enteroclysis for the detection of SB involvement proximal to the terminal ileum (16%) [129].

MRE, however, may have a lower diagnostic yield for CD, as compared to CE. A study that evaluated 18 patients with established or suspected CD, using CE and MRE, found that CE detected more inflammatory lesions in the proximal and mid-SB as compared to MRE (12 vs. 1 patient; $p=0.016$). There was no significant difference in the detection of lesions in the distal SB, including terminal ileum, which may have been related to poor visualization on CE of the distal SB mucosa [130].

Additional prospective studies are necessary to determine the future role of MRE in the evaluation of SB Crohn's. Performance of MRE, with its relatively high expense, can currently be justified in patients with contraindications to CTE, those who may require sequential scanning and in those with coexistent perianal CD.

CT Colonography and MR Colonography

CTC is a useful radiologic test for colorectal cancer screening and surveillance, particularly in patients with incomplete colonoscopies, patients with suspected colonic obstruction, and high risk patients on anticoagulation. CTC has the ability to demonstrate colonic wall thickening, ulcerations, sinus tracts, fistulae, pseudopolyps, and loss of haustrations, and may hence be useful in the diagnosis of active CD or UC in a relatively noninvasive manner [131]. Biancone et al. compared colonoscopy and CTC in 16 patients with suspected postoperative recurrence of CD. Although colonoscopy detected a higher number of patients with colonic recurrence (15 vs. 11), CTC was comparable to colonoscopy (7 vs. 8 patients) in the detection of stenosis and/or narrowing of the anastomotic site [132].

MRC is another potential diagnostic tool in IBD, which is currently being evaluated for CRC surveillance. A feasibility study was conducted by Schreyer et al. in 22 patients with suspected IBD, with performance of MRC immediately before colonoscopy. The sensitivity for accurate identification of inflammation, on a per segment analysis of the colon, was 31.6% for CD and 58.8% for UC. MRC sufficiently identified only severe inflammatory changes with CD, whereas even severe inflammation was not detected accurately in patients with UC [133]. Another study conducted by Ajaj et al. quantified inflammatory changes in the colon (MRC-based score) based on colon wall thickness, colonic wall contrast enhancement, loss of haustral folds, and presence of perifocal lymph nodes. In contrast to the study by Schreyer et al., the authors found that more than 90% of the colonic segments with IBD involvement could be diagnosed and categorized accurately as mild, moderate, or severely inflamed compared to histopathologic data [134]. Additional studies are necessary to determine the true value of MRC in the diagnosis of IBD.

Conclusions

Diagnostic testing of IBD has significantly improved with the introduction of new laboratory, endoscopic, and radiologic modalities. These novel diagnostic modalities have complementary roles in the diagnosis of IBD. In addition to facilitating earlier diagnosis of IBD, these tests provide additional benefits including the accurate determination of severity and extent of small bowel involvement, simultaneous evaluation of luminal and extraluminal disease, objective monitoring of response to therapy, performance of therapeutic interventions, and better surveillance techniques for CRC. Further studies and longer follow-up are necessary to determine the true utility and potential of these tests in the diagnosis and long-term management of patients with IBD.

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Chapter 16
Inflammatory Bowel Disease Pathology Slideshow

Christopher R. Weber

Keywords Crohn's disease • Ulcerative colitis • Esophagus • Antrum • Duodenum • Ileum • Colon • Pouchitis • Dysplasia • Ischemia • Radiation colitis • Infectious colitis • Pseudomembranous colitis • Cytomegalovirus superinfection • Lymphocytic colitis • Collagenous colitis • Solitary rectal ulcer syndrome

Introduction

The diagnosis of inflammatory bowel disease (IBD) relies as much on histological findings as it does on clinical presentation and endoscopic appearance. The features of IBD were reviewed in the previous version of this book, and will not be exhaustively reviewed here. However, the most important histological features to consider include the presence or absence of chronic injury, distribution of disease, nature and extent of inflammation, presence of granulomas, and assessment for the presence of dysplasia. A selection of some examples which highlight these important features are shown in some typical examples of ulcerative colitis and Crohn's disease in Figs. 16.1–16.8. When making a diagnosis of IBD, it is also important to consider other conditions which may mimic the features of IBD clinically, or even may coexist with IBD. Some of these diseases are reviewed in Figs. 16.9–16.16.

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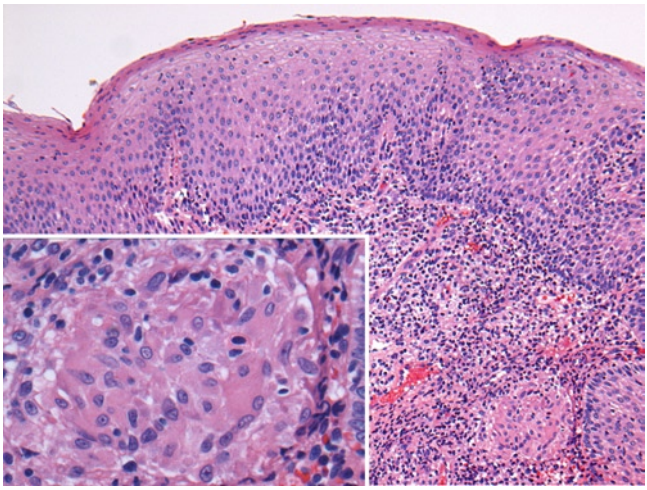

Fig. 16.1 Crohn's disease of the esophagus. Squamous mucosa has increased intraepithelial lymphocytes compared to normal mucosa and numerous inflammatory cells are present in the lamina propria. Epithelial cells appear reactive, with mild hyperplasia of the basal cell layer. A granuloma is present in the lamina propria (*inset*). (magnification 100×)

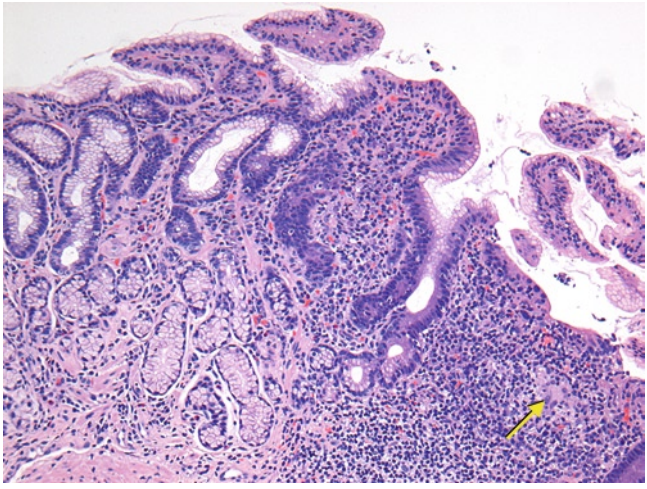

Fig. 16.2 Crohn's disease of the gastric antrum. The antral mucosa in the left portion of the image appears normal with clear mucous and bicarbonate secreting foveolar cells, which normally line the entire gastric mucosa. In this area, the lamina propria contains a normal number of inflammatory cells, which are predominantly composed of macrophages, lymphocytes, and plasma cells. Focal active Crohn's disease with ulceration is present in the *right portion* of image. The regenerating foveolar epithelial cells appear mucin depleted. The lamina propria has a dense lymphoplasmacytic infiltrate, a small granuloma (*arrow*), and antral glands have been destroyed in this area. (magnification 100×)

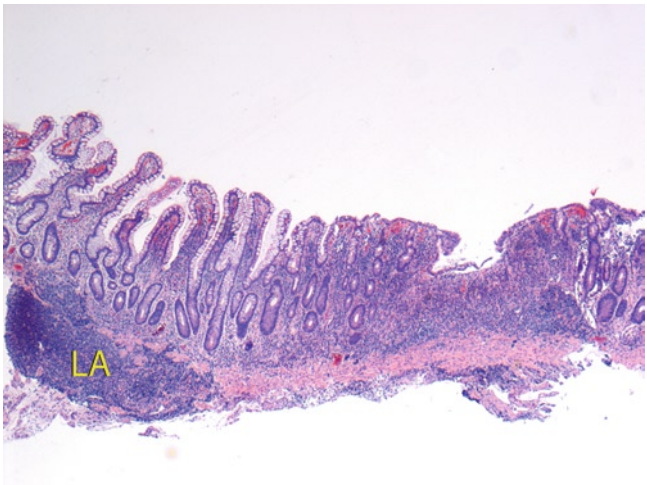

Fig. 16.3 Crohn's disease of the ileum. In the left portion of the biopsy, small intestinal villus architecture is relatively preserved and lamina propria inflammatory cells are normal in number. A lymphoid aggregate (LA) is present in the submucosa. In the right portion of the biopsy, villi are absent and a dense lamina propria lymphoplasmacytic infiltrate is present in a patch of mucosa involved by Crohn's disease. (magnification 50×)

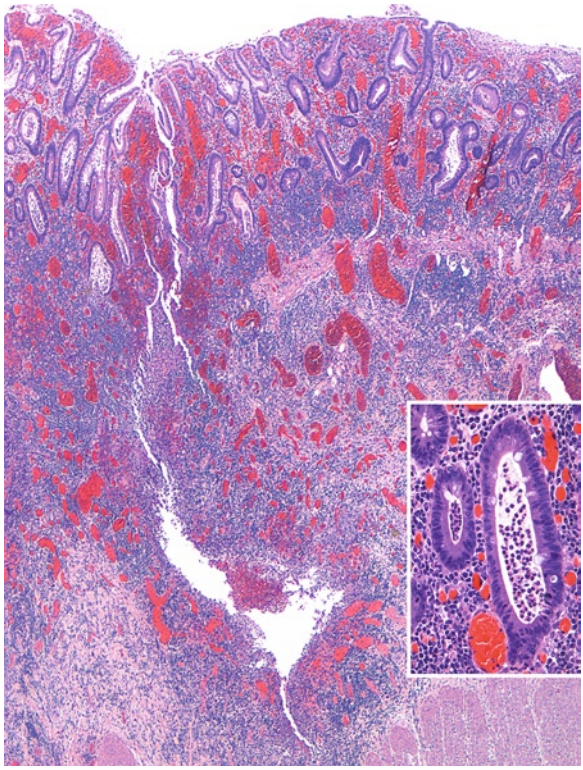

Fig. 16.4 Crohn's disease of the colon. A dense lymphoplasmacytic infiltrate is present in the mucosa and submucosa and multiple crypt abscesses are filled with neutrophils (*inset*). Architectural distortion indicates the presence of chronic injury, but more distal areas of colon appeared normal (not shown). In Crohn's disease, ulceration is often "knife-like" and deep. (magnification 25×)

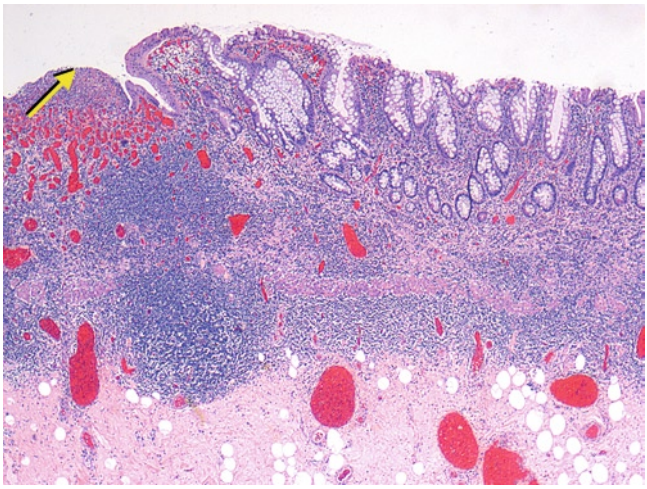

Fig. 16.5 Ulcerative colitis. A diffuse basal lymphoplasmacytic infiltrate is present within the colonic mucosa, but it does not extend deep into the submucosa. Disease was continuous from the right colon to the rectum. An area of shallow ulceration (*arrow*) with underlying granulation tissue is evident in the left part of the image. There are no granulomas. (magnification 25×)

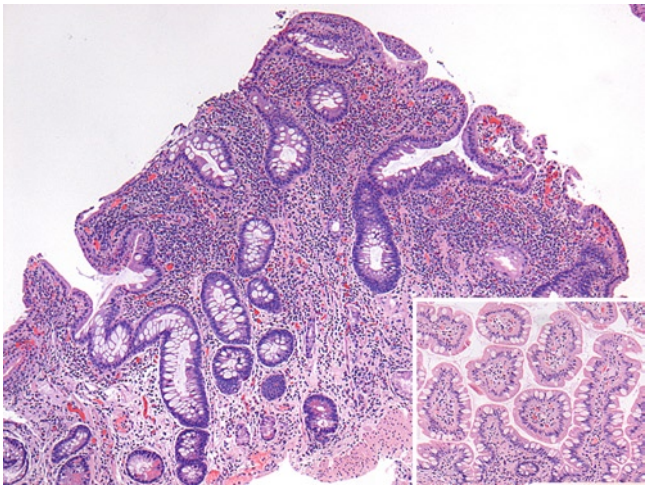

Fig. 16.6 Pouchitis. This pouch biopsy shows diffuse chronic mucosal injury with severe activity. The presence of normal appearing prepouch mucosa (*inset*) and the absence granulomas supports the diagnosis of pouchitis. (magnification 50×)

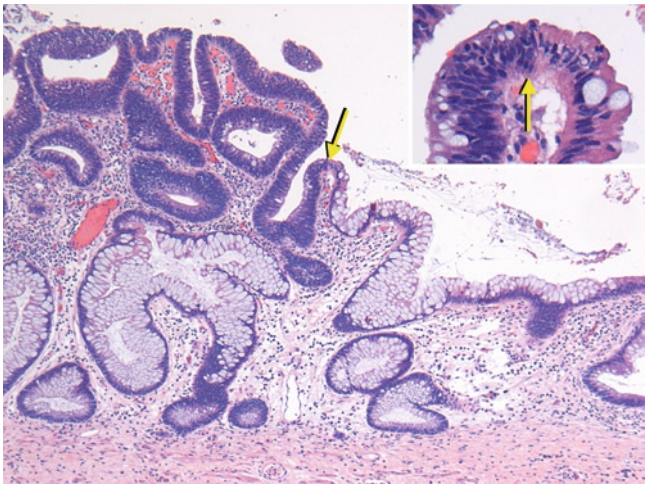

Fig. 16.7 Low grade dysplasia in ulcerative colitis. Low grade dysplasia arising in a background of inactive inflammatory bowel disease is present in the *upper left* portion of the image. Nuclei are hyperchromatic and enlarged, with some stratification (*inset*), but all dysplastic cells are similar in shape, oriented in the same direction, and have basally located nuclei. The transition between dysplastic and nondysplastic epithelium is indicated by the *arrow*. (magnification 50×)

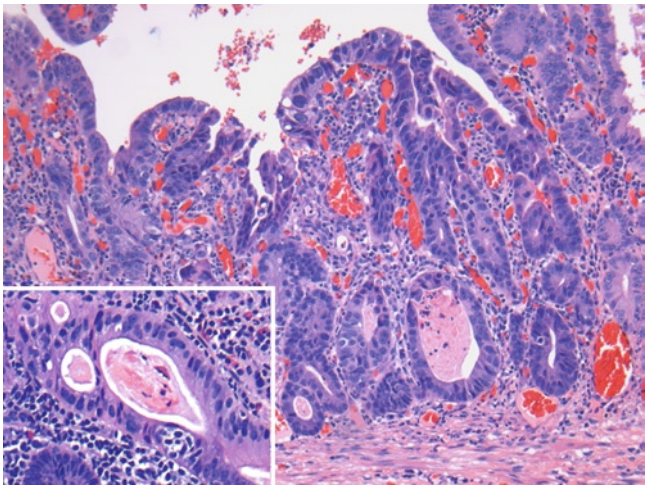

Fig. 16.8 High grade dysplasia in ulcerative colitis. Cells are markedly pleomorphic and haphazardly oriented with respect to the basement membrane in this example of high-grade dysplasia. In other areas (*inset*), glands had a cribiform architecture. (magnification 100×)

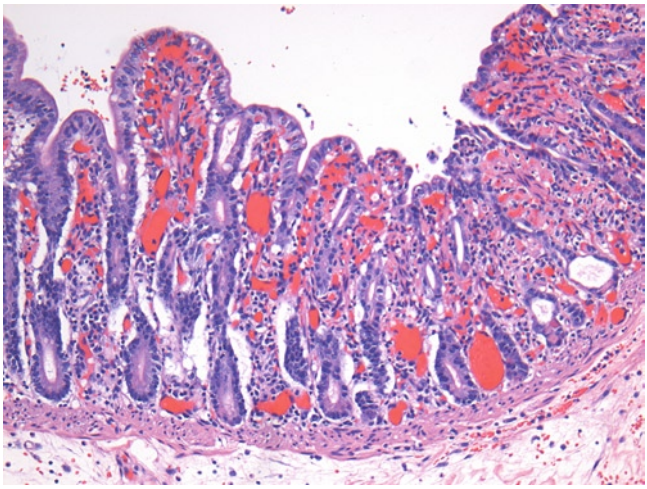

Fig. 16.9 Ischemia of the colon. Acute ischemia affects surface epithelial cells more than the epithelial cells of the crypts, where pO_2 is the highest. This is apparent as relative preservation of crypt epithelium, with mucin depletion and cell attenuation towards the surface. Separation of the epithelium from the lamina propria is another feature of ischemia. (magnification 100×)

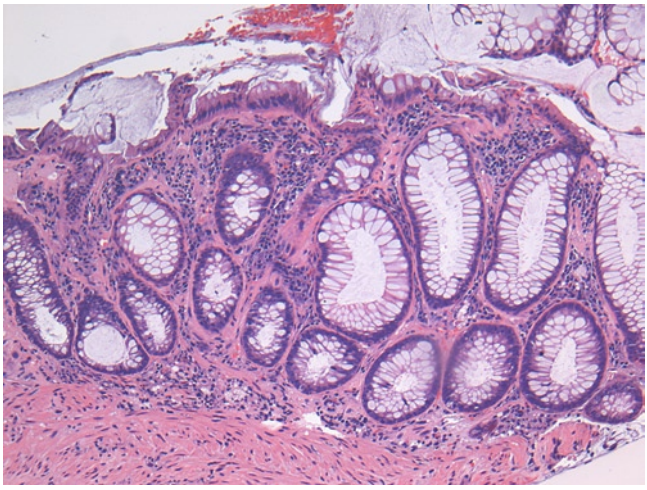

Fig. 16.10 Radiation colitis. Chronic colonic injury might occur secondary to radiation therapy and can resemble IBD histologically. In this example, features which are particularly suggestive of radiation injury include fibrosis of the basement membrane, mild surface cytological atypia, and thickening of the muscularis mucosae. (magnification 100×)

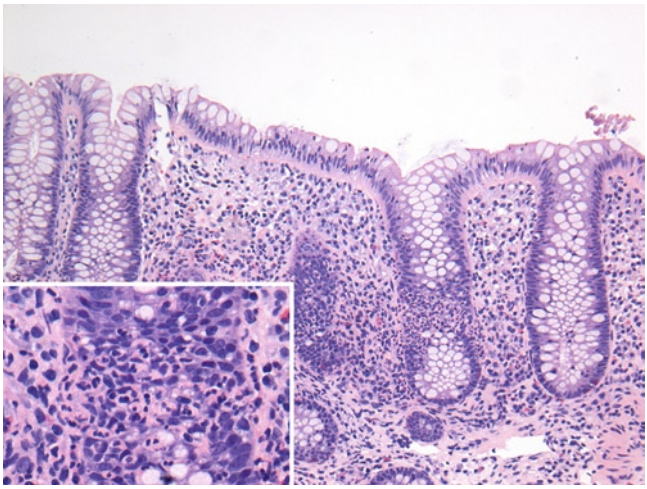

Fig. 16.11 Infectious colitis. Neutrophils are present within the colonic epithelium (*inset*), however, spacing of crypts is normal, and there is no evidence of chronic injury. (magnification 100×)

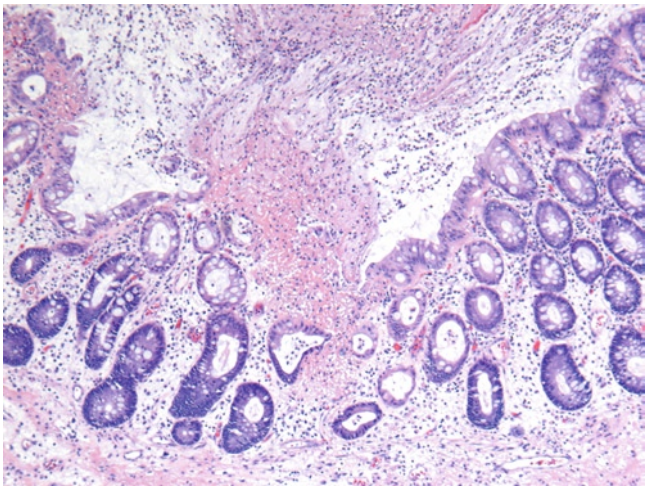

Fig. 16.12 Pseudomembranous colitis. A "volcanic-like" eruption of pseudomembrane composed of fibrin and inflammatory cells present in the center of the image is a typical feature of pseudomembranous colitis. (magnification 50×)

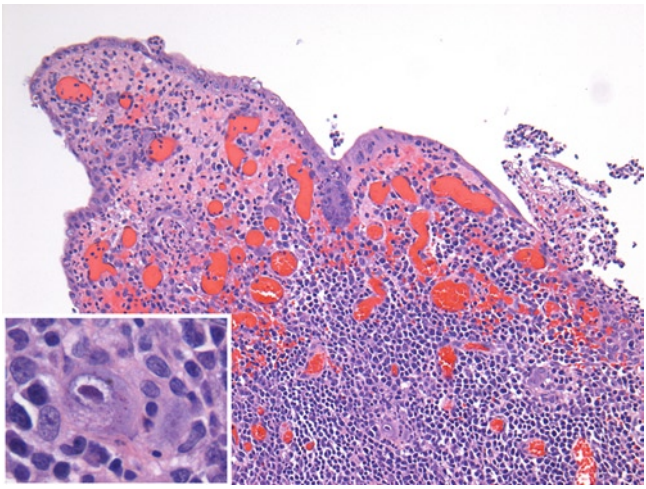

Fig. 16.13 Severely active inflammatory bowel disease with cytomegalovirus superinfection. Disease activity is severe in this biopsy and there is focal epithelial ulceration apparent at the right side of the image. A macrophage with an intranuclear Cowdry type B viral inclusion body is present (*inset*). (magnification 100×)

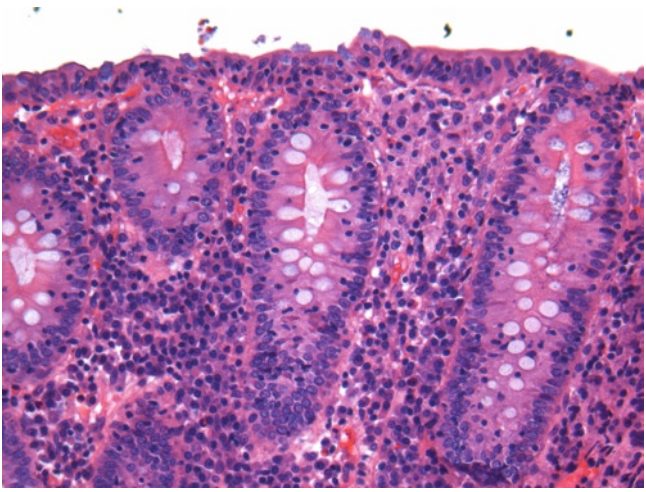

Fig. 16.14 Lymphocytic colitis. Intraepithelial lymphocytosis is present in this patient with watery diarrhea and a normal appearing colonoscopy. (magnification 200×)

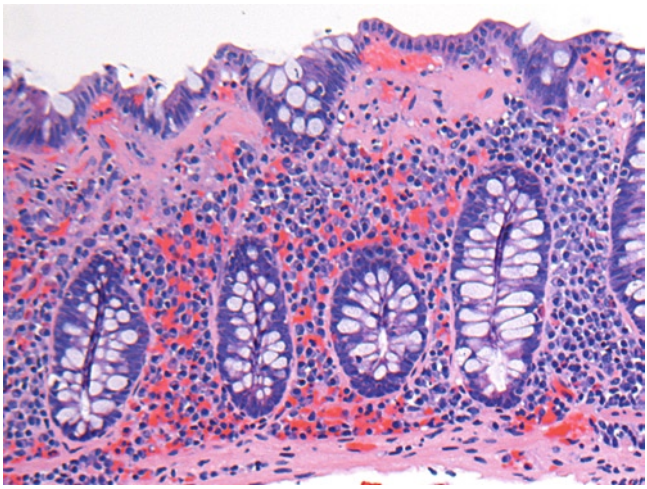

Fig. 16.15 Collagenous colitis. In this patient with watery diarrhea, a thickened and irregular subepithelial fibrous band is present beneath the surface epithelium. Overall crypt architecture is preserved. Lamina propria plasma cells are numerous. (magnification 150×)

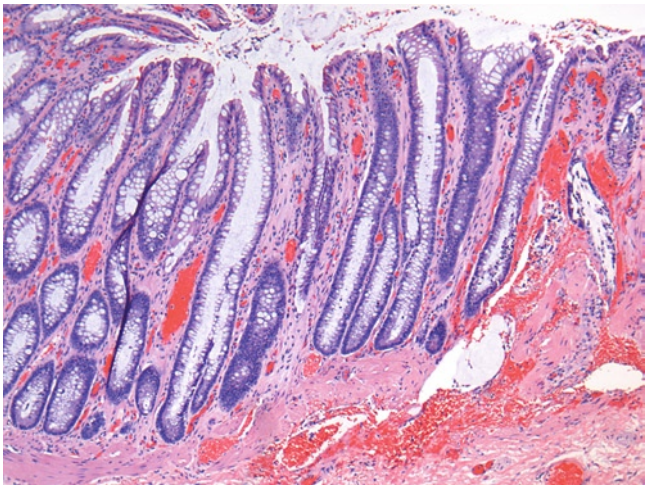

Fig. 16.16 Solitary rectal ulcer syndrome. Smooth muscle fibers extend upward from the muscularis mucosae into the lamina propria and is the hallmark of prolapse. Architectural distortion is present in the form of crypt elongation and branching, and the surface epithelium is mildly hyperplasic. (magnification 100×)

Chapter 17
New Findings in the Diagnosis and Prevention of Colorectal Cancer in IBD

David T. Rubin and Jami A. Rothe

Keywords Ulcerative colitis • Crohn's disease • Chromoendoscopy • Magnification endoscopy • Confocal laser endomicroscopy • Colon cancer • Colorectal cancer • Dysplasia • Neoplasia • Surveillance • Narrow band imaging • Adenoma-like masses • Dysplastic-associated lesions or masses • Chemoprevention

Key Points

- The risk of colorectal cancer in chronic ulcerative colitis and Crohn's disease of the colon is increased compared to the noninflammatory bowel disease population, but appears to be less than previous estimates.
- Our current approach is secondary prevention with screening and surveillance colonoscopies, yet this approach remains inaccurate and time consuming.
- Unlike traditional teaching, dysplasia of the colon in colitis is visible with current technologies, and can be identified with greater success using dye-spray chromoendoscopy.
- The evolving understanding of dysplasia detection may allow some patients with dysplasia to be followed with serial examinations rather than undergoing colectomy.
- Incorporation of degree of inflammation into prevention strategies will enable risk stratification for future follow-up.
- Chemoprevention with aminosalicylates remains a great interest. The role of other medical therapies in primary cancer prevention has been insufficiently studied.

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Introduction

Patients with inflammatory bowel disease (IBD) are at an increased risk for developing colorectal cancer (CRC). This is an important topic that is undergoing continued investigation in the field. Although only 1% of all cases of CRC occurs in patients with IBD, these patients represent a high risk group for developing this complication, and these patients develop cancer at a younger age than the non-IBD population [1]. Therefore, it is essential to reduce or prevent complications associated with cancer in this population. Currently, consensus-based guidelines suggest routine surveillance colonoscopy and biopsies as the cornerstone of prevention in this population, with proctocolectomy when dysplasia or early stage cancer is found. Patients in whom a precancerous lesion or early cancer are detected, surgical removal of the colon can be a potentially curative procedure for both the colitis and the cancer. However, this secondary prevention strategy has several drawbacks. The detection of neoplasia in chronic colitis is time consuming, inexact, and not performed uniformly by physicians and patients. Every aspect of the procedure warrants better understanding and more efficient approach. This chapter will review current and evolving understanding of this important topic.

Risk of Dysplasia and CRC in Ulcerative Colitis and Crohn's Disease

Ulcerative Colitis

The increased risk of developing CRC in ulcerative colitis (UC) has been recognized by researches for decades, although the estimates of the magnitude vary considerably in the literature, with more recent estimates considerably less than historical reports [2, 3]. A 2001 meta-analysis of 116 studies (41 were included in final analysis) including 54,478 patients with UC and 1,698 cases of CRC calculated an overall prevalence of cancer in UC of 3.7% [4]. Of the studies reporting duration of disease, a cumulative probability of CRC in UC of 2% at 10 years, 8% after 20 years, and 18% after 30 years of disease. However, a large population-based study in Manitoba, Canada, including 19,655 person-years of follow-up only found an incidence rate ratio for CRC of 2.75 [95% confidence internal (95% CI), 1.91–3.97] compared to the general population [5]. Additional studies have similarly suggested substantially lower rates of CRC [3, 6, 7]. In the population-based study from Denmark of 22,290 person-years of follow-up, the 30-year cumulative probability of CRC in UC was only 2.1%, which was not significantly more than the non-IBD population. More recent reports from referral centers suggest lower rates of dysplasia and cancer as well. From the 30-year surveillance experience at the St. Mark's Hospital in the United Kingdom identified a cumulative incidence of CRC of only 2.5% at 20 years, 7.6% at 30 years, and 10.8% after 40 years of disease [8].

A variety of reasons for this apparent decrease in CRC incidence have been proposed, and may included the more widespread use of surveillance colonoscopy, the chemoprotective effect of maintenance therapies, access to surgical intervention, or as yet unidentified dietary or environmental factors. One should interpret the results of these more recent studies with caution. These reports should not result in a more relaxed approach to prevention of CRC in UC, but because this may represent the result of successful cancer prevention, ongoing efforts, and current guidelines-based practice should continue [9].

Several factors have been identified that increase the risk of CRC in patients with UC. The risk of CRC in UC has been linked to increased duration of disease, younger age at diagnosis, and greater extent of colitis. In addition, increased disease activity, family history of CRC, diagnosis of primary sclerosing cholangitis (PSC), and the presence of backwash ileitis or stricture have also found to be risk factors in developing CRC. The observation that cumulative risk of cancer increases over time establishes that increasing duration of disease is an important risk factor [4, 10]. Consistent with the understanding of CRC risk being associated with cumulative effect of chronic inflammation, the extent of colon involvement in UC is an independent predictor of cancer risk [10]. Ekbom and colleagues reported that the relative risk of CRC in ulcerative proctitis was 1.7, whereas the risk in left-sided colitis was 2.8 and rose to 4.8 in those with extensive colitis [10]. Despite this greater risk associated with greater extent of disease, when CRC occurs in UC, it is more often in the rectum or sigmoid colon [11]. Degree of inflammation, a relative recent addition to the list, correlates with cancer risk. Three recent studies have confirmed this association. Rutter and colleagues, from St. Mark's Hospital in UK, performed a retrospective analysis demonstrating that severity of inflammation on biopsy is independently a predictive risk factor for CRC [12]. This finding was reinforced by studies from the University of Chicago and Mt. Sinai Medical Center in New York in which inflammatory activity was shown to be independently associated with CRC risk [13, 14]. Several studies have shown that younger age at diagnosis of UC is associated with an elevated risk of CRC, independent of disease duration [10]. The reason for this association is not known; however, Rutter and colleagues attribute the finding to that the early age of diagnosis tends to have more severe inflammation [12]. Several studies have demonstrated that a family history of CRC, independent of a family history of IBD, doubles the risk of developing cancer [15–18]. Additionally, it has been found that coexistent PSC confers to an elevated risk of CRC in UC patients, with a meta-analysis by Soetikno et al. [19] describing an odds ratio of 4.09 (95% CI, 2.89–5.76) when compared to UC patients without PSC. The reason for the increased risk of subsequent PSC is that PSC is a marker for longstanding subclinical disease [20]. This finding has led to the recommendation of closer surveillance in this unique high-risk subset of UC patients. However, the finding that treatment with ursodeoxycholic acid (UDCA) can lessen CRC risk suggests that the altered bile acid milieu of PSC may play a role in the carcinogenesis [21, 22]. Additionally, one study has demonstrated that backwash ileitis may be an independent predictor of increased CRC risk [23]. The finding of a stricture or dysplasia during colonoscopy also carries a heightened risk of malignancy, one study showing that 24% of strictures were malignant [24–26].

Thus cancer risk in UC appears to result from the combined effects of chronic inflammation (as estimated by the extent and duration of disease and the degree of histologic inflammation) and an individual's underlying genetic predisposition (as suggested by family history, coexistent PSC, and early age at diagnosis). Unfortunately, severity of inflammation appears to be the only modifiable risk factor, underscoring the importance of medical management in mitigating cancer risk, and highlighting the need for a preventive approach to cancer and precancer detection.

Crohn's Disease

While the relationship between UC and CRC has been appreciated for many years, the association between CD and CRC has gained increasing recognition recently. Measuring the risk of CRC in CD poses several challenges, relating to the patchy nature of the disease, difficulty in controlling disease extent, with many patients having no colonic involvement. Despite these challenges, several studies have been able to adjust for disease location and offer estimates of CRC risk in colonic CD. Gyde and colleagues reported the relative risk of CRC in Crohn's colitis to be 23.8, whereas the risk was 4.3 in the general Crohn's population [27]. Greenstein and colleagues calculated a relative risk of 6.9 for developing CRC in isolated colonic Crohn's [28]. A landmark study from Sweden demonstrated a relative risk of CRC of 5.6 for those with exclusively colonic involvement, as compared to a relative risk of 3.2 for patients with ileocolitis and 1.0 for patients with ileal involvement only [29]. This study not only established that Crohn's colitis carries a higher risk of CRC but also that this risk correlates with the extent of colonic involvement. Additionally, a subset analysis revealed that patients whose IBD was diagnosed prior to age 30 had a higher relative risk than patients diagnosed at an older age, similar to patients with UC. The risk of CRC in Crohn's is equivalent to that in UC when comparison is controlled for similar extent of disease. In a study by Gillen and colleagues from the UK, patients with extensive Crohn's colitis were compared to patients with extensive UC with regard to CRC risk [30]. The results were astonishingly similar with a relative risk of developing CRC of 18 for Crohn's colitis and 19 for UC. The cumulative risk of CRC was 8% at 22 years for patients with Crohn's versus 7% at 22 years for patients with UC. In addition to a similar magnitude of risk, Crohn's patients share many of the same risk factors for CRC as UC patients, including younger age at diagnosis, greater extent of colonic involvement, and longer duration of disease.

In addition, it appears that bypassed segments of bowel [31] and perianal fistulae [11] in CD may also be sites of increased risk for neoplastic transformation and warrant heightened vigilance. Furthermore, bowel strictures in CD may harbor dysplasia or cancer [32] and should be carefully biopsied and resected if a pediatric or upper endoscope cannot traverse them. Different from UC, however, is that benign strictures are considered a possible manifestation of the disease so may not

Table 17.1 Risks of dysplasia or colorectal cancer (CRC) in UC and Crohn's colitis

Confirmed risk factors
Longer duration of disease
Greater extent of disease
Increased activity of disease
Mass/stricture
Presence of dysplasia
Family history of CRC
Primary sclerosing cholangitis (PSC)
Presence of pseudopolyps
Possible risk factors
Younger age of diagnosis
Backwash ileitis

need resection otherwise. In addition, patients with CD have an increased risk of small bowel adenocarcinoma as well as an increased risk of squamous cell carcinoma in the perianal region. In 1999, Sigel and colleagues reported 30 cases of resected adenocarcinoma in patients with CD and concluded that most (86%) of CD-related colorectal adenocarcinomas exhibit dysplasia in adjacent mucosa and that 41% of CRCs exhibit distant dysplasia [33]. Due to this finding, they were able to conclude that the dysplasia-carcinoma sequence in CD is similar to the sequence described in UC and that prevention using dysplasia as a marker is justified. With the exception of strictures as described above, screening and surveillance of CRC in patients with Crohn's should be handled identically to patients with UC, matched for the extent of colonic involvement. Table 17.1 is a summary of both confirmed and possible risk factors for dysplasia in IBD.

The Evolving Understanding of Dysplasia as a Marker of Cancer Risk

Traditionally, we have thought that CRC occurs in long-stating UC and Crohn's disease; it is associated with dysplastic changes in the epithelium, and the biology of IBD-associated CRC is different than hereditary or sporadic CRC. In chronic IBD, the mucosa undergoes change and development of precancerous cytologic or architectural abnormalities known as dysplasia. The current approach to surveillance is grounded in the concept of an inflammation-dysplasia-carcinoma sequence, during which intervention can prevent or minimize the complications associated with invasive cancer. What we are learning now is that risks of CRC in IBD are lower than the risks previously reported, that there is a predictive value of dysplasia in colitis, new imaging methods help guide endoscopists in mucosal sampling, and that dysplasia is "visible" with modern imaging techniques. An understanding of the definition, diagnostic challenges, and natural history of dysplasia in IBD is therefore essential when contemplating complex clinical management decisions.

Dysplasia is defined as unequivocal neoplasia of the epithelium confirmed to the basement membrane, without invasion into the lamina propria [34]. Dysplasia in IBD can be thought of as flat and "invisible" or as raised and "visible" dysplasia. "Invisible dysplasia" is indistinguishable from surrounding inflamed or quiescent mucosa, detected only on random biopsy specimens. However, at least two studies have shown that many of these lesions are in fact visible through standard white light endoscopy using newer generation colonoscopy techniques [35, 36]. Visible dysplastic lesions can be categorized as polypoid "adenoma-like" lesions or masses (ALMs), non-resectable dysplastic-associated lesions or masses (DALMs), or strictures. The newer term ALM was introduced to describe the finding of an endoscopically discreet polypoid lesion resembling a sporadic adenoma that is found in an area of colon involved or not involved by chronic colitis. Regardless of the endoscopic appearance of a lesion that is raised or flat, pathologists use the same set of criteria to describe the histologic appearance of dysplasia in IBD. The standardized classification system of dysplasia in IBD was established by Riddell and colleagues in 1983 and divided dysplasia into categories, including indefinite dysplasia (IND), low grade dysplasia (LGD), high grade dysplasia (HGD), and cancer [34]. IND was later broken down into "probably positive IND" and "probably negative IND" based on histologic appearances of the epithelial cells and their nuclei [37]. Although this system remains widely used today, it has several acknowledged limitations, including poor inter-observer agreement and intra-observer reliability, even among expert pathologists [34, 38]. This lack of concordance of biology interpretations has led to the routine practice of more than one expert GI pathologist reviewing the biopsies to confirm the diagnosis before making critical treatment decisions, especially in cases of LGD or IND, in which inter-observer agreement is poorest.

Management of dysplasia, once diagnosed, relies on an understanding of the natural history. In 1994, two groups published data revealing that approximately 1 in 8 patients with UC will have dysplasia or cancer found on their initial screening colonoscopy, but that those with a negative initial exam have a low incidence (~3%) of developing HGD or cancer on subsequent surveillance colonoscopies [24, 39]. Among patients with LGD who undergo immediate colectomy 19% will already harbor concurrent CRC or HGD [8, 24], and an additional 29–54% will subsequently develop advanced neoplasia over the next 5 years [24, 39, 40]. HGD carries a 43% risk of synchronous malignancy and is therefore considered to be an indication for immediate colectomy [24]. DALMs are associated with a similarly high rate of CRC and are likewise an indication for total proctocolectomy [24, 41]. In contrast to DALMs, however, it appears that adenoma-like lesions maybe safely managed by polypectomy with biopsies of the surrounding flat mucosa [42]. If the lesion is successfully removed in its entirety and the surrounding mucosa is free of dysplasia, a regimen of more frequent surveillance colonoscopy is recommended. The finding of adjacent dysplasia in the flat mucosa prompts immediate colectomy by most experts, given the likelihood of concurrent cancer or progression to cancer.

Strictures represent a unique circumstance that merits a higher degree of vigilance. Colonic strictures in UC often harbor malignancy and are considered a strong indication for surgery, even if biopsies and brushing of that area are unrevealing [26]. In Crohn's disease, colonic strictures may be followed with annual surveillance and biopsy if the lesion can be traversed with a standard pediatric colonoscope. In the setting of longstanding Crohn's disease, consideration should be given to surgical resection of a stricture due to the heightened risk of CRC [26].

Technological Advances in the Detection of Dysplasia

The current foundation of cancer prevention in IBD is periodic surveillance colonoscopy. This strategy relies on the ability to detect CRC at a preclinical phase of dysplasia during which intervention can avert the adverse consequences of invasive cancer. Detection of dysplasia depends on the frequency and technique of surveillance colonoscopy, as well as the quality of pathologic review. Itzkowitz and Harpaz [43] report that a typical surveillance exam and biopsies samples less than 0.05% of the colon, highlighting the great likelihood for sampling error associated with a nontargeted biopsy approach to identify flat dysplasia. Rubin et al. [44] retrospectively determined that 33 biopsies are required to detect dysplasia with 90% sensitivity and 64 biopsies are needed to achieve 95% sensitivity. Although consensus guidelines incorporate this finding and recommend 30–40 biopsies, this can be quite cumbersome to perform. Additionally, many gastroenterologists are either not fully aware of these recommendations or intentionally do not adhere to them [45, 46]. Newer imaging technologies such as chromoendoscopy, magnification endoscopy, and confocal laser microscopy offer the potential to enhance detection of dysplasia during surveillance colonoscopy, allowing endoscopists to take fewer high-yield biopsies of targeted abnormal mucosa.

The technique of chromoendoscopy involves the application of dye during colonoscopy to highlight subtle mucosal changes that cannot be appreciated by standard white light imaging techniques. Indigo carmine is a contrast dye that augments subtle mucosal alterations, whereas methylene blue is an absorptive dye that is avidly taken up by normal mucosa but does not stain areas of inflammation or dysplasia, thereby creating a contrast gradient that enhances visualization. Images of a rectal polyp using standard white light technology and chromoendoscopy can be seen in Fig. 17.1. At least three prospective studies have demonstrated that chromoendoscopy improves the sensitivity of detecting neoplasia in UC patients [47–49]. These studies show an improved sensitivity of 93% and specificity of 88–93%, by facilitating enhanced endoscopic characterization of lesions, thereby allowing the endoscopist to perform fewer biopsies that are more targeted. The combination of chromoendoscopy with magnification permits a detailed analysis of the mucosal architecture, and can assist gastroenterologists in differentiating benign from neoplastic lesions during colonoscopy, improving the yield of targeted biopsies [50].

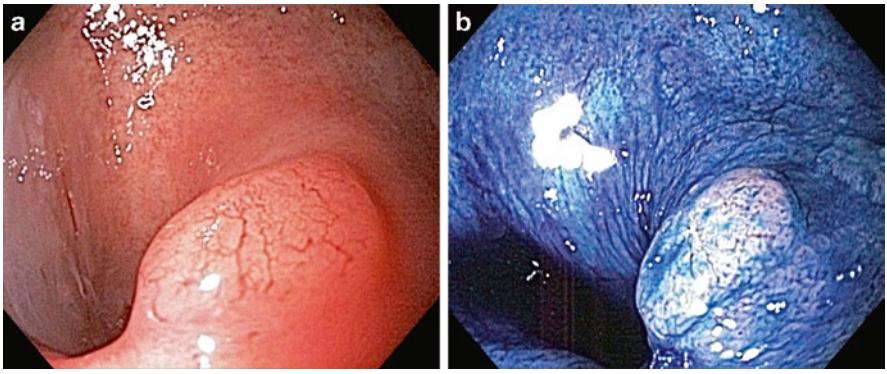

Fig. 17.1 (**a**) Rectal polyp using white light optical colonoscopy. (**b**) Rectal polyp visualized with methylene blue chromoendoscopy, demonstrates enhanced margins and satellite raised areas

Narrow band imaging (NBI) uses specialized light filters to enhance visualization of the tissue microvasculature, facilitating distinction between normal mucosa and neoplasia. Dekker and colleagues performed a prospective, randomized, crossover study in 2007 on 42 patients with longstanding UC and found that first-generation NBI has comparable sensitivity to conventional colonoscopy, noting that more suspicious lesions were found during NBI [51]. Although this novel and innovative technology remains to be thoroughly evaluated in the setting of surveillance in IBD, it holds the potential to offer the same benefits as chromoendoscopy with greater ease of application. Figure 17.2 compares an image of rectal mucosa using white light optical colonoscopy, NBI, and methylene blue chromoendoscopy.

Confocal laser endomicroscopy (CLE) enables real-time histologic evaluation of the colonic mucosa during endoscopy and can be combined with chromoendoscopy. Suspicious lesions identified through application of dye can be subsequently examined with extreme detail at the subcellular level of resolution with CLE prior to targeted biopsy. In a randomized trial in UC patients of chromoendoscopy in conjunction with CLE compared to conventional colonoscopy, the presence of neoplasia could be predicted with 94.7% sensitivity, 98.3% specificity, and 97.8% accuracy [52]. In this study of 153 patients, the mean examination time was 42 min using chromoendoscopy with CLE compared with 31 min in the standard colonoscopy group. This innovative imaging technique has major implications for the future of colonoscopic surveillance in IBD.

Despite the promise and emerging information about these new techniques, factors of cost and training remain far from answered, and chromoendoscopy is not yet considered a standard of care approach to surveillance in the United States. Of interest as well is the issue of whether dysplastic lesions seen on chromoendoscopy have the same predictive value as those historically described on random biopsy or with older optical colonoscopes.

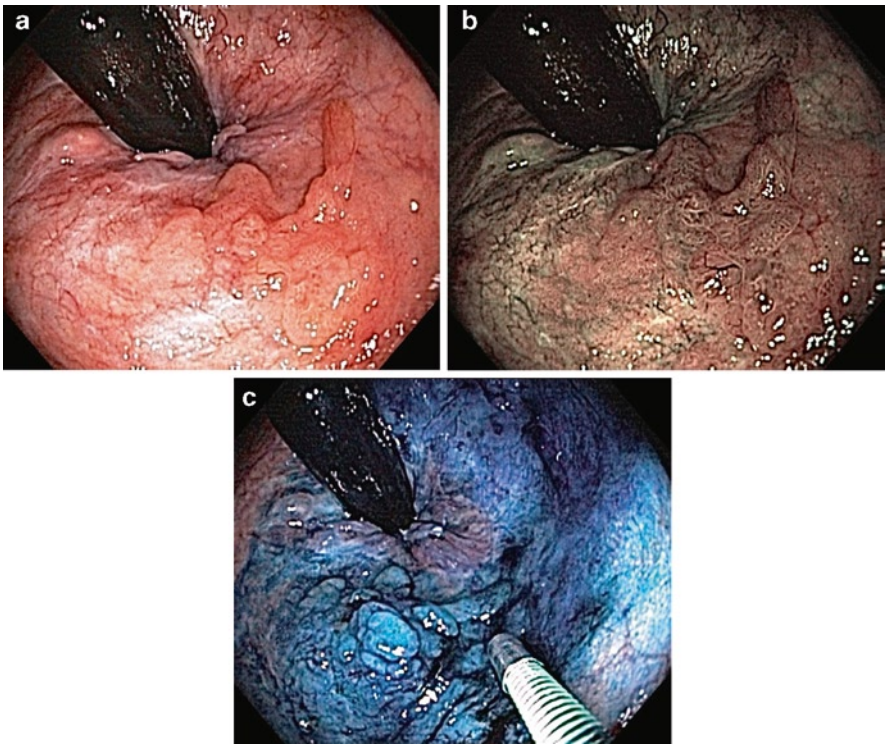

Fig. 17.2 Patient with Crohn's colitis and multifocal polypoid low grade and high grade dysplasia in the distal rectum. (**a**) Rectum using white light optical colonoscopy. (**b**) Rectum visualized with narrow band imaging (NBI). (**c**) Rectum visualized with methylene blue chromoendoscopy

Current Consensus Guidelines

The recommendation to perform surveillance in IBD patients comes from consensus expert opinion, supported by solid rationale and an ethical imperative to attempt prevention in an at-risk population [53]. However, hard evidence of efficacy is lacking. A Cochrane review concluded that although there is no clear evidence that surveillance colonoscopy prolongs survival in IBD patients, there are data to suggest that cancers tend to be detected at an earlier stage with a correspondingly more favorable prognosis [54]. The authors include the caveat that lead time bias may contribute substantially to these results. Additionally, they conclude that indirect evidence supports surveillance as a cost-effective endeavor [54].

A number of guidelines have been published over the past decade in the United States and United Kingdom to assist gastroenterologists in their approach to surveillance of dysplasia and cancer in IBD [26, 55–58]. With the goal of developing standardized consensus guidelines, the Crohn's and Colitis Foundation of America commissioned an international group of experts who published their

conclusions in 2005, suggesting that an initial screening colonoscopy be performed in all UC patients 8–10 years after onset of symptoms attributable to UC [26]. The dual purpose of this initial screening exam is to identify dysplasia or cancer, if present, as well as to evaluate possible reclassification of disease extent. The extent of disease in a given UC patient should be considered the greatest extent of involvement documented on either gross or histologic exam at the time of diagnosis of UC or at initial screening colonoscopy. Patients with Crohn's disease of the colon should be managed in an identical manner to UC patients of comparable extent of colonic involvement. Crohn's patients with at least one third of their colon involved are considered to have extensive colitis. Those patients with left-sided or extensive colitis (UC or Crohn's) who have a negative screening examination should continue periodic surveillance at an interval of every 1–2 years, the interval determined based on compounded risk factors. The exceptions are patients with colitis and coexistent PSC, in whom annual surveillance should begin at the time of PSC diagnosis. Because of the traditional understanding of dysplasia occurring in flat mucosa, a systematic approach to mucosal sampling has been recommended, which involves 4 quadrant random biopsies at 10 cm increments throughout the colon in addition to targeted biopsies of suspiciously abnormal mucosa. All abnormal biopsies results should be confirmed through independent review by a second pathologist. A finding of IND should prompt accelerated surveillance with a repeat exam in 3–6 months. Management of LGD is a subject of debate among experts with no clear consensus on optimal management. In the setting of LGD, physicians should initiate an informed discussion with their patients regarding the risks and benefits of immediate surgery versus heightened colonoscopic surveillance. Prophylactic colectomy should be discussed due to the approximately 20% prevalence of concurrent malignancy [8], with counseling about possible surgical complications including incontinence, adhesions, pouchitis, and decreased fecundity in female patients. Patients who elect nonoperative management should be informed regarding the limitations of surveillance, including difficulties with endoscopic detection and sampling and challenges with histologic interpretation. An accelerated program of surveillance colonoscopy every 3–6 months should be pursued with adherence to an extensive biopsy protocol mentioned earlier. Endoscopically discreet polyps may be removed as they would be in non-IBD patients, but if the polypoid lesion contains dysplasia, the follow-up and recommendations will depend on the age of the patient, the number of lesions (including pseudopolyps), and the presence or absence of dysplasia in flat mucosa. Available evidence suggests that complete removal of polypoid dysplasia may be safely followed, albeit with more intense surveillance [42, 59, 60].

Our evolving understanding of risks and outcomes may lead to an approach in the near future that incorporates stratified follow-up based on degree of inflammation and the possibility of serial colonoscopic exams in patients with visible or clearly polypoid dysplasia.

Chemoprevention

The use of chemoprevention as a primary prevention of CRC in IBD means to use chemical compounds to prevent, halt, or reverse the development of cancer. One advantage of chemoprevention over the current secondary prevention strategy of routine colonoscopy is the potential to intervene early enough in the carcinogenic sequence to avoid not only cancer but also the need for colectomy. The goal of chemoprevention should be to reduce CRC risk, allowing for less frequent surveillance exams and a reduction in the number of invasive cancers. And its use is important in the prevention of cancer in IBD but does not ultimately change the surveillance approach to these patients. Most importantly, many of the studies have looked at the chemoprotective effects of agents in UC, little data exists for CD patients. The bulk of evidence for chemoprevention in IBD relates to the use of 5-aminosalicylates (5-ASA). Unfortunately no prospective data exist, and retrospective studies have yielded mixed results with regard to the protective effect of 5-ASA medications. A 2005 meta-analysis by Velayos et al. [61] including nine case control and cohort studies revealed a pooled odds ratio of 0.51 (95% CI 0.38–0.69) for the development of dysplasia or cancer in patients with regular use of 5-ASA medications. Rubin et al. [62] conducted a retrospective case–control study in 2006 concluded that aminosalicylate use of 1.2 g/day or more was associated with 72% reduction in the odds of dysplasia/CRC, with increasing aminosalicylate dose the odds of dysplasia/CRC decreasing. Given the substantial heterogeneity of individual study results, this pooled estimate signifies the most accurate estimate of the protective effect of 5-ASA.

The most compelling evidence for chemoprevention in IBD comes from a prospective randomized placebo-controlled trial of UDCA in the high-risk subset of UC patients with coexisting PSC [21]. Compared to the placebo group, patients who received UDCA had a relative risk of 0.26 (95% CI 0.06–0.92) for developing CRC or dysplasia. A retrospective study performed at the University of Washington included patients with PSC and UC and corroborated these results by demonstrating a strong negative association between UDCA use and dysplasia, with an odds ratio of 0.18 ($P=0.005$) [22]. UDCA is considered standard of care in patients with UC and PSC.

While other medications have been explored as potential chemopreventive agents, none have yet yielded satisfactory results. The adverse effects of corticosteroids and nonsteroidal anti-inflammatory drugs preclude their long-term use for chemoprevention in IBD patients, despite some evidence to suggest a protective effect in both IBD and non-IBD patients. The use of folate for chemoprevention has sound rationale and an excellent safety profile, but inadequate evidence of a protective benefit. Likewise despite the rationale of medically controlling inflammation as a potential mechanism of cancer prevention, there are insufficient data to recommend azathioprine or 6-mercaptopurine for chemoprevention. There remains interest in the possibility of early, effective control of inflammation with immune modulation or biologic therapy altering neoplasia risk.

The Future of Cancer Detection in IBD

Although we have made good progress, there is clearly much room for improvement in our understanding of the neoplastic risks in patients with IBD. A variety of approaches are being explored, although none are likely to change our current practice at this time. There has been much interest in the identification of biomarkers that are associated with dysplasia or early stage cancer development. Some have been in peripheral blood and others have been in tissue. Unfortunately, none have been sufficiently sensitive or specific to warrant their use in this field [63, 64]. In addition, despite the positive studies in patients with sporadic polyps and cancer, an array of fecal DNA and molecular markers has not been sufficiently sensitive for use in IBD [65]. As we incorporate our evolving understanding of the "new" meaning of dysplasia in our patient populations and the importance of distinguishing between polypoid and flat dysplasia, it will also become essential that physicians are able to communicate these complicated issues to patients so that they may actively participate in these discussions. Since the prospect of surgical colectomy is so frightening to patients, exploration of the degree of risk that they are willing to accept before having surgery is an important issue. In a survey of 199 patients with UC for more than 8 years seen at Dartmouth Hitchcock Medical Center and at the University of Chicago Medical Center, Siegel and colleagues identified that patients were on average willing to accept an approximately 60% risk of cancer before they would undergo proctocolectomy and restorative ileo-anal pouch. This is significantly different than the risk currently understood of low-grade dysplasia (20%) [66]. It is clear that improved methods of communicating risk must be incorporated into our future approaches in this field (Table 17.2).

Table 17.2 Unanswered questions in cancer prevention in inflammatory bowel disease (IBD)

Is any dysplasia truly invisible or have new technologies allowed for direct visualization of all lesions?
Is degree of inflammation a cumulative risk of neoplasia or can a single episode of severe inflammation alter the future risk?
Does effective control of inflammation decrease the risk of cancer in ulcerative colitis and Crohn's colitis?
What is the ideal interval of follow-up for surveillance exams in an individual patient?
What is the best way to incorporate chromoendoscopy into clinical practice? What is the learning curve for this approach?
If dysplasia is visible, what is its predictive value for synchronous or metachronous cancer? Can any dysplasia be followed safely without colectomy in patients?
Do immunomodulators or biologic therapies have unique chemoprevention properties, or is control of inflammation the primary mechanism?

Conclusion

Patients with IBD have an increased risk of developing CRC. This risk appears to be related to the cumulative effect of chronic inflammation and correlates directly with the extent and duration of disease as well as the severity of inflammatory activity. Despite varying estimates of the magnitude of cancer risk in IBD, it remains widely accepted that patients with IBD represent a high-risk group for developing CRC in whom current therapies and surgical techniques may be affecting the incidence of this complication, so a careful approach to prevention and surveillance is still warranted. The overall approach to cancer prevention in IBD should be a comprehensive strategy, including regular follow-up visits and intensive control of disease activity through medical therapy, in concert with routine surveillance colonoscopy involving extensive biopsies. Cancer risk reduction through regular use of chemopreventive medications remains an attractive concept, and the most compelling data is in the setting of PSC and IBD, in which UDCA offers substantial benefit. The accumulated data appear to favor 5-ASA as a chemopreventive agent, but this remains inconclusive due to the retrospective nature of these studies. Novel endoscopic imaging technologies to enhance detection of neoplasia are under investigation and hold promise for improving the yield of surveillance colonoscopy.

In recent years, the cumulative probability of cancers in chronic colitis appears to be less than previously reported, and it is suspected that this is due to access to effective medical and surgical therapy. Better characterization of the appearance and behavior of dysplasia improves our understanding and approach to risk stratification and prevention, but there remain substantial challenges in this field.

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Chapter 18
Managing the Patient with a Fecal Diversion

Janice C. Colwell

Keywords Ostomy • Ileostomy • Colostomy • Stoma • Loop stoma • Peristomal • Irritant contact dermatitis • Peristomal candidiasis • Peristomal pyoderma gangrenosum • Parastomal hernia • Wound Ostomy and Continence Nursing Society

Key Points

- An effective pouching system requires an adequate seal and intact skin around the stoma.
- Preoperative evaluation for stoma location is important to ensure that the area is free of skin folds in the sitting, standing, and prone positions.
- The adhesive/hydrocolloid should be inspected for erosion upon removal of the pouching system, with shorter time between changes if there is evidence of skin barrier breakdown.
- Postoperatively, patients are advised to adhere to a low-residue diet; many can extend their diet after 6-weeks.
- Patients with high-output ostomies are advised to eat foods that thicken their effluent, especially when drinking liquids.
- Risk factors for complications include obesity, the presence of inflammatory bowel disease, and emergently created stomas.
- The most common peristomal complication, irritant contact dermatitis, is due to an inadequate seal and requires reevaluation of the pouching system and patient technique.
- Social support is important for patients to adapt to their new ostomy.

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- The Wound Ostomy and Continence Nursing Society (WOCN) and the United Ostomy Associations of America provide valuable resources to caregivers and their patients with ostomies.
- The input of a trained WOC nurse is important in each step of the process for the patient who requires an ostomy.

Introduction

A number of patients with ulcerative colitis or Crohn's disease may require a temporary or permanent fecal diversion. The creation of a stoma, either an ileostomy or a colostomy, requires a planned patient care approach; the plan should include the patient, family or identified support person, gastroenterologist, surgeon, and certified ostomy care nurse. The patient must understand the reason that the stoma will be created and the final outcome, as well as the process that will be in place to help him or her achieve the outcome. A person anticipating the creation of a fecal diversion needs to have adequate preoperative preparation, postoperative education, and support as well as ongoing access to the health care team for ongoing monitoring and intervention if problems should be encountered. An important member of this team is the certified ostomy care nurse, a nurse specializing in the management of a person with a stoma, who has attended an advanced nursing course and has achieved certification in ostomy care. Ostomy care nursing has evolved into the specialty of wound, ostomy, and continence care referred to as the Wound, Ostomy, and Continence Nurse or WOC nurse. The WOC nurse should be involved in preparing the patient for surgery, teaching, and supporting the patient after surgery and providing interventions should problems arise.

In order to live successfully with a stoma, the person must have a pouching system that maintains the seal around the stoma for a predictable period of time, and the skin around the stoma must remain intact. The predictable wear time will provide the patient with the security that he or she can return to preillness activities without fear of pouch failure. Once the patient has achieved security in wearing an ostomy pouching system, the adaptation to living with a stoma can begin. Factors that will impact a secure pouching system are the location of the stoma on the abdominal wall, the amount of protrusion of the stoma, the amount and consistency of the stoma effluent, the choice of pouching system, and the ability of the patient to manage the stoma.

Stoma Location

The stoma location on the abdominal wall affects the seal of the pouching system as well as the patient's ability to manage the stoma [1]. The site for the stoma should be chosen before the surgical event. Most pouching systems have

approximately 4 in. of adhesive that should be placed on a flat abdominal area around the stoma. A four inch area should remain flat in a standing, sitting, or prone position to maintain the pouch seal. Therefore, the location of a stoma in an area that is free of creases and folds is key to securing the pouching seal. Other considerations for stoma site selection include placement through the rectus muscle, in a location that the patient can see the stoma and thus become independent in care and if possible below the belt line to provide for concealment. At the preoperative session, the patient's abdomen is assessed in a sitting, standing, and prone position and an area is chosen that remains relatively flat in each position. Once the site is chosen, it is marked with a surgical marking pen and covered with a transparent dressing. This will allow the spot to be in place on the day of surgery. A resource for stoma siting has been collaboratively developed by The American Society of Colorectal Surgeons and the Wound Ostomy and Continence Nurses Society and covers the importance of stoma site marking as well as the procedure to ensure proper site selection [1].

Stoma Creation

A stoma that is created to protrude at least 2 cm above the skin should allow the effluent to drain out of the stoma, over the adhesive seal of the pouching system and into the pouch. A flush stoma may drain the effluent out of the stoma at the level of the adhesive seal, undermining the seal and causing stool to leak out from under the pouching system. This principle of stoma creation refers to either an end colostomy or ileostomy. When a loop stoma is created, the amount of protrusion maybe compromised. A loop stoma may be created for several reasons, including to divert the stool from a newly created anastomosis to allow for healing or to divert stool from diseased or infected intestine. In creating an ileal pouch anal anastomosis, a diverting loop stoma is generally created to provide temporary diversion of the fecal stream from the healing internal pouch. A loop stoma is fashioned by bringing a loop of bowel out to the abdominal wall, thus the side rather than the end of the intestine is used to fashion the stoma. A support bridge is used to hold the bowel to the skin until healing is completed. Because the opening in the bowel is on the side rather than at the end of the bowel, the loop stoma may not protrude above the skin level.

The obese patient who requires the creation of a stoma may encounter problems related to stoma creation and location. In one analysis of patients with stoma complications, a high BMI was found to be independently associated with an increased rate of retractions (stoma at the level or below the skin) [2]. Duchesne et al. [3] reported that common problems encountered in obese patients were necrosis, prolapse, and skin irritation. These studies suggest that a short and fatty mesentery can cause a comprised circulation and may prevent the creation of a stoma that protrudes above the skin level.

Preoperative Patient Preparation

All patients scheduled to have surgery that will create a stoma will need preoperative patient education, most likely done by the WOC nurse. Given the speed in which patients are discharged from inpatient acute care facilities, it is important to introduce the patient to the principles of managing a stoma and to begin to help the patient understand how he or she will live with a stoma. The topics covered in the preoperative teaching session should include how the gastrointestinal tract will function once a stoma is created, what the stoma will look like, how it will function, how it will be managed, and the skills that will need to be acquired to manage the stoma. The use of a teaching guide with pictures or illustrations of a stoma will help the patient understand the appearance of the stoma. Showing the patient a pouching system, how it is changed and emptied, helps the patient actualize the stoma and the skills that he or she needs to acquire. Sending the pouching system home with the patient allows him or her to practice opening and closing the bottom of the pouch, moving toward mastering the emptying of the pouch. Some patients benefit from meeting or talking with a person who has had a stoma. Such visits can be arranged through the United Ostomy Associations of America, by contacting a local chapter who has a visitors group. The members of the visitors group undergo a training session that help them address the concerns of the patient anticipating surgery.

The two most frequently asked questions by patients anticipating ostomy surgery are will I have an odor and will others be able to see that I am wearing a pouch? If a patient does not ask these questions, both of these topics should be addressed. The patient must understand that the pouching system is air tight, if placed on correctly no odor will seep from under the pouch adhesive seal, or from the bottom of the pouch. The plastic of the pouch is odor proof. The pouch is concealed beneath properly fitting under clothing, the under clothing when fitted to the body will keep the pouching system flat and allow the effluent to be distributed evenly through the pouch, keeping a flat profile under the clothes. The pouch is emptied when one-third full to avoid overfilling the pouch.

Stoma Function

Stoma function will depend upon the anatomical location of the stoma and the amount of functioning bowel. Typically, once a person with a new ileostomy is out from surgery approximately 3 weeks, he or she can expect 1,000–1,200 ccs of pasty effluent in a 24-h period. During the first few weeks after surgery, the initial output from an ileostomy maybe over 1,200 ccs/24 h and the consistency will be liquid. Colostomy output will vary from a right-sided stoma with output close to 1,000 ccs in 24 h to a sigmoid colostomy with 500 ccs in 24 h and a semi-formed stool. Normal output for a person with previous bowel resections will vary depending upon the amount of intact and functioning intestine. A high volume, liquid output will erode the pouching seal after several days, whereas stoma output that is pasty will not loosen the seal of the pouching system quickly allowing for a longer wear time.

Pouching Systems: Basic Stoma Management

A pouching system consists of the collection device that contains the stoma drainage and the skin barrier that provides a secure seal and protects the peristomal skin (see Fig. 18.1). The most important part of the pouching system is the skin barrier as this provides the patient with security. If chosen appropriately, the skin barrier protects the skin from the stoma effluent and seals the pouch to the skin for a predictable period of time. The pouch, although the more obvious portion of the pouching system, does not contribute in a direct way to the pouch seal.

The skin barrier contains several materials that include adhesives and hydrocolloids. The adhesive provides the bonding agent between the pouch and the skin. The hydrocolloid slowly absorbs moisture to prevent the stoma effluent from making contact with the skin and absorbs skin moisture. Most pouching systems have a tape border around the skin barrier to allow the patient to bathe without loosening the inner seal. The skin barrier is fitted around the stoma and should cover all of the skin around the stoma. Thus as the stoma effluent drains, the output will be in contact with the skin barrier, protecting the peristomal skin from damage. The size of the opening in the skin barrier should match the stoma, if the stoma is round, the opening is round; if the stoma is oval, the opening should be cut to match. Skin barriers are available on pouching systems as cut-to-fit and precut. Immediately after surgery, it is advisable to use a cut-to-fit system to allow the patient to downsize the skin barrier opening as the stoma heals and changes size. Once the stoma edema has subsided, a precut round opening skin barrier can be used, or if the stoma remains oval, the oval shape can be cut by the patient.

The amount of time that a patient wears the pouching system is related to how quickly the adhesive/hydrocolloid erodes. The erosion occurs when the stool makes

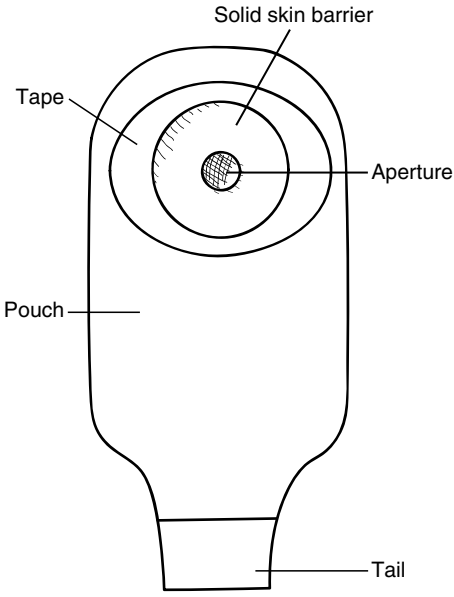

Fig. 18.1 Ostomy pouching system

Patient resources

Organization	Description
United Ostomy Associations of America (UOAA) P.O. Box 66 Fairview, TN 37062-0066, USA www.uoaa.org	UOAA is an association of affiliated, nonprofit, support groups that are committed to the improvement of the quality of life of people who have, or will have, an intestinal or urinary diversion It is dedicated to the provision of information, advocacy, and service to, and for, its affiliated support groups, their members and the intestinal/urinary diversion community at large. The support groups are located geographically around the United States and a local support group can be located at the UOAA web site. Monthly educational meetings are held that provide support and information. The Phoenix, a quarterly magazine is published, which provides the person with an ostomy a mechanism to keep up-to-date on ostomy-related issues as well as exposure to the newest ostomy equipment
Wound Ostomy and Continence Nurses Society 15000 Commerce, Suite C Mount Laurel, NJ 08054, USA 888-224-WOCN (9626) www.wocn.org	The WOCN Society is a professional nursing society that supports its members by promoting educational, clinical, and research opportunities to advance the practice and guide the delivery of expert health care to individuals with wounds, ostomies, and incontinence. The WOC nurse provides ostomy care services to people with ostomies in the preoperative period, the postoperative period and postdischarge. A referral to a WOC nurse can be obtained by calling the national office or by searching the database at the web site

contact with the skin barrier, the more liquid the stoma output the faster the erosion occurs. Thus a patient with a high volume liquid output from the stoma may not wear the system as long as someone with pasty stool that passes from the stoma once or twice a day. The wear time is determined by the patient and the ostomy nurse; upon removal of the pouching system, the adhesive/hydrocolloid is examined to see how much erosion has occurred. Should the opening in the skin barrier be larger than it was when placed on, erosion has occurred with the potential for skin exposure. Thus the patient will be instructed to wear the system for at least one less day. On average a person with a normal functioning ileostomy and colostomy, with a stoma with adequate protrusion and location, should have an average wear time of 4 days.

Pouches are available in many shapes, configurations, fabrics, and films. Pouches that are sealed to the skin barrier are classified as a one-piece system and pouches that are separate from the skin barrier but are attached to the skin barrier with a flange or an adhesive seal are classified as a two-piece system [4]. Pouch options include a drainable pouch allowing the effluent to be emptied, without the removal of the pouch, or a closed-end pouch requiring removal and disposal of the pouch when filled. Drainable pouches are available in several lengths and the length of the pouch depends upon the person's personal preference and the volume of the stoma output. A person with an ileostomy generally chooses to wear a drainable pouch because he

or she needs to empty the pouch approximately 5 times a day. Closed-end pouches require the person to remove and discard the pouch when filled and thus become more appropriate for a person to use when he or she has a left-sided colostomy with one to two bowel movements per day. There is a variety of cloth fabric-covered pouches (to absorb moisture, to conceal the pouch contents) as well as beige pouch films also to provide concealment. Other features of pouches include gas filters (to vent and deodorize flatus) and integrated closures (vs. a pouch clamp). Most people with a new ostomy try several pouch types before deciding upon the best fit (Tables 18.2–18.3).

Table 18.2 Ostomy product manufacturers

Coloplast 200 South Sixth Street, Suite 900 Minneapolis, MN 55402, USA 1-612-337 7800 www.coloplast.com	ConvaTec Professional Services P.O. Box 5254 Princeton, NJ 08543-5254, USA 1-800-422-8811 www.convatec.com
Hollister 2000 Hollister Drive Libertyville, IL 60048, USA 1-888-740-8999 www.hollister.com	Nu-Hope Laboratories Nu-Hope Laboratories, Inc.P.O. Box 331150Pacoima, CA 91333-1150, USA 1-800-899-5017 www.nu-hope.com

Table 18.3 Ostomy products

Product	Purpose	Clinical tips
One-piece cut to fit pouching system	Pouch and skin barrier are one unit, can be cut to fit stoma size	Appropriate for postop use. Can be used to fit irregular stoma shapes. Opening in skin barrier cut to exact stoma size/shape
Two-piece pouching system	Skin barrier and pouch are two separate pieces, allowing skin barrier to be placed on prior to pouch application. Skin barrier can be cut to fit or precut	Use when patient wants to remove the pouch on a frequent basis, prevents the need for the skin barrier to be removed before wear time achieved
Skin barrier paste	Used to "caulk" the opening in the skin barrier to prevent undermining of the stool. Can be used to fill in uneven areas around the stoma	Paste contains alcohol which will cause burning if applied to denuded skin, avoid use if possible on irritated skin
Skin barrier powder	Used to dry denuded weepy skin and to allow the seal of the pouching system	Sprinkle a small amount of powder to the affected skin, rub in and brush off excess, prior to pouch application
Convex pouching system	The convex shape can enhance the pouch seal, by flattening an uneven peristomal area, or causing a retracted stoma to protrude into the skin barrier opening	The convex shape of the skin barrier is used if after assessing the patient in a sitting position, a crease or fold is noted. The convex barrier is placed when the skin is flat, such as when standing
Pouch deodorant	Neutralizes odor when the pouch is emptied	Placed in pouch upon application and after each emptying

Day-to-Day Management of a Fecal Stoma

On a daily basis, a person with a fecal stoma must empty the output from the pouching system. A person with an ileostomy and an intact small bowel will have a pasty effluent that will need to be emptied from the pouch approximately 5 times a day. Most people with an ileostomy empty their pouching system when it is one-third full, which in a regular length pouch is approximately 200 ccs. To empty the pouch, they sit back on the toilet, open the end of the pouch, and allow the output to drain into the toilet. The end of the pouch is wiped with a tissue and the pouch tail closed. The skill of emptying the ostomy pouch is the first skill that a person learns after surgery and must be mastered before discharge. A person with an ascending or transverse colostomy empties the pouch in the same manner as the effluent is generally loose and can easily be emptied. The person with a left-sided colostomy and a pasty stool passing once or twice a day may opt to remove the pouch and discard into a receptacle (in a plastic bag provided for this purpose) because emptying a pasty to semi-formed stool can be difficult.

When the pouch seal is intact and the closure is properly fashioned, the person with an ostomy will have no odor. However when emptying the pouch, odor can be present. Some patients opt to use a pouch deodorant that is placed into the pouch upon application and after each time the pouch is emptied. The pouch deodorant neutralizes the odor.

After healing has taken place and the person with an ostomy has made a decision upon what pouching system best works for his or her situation, he or she will develop a pattern for the pouching system change. Most people change their system approximately every 4 days, and thus develop a routine of changing about twice a week. When a person changes his or her pouching system, he or she prepares all of the equipment prior to the removal (as the stoma function is unpredictable). The pouching system is removed, the skin cleansed with water (most soap has moisturizing agents which will interfere with the seal), dry the area, and place the pouching system on. The pouch change is done in the washroom, while standing at this position allows visualization of the stoma and keeps the peristomal skin flat.

The material on the outside of the skin barrier is water resistant and will maintain the seal when the patient showers, bathes, or swims. Most patients leave the pouching system in place when showering or bathing, while some will shower without the pouch on the day they choose to change their pouch. This allows water to contact the skin and facilitate adhesive removal.

Postoperatively most patients with a fecal diversion are on a low residual diet while the stoma is edematous to prevent cramping or a possible bowel obstruction. Once the postoperative edema has subsided (usually 6 weeks after the surgical procedure), the patient is instructed to slowly reintroduce high fiber foods, chewing well and including liquids when eating high fiber foods. A normal diet for a person with a fecal diversion will depend upon the presence of active disease or strictures. For some patients with active inflammatory bowel disease or strictures, a low residual diet is recommended. Patients with a temporary loop ileostomy following the creation of an

ileal anal anastomosis may encounter high liquid output that can lead to dehydration. These patients are advised to include foods that thicken the output such as complex carbohydrates, pretzels, bread products, bananas, cheeses, and applesauce. They are further advised not to drink without eating some of the aforementioned products, as a significant increase in fluid intake without eating can cause an increase in output.

Complications

The incidence of stoma complications is difficult to determine. The frequency of reported complications varies between 6 and 77%, and this variation appears to be a result of inconsistent reporting of definitions, types of stoma, and the time frame of complications [1, 5, 6]. The known risk factors for the occurrence of complications include obesity, the presence of inflammatory bowel disease, and emergently created stomas [2, 3]. It is therefore likely that a person with inflammatory bowel disease and a fecal diversion will at some point encounter a peristomal or stomal complication.

Selected Peristomal Complications

Irritant Contact Dermatitis

The most common peristomal complication is the loss of skin around the stoma: irritant contact dermatitis, seen in 30–40% of patients [3]. The skin is exposed to the fecal output for a prolonged period of time, causing epidermal erosion. The patient complains of pain and burning in the involved area. The skin damage can result from an inadequate pouch to skin seal that allows stool to remain in prolonged contact with the skin. Assessment of the peristomal area finds the loss of epidermis in the area of leakage, resulting in a moist area, and the patient notes frequent leakage under the pouching system seal. The cause of the inadequate seal is usually not matching the opening on the skin barrier exactly to the stoma (the opening should be the same size and shape as the stoma to prevent the effluent form contacting the skin), allowing the skin barrier to be worn for an excessive amount of time causing the skin barrier to erode, or not matching the shape of the skin barrier to the shape of the peristomal skin [7]. When evaluating a patient for the proper shape of the skin barrier, the peristomal area is visualized while the patient is sitting to see if the skin barrier shape should be flat or convex. The shape is matched to the shape of the peristomal skin, if when the patient is sitting the skin is flat, a flat skin barrier is chosen, and if the skin around the stoma is concave a convex skin barrier is used. The fitting of the shape and size of the skin barrier is best done by a certified ostomy care nurse. Once the correct shape and size of skin barrier is determined, the denuded peristomal skin should be treated using a skin barrier powder. The skin barrier powder is a hydrocolloid and will absorb the skin moisture, drying the area

to allow for a seal. The powder is liberally applied to the affected skin, rubbed into the skin with a gauze pad, and the excess powder is wiped off leaving a light dusting on the skin. The correct pouching system is then put in place.

Peristomal Candidiasis

Peristomal Candidiasis is an overgrowth of a Candida organism of sufficient magnitude that causes an inflammation or infection of the peristomal skin. The patient may complain of itching, pain, or excessive moisture in the skin around the stoma. Assessment of the area finds papules, erythema, and maceration with satellite lesions at the edges of the advancing Candidiasis. Location is generally limited to the area of the skin barrier as moisture is trapped under the skin barrier. Risk factors for development include long-term antibiotic administration, diabetes mellitus, use of immunosuppressive drugs, and a moist environment. The moist environment may be caused by an improper pouch seal, from cutting the skin barrier larger than the stoma or prolonged wear time, both of which can cause a moist environment. A topical antifungal preparation that will not interfere with the pouch adhesion is recommended, such as nystatin powder. The involved area is cleansed with warm water, dried, and powder rubbed into the area and the excess is removed. The powder is applied at pouch change until the peristomal area appears dry and intact.

Peristomal Pyoderma Gangrenosum

Peristomal pyoderma gangrenosum is a rare, ulcerative skin condition of unknown etiology that occurs in the area surrounding the stoma. There is no clear understanding of the pathogenesis. The majority of patients with peristomal pyoderma have been diagnosed with inflammatory bowel disease, more often with Crohn's disease than ulcerative colitis [6, 8, 9]. Full thickness ulcers with irregular ragged overhanging edges occur in the area covered by the skin barrier. The ulcers frequently undermine with loss of skin between them. The skin around the ulcers have a distinct purple hue, and the patients report the area to be very painful (Fig. 18.2).

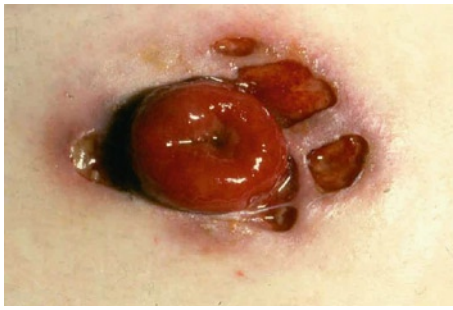

Fig. 18.2 Peristomal pyoderma gangrenosum, purple discoloration around full thickness wounds with epidermal undermining between ulcers

The ulcer base is red and moist, and because of the inflammatory process there is significant drainage present. Healing results in a cribriform scar that can cause pouch seal problems after the area is healed. No single therapy has been demonstrated to be effective in the treatment of peristomal pyoderma [10]. The challenge is to provide systemic and local therapy while maintaining an adhesive seal over the ulcers. Topical therapy should be geared toward decreasing the inflammatory process, absorbing the excessive moisture, and maintaining a pouch seal. Topical treatments may include the use of steroid preparations in a paste (e.g., Orabase® in triamcinolone), or topical immunomodulators such as pimecrolimus (e.g., Elidel®). Products are used to absorb excessive moisture and can include hydrofiber or alginate products. A secondary dressing is used to provide a dry surface to adhere the pouching system and may include hydrocolloid or a foam dressing. In cases of small areas of involvement, topical therapy is instituted to determine response. In cases of no response with topical therapy or in involved cases, systemic medical therapy is instituted. Therapy may include administration of prednisone, cyclosporine, dapsone, or infliximab [11]. Healing rates are variable and the patient requires ongoing support during the treatment process.

Parastomal Hernia

A parastomal hernia is a defect in the fascia that allows loops of intestine to protrude into the area of weakness. The cause of a peristomal hernia is unclear; however, several factors have been implicated and include: siting the stoma outside of the rectus muscle, the creation of a large fascial opening, a weak abdominal musculature, obesity, corticosteroid use, and chronic respiratory disorders [12, 13]. The reported rate of peristomal hernia varies between 5 and 52% [12]. The patient presents with a bulge in the area surrounding the stoma. This bulge is most prominent in a standing or sitting position. Patients may encounter difficulty maintaining the seal of the pouching system because the abdominal skin of the area alternates between stretching and relaxing, thus shifting the pouch seal [7]. The difficulty in maintaining the pouching system seal can cause leakage and irritated peristomal skin. Many patients are distressed by the unsightly bulge that may be noticeable under clothing. Some patients report occasional pain in the area of the hernia and in extreme cases patients report intense pain at the site of the parastomal hernia due to obstruction or ischemia of an intestinal loop.

If the patient with a parastomal hernia is asymptomatic (maintains a seal on the pouching system, has minimal discomfort in the area), no interventions are generally considered. If the bulge is unsightly or affects the pouch security, a hernia support belt can be worn over the hernia. The belt provides support over the herniation and around the stoma. It is placed on when the hernia is reduced (patient is in a flat position), and looks much like an abdominal binder with a hole for the pouch to be worn outside of the support belt. Surgical options include primary fascial repair, local repair with prosthetic material and relocation of stoma, and long-term results that are not encouraging due to a high reoccurrence rate [12].

Adjustment

A patient undergoing ostomy surgery is faced with a profound change in body image and physical functioning. Adaptation to life with a stoma necessitates acquisition of new skills to maintain the pouch seal (security) and the presence of social support [14]. Pieper and Mikols [15] reported the top three concerns that patients with new ostomies identified: fear of stool leaking, presence of odor, and participation in sports. In order to start working on adjustment of life with a stoma, the person with a new stoma needs the skills and knowledge that will prevent stool from leaking or the presence of odor (how to change and maintain the pouching system) and then the encouragement that he or she can participate in all activities. The acquisition of new skills can be facilitated by consultation with a certified ostomy care nurse. Once the person with an ostomy feels comfortable that he or she has gained control over the pouching system, adjustment can move forward. The encouragement to resume preillness activities may be best accomplished by offering the person with a new ostomy the opportunity to talk or meet with someone who has had an ostomy for some time and has resumed activities. This can be accomplished by working with the United Ostomy Associations of America that provide networking opportunities for people with fecal and urinary diversions.

Nichols and Riemer [16] surveyed 1,495 people with ostomies to identify stabilizing forces on the recovery of ostomy patients. They reported that a stable spouse/partner relationship positively influenced life satisfaction scores after ostomy surgery as did the stability in occupation (returning to presurgical employment). Piwonka and Merino [17] found that predictors for adaptation for patients with colostomies included the presence of social support. Inclusion of the patient's significant other appears to positively influence the adjustment process, and part of the plan of care for the person with a new ostomy should include identification and inclusion of the patient's significant other. If agreeable with the patient, the identified support person should be present during the preoperative consultation as well as at least one ostomy care lesson and at the return outpatient visit. While the goal for most people with a new ostomy is to learn selfcare, the presence of support appears to contribute to the adjustment to living with a stoma.

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Chapter 19
The New Economic Reality in the World of IBD

Nanda Venu and Russell D. Cohen

Keywords Crohn's disease • Ulcerative colitis • Inflammatory bowel disease • Costs • Direct costs • Indirect costs • Charges • Reimbursements • Healthcare economics • Hospitalization • Surgery • Pharmacy • Resource utilization • Disability • Quality adjusted life years • Quality of life

Key Points

- The treatment of inflammatory bowel diseases over a lifetime adds a considerable amount of costs to the total healthcare burden.
- There is disparity in the usage of healthcare dollars whereby a small percentage of patients account for a majority of the total direct costs.
- In the prebiologic era, most costs were due to hospitalizations and surgeries. Currently, pharmaceuticals may account for the most costs.
- Crohn's patient with fistulas accrue higher treatment costs than patients with solely luminal disease.
- Indirect costs contribute to over ½ of overall costs, yet are not measured in most economic analyses.
- Medication costs for biological therapies are higher than that of traditional agents. However, these drugs may decrease utilization of high cost items such as surgeries and hospitalizations.
- The cost-effectiveness of the different biological agents in Crohn's disease may differ between drugs over long-term use. More studies are needed before this can be confirmed.

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Introduction

Until the past decade, the issues regarding the economics of inflammatory bowel disease (IBD) were far below the radar screen of even the most stingy budget hawk. The diseases were rare, the medications were cheap (and for the most part only modestly effective), and the options were very few. Ulcerative colitis (UC) patients might wax and wane between flares, until they ultimately had a surgical "cure," while Crohn's disease patients would mark their "life calendars" with an occasional surgery, followed by a number of years of relative quiescence, punctuated by an occasional need for corticosteroids.

So what changed? The introduction of the biological agents into the arena in the last 1990s suddenly cast the vision of large dollar sign costs for these exciting but expensive agents. Suddenly, doctors were transformed into economists, balancing their Hippocratic oaths against fears of exhausting their health plan's budgets, or even their nation's treasuries. Perhaps most exciting for authors, there was suddenly a need for a chapter addressing the economic issues surrounding IBD in the textbooks that previously only spoke of "knock-out mice," NOD-genes, and "moon-like facies."

Lost among the details were the patients. With these new therapies, the patients with colitis may be awaiting their next flare… perhaps not to come. Crohn's patients are now being told, "Now we may be able to prevent another surgery"; words that just 10 years ago were rarely muttered. As readers of this textbook have hopefully learned from the previous chapters, exciting advances in the treatment of these diseases are upon us, and may ultimately result in a change in the natural course of disease…that is, treated disease. Perhaps we have not reached that point just yet. But the opportunity to greatly improve the quality of life and lessen the burden of disease for our patients is upon us.

"But can we afford it," say the nay-sayers. "What will it cost…and is it *worth it* ?" Ethical debates aside, a responsible evaluation of the economic impact of new technology is required, and that is the purpose of this chapter. A variety of economic questions have been asked, and answered (sometimes) by different study designs, in various populations (real and imaginary), and across numerous continents. The researchers' conclusions don't always coincide, and may not be entirely supported by their findings. This chapter attempts to organize the best studies to date, with the intent on providing some guidance, and perhaps some incentive for better, more comprehensive analyses.

IBD Economics

Studies Using Cost-Modeling and Databases

Two of the earliest landmark studies in IBD economics were published in 1992 by Hay and Hay [1, 2] utilizing cost-modeling and data from the United States in the late 1980s. While often referenced in the field, in reality these studies predated the

use of not only the biological therapies, but also the "branded" nonsulfa containing mesalamine derivative, as well as the immunomodulators, with rare exceptions. Surgical approaches to IBD also have dramatically changed since that time, with the adoption of "bowel-sparing" procedures in disease, and the restorative proctocolectomy with ileoanal pouch in patients with ulcerative colitis. In addition, the vast changes in the US healthcare system have effectively moved IBD management to the outpatient arena whenever possible. Patient management changes such as the shortening of hospital stays, improving postoperative management, expansion of home-based intravenous and nursing therapies, and the creation of advanced nutritional formulas, all result in the decreased emphasis upon inpatient delivery of care [3, 4]. In their first study [1], these authors created medical cost algorithms to simulate the costs of illness in IBD care. They then applied the algorithms to 100 hypothetical Crohn's disease and UC patients, and estimated an annual cost per patient at $6,561 and $1,488, respectively (priced in 1990 dollars). Total annual costs were estimated to be $1–$1.2 billion for Crohn's disease and $400–$600 million for UC. These costs increased to $9,000 per patient, and over $1.7 billion when updated to 1996 dollars [5]. Adjusting for productivity losses, the total cost for IBD care was projected at $1.8–$2.6 billion [1]. IBD costs were disproportionately high due to surgery and hospitalization, which accounted for 80% of overall costs in Crohn's disease and 47% in ulcerative colitis. Outpatient medical care accounted for 3–7%, diagnostic tests accounted for 2–8%, and medication accounted for 10% of the total costs. Overall, hospitalization and surgery accounted for more than 50% of the total IBD-related costs. Looking to the future, the authors then performed a regression analysis whereby doubling medication costs with a new agent whose increased efficacy resulted in a decrease of utilization of healthcare services by 20% resulting in an overall cost savings of 11–13%.

Their accompanying article studied the medical claims database of a large commercial health insurer (CIGNA Corporation), with over 4,000 IBD-related claims over a period of 1988–1989 [2]. They found that a very small percentage of patients (2%) accounted for a disproportionately high amount of charges and payments; 29% of the total charges and 34% of the total amount paid amongst patients; for ulcerative colitis, the values were 36 and 39%, respectively. Targeting more effective medical care to these presumably sickest patients could potentially have a profound effect upon lowering overall costs.

The disparity in utilization of the healthcare dollars was reinforced by a 1994 medical claims Hewitt Associates database study in disease [6]. Patients requiring hospitalization accrued charges that were triple those of patients on chronic immunosuppression, and six-times higher than those patients who never underwent either intervention. Approximately 25% of the patients accounted for 80% of the total charges, with hospitalizations accounting for over one-half of all charges.

Similar trends have been shown in European analyses. A study from the United Kingdom over a 6-month period in 2000 looked at a cohort of 307 cases of UC or indeterminate colitis and 172 cases of Crohn's disease [7]. The study was based at University Hospital Liverpool U.K. Cases were identified retrospectively from the hospital database. They found the 14% of patients who required inpatient care accounted for 49% of all costs, with medication costs contributing less than

one-fourth of the total. Mean 6-month costs for outpatient care in Crohn's disease was £516, while for UC they were £539. For the hospitalized group, the costs were £6,923 for Crohn's disease and £7,658 for UC. This study supports the conclusion that a minority of IBD patients were hospitalized but they accounted for almost half of the total direct costs.

A 2008 review of the cost of Crohn's disease in the United States and other western countries projects the total economic burden at $10.9–$15.5 billion in the USA and 2.1€–16.7€ billion in Europe [8, 9]. After reviewing the data, costs were adjusted to 2006 values. The authors concluded that annual per patient direct medical costs for disease was close to $19,000 in the United States and 7,000€ in other Western countries. Hospitalizations accounted for 53–66% of direct medical costs, with average cost for hospitalization in the United States around $37,459. Indirect costs were estimated at 28% of total costs in the USA and 64–69% in Europe.

A retrospective PharMetrics database analysis in UC estimated total all-cause healthcare costs at $13,233, compared to $3,214 for the control group [9]. Data were collected for 15,105 patients from January 2000 to 30 June 2005. Inpatient hospitalization constituted 43.6% of the costs. Resource utilization was highest for adults older than 65 years, followed by pediatric–adolescent patients and lowest for adults aged 18–64 years. On the other hand, median total healthcare costs were highest for the pediatric–adolescent patients ($23,113) and lowest for adults in the 18–64 age groups ($12,693). The increased costs in the pediatric–adolescent age group were primarily due to hospitalizations.

Crohn's disease patients who suffer from fistulae have additional utilization and costs to consider, as reflected in a healthcare cost analysis by Cohen et al. [10]. Using the PharMetrics database, a retrospective analysis over a 5-year period from 2000 to 2005 compared paid claim costs and resource utilization in patients with and without fistula during the first 12 months following diagnosis. Median cost per patient was higher in the patients with fistulae ($10,863 vs. $6,268). The costs were largely driven by hospitalization and surgical costs. Hospitalization was the largest cost driver in Crohn's disease. The cost of hospitalization accounted for 60.2% of the mean costs in the fistula cohort and 45.4% in the nonfistula cohort. Resource utilization and paid claims were higher in the patients with fistulas, as was length of hospital stay. Surgical rates and costs were also substantially higher for patients with fistulas; the increased costs were due to the increased number of procedures needed in this group.

The 2008 study by Kappelman et al. [11] gives an updated direct cost estimate for IBD in the United States. Data was extracted from the medical and pharmacy claims administrative database (PharMetrics Patient-Centric Database) from 87 health plans spread over 33 states throughout the country. The period of analysis for the data was between January 2003 and December 2004. The study identified 9,056 patients with Crohn's disease and 10,364 UC patients using international classification of disease (ICD-9) codes. Adequate numbers of matched controls were identified. The claims were classified as inpatient, outpatient, or pharmaceutical using current procedural terminology (CPT) and national drug codes. Inflammatory bowel disease (IBD) attributable costs were estimated by subtracting

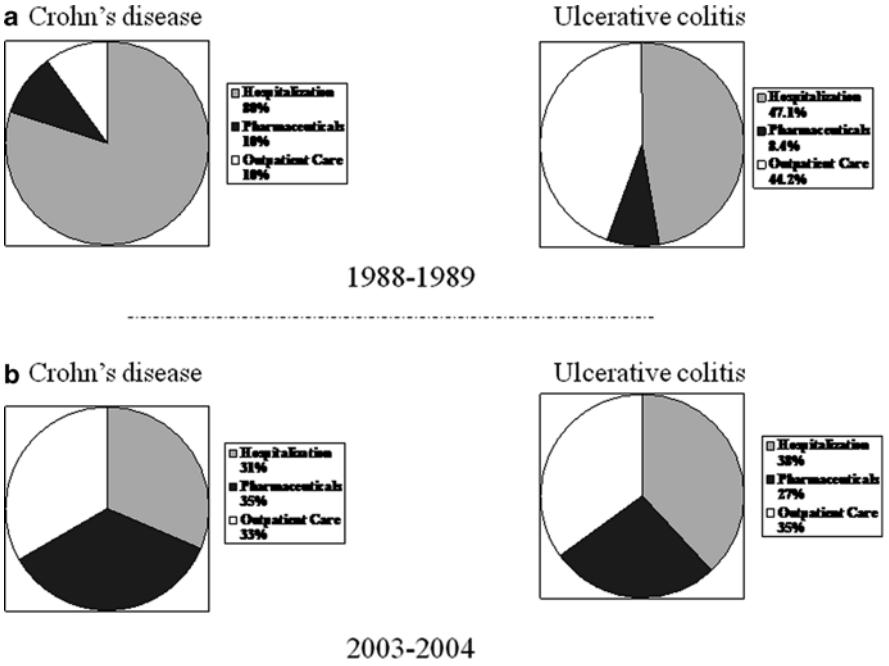

Fig. 19.1 Comparison of annual cost percentages attributable to hospitalizations, pharmaceuticals, and outpatient care in patients with Crohn's disease and ulcerative colitis (UC) from 1988 to 1989 (**a**) [1] to those from 2003 to 2004 (**b**) [11]

cost for non-IBD patients from patients with IBD. Logistic regression analysis is used to identify the social and demographic factors influencing the data. Mean total annual direct costs for Crohn's disease were $8,265, while for UC they were $5,066. Extrapolating this data, total IBD-associated treatment costs in the United States are estimated at $6.3 billion ($3.6 billion for Crohn's disease and $2.7 billion for UC). These were based on year 2004 value of the U.S. dollar. In patients with Crohn's disease, hospitalization and surgery accounted for 31% ($2,593), outpatient services accounted 33% ($2,753), and pharmaceutical claims accounted for 35% ($2,919) of total costs. In patients with ulcerative colitis, hospitalization and surgery accounted 38% ($1,925), outpatient services accounted for 35% ($1,773), and pharmaceutical claims accounted for 27% ($1,368) of the total costs.

In Crohn's disease, the largest share (35%) of the costs were due to pharmaceuticals. The costliest medication was infliximab. The other medications included adalimumab, aminosalicylates, thiopurines, methotrexate, and budesonide. The share of total costs in UC accounted for by pharmaceuticals (27%) also increased compared to previous studies. This change in the pattern of total costs is notable compared to previous studies (Fig. 19.1). In the index study by Hay and Hay [2], outpatient pharmaceuticals accounted for only 4% while hospitalization and surgery accounted for majority (>50%) of the total direct costs. Although it is difficult to compare these studies due to differing methodologies, extrapolation of the costs in the Hay and

Hay studies was done using the medical consumer price index for year 2004. Based on this, total direct costs for Crohn's disease was $13,844 and for UC it was $3,140. Comparing Kappelman's study and the Hay study, the direct cost for Crohn's disease would suggest a decreasing trend from $13,844 to $8,265 while for UC an increasing trend from $3,140 to $5,066. This trend may suggest a shift in resource utilization; increasing pharmaceutical costs offsetting hospitalization, and surgery costs. One explanation is that this is due to the selective use of biological therapies in Crohn's disease (as compared to ulcerative colitis) resulting in the higher pharmacy-related costs but potentially lower utilization of healthcare services.

The new biologic drugs improve quality of life and may decrease the overall costs of disease. The initial excitement that surrounded the release of these highly efficacious agents has been tempered by their costs [12]. The three anti-TNF monoclonal antibody biological agents currently approved in the United States for the treatment of IBD are infliximab, adalimumab, and certolizumab. All three are FDA-approved for Crohn's disease while infliximab is also FDA-approved for UC. Infliximab, the first of this class to be approved, is an intravenous agent that requires weight-based dosing. The standard 5 mg/kg dose in a 70-kg individual carries a drug cost of $2,800 per infusion [13], which is given every 8 weeks after an initial 3-dose load over the first 6 weeks. Adalimumab is available only as a 40-mg subcutaneous dose ($687) [14]. After an initial loading dose of 160 mg, patients receive a second dose of 80 mg, followed by 40 mg doses every 14 days. Certolizumab costs $1,316 for the standard 400 mg dose [15], and is given as a subcutaneous injection every 28 days, with an additional loading dose given after the first 14 days of therapy.

The other biologic agent currently approved for the treatment of Crohn's disease and available is natalizumab, a monoclonal antibody targeting alpha-4 integrins. Natalizumab is an intravenous infusion dosed 300 mg every 4 weeks, at a drug cost of $1,619 per infusion [16]. The costs associated with the biological therapies raise concern about their cost-effectiveness in our financially conscious healthcare environment.

Indirect Costs and Disability

Patients with IBD are typically young, in school, or part of the work force when first diagnosed [17]. Their illness may have a negative impact upon their future productivity. Family and caregivers may also be affected, due to extensive outpatient testing or hospitalizations. These indirect costs are often hard to quantify and are left out in many IBD economic studies. The vast majority of studies on IBD economics focus on direct costs (such as hospitalizations, surgeries, medications, outpatient visits etc), as this data is easier to access and to quantify. However, due to the universal impact of this chronic disease on the patients' productivity and family life, the financial impact upon the family, other caregivers, and employers (through employer-sponsored insurance or loss of job productivity) can be substantial.

One of the earliest and most comprehensive studies on indirect costs was from Sweden [18]. This study calculated direct healthcare costs and indirect 1-year costs resulting from disease morbidity in Sweden. Indirect costs were calculated to account for 68% of overall costs, primarily due to sick leave and early retirement. Patients with Crohn's disease missed more work days than UC patients. Early retirement in 1994 was 2.5 per 100,000 and lasted on average 14 years, with early pensions received by 1% of Crohn's and 0.03% of UC patients.

A substantial adverse impact of disease upon patients' education was the focus of a study from Scotland [19]. They looked at the impact of IBD on education and employment at a mean 14 years after diagnosis. Among the 70 patients (50 Crohn's disease, 20 UC) interviewed and examined they found that 60% of Crohn's patients and 50% of UC patients reported adverse impact on education; work loss was reported by 70 and 74%, respectively. Fifty-seven percent of patients reported absence from school for 2 months or more. A separate study reported higher disability rates in females and white collar workers with IBD [20].

The ACCENT I trial for infliximab in 573 Crohn's patients with moderate to severely active luminal disease provided important data on the indirect costs associated with disease [21, 22]. At baseline (prior to starting therapy), only 48.5% of patients reported full-time employment while 13.1% reported part-time employment. Greater than one-third (38.4%) of patients were unemployed, and 25% were receiving disability compensation. Only 14% of the 222 unemployed patients felt well enough to work if work were available. Encouraging trends in employment rates were seen with induction of remission [23]. Of the 38.4% patients initially unemployed, 31% of those who achieved remission at week 54 were employed compared to the 16% who were not in remission at the same endpoint ($p<0.05$) (Fig. 19.2). At week 54 an upward trend was also noted in achieving full-time employment, 29% of those in remission had obtained full-time employment compared to 18% among those not in remission ($p=0.07$). The number of work hours lost was also significantly lower among those in remission. The mean work hours lost during the study period were 35, 49, 26, and 12 h for Crohn's patients who

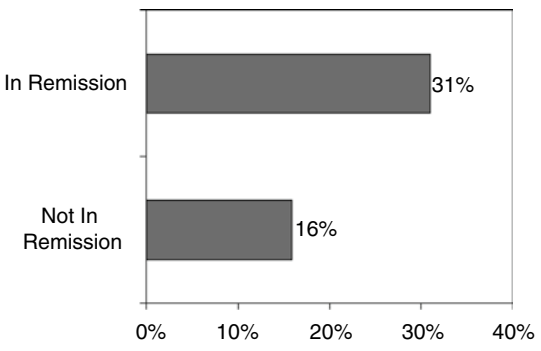

Fig. 19.2 Employment status at week 54 in the ACCENT I clinical trial. Patients who were in remission at week 54 had significantly higher employment rates (31%) than those not in remission (16%) [22]

spent 25% or less, more than 25–50%, more than 50–75% and more than 75% respectively of their time in remission ($p < 0.05$).

The ACCENT II trial for infliximab in fistulizing Crohn's showed similar baseline disability and unemployment figures [24]. Among the 306 patients, 55% worked full-time, 33% were unemployed, and 11% worked part-time. Approximately 18% of patients received disability compensation.

Disability rates were much lower in a 2008 study by the group at the Medical College of Wisconsin. This retrospective database analysis of Crohn's patients receiving care at their medical center found that 5.3% of patients received permanent work disability administered through the social security administration [25]. They included 185 Crohn's patients in the study. Multivariate analysis showed that a Short Inflammatory Bowel Disease Questionnaire (SIBDQ) score ≤50, two or more GI surgeries, and two or more medical hospitalizations were significantly associated with work disability in Crohn's disease. Disease location (small bowel or Colon), type (inflammatory, structuring or fistulizing), or specific treatment strategies were not associated with work disability.

Resource Utilization

Crohn's disease and UC are chronic diseases, which typically follow repeated courses of remission and relapse. Patients often require hospitalization, with approximately 70% of Crohn's patients ultimately requiring at least one surgery and 25% of UC patients requiring a colectomy [26]. Annual medical costs estimates for the year 2000 were US $0.7 billion to $1.7 billion for Crohn's disease and US $400 million for UC. A large share of this was accounted for by medical costs due mostly to hospitalization and surgery [27]. The rest was accounted for by indirect costs such as loss of work, disability, etc.

One of the earliest analysis of actual costs and resource utilization of hospital resources in Crohn's disease was conducted by our group at the University of Chicago, a quaternary referral center for IBDs [28]. The study looked at the cost, charges, revenues (reimbursements), and resource utilization for patients hospitalized at the University over a 1-year period July 1996 through June 1997. There were 75 Crohn's disease admits among 147 patients. Mean cost were $12,528, charges were $35,378 while reimbursements were $21,968. Surgery accounted for 57% of the hospitalizations and 40% of costs. Medical costs were mainly accounted for by the pharmacy, total parenteral nutrition (TPN), and physician charges. Pharmacy accounted for 19% of overall costs. TPN was given in 27% of hospitalization and but accounted for 67% total pharmacy costs. Patients requiring TPN required hospitalization stays three times as long compared to non-TPN admissions. Physician charges were only 9% of the total dollars charged while surgeons accounted for 18% of the total charges.

A similar study but also looking at UC and indeterminate colitis was done by the group at Saint Boniface Hospital in Manitoba, Canada [29]. They looked at 325

patients over a 2-year period from 1994 to 1995. There were a total of 362 admissions for the 325 patients. Surgery accounted for nearly 50% of admissions, 58% of hospital days and 61% of the costs. TPN was used in 9.5% of the cases (7.1% in Crohn's, 13.9% in UC) accounting for 27% of overall costs (21% Crohn's disease, 36% UC). Mean length of stay was four times longer in patients receiving TPN.

Since the release of the first biological agent in IBD, infliximab, in 1998 there have been more recent economic studies, which look into the trends in hospitalization and resource utilization in IBD [30–33]. Bewtra et al. [30] looked at the trends in hospitalization and surgery for Crohn's disease and UC for a 13-year period using the National Hospital Discharge Survey (NHDS) data from 1990 to 2003. The NHDS data base is produced by the centers for disease control and prevention and incorporates data from approximately 500 hospitals and 270,000 patients annually from all over the United States. The complex sampling used allows population level estimates using the data. This database was searched using the ICD-9 codes for Crohn's disease and UC. For Crohn's disease, the annual hospitalization rates varied from 24,828 to 48,863 and for UC hospitalization rates varied from 20,839 to 35,096 during the study period. After applying sample weights and approximating the data for the US population; the hospitalization rates for Crohn's varied from 9.3 to 17.7 per 100,000 for Crohn's and 8.2 to 12.4 per 100,000 for UC; there was trend to increasing rates for Crohn's but not for UC. When hospitalization rates related to age were analyzed, they showed increasing rates regardless of age for Crohn's patients, while an increasing trend in UC for those aged 40 or above. The rates of bowel surgeries were 2.8–5 per 100,000 and 1.6–3.4 per 100,000 for Crohn's and UC, respectively with no significant trend for Crohn's or UC. As the introduction of infliximab to the market could have resulted in the hospitalizations of 1-day or less for administration of the medication, a sensitivity analyses excluding any admits less than 2 days were done and still the increasing trend persisted. The authors conclude that the overall trend towards increased rates may reflect an increase in the US population, aging of the population, tendency for hospitalizations at referral centers, hospitalizations due to complications of medical therapy, and readmissions.

Another study looking into hospitalization trends in the infliximab era was done by the Johns Hopkins Group [31]. They utilized data from the nationwide inpatient sample (NIS), maintained by the Agency for Healthcare Research and Quality (AHRQ), the largest all-payer database of national discharges. The database searched using ICD-9 codes for Crohn's disease and UC diagnosis. The results were extrapolated for providing national estimates. A sensitivity analysis was performed excluding 1-day admissions, to remove any bias for inpatient infliximab infusion. Overall hospitalization rates for Crohn's disease were 18 per 100,000 and for UC were 10.8 per 100,000, representing an annual increase of 4.3% for Crohn's and 3% for UC. Using this data, an economic analysis in 2005 US dollars was done to evaluate the impact of this increasing trend in hospitalization rates. The cost of hospitalization for Crohn's increased from $762 million in 1998 to $1,330 in 2004, while that of UC increased from $592million to $945million, reflecting annual increases of 10.5 and 8.6%, respectively. Bowel surgery increased hospital charges

by 93% for Crohn's and 81% for UC. Admission to an urban hospital was costlier by 44% compared to a rural center. This increasing trend in hospital admissions may have been due to an increasing prevalence of IBDs, which would translate into an increasing economic burden to patients and society.

This may be answered in part by the biological therapies. While biological therapies may substantially increase medication costs, they have been shown to decrease the use of healthcare resources and increase the quality of life. A study from the University of Chicago which looked into the effect of infliximab on healthcare resources compared the rates of hospital resource use 1-year before and 1-year after their initial infliximab infusion [34]. The year after infliximab all surgical rates reduced by 38%, gastrointestinal surgeries by18%, emergency room visits by 66%, outpatient visits by 16%, gastrointestinal outpatient visits by 20%, endoscopies by 43%, and radiographs by 12% (Fig. 19.3). Crohn's patients with fistulizing disease showed a 59% decrease in hospitalizations. There was a trend toward a 9% decrease in days of hospitalization among all Crohn's patients. A subsequent 3-year controlled analysis before and after infliximab showed similar decreasing trends [35]. This study compared results with those of infliximab naïve controls. Crohn's disease patients on infliximab had fewer hospitalizations (37%), outpatient visits (gastrointestinal 41%, rheumatology 54%, total 33%), endoscopies (52%), and radiographs (58%).

Analysis of the data from the two-large multicenter studies of infliximab in Crohn's disease (ACCENT I and II [22, 24]) also showed significant reduction in the number of hospitalizations and surgeries in patients on maintenance therapy [36, 37]. ACCENT I showed a hospitalization rate three times less for those in remission, 75% or more of the time compared to those in remission 25% or less of the time. Surgery rates for those in remission 75% or more of the time were

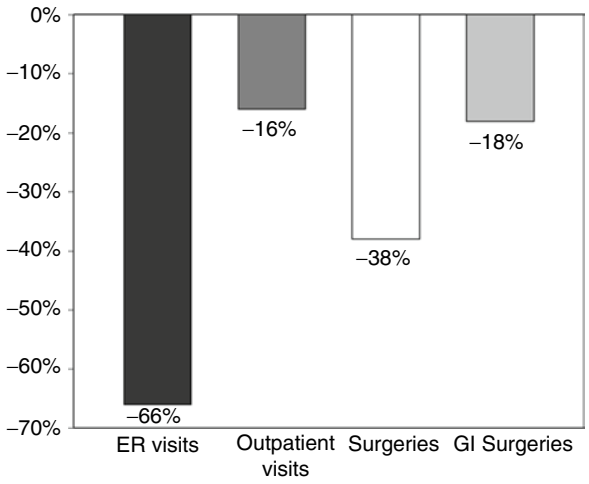

Fig. 19.3 Infliximab markedly reduced emergency room visits (ER), outpatient visits, overall surgery rates, and GI surgery rates in patients with Crohn's disease [34]

five-times less than those in remission 25% or less of the time. The average number of days hospitalized was also significantly lower among those in remission. In the ACCENT II study for fistulous disease, maintenance treatment was shown to result in fewer days in the hospital in patients responding to infliximab. The study reported hospitalization rates of 18.9% in the placebo group and 8.6% in the infliximab maintenance group at 54 weeks ($p<0.05$). There was also a significant reduction in surgical procedures such as fistula excision and fistulotomy (13.0 vs. 2.0 per 100 patients; $p<0.05$).

The Impact of Biological Therapies upon Costs

Various studies of disease-related costs have been conducted since the inception of biologics into the treatment of IBD in late 1998. Most have shown that resource utilization is generally decreased with the use of these biologics. The drug cost of the biologics is much higher than with traditional therapies, and a contentious issue is whether these therapies are cost-effective or at least cost neutral with increased quality of life (Table 19.1).

A study at the University of Chicago showed higher median charges for patients on infliximab with over half the cost associated with drug cost [35]. Medical records of all Crohn's disease patients treated with infliximab and managed at the University of Chicago were reviewed and data abstracted up to 3 years prior to and post-first infusion of infliximab. The study showed a decrease in the utilization of healthcare resources as described earlier in this chapter, Although mean total charges *including* infliximab increased by 75% ($p<0.0001$), the charges *excluding* infliximab decreased by 23%, while they increased in Crohn's disease control

Table 19.1 Annual treatment costs per patient

Reference	Country	Database	Disease	Mean annual cost per patient
Hay and Hay [2]	United States	Claims database US insurer	Crohn's disease	$6,561
			Ulcerative colitis	$1,488
Berstein et al. [29]	Canada	Hospital database	Crohn's disease	$CAN 3,149
			Ulcerative colitis	$CAN 3,726
Bassi et al. [7]	United Kingdom	Hospital database	Crohn's disease	£1,652 (6 month data)
			Ulcerative colitis	£1,256 (6 month data)
Odes et al. [66]	Europe	Population based prospective cohort	Crohn's disease	2,548 €
			Ulcerative colitis	1,524 €
Stark et al. [67]	Germany	Cost diaries of affected patients	Crohn's disease	1,425 € (4 week data)
			Ulcerative colitis	1,015 € (4 week data)
Bickston et al. [9]	United States	PharMetrics	Ulcerative colitis	$13,323
Kappelman et al. [11]	United States	PharMetrics	Crohn's disease	$8,265
			Ulcerative colitis	$5,066

Studies from different countries summarized. $CAN indicates Canadian dollars

patients (who did not receive infliximab) by 56%. One of the conclusions from the study was that future economic analysis should include indirect costs also to evaluate if this would offset infliximab costs.

In a different study, retrospective audit of healthcare utilization and costs in Crohn's disease was conducted in seven centers in 205 patients in the United Kingdom [38]. The study compared the time period 6 month prior to an initial infliximab period to the 6 months following the first infusion. and 6 after an initial infliximab infusion. The audit showed a reduction in hospitalized days (1,435 vs. 342), outpatient visits (555 vs. 534), and in surgical procedures after infliximab was initiated. There was an estimated direct total cost reduction of £591,006; when tallied against the total cost of the 353 infliximab infusions received by the patients, there was a net cost reduction of £28,287, or £137.98 per patient.

More complex models have been used in an attempt to predict the cost-effectiveness of these drugs. These models often used the Markov model by Silverstein to estimate long-term cost of infliximab [39]. One example is the cost-utility analysis which attempts to measure both quantity and quality by measuring the "quality adjusted life years" (QALYs). The utility gained by healthcare intervention is calculated by multiplying life years gained by the increase in utility that the intervention causes. The incremental cost per QALY or the incremental cost-utility ratio (ICUR) can be calculated and then employed to theoretically compare the value of different healthcare interventions. A drawback of the cost-utility analysis is that ICUR alone is an abstract value and relies on decision makers to determine what the society is prepared to allocate in order to gain a QALY. [40]. There are no firm guidelines for an acceptable QALY, but a commonly cited value is $50,000 and UK NICE reported threshold is £20,000–£30,000 [41].

The United Kingdom National Institute for Health and Clinical Excellence (NICE) calculated ICUR over 1 year to be £35,371 (2001 values) for single dose therapy with infliximab and £59,219 for retreatment of relapsing disease. Extending the model over 5 years reduced the values to £16,179 for one-time treatment and £32,274 for episodic treatment. A cost-utility model referred to by the NICE guidelines on infliximab in fistulizing Crohn's calculated the ICUR £102,000–123,000 (2001 values) for initial treatment and from £82,000 to £96,000 with the most positive assumptions of treatment success (90% success rate assumed) [42, 43]. A model by the Canadian Coordinating office for Health Technology Assessment predicted an ICUR of $CAN 181,201 for single infusion and infusion upon relapse was $CAN 480,111 and the ICUR for maintenance infusions every 8 weeks was $696,078 (2001 values) [44].

A 2008 cost-utility analyses from the United Kingdom suggests that the standard 8 eight week maintenance treatment with infliximab may be a cost-effective treatment for adult patients with active luminal and fistulizing Crohn's disease [45]. This was based on a Markov model construct to simulate progression of Crohn's disease on infliximab 5 mg/kg in patients with and without fistulizing disease. Calculations were done using an average weight of 60 kg. The costs and outcomes were discounted at 3.5% over 5 years. In luminal, Crohn's scheduled infliximab

maintenance dosing (i.e., every 8 weeks) derived a mean additional 0.19 QALYs at an additional cost of £4,873 compared to standard care without infliximab. The incremental cost per QALY gained for infliximab was £26,128. In fistulizing Crohn's disease maintenance therapy with infliximab gained an additional 0.20 QALYs with added costs of £5,998, compared to standard care without infliximab. In patients with fistulizing Crohn's disease, the incremental cost per QALY gained for infliximab was £29,752.

Infliximab use may be limited by infusion reactions; response to therapy may be lost due to low serum drug levels or due to antibody formation. Options in such situations are to increase the frequency of administration, increase the dose, or change to another biologic agent. To look at the cost-effectiveness such alternative options a decision-analysis model for 100,000 hypothetical patients was constructed by the Massachusetts General Hospital group [46]. The study looked at two cohorts of Crohn's patients: one with increased dose of infliximab (10 mg/kg) and the other started on therapy with a different biological agent (adalimumab). At the end of the first year, dose escalation of infliximab resulted in 13,989 more patients in remission with 6,428 fewer surgeries compared to the adalimumab group. The infliximab strategy resulted in greater QALY per patient compared to adalimumab (0.79 vs. 0.76). The cost for dose escalation was $28,367 per patient vs. $18,074 per patient in the adalimumab group. The incremental cost-effectiveness ratio (ICER) was $332,032/QALY, suggesting that the dose escalation of infliximab was not cost-effective compared to change to adalimumab.

A 2009 study from the United Kingdom looked at the cost-effectiveness of infliximab and adalimumab from the cost-conscious U.K. National Health Service perspective using a Markov Model analysis [47]. In this study, a Markov model for moderate to severe Crohn's disease with 4 disease states (full response, partial response, nonresponse, surgery and death) was created. Based on this model a lifetime analysis to simulate quality adjusted life years (QALY) and costs was done. Direct medical costs related to inpatient and outpatients services, investigations, medications, and surgery without biological therapy was calculated, then recalculated with biological care. The doses of the biologics in the model were infliximab 5 mg/kg and adalimumab 40 mg every other-week per U.K. NICE guidelines. Although a loading dose regimen was assumed for the infliximab therapy, the authors did not adjust their data for the standard adalimumab load of 160 mg (quadruple dose) followed by 80 mg (double-dose) for the first month. The initial costs were based on year 2000–2001 values. These values were then inflated for the year 2006–2007 values using an annualized inflation rate of 5.6%. The mean discounted lifetime cost for standard care was £43,490 for 14.209 QALYs; the mean lifetime discounted cost for infliximab was £50,330 for 14.568 QALYS. The ICER for infliximab was £19,050 per QALY gained. The mean life cost associated with adalimumab was £46,730 for 14.682 QALY's, with an ICER of £7,190. A sensitivity analysis predicted that after 4 years infliximab may not be cost-effective at a threshold of £30,000 per QALY gained; suggesting that adalimumab was more cost-effective when used long-term.

Quality of Life in IBD

Health-related quality of life (HRQOL) is an important component in determining the impact of therapy upon the lives of the patients, their families, and caregivers. An objective assessment of the impact of IBD upon quality of life is an essential factor in understanding IBD economics. Most clinical trials in IBD use one or more scales to assess HRQOL. While the Crohn's Disease Activity Index (CDAI) is used to assess the clinical activity of Crohn's disease in clinical trials, the Inflammatory Bowel Disease Questionnaire (IBDQ) is the standard quality of life scale utilized in clinical IBD studies. The IBDQ is a disease-specific scale that was specifically designed to assess overall HRQOL in patients with IBD and consists of 32 questions. The subscales of the IBDQ cover four general aspects of HRQOL: *bowel-related* symptoms (i.e., looseness of stool, frequency, abdominal pain or cramps), *systemic symptoms* (i.e., fatigue, lack of energy, poor sleep patterns, avoiding or canceling social engagements), *social function* (i.e., ability to attend work and social events), and *emotional state* (i.e., anger, frustration, depression, worry about surgery). The total scores can vary from 32 to 224 with greater scores indication better HRQOL, with a score greater than 170 correlating with remission [48].

The Short Form-36 (SF) scale is also commonly used as a general quality of life measurement when comparing the impact that different diseases have upon health-related quality of life. The SF-36 consisting of 36 questions is a commonly used generic instrument for HRQOL measurement. The questions span 8 domains; physical function, role limitations-physical, role limitations-emotional, vitality, general health perceptions, pain, social function, and mental health. SF-36 is usually summarized into two component scores: Physical and mental [49]. Greater the summary score the better HRQOL. Normalized SF-36 score permit the comparison of HRQOL of patients with Crohn's disease with the HRQOL of the general U.S. population [50].

Studies of HRQOL in IBD patients have suggested that they experience worse quality of life when compared with health maintenance organization controls [51]. Crohn's patients experience a quality of life worse than UC patients and healthy controls [48, 52, 53], and UC patients score lower in HRQoL scales compared to health maintenance organization controls, with the quality directly correlating to disease activity [48, 54]. Patients often score lower in the emotional and social functioning components of the QoL scales than the physical components. The presence of psychological distress in IBD patients contributes to poor QoL, along with IBD clinical activity [55]. Controlling and minimizing the symptoms of the disease, along with identification and treatment of psychopathology, should become integral aspects of IBD care to improve QoL of these patients. In a study to assess the relationship between disease type and activity with psychological functioning and quality of life it was found that UC and Crohn's patients do not differ in their psychological profiles [56]. This study also found that patients with active disease had poorer QOL.

Patients with moderate to severely active disease are the cohorts for trials of the newer biologic drugs and they have poor baseline QOL. The ACCENT I population had a score of 297 on the CDAI and a score of 34 and 39 respectively on the physical component and mental component of the SF-36 scale, which is 1.5 and 1 standard deviation lower respectively compared with the general US population [57].

Table 19.2 Mean IBDQ scores summarized from clinical trials of biologics for Crohn's disease

Agent – dose	Baseline	4 weeks	12 weeks	24 weeks
Infliximab [58]				
5 mg/kg every 8 weeks	127	175	170	174
10 mg/kg every 8 weeks	127	155	165	160
Adalimumab [62]				
40 mg every week	124	165	170	175
40 mg every 2 weeks	124	170	175	175
Certolizumab [64]				
400 mg every 4 weeks	123	175	169	176
Natalizumab [65]				
300 mg every 4 weeks	123	–	182	175

Each of the biological agents showed a significant improvement in scores from baseline indicating improved quality of life

Patients who attain remission on infliximab have higher QOL life scores than patients not in remission [23]. There was significant improvement in the IBDQ scores of those who received the three dose induction and maintenance doses at week 30 and 54 [58]. The baseline IBDQ score for the cohort was 129. There was a mean increase in the score by 22.1 ($p<0.05$) in the 5 mg/kg maintenance group and increase of 30.2 ($p<0.01$) in the 10 mg/kg maintenance group at week 54 compared to the single dose group (placebo maintenance after initial induction). Similar increases in quality of life are seen with therapy in patients with fistulizing disease who receive infliximab [59, 60] (Table 19.2).

The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission and Maintenance (CHARM) trial assessed the efficacy and safety of adalimumab in patients with moderate to severe Crohn's disease [61]. The trial showed considerable improvements in the HRQOL indices. A subsequent analysis study assessed the effect of adalimumab maintenance therapy on HRQOL of the patients enrolled in the CHARM trial [62]. The mean baseline IBDQ score was 124, which is consistent with impaired quality of life. With maintenance adalimumab therapy the scores increased to over 170 ($p<0.05$) compared to the induction only group.

Certolizumab pegol also shows significant improvement in HRQOL as demonstrated by the higher IBDQ scores in the Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy (PRECISE 2) trial [63]. In the PRECISE 2 trial, the IBDQ scores improved from 123 at baseline to 176 at 26 weeks of maintenance therapy. A post-hoc analysis of the intent-to-treat population via their IBDQ scores showed higher HRQoL from baseline at 12 weeks for patients receiving the highest dose (400 mg) of the drug. The baseline IBD score was 123 in all those who received certolizumab; by week 12 the mean score increased by 28 ($p \leq 0.05$). This substantial increase suggests markedly improved quality of life [64].

Natalizumab, a humanized monoclonal antibody against α4 integrin which inhibits leukocyte adhesion and migration into inflamed tissue is also used in Crohn's disease. A study evaluating the effects of treatment on HRQOL showed improvement of the

HRQoL indices [65]. The study looked at the 339 patients who responded to natalizumab in ENACT-1(Efficacy of Natalizumab as Active Crohn's Therapy) were rerandomized in ENACT-2 (Evaluation of Natalizumab as Continuous Therapy) to receive either natalizumab 300 mg or placebo every 4 weeks for an additional 48 weeks. Outcome measures were a change in from baseline of IBDQ or SF-36. Subjects on entry into ENACT-1 had substantially low HRQoL. The natalizumab responders showed substantial improvement in HRQOL over the course of ENACT-1. During maintenance, the IBDQ and SF-36 scale scores of those rerandomized to receive the drug remained stable while those who got placebo worsened. The mean IBDQ score at baseline for the enrolled patients was 123; at week 60 the score increased to 177 ($p<0.001$)At week 60 the scores of those received maintenance natalizumab treatment were not statistically different from those of a cross-section of the U.S. population for 6–8 scales of the SF-36, suggesting normalization of quality of life.

Conclusions

The economic story behind IBD care has dramatically changed as we have adopted new therapies with higher drug costs, but potential savings of direct costs by decreasing medical resources, and indirect costs by sustained remission, corticosteroid-sparing qualities, and improving quality of life. One cannot overlook the economic implications of a chronic relapsing disease with early age of onset but normal life expectancy that tends to afflict those in industrialized nations has upon accurate modeling of true overall costs.

The recipe is complicated by a wide variation in healthcare models around the world, currency fluctuations, and an overall modernization of the industry. Exposing the overwhelming contribution of indirect costs, coupled with the acknowledgement that few analyses even include attempts at measuring such costs, leaves many such studies as potentially grossly underestimating the true economic impact of these advances in care.

And finally, adding in the "human" side, the underlying reason why we are even bothering, further bolsters the notion that there is great promise in the medical treatments of these diseases, and the investment in effective interventions may indeed be "priceless"…. and well worth the cost. Normalization of quality of life is of prime importance to patients with IBD, and now achievable without the ravages of chronic corticosteroid therapy.

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