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THE STATE OF THE ART IN THE MANAGEMENT OF

Inflammatory Bowel Disease

Based on the proceedings of a roundtable held
December 12–13, 2001

PRESENTED BY:

The Office on Women's Health
of the
U.S. Department of Health and Human Services
and
The Society for Women's Health Research

IN COOPERATION WITH:

Crohn's & Colitis Foundation of America
American College of Gastroenterology
American Gastroenterological Association
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

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SOCIETY FOR WOMEN'S HEALTH RESEARCH

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July 2002

Dear Colleague:

Strategies for the management of inflammatory bowel disease (IBD) are continuing to evolve as our scientific and clinical experience grows and new agents are added to the therapeutic armamentarium. This progress is paving the way for new approaches that enable the accurate differential diagnosis of IBD and more effective methods of inducing and maintaining remission. The need to consider the special concerns and issues of women, children, and the elderly also is gaining greater recognition. Knowledge of these ongoing developments is crucial so that physicians may optimize treatment, reduce the risk of complications, and improve the quality of life for the 1 million Americans who suffer from ulcerative colitis or Crohn's disease.

This CME-certified monograph provides a comprehensive review of key issues, including the epidemiology and etiology of IBD, clinical manifestations and diagnosis, traditional and evolving therapeutic options, extraintestinal manifestations and long-term complications, and special considerations in management of IBD across the life span. It is a continuation of the series of educational initiatives based on a roundtable presented by The Office on Women's Health of the U.S. Department of Health and Human Services and The Society for Women's Health Research. The University of Chicago Pritzker School of Medicine and SynerMed Communications jointly sponsored this roundtable in cooperation with the Crohn's & Colitis Foundation of America, the American College of Gastroenterology, the American Gastroenterological Association, and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Funding for the roundtable and subsequent enduring materials has been made possible by an unrestricted educational grant from Procter & Gamble Pharmaceuticals, Inc.

We hope that you find this monograph to be a useful educational resource for your practice, and that it well help you define the optimal strategies not only for treating IBD, but for improving the overall well being and quality of life of the many patients who suffer from these chronic disorders. For further educational publications based on this roundtable, please visit http://www.4woman.gov/owh/gastro/.

Sincerely,

Stephen B. Hanauer, MD
Program Chair
Member, Steering Committee
Professor of Medicine and Clinical Pharmacology
Director, Section of Gastroenterology and Nutrition
University of Chicago
Pritzker School of Medicine
Chicago, Illinois

Daniel H. Present, MD
Program Chair
Member, Steering Committee
Clinical Professor of Medicine
Mount Sinai Medical Center
New York, New York

Jacqueline L. Wolf, MD
Member, Steering Committee
Associate Professor of Medicine
Harvard Medical School and Beth Israel Deaconess Medical Center
Boston, Massachusetts

Wanda K. Jones, DrPH
Member, Steering Committee
Deputy Assistant Secretary for Health
Office on Women's Health
U.S. Department of Health and Human Services
Washington, DC

Sherry A. Marts, PhD
Member, Steering Committee
Scientific Director
Society for Women's Health Research
Washington, DC

Steering Committee

Stephen B. Hanauer, MD
Professor of Medicine
and Clinical Pharmacology
Director, Section of
Gastroenterology and Nutrition
University of Chicago
Pritzker School of Medicine
Chicago, Illinois

Daniel H. Present, MD
Clinical Professor
of Medicine
Mount Sinai
Medical Center
New York, New York

Jacqueline L. Wolf, MD
Associate Professor of Medicine
Harvard Medical School
Beth Israel Deaconess
Medical Center
Boston, Massachusetts

Wanda K. Jones, DrPH
Deputy Assistant
Secretary for Health
Office on Women's Health
US Department of
Health and Human Services
Washington, DC

Sherry A. Marts, PhD
Scientific Director
Society for Women's
Health Research
Washington, DC

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Faculty

Maria T. Abreu, MD 13, 42
Director, Basic and Translational Research
IBD Center
Cedars-Sinai Medical Center
Los Angeles, California

Theodore M. Bayless, MD 13, 42, 53
Professor of Medicine
Johns Hopkins University School of Medicine
Director, Meyerhoff IBD Center
Johns Hopkins Hospital
Baltimore, Maryland

Charles N. Bernstein, MD 3, 5, 9, 16, 42, 49
Professor of Medicine
University of Manitoba
Inflammatory Bowel Disease
Clinical and Research Centre
Winnipeg, Manitoba, Canada

Judy Cho, MD *
Assistant Professor of Medicine
University of Chicago
Chicago, Illinois

Robynne Chutkan, MD *
Assistant Professor of Medicine
Georgetown University Medical Center
Washington, DC

Bess Dawson-Hughes, MD 19, 34, 42, 44
Professor of Medicine
Chief, Calcium and Bone Metabolism Laboratory
US Department of Agriculture Human Nutrition
Research Center on Aging
Tufts University
Boston, Massachusetts

Victor W. Fazio, MD *
Rupert B. Turnbull Professor and Chair
Chairman, Department of Colorectal Surgery
Co-Chairman, Digestive Disease Center
Cleveland Clinic Foundation
Cleveland, Ohio

Susan Galandiuk, MD 1, 4, 28, 30, 32,
Professor of Surgery, Program Director 40, 41, 47, 52
Section of Colon and Rectal Surgery
Department of Surgery
University of Louisville
Louisville, Kentucky

Stephen B. Hanauer, MD 4, 13, 42, 45
Professor of Medicine and Clinical Pharmacology
Director, Section of Gastroenterology and Nutrition
University of Chicago
Pritzker School of Medicine
Chicago, Illinois

E. Jan Irvine, MD 8, 22, 39, 42
Professor of Medicine
Division of Gastroenterology
McMaster University
Hamilton, Ontario, Canada

Stephen P. James, MD *
Deputy Director
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive
and Kidney Diseases
Bethesda, Maryland

Sunanda V. Kane, MD 4, 13, 27, 42
Assistant Professor of Medicine
University of Chicago
Chicago, Illinois

Seymour Katz, MD 4, 13, 39, 42
Clinical Professor of Medicine
New York University School of Medicine
North Shore University Hospital
Long Island Jewish Health Systems
St. Francis Hospital
Great Neck, New York

James F. Marion, MD 13, 42
Assistant Clinical Professor of Medicine
Mount Sinai School of Medicine
New York, New York

Lloyd Mayer, MD 13, 37
Professor and Chairman
Immunobiology Center
Mount Sinai Medical Center
New York, New York

Daniel H. Present, MD 10, 12, 13, 15, 17, 21, 25,
Clinical Professor of Medicine 28, 31, 33, 42, 43, 44,
Mount Sinai Medical Center 45, 46, 50, 53, 54
New York, New York

Robert H. Riddell, MD 34
Professor of Pathobiology and Laboratory Medicine
Mount Sinai Hospital
Toronto, Ontario, Canada

David B. Sachar, MD 4, 42, 43, 54
Clinical Professor of Medicine and
Director Emeritus
Gastroenterology Division
Mount Sinai School of Medicine
New York, New York

William J. Sandborn, MD 2, 4, 6, 7, 11, 12,
Head, Inflammatory Bowel 13, 18, 20, 23,
Disease Research 24, 25, 28, 29,
Mayo Clinic 30, 32, 35,36,
Director, IBD Clinical Research Unit 40, 42, 43, 45,
Professor of Medicine 48, 51, 55, 56
Mayo Medical School
Rochester, Minnesota

Ernest Seidman, MD 26, 38, 42, 43
CCFC/CIHR IBD Research Chair
Chief, Division of Gastroenterology,
Hepatology and Nutrition
Professor, Department of Pediatrics
University of Montreal
Montreal, Quebec, Canada

Charles A. Sninsky, MD 13, 42, 53, 54
Digestive Disease Associates
Gainesville, Florida

Christina Surawicz, MD 4
Professor of Medicine
University of Washington School of Medicine
Section Chief, Gastroenterology
Harborview Medical Center
Seattle, Washington

Douglas C. Wolf, MD *
Atlanta Gastroenterology Associates
Clinical Assistant Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

Jacqueline L. Wolf, MD 4, 14, 27, 39, 42
Associate Professor of Medicine
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

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The State of the Art in the Management of Inflammatory Bowel Disease

CME Information

Statement of Need

Strategies for the management of inflammatory bowel disease (IBD) are continuing to evolve as the result of research advances, growing clinical experience, and an expanding therapeutic armamentarium. This progress is paving the way toward more efficient approaches to the differential diagnosis of IBD as well as more effective methods of establishing and maintaining remission. Unique treatment considerations in special populations such as women, children and adolescents, and the elderly are also gaining greater recognition. An appreciation of these ongoing developments is crucial to optimizing therapeutic responses, reducing the risk of complications, and improving quality of life for the approximately 1 million Americans who suffer from IBD. Awareness of these issues will help physicians become better equipped to meet the challenges of IBD in daily clinical practice and will support the practice of evidence-based medicine.

Educational Method

The State of the Art in the Management of Inflammatory Bowel Disease as published in this *CLINICIAN*® is based, in part, on the proceedings of a roundtable that was held on December 12-13, 2001 in Washington, DC.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Chicago Pritzker School of Medicine and SynerMed Communications. The University of Chicago Pritzker School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Chicago Pritzker School of Medicine designates this educational activity for a maximum of 2 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit he/she actually spent on the educational activity.

Target Audience

Target audience: US and Canadian gastroenterologists and fellows

Learning Objectives

After completing this program, participants will be able to discuss what is known about and be able to summarize current findings and identify knowledge gaps as they apply to the

- Epidemiology and proposed etiologies of ulcerative colitis and Crohn's disease
- Clinical and diagnostic findings in adults and children with inflammatory bowel disease
- Clinical utility of traditional and evolving therapies in the everyday management of ulcerative colitis and Crohn's disease
- Use of surgical procedures in the management of inflammatory bowel disease
- Psychosocial challenges facing patients with inflammatory bowel disease
- Relationship between adherence and disease relapse and optimizing adherence in clinical practice

This *CLINICIAN*® is presented by The Office on Women's Health of the U.S. Department of Health and Human Services and The Society for Women's Health Research. It is jointly sponsored by The University of Chicago Pritzker School of Medicine and SynerMed Communications in cooperation with the Crohn's & Colitis Foundation of America, the American College of Gastroenterology, the American Gastroenterological Association, and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

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The Epidemiology of IBD

Epidemiologic studies of inflammatory bowel disease (IBD) have not only supplied data on the incidence and prevalence of ulcerative colitis (UC) and Crohn's disease (CD), but also have revealed associations that may provide clues to the etiologies of these diseases. The most recent estimates of the incidence and prevalence come from studies in Olmsted County, Minnesota by Loftus and colleagues.[1,2] The incidence rate for UC was 7.6 cases per 100,000 person years, and the prevalence rate was 229 per 100,000. The incidence rate of CD was estimated to be 5.8 cases per 100,000 person years, with a prevalence rate of 133 per 100,000.[1,2]

The peak onset of IBD is bimodal, and most cases develop during the second and third decades of life. A second, smaller peak occurs in the sixth decade (Figure 1).[3] In general, there are few sex differences in incidence and prevalence of IBD, though males have a 20% higher incidence of UC, and females have a 20% higher incidence of CD.[3] Patients who undergo appendectomy in childhood or adolescence have a lower incidence of UC, although the surgery has been shown to be protective only if it was performed for an inflammatory condition such as appendicitis or lymphadenitis and if a patient had surgery before 20 years of age.[4] Overall rates of IBD are similar for Whites and African Americans and are higher among Ashkenazic than among Sephardic Jews. As many as 25% of affected individuals have positive family histories of IBD.[3] These ethnic and familial aggregations suggest that shared genetic and environmental factors may play roles in the etiology of IBD.

The Burden of IBD

A recent report from the American Gastroenterological Association provided estimates of the socioeconomic impact in the United States of 17 common gastrointestinal (GI) disorders (all costs given in year 2000 dollars). Direct and indirect costs of IBD exceeded $1.25 billion.[5] The total direct cost of treating UC was $404.9 million. The total indirect cost was $37.8 million.[5] Healthcare utilization and associated costs are even higher for CD. The total direct cost was estimated to be $736.4 million. The indirect cost of healthcare services and lost work time totaled $78.8 million.[5]

The Etiology and Pathogenesis of IBD: A Complex Interplay of Factors

Although the etiologies of UC and CD are not known, complex interactions between environmental, genetic, and immune factors are necessary for disease development (Figure 2).[6] Pathogenesis is believed to involve precipitating and perpetuating events. Any of several exogenous insults, such as infectious agents, toxins, and nonsteroidal anti-inflammatory drugs (NSAIDs), may trigger disease in genetically susceptible individuals. It is perpetuated by a dysregulated mucosal immune response.[6,7] It is important to note that IBD is considered to reflect a dysregulated, but not autoimmune, inflammatory process.

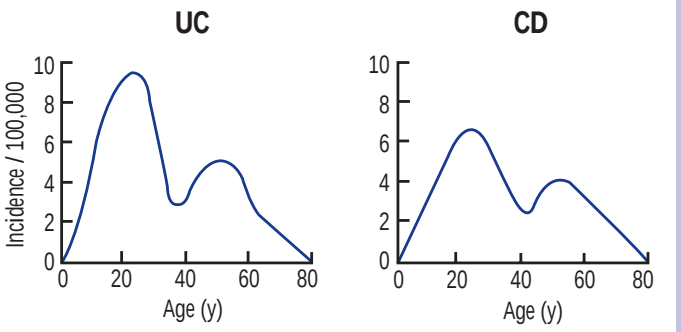
Genetic Factors

As mentioned earlier, epidemiologic studies of IBD show that up to 25% of affected individuals have positive family histories.[3,8,9] Within a family with multiple affected members, 75% to 80% are concordant for disease type: Most affected members have either UC or CD.[9] Monozygotic twin concordance for CD is 42% to 58%, and concordance among monozygotic twins for UC is 6% to 17%.[10,11]

The evidence for genetic factors has spurred the search for disease-associated genes. To date, the results of 7 genome-wide scans have been reported and have identified a number of chromosomal locations associated with UC, CD, or both.[12-18] These studies indicate that there are many susceptibility loci. Whereas a number of loci are shared, some are not, supporting the idea that UC and CD are closely related but distinct polygenic disorders.

Figure 1

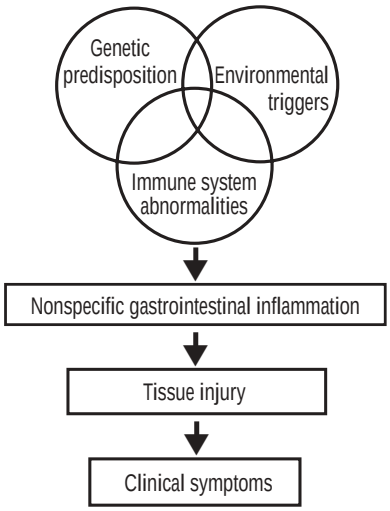
UC and CD Display Bimodal Age-Specific Incidence



Adapted with permission from Lashner, BA. In: Stein SH and Rood RP, eds. *Inflammatory Bowel Disease: A Guide for Patients and Their Families.* Philadelphia, Pa: Lippincott-Raven Publishers; 1999:23-29.

Figure 2

Pathogenesis of IBD: Implicated Factors



Elson CO, et al. *Ann NY Acad Sci.* 1998;859:85-95. Sartor RB. *Am J Gastroenterol.* 1997;92:5S-11S.

Several independent research groups have established that the *NOD2* gene in the pericentromeric region of chromosome 16 confers increased susceptibility to CD.[19-21] *NOD2* is a particularly apt candidate gene. It is expressed in monocytes and appears to be involved in the innate immune response to microbial pathogens.[21,22] If aberrantly produced or expressed, *NOD2* could contribute to the development of the inflammatory process in CD.

The discovery that mutations in *NOD2* confer increased susceptibility to CD is an important first step in understanding the genetic contribution to IBD. Identification of *NOD2* and similar genes will make it possible to determine whether patients who carry these alleles have a more or less benign course of disease, require more frequent surgeries, or have better responses to certain treatments. This area of investigation promises to be among the most exciting—and fruitful—in IBD research.

Environmental Influences

Many environmental factors have been implicated in the pathogenesis of IBD, including a sedentary lifestyle; higher socioeconomic status; diet; and use of antibiotics, NSAIDs, or tobacco.[3,7] Among these various factors, tobacco use is the best characterized. Both active and passive cigarette smoking have a protective effect on the risk of UC[23,24]; however, smoking has the opposite effect in CD—it increases the risk of disease and affects its course adversely.[25]

Immunologic Dysfunction in IBD

In IBD, immunoregulation appears to be defective. After an immune response is stimulated, it is perpetuated rather than down-regulated. The processes that occur in UC and CD resemble a vicious cycle that leads to a chronic, self-perpetuating inflammatory state.[7] Helper ($CD4^+$) T cells have been implicated as key mediators of this unrestrained response.[26] These helper T cells are divided into 2 major classes, depending on the profile of cytokines they produce. Th1 cells produce interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, which promote cellular or delayed-type hypersensitivity responses. Th1 cells and their cytokines promote macrophage activation and granuloma formation, histology that is most commonly associated with CD.[7,26] In contrast, Th2 cells secrete cytokines such as IL-4, IL-5, IL-6, and IL-10, which promote antibody-mediated immune responses. This type of response, characterized by antibody-mediated tissue injury and complement activation, is more consistent in UC.[7,26] It is still unclear why chronic inflammation occurs in IBD. One hypothesis is that there is a dysregulated $CD4^+$ T-cell response to enteric bacterial flora.[6] A second theory suggests that there may be a defect in the suppression of disease-causing $CD4^+$ T cells. Both hypotheses are under active investigation in humans and in animal models of disease.

Diagnosis and Differential Diagnosis of IBD

Although UC and CD share many disease dimensions, the 2 disorders are clearly distinct. They differ in anatomic location, symptoms, prognosis, and how they respond to treatment.[27] Based on the limited number of clinical patterns with which it presents, UC is relatively homogeneous. In contrast, CD has a wide spectrum of clinical forms.[27]

Clinical and Radiologic Features

UC is a diffuse mucosal inflammation limited to the colon. It almost always affects the rectum, and it may extend proximally in a symmetric, uninterrupted pattern to involve all or part of the large intestine (Figure 3).[27] A long-term follow-up study of 1116 patients (609 male, 507 female) found that 46.2% had proctosigmoiditis, 36.7% had colitis of the entire large intestine, and 17.0% had left-sided colitis.[28] The extent of UC increased over time. At follow-up, 34% of patients with initial diagnoses of proctitis and 70.4% of patients with initial diagnoses of left-sided colitis were found to have pancolitis.[28] No differences in disease location were reported between men and women. The most common symptoms of UC are rectal bleeding, diarrhea, abdominal cramping, weight loss, and fever.[28]

CD is a chronic transmural inflammation that can affect any part of the GI tract from the mouth to the anus. In approximately 30% of cases, disease is confined to the small intestine. In about 50% of cases, it will involve both the small intestine and colon (ileocolitis), and, in approximately 20% of cases, CD involves only the colon.[29] Perianal disease occurs in one third of cases and is more common in patients with colonic involvement.[29,30] Most patients present with symptoms of abdominal pain and tenderness, chronic or nocturnal diarrhea, rectal bleeding, weight loss, and fever.[31] CD evolves over time from a primarily inflammatory disease into 1 of 2 clinical patterns: stricturing (obstructive) or penetrating (fistulizing).[32] Figure 4 shows the range of clinical presentations and patterns with corresponding radiologic manifestations.

Because of its heterogeneous manifestations, attempts have been made to classify subpopulations in CD. The most recent classification was proposed by an international group of 13 specialists at the World Congresses of Gastroenterology in Vienna.[33] Three outcome-related variables were selected for the classification scheme: age at diagnosis (< 40 years or ≥ 40 years), anatomic location (terminal ileum, colon, ileocolon, or upper GI tract); and principal clinical behavior (nonstricturing, nonpenetrating, stricturing, or penetrating). This classification scheme, which was validated internally, provides distinct definitions that categorize patients into 24 subgroups.[33] However, due to evolution over time, to stricturing or penetrating factors, and to an absence of correlations with genetic patterns (ie, *NOD2*), the utility of this classification has been questionable.

The Role of Endoscopy

Endoscopy is a key diagnostic tool for excluding other causes of colitis and differentiating between UC and CD.[34] Along with radiologic studies, endoscopy is used to evaluate the location and extent of disease and to obtain tissue for histologic evaluation. The endoscopic findings in UC cover a wide spectrum. In mild disease, erythema, edema, and pinpoint friability are seen. In moderate UC, the colon appears superficially denuded and eroded. It is diffusely friable and bleeds readily. In severe disease, there is marked inflammation accompanied by gross ulceration and spontaneous hemorrhage. When one is diagnosing UC, there are 3 key points:

– Discrete ulcers are not seen in mild disease. The "ulcerative" in UC refers to micro-ulcers that are visualized by histology.

– Rectal sparing can occur after local (rectal) therapy in UC but is uncommon.[35]

– UC and infectious colitis can appear similar.[36] In difficult cases, histology is useful in making the diagnostic distinction.

The endoscopic appearance of CD is highly variable and changes with disease activity and/or duration. The most distinctive endoscopic signs are the discontinuous distribution of aphthous or irregular-shaped or linear ulcers, cobblestoning, and the potential for rectal sparing or anal lesions.[34,37]

Histology

Biopsies of the large bowel in patients with IBD are used to establish a primary diagnosis; to determine whether there has been a change in the extent, activity, or diagnosis of disease; and for dysplasia surveillance. Morphologic criteria have been developed to distinguish IBD from other forms of colitis and to distinguish UC from CD. Features useful in distinguishing IBD from other forms of colitis are crypt atrophy, crypt distortion, basal plasmacytosis with severe mononuclear cell infiltration, and Paneth cell metaplasia.[38] For UC versus CD, useful criteria are segmental distribution of crypt atrophy or distortion, segmental distribution of mucin depletion, mucin preservation at the ulcer edge or in the crypts with surrounding neutrophils, and the ratio of biopsies with crypt atrophy to biopsies with mononuclear cell infiltration.[38] Noncaseating granulomas are seen in 15% to 40% of mucosal biopsies in CD. When they are identified, their presence is useful in distinguishing UC from CD.

Serologic Markers

Although the diagnosis of IBD is based on clinical, endoscopic, histologic, and radiologic criteria, these tests are invasive and expensive. Serologic markers, if they could accurately identify IBD and distinguish CD from UC, would be a welcome diagnostic tool. Serologic testing would be particularly desirable for the pediatric population. Children often have unique, sometimes difficult-to-diagnose presentations of IBD, and the use of noninvasive techniques to distinguish disease would be most valuable to clinicians.[39] In addition, serologic testing to classify patients with indeterminate colitis would have clinical utility.[40]

Several IBD-specific antibody markers have been identified, of which 2, perinuclear antineutrophil cytoplasmic antibody (pANCA) and anti-*Saccharmomyces cervisiae* antibody (ASCA), have been studied most. pANCA is detected in about 80% of patients with UC and approximately 45% of patients with CD.[41,42] ASCA antibodies are present in 60% to 70% of patients with CD and 8% to 14% of patients with UC.[40,43,44] Two recent studies assessed the value of serologic testing in diagnosis using both pANCA and ASCA antibodies.[40,45] The combination of positive pANCA and negative ASCA had a positive predictive value for identifying UC patients of 88% to 92%. Conversely, the combination of positive ASCA and negative pANCA had a positive predictive value of 95% to 96% for identifying patients with CD.[40,46] Unfortunately, although these assays primarily classify patients with "classical presentations," they have not been useful in classifying patients with indeterminate colitis. As the roles of pANCA, ASCA, and other serologic markers for IBD are defined better, it is anticipated that serologic testing may become an integral part of the diagnostic tool kit for IBD.

Differential Diagnosis

Diagnosis is made using complementary methods that include clinical, radiologic, endoscopic, and histologic examination. Infection, ischemia, physical damage, or specific immunologic sensitivity must be excluded.[27] Diagnosis also must distinguish between the several types of IBD. (Table 1, and Table 2 on page 4).[27]

Figure 3

Anatomic Distribution of UC

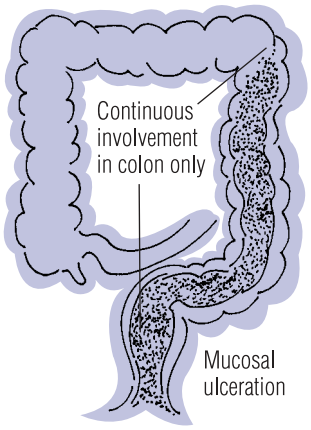
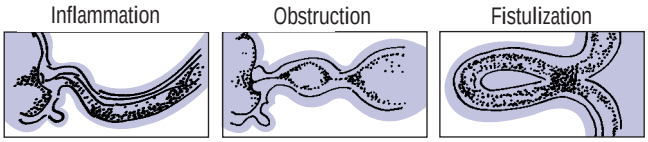


Figure 4

Clinical Presentations, Patterns, and Radiologic Manifestations in CD



- Pain
- Tenderness
- Diarrhea

- Cramps
- Distension
- Vomiting

- Diarrhea
- Damage to skin
- Air/feces in urine
- Types
  - Enteroenteric
  - Enterovesical
  - Retroperitoneal
  - Enterocutaneous

Table 1

Classification of Nonspecific IBD

UC (proctitis)	
CD	
Collagenous colitis	
Eosinophilic enteritis	
Behçet's disease	
"Transient" colitis	Prestomal ileitis
"Microscopic" colitis	Pouchitis
Solitary rectal ulcer	

Adapted with permission from Lennard-Jones JE. 1989; 24 (suppl 170):2-6. Taylor & Frances Ltd, http://www.tandf.co.uk/journals.

Table 2

Criteria for the Differential Diagnosis of UC and CD

UC	CD
Exclusion: - Infective colitis (microbiology) - Ischemic colitis (predisposing factors, disease distribution, histology) - Irradiation colitis (history) - Solitary ulcer (situation, histology) - Abnormalities suggesting CD, such as small-bowel disease (X-ray) - Complex anal lesion (physical examination) - Granulomata (biopsy)	Exclusion: - Infections (microbiology, including *Yersinia* antibodies when appropriate) - Ischemia (predisposing factors, distribution of disease, histology) - Irradiation (history) - Lymphoma/carcinoma (previous celiac disease, suggestive radiologic features, prognosis)
Inclusion: a) Continuous mucosal inflammation without granulomata (biopsy) b) Affecting rectum (endoscopy) and some or all of colon in continuity with rectum (endoscopy or barium enema)	Inclusion: a) Mouth to anus - Chronic granulomatous lesion of lip or buccal mucosa (inspection, biopsy) - Pyloroduodenal disease (radiology, endoscopy, biopsy) - Small-bowel disease (radiology, endoscopy, specimen) - Chronic anal lesion (clinical examination, biopsy) b) Discontinuous - Lesions separated by normal mucosa, which may be widely separate, "skip lesions" along length or around circumference, or discrete ulcers (endoscopy, radiology, specimen) c) Transmural - Fissuring ulcers (radiology, specimen) - Abscess (clinical, imaging) - Fistula (clinical, radiology, specimen) d) Fibrosis - Stricture (to be distinguished from carcinoma or concentric muscular thickening in UC), which can be asymmetric and multiple (endoscopy, radiology, specimen) e) Lymphoid - Biopsy of small aphthoid ulcer or showing lymphoid aggregates f) Mucin - Retention of colonic mucin on biopsy in the presence of active inflammation (biopsy, specimen) g) Granulomata - Not present in all cases of CD; distinguish from caseating granulomata of TB, foreign-body granulomata, or other causes (biopsy, specimen)

The method(s) used to determine various aspects are noted in parentheses.

TB = tuberculosis.

Lennard-Jones JE. *Scand J Gastroenterol.* 1989;24(suppl 170):2-6.

Traditional and Evolving Management Strategies

Ulcerative Colitis

The 2 principal clinical goals in UC are to induce and maintain remission. It is equally important to achieve a good quality of life (QOL). A third key goal is to prevent complications—both disease related and those that are associated with long-term use of medication. A final goal is to optimize the timing of colectomy for the 20% of patients who may require surgical "cures." To provide the best possible clinical care, it is essential that clinicians know the pharmacology, side effects, and appropriate use of the available agents.

The approach to therapy is determined by the extent and severity of disease (Table 3). Extent is characterized as distal (in which inflammation is limited to below the splenic flexure and thus within the reach of topical therapy) or extensive (extending proximal to the splenic flexure and thus necessitating systemic therapy).[47] Severity is graded as mild, moderate, or severe.[48] Mild disease is characterized by fewer than 4 stools daily, with or without blood; no systemic signs of toxicity; and a normal erythrocyte sedimentation rate. Patients with moderate disease have more than 4 stools daily but with minimal signs of toxicity. Severe disease is defined as more than 6 bloody stools daily and evidence of toxicity as demonstrated by fever, diarrhea, tachycardia, anemia, or an elevated erythrocyte sedimentation rate.[48] It is important that before moving in sequence from induction to maintenance therapy, the patient is documented to have indeed achieved remission. Remission is achieved when inflammatory symptoms are absent (patients may have residual symptoms of irritable bowel syndrome), there is regeneration of intact mucosa, and histology reveals absence of crypt abscesses.

Induction of Remission: Mild to Moderate Disease

The aminosalicylates are the cornerstone of treatment in mild disease. The first to be used was sulfasalazine (Azulfidine®), which contains sulfapyridine linked to 5-ASA (mesalamine).[49] It is cleaved by gut bacteria into 5-ASA and sulfapyridine. The 5-ASA moiety is responsible for its anti-inflammatory properties, and the sulfapyridine moiety accounts for most of the drug's toxicity.[49,50] Sulfasalazine at dosages ranging from 2 to 6 g/day induces remission in 64% to 80% of patients, particularly when dosages are higher than 3 g/day.[49] Although increasing the dose increases the response, there also is a dose-dependent increase in the rate of adverse events, principally due to the sulfapyridine component.[49-51] The most common side effects, which occur in approximately 15% to 30% of patients, are anorexia, headache, nausea, vomiting, gastric distress, and oligospermia.[51]

The dose-limiting side effects of sulfasalazine led to the development of sulfa-free aminosalicylate formulations. Oral preparations include mesalamine (Asacol®, Pentasa®), balsalazide (Colazal™), and olsalazine (Dipentum®). Clinical improvement or remission with mesalamine compounds is attained at dosages of 1.5 to 4.8 mg/day, with greater improvement at dosages greater than 2 g/day.[49] 5-ASA compounds are safe and well tolerated, even by sulfasalazine-intolerant patients. Doses can be increased without a corresponding increase in side effects.[49,52] In 2 studies of 5-ASAs,further analyses were performed to determine whether clinical response was affected by factors such as sex, age, and total disease duration. No factors, including sex, were found to

have significant effects on treatment outcomes.[53,54] A compilation of data across 3 studies that used varying doses of mesalamine is shown in Figure 5, page 6.[53-55] Increasing doses were associated with higher rates of remission and improvement. Because there is no dose-toxicity response and thus no concern regarding increased side effects with higher doses, it is possible to initiate or titrate therapy at dosages up to 4.8 g/day according to clinical response. A trial is currently under way exploring higher initial dosages of mesalamine (4.8 g/day) using an 800-mg tablet.

Topical 5-ASA preparations are available for patients with distal disease. In a meta-analysis and literature review, Cohen et al found convincing evidence that mesalamine suppositories and enemas were associated with higher remission rates and greater clinical improvement than steroid-based topical therapies. A 60% to 89% response was achieved with suppositories (0.5 to 2 g/day) or enemas (1 to 4 g/day) by patients with mild to moderate ulcerative proctitis or proctosigmoiditis. Both efficacy and side effects were dose independent.[56] Topical mesalamine therapy was shown to be more effective than oral therapy,[56] although combined oral/topical therapy produced greater improvement than either therapy alone. Safdi and colleagues compared oral mesalamine, 2.4 g/day; topical mesalamine, 4 g/day; and combination treatment for 60 patients with mild to moderate distal UC.[57] Although patients treated with topical mesalamine improved more than those treated with oral mesalamine, combination therapy provided the best response, as evidenced by the absence of rectal bleeding over the course of the trial.[57]

Induction of Remission: Moderate to Severe Disease

Corticosteroids are recommended for patients who do not respond to optimized doses of aminosalicylates. Even though corticosteroids are widely used, their mechanisms of action are not completely understood. They have a range of anti-inflammatory effects, including inhibition of cytokine gene transcription, arachidonic acid release, neutrophil phagocytosis, and leukocyte trafficking.[49] They also may decrease diarrhea by enhancing sodium and water absorption.[49] Clinical improvement or remission is achieved by 45% to 90% of patients with 15 to 60 mg/day of prednisone, 300 mg/day of hydrocortisone, 40 to 60 mg/day of methylprednisolone, or 80 to 120 µg/day of ACTH.[49] The side effects of corticosteroid therapy, however, are numerous and include fluid and electrolyte disturbances and GI, dermatologic, neurologic, endocrine, ophthalmic, and metabolic adverse effects.[58] Corticosteroids accelerate the rate of bone loss, and osteoporosis is one of the most serious complications of this treatment.[59] These side effects have spurred the search for more potent steroids that are less well absorbed and have greater first-pass hepatic metabolism. In this regard, a topical formulation of a newly available corticosteroid, budesonide, has been shown to be effective in distal UC.[60,61] Oral formulations of budesonide have not been efficacious for UC.

Induction of Remission: Severe or Fulminant Disease

There have been few clinical trials with patients with severe disease. Consensus is that patients who continue to have severe symptoms should be hospitalized for further treatment.[47] The standard of care is IV steroids. Several controlled clinical trials have shown that the addition of antibiotics to IV steroids provides no therapeutic benefit.[47] Total parenteral nutrition also is not beneficial, except for patients with severe nutritional depletion.[47]

Table 3

Inductive and Maintenance Medical Therapies for UC

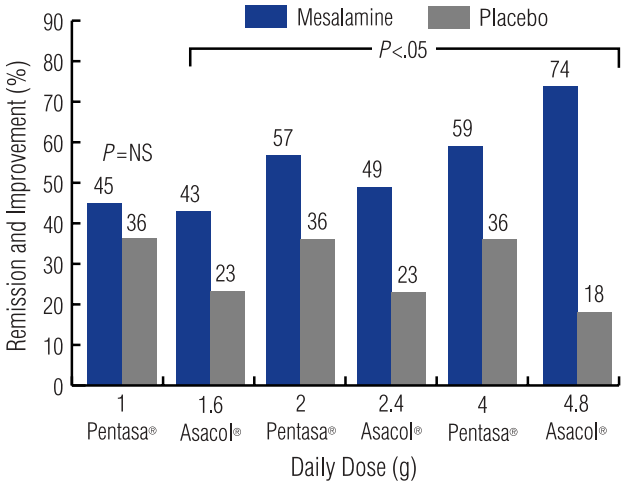
Drug	Dose Range	Response Rate
	Inductive Therapies	
Sulfasalazine	Clinical improvement or remission of mild to moderate UC at dosages of 2-6 g/day (with improved efficacy at dosages >3 g/day)	64% to 80%
Oral 5-ASA	Clinical improvement or remission of mild to moderate UC at dosages of 1.5-4.8 g/day (with improved response at dosages >2 g/day)	40% to 74%
Topical 5-ASA	Response to suppositories (0.5-2 g/day) or enemas (1-4 g/day) for mild to moderate proctitis or proctosigmoiditis	60% to 89%
Corticosteroids (oral or IV)	Clinical improvement or remission with 15-60 mg/day of prednisone (with increased response at 40-60 mg/day), hydrocortisone 300 mg/day, methylprednisolone 40-60 mg/day, or ACTH 80-120 µ/day for moderate to severe UC	45% to 90%
Corticosteroids (topical)	Clinical response using hydrocortisone enemas or cortisone foam preparations at variable doses for moderate proctitis or proctosigmoiditis	41% to 89%
AZA/6-MP	Clinical improvement or reduction in steroid dosage while receiving AZA/6-MP at dosages of 1.5-2.5 mg/kg/day	29% to 78%
Cyclosporine	Clinical response in 1 placebo-controlled trial using IV cyclosporine 4 mg/kg/day for severe, steroid-refractory UC	82%
Placebo	Clinical improvement from a review of 11 placebo-controlled trials	16% to 52%
	Maintenance Therapies	
Sulfasalazine	Maintenance of remission at 6-12 mo at dosages of 1-4 g/day (with slightly increased efficacy at the 4-g/day dosage)	71% to 88%
Oral 5-ASA	Maintenance of remission at 12 mo at dosages of 1.5-4 g/day (with slightly increased efficacy at the 4 g/day dosage) in a review of controlled trials, comparative trials, and meta-analyses	54% to 80%
Topical 5-ASA	Maintenance of remission at 12 mo using 1-4-g enemas nightly 1 wk/mo, 4-g enemas every 3rd night	74% to 80%
AZA/6-MP	Maintenance of remission for up to 12 mo while receiving a mean dosage of AZA 100 mg/day in 1 controlled trial	64%
Placebo	Maintenance of remission at 6-12 mo in a review of 6 placebo-controlled trials	25% to 51%

IV = intravenous; 5-ASA = 5-aminosalicylic acid; AZA/6-MP = azathioprine/6-mercaptopurine.

Adapted with permission from Stein RB, Hanauer SB. *Gastroenterol Clin North Am.* 1999;28:297-321.

Figure 5

Effect of Mesalamine Dose on Remission and Improvement in UC



Hanauer S, et al. *Am J Gastroenterol.* 1993;88:1188-1197. Schroeder KW, et al. *N Engl J Med.* 1987;317:1625-1629. Sninsky CA, et al. *Ann Intern Med.* 1991;115;350-355.

Cyclosporine provides an alternative treatment for patients with severe UC who do not respond to IV corticosteroids. Cyclosporine is a potent inhibitor of T-cell-mediated immune responses: it blocks T-cell production of IL-2, IL-3, IL-4, IFN-γ, and TNF-α and prevents the recruitment of cytotoxic T cells.[49] In one placebo-controlled trial using IV cyclosporine at 4 mg/kg/day, 82% of patients achieved response to therapy.[62] A recently published report of 5 years' experience using cyclosporine for severe, intractable UC suggests that it allows most patients to avoid surgery or provides time for "elective" colectomy for others.[63] AZA/6-MP is indicated for maintenance in refractory UC or for corticosteroid-dependent patients and after inductive therapy with cyclosporine.[64]

Cyclosporine therapy is associated with significant toxicity, and it should be used in centers where drug blood levels can be monitored. There are multiple warnings regarding its use. Cyclosporine can cause nephrotoxicity and hepatotoxicity. The risk increases with increasing dose.[65] Patients also may be at increased risk for convulsions, particularly patients who have low serum cholesterol levels. Encephalopathy also has been described, both in the literature and in postmarketing reports.[65] The principal adverse reactions are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.[65] Drug-drug interactions with cyclosporine are common, and opportunistic infections in patients using concomitant immunosuppressive therapies have led to recommendations for prophylaxis therapy for those infections.[49]

Maintenance Therapies

Maintenance therapy is individualized based on the extent of disease, the induction therapy that was used, and the response to prior treatment, including any history of relapse or issues with adherence. Complete remission must be established before maintenance therapy is initiated—incomplete remission is a guarantee that maintenance will fail. A second extremely important point is that *corticosteroids are ineffective as maintenance therapy* and, as a rule, should be avoided.[47] Steroids should be tapered according to the rapidity of the response and before topical mesalamine is tapered.

Aminosalicylates

5-ASAs are the mainstays of maintenance therapy. Sulfasalazine, at dosages ranging from 1 to 4 g/day, is associated with maintenance of remission in 71% to 88% of patients at 6 to 12 months.[49] In a review of controlled trials, comparative trials, and meta-analyses, oral mesalamine treatment maintained remission in 54% to 80% of patients at 12 months at dosages ranging from 1.5 to 4 g/day.[49] As is seen for inductive therapy, there is a dose-response effect for oral 5-ASAs.[66,67]

A randomized study compared mesalamine at 0.8 g/day or 1.6 g/day with placebo for the maintenance of remission. At 6 months, 70% of patients in the 1.6-g group, 63% in the 0.8-g group, and 48% of placebo-treated patients were in remission. Differences were statistically significant from placebo for both the 0.8-g dose and the 1.6-g dose ($P = .05$). There were no differences between the treatment groups for side effects.[66] More recent research further reinforced the dose-response relationship of the oral mesalamine preparations.[67] High doses of oral 5-ASA (balsalazide 3.0 g administered twice daily) were significantly more effective than lower doses (0.5 g mesalamine 3 times per day; $P = .006$). This study underscores the need to use doses of aminosalicylates that will control disease adequately, particularly using agents that will be most efficacious on the specific location of disease based on that agent's profile. Oral mesalamine can be used safely at dosages up to 4.8 g/day without dose-related side effects.

Topical mesalamine is effective for the maintenance of remission in distal UC.[68,69] Rates for maintenance of remission with topical 5-ASA agents range from 74% to 80% at 12 months.[49] Combined oral/topical mesalamine is more effective than oral therapy alone. d'Albasio and colleagues compared continuous oral mesalamine 1.6 g/day, plus 5-ASA enemas (4 g/100 mL twice weekly) to oral therapy alone. A twice-weekly topical regimen was evaluated, because it was hoped that less frequent treatment would be better accepted than daily therapy.[70] At both 6 months and 12 months, patients on combined therapy had lower relapse rates than patients using oral therapy alone. The difference in the cumulative relapse-free survival was statistically significant between the 2 groups ($P = .02$). It should be noted that the rectal route often is not preferred by patients. Fortunately, oral therapy also is effective for most patients with distal disease. Superior maintenance rates are achieved with higher doses. For example, 3.2 g/day of mesalamine achieved a 92% maintenance rate, compared with 78% for 1 g/day of olsalazine.[56]

In the past, physicians reduced the 5-ASA dose when patients began maintenance therapy, largely because of the dose-related side effects of sulfasalazine. Because there is a dose response for efficacy but not for side effects with oral mesalamine, the current approach is to use the *same* dosage for maintenance therapy that was required for induction. For example, a patient whose induction dosage was 4.8 g/day can be safely and effectively maintained on the 4.8-g/day dosage. Indeed, the ultimate dose potential of mesalamine is not known.

Immunomodulators: AZA and 6-MP

AZA and 6-MP are purine analogues that modulate immune responses by inhibiting natural killer cell activity and suppressing cytotoxic T-cell function.[49] They have been effective for steroid-dependent patients and can be used in patients who have not

responded to 5-ASAs despite optimized oral and/or topical therapy. One randomized, controlled trial found that 64% of AZA-treated patients maintained remission, compared with 41% of placebo-treated patients.[71] A retrospective study analyzed the long-term use of 6-MP for both induction therapy and maintenance of remission in 105 patients with chronic refractory symptoms. Most patients (89%) had been taking steroids before 6-MP therapy was initiated. Remission or improvement was achieved by 89% of patients. Of the 68 patients who achieved complete remission and were maintained on 6-MP, 65% achieved long-term remission.[72] Fifty-five percent of patients in this study were men and 44% were women. No sex-related differences in safety or efficacy were reported.[72] A third study demonstrated the utility of AZA in steroid-resistant and steroid-dependent UC. In a retrospective analysis of 56 patients, all of whom were taking corticosteroids when AZA treatment was initiated, remission with complete elimination of steroids was achieved by more than 60% of patients with continued AZA treatment.[73] In this study, 67% of patients were male and 30% were female. No sex-related differences in efficacy or safety were reported.[73]

Side effects of AZA and 6-MP include pancreatitis, nausea, fever, rash, allergic reactions, and drug hepatitis.[49,74] Another complication is bone marrow suppression, which occurred in approximately 2% of a large series of 6-MP-treated patients.[74] The potential for this side effect necessitates regular monitoring of complete blood count during treatment.[49] A further issue relates to levels of thiopurine methyltransferase (TPMT), an enzyme that transforms active metabolites of 6-MP into inactive products.[75] Approximately 11% of the population is heterozygous for alleles that result in intermediate enzyme activity (0.3% of the population is homozygous and thus has little or no TPMT activity). Such patients may be unusually sensitive to standard therapeutic doses, placing them at increased risk for bone marrow suppression.[75] Some clinicians suggest that careful monitoring of complete blood count is sufficient to ensure safe treatment, but others suggest that it may be useful to determine the TPMT phenotype before long-term 6-MP therapy is initiated or to measure MP metabolites (6-thioguanine and 6-methylmercaptopurine) directly during therapy.[31,75]

A final issue is the drug-drug interaction between 5-ASA-containing compounds and 6-MP and AZA.[75-77] 5-ASA-containing compounds are competitive inhibitors of TPMT. Clinical experience suggests that, with careful monitoring, combined therapy is safe. In addition, this combination confers a potential benefit: A lower dose of 6-MP/AZA can be used, thereby decreasing the overall cost of therapy. In addition, a more rapid therapeutic response may be possible.[77]

Refractory Colitis

A subset of patients have UC that is refractory to both inductive and maintenance therapies, despite adequate doses and duration of treatment and optimal drug delivery. In these cases, "pseudorefractory UC" must be considered. These patients may be refractory for a variety of reasons, including use of NSAIDs; intolerance to 5-ASAs; irritable bowel syndrome; intercurrent infections; cyclical symptoms associated with the menstrual cycle; or nonadherence to therapy. For these patients, treatment options for distal disease include rectal mesalamine or AZA/6-MP. For patients with extensive disease, high dosages of oral mesalamine (4.8 g/day to 6.0 g/day or higher) can be tried. AZA/6-MP can be used by steroid-dependent or 5-ASA-intolerant patients. Irrespective of the extent of disease, colectomy is an option.

Crohn's Disease

The overall goals of therapy in CD are to eliminate symptoms, maintain patients' health and QOL, limit side effects of therapy, and prevent long-term complications.[31] These goals are met by reaching an accurate diagnosis, inducing complete remission, and maintaining remission. A good working knowledge of the side effects of various agents is necessary to minimize adverse effects of therapy. In this regard, avoidance of steroids is an important aim.

Therapeutic choices are based on the extent and severity of disease and response to prior therapy. Categories of disease and their severity follow[31]:

Mild to moderate disease: Patients are ambulatory and able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or >10% weight loss.

Moderate to severe disease: Patients have not responded to treatment for mild to moderate disease or have more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

Severe to fulminant disease: Patients have persistent symptoms despite the introduction of steroids, or patients present with high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

Treatment follows a sequence comprising induction and maintenance of remission. Commonly used agents, dose ranges, and response rates are listed in Table 4, page 8. Remission is reached when patients are asymptomatic or without inflammatory sequelae. Remission is achieved through either medical intervention or surgery. Patients who require steroids to maintain well-being are steroid dependent and are not considered to be in remission.[31]

Induction of Remission: Mild to Moderate Disease

Aminosalicylates

The efficacy of mesalamine for induction of remission is well established. In a double-blind, placebo-controlled trial with 310 patients, Singleton and colleagues demonstrated that mesalamine at 4 g/day, but not at 1 or 2 g/day, had significant efficacy compared with placebo ($P < .01$). Mesalamine at 4 g/day was not associated with clinically significant toxicity.[78] These data were confirmed in a randomized, double-blind, placebo-controlled, 16-week trial using 3.2 g/day of mesalamine. Sixty percent of mesalamine-treated patients achieved partial or complete remission, compared with 22% of placebo-treated patients. Mesalamine treatment was well tolerated, and no patients discontinued study medication because of side effects.[79] A third study compared 4 g/day of mesalamine (tablet or microgranular formation) with 40 mg of 6-methlyprednisolone in 94 patients with Crohn's ileitis.[80] The microgranular formulation preferentially deposits drug in the terminal ileum. After 12 weeks of treatment, 61% of steroid-treated patients, 60% of patients receiving mesalamine tablets, and 79% of patients receiving microgranular mesalamine had achieved remission (Figure 6, page 9). The microgranular formulation was safe and well tolerated.[80] No sex-related safety or efficacy data were reported in these studies. Further studies have not replicated mesalamine's superiority over placebo in inducing remission in CD; however, trials using higher doses of mesalamine—up to 6.0 g/day—are currently under way. It is anticipated that results of these trials may help define the role of mesalamine in the induction and maintenance of remission in CD.

Table 4

Inductive and Maintenance Medical Therapies for CD

Drug	Dose Range	Response Rate
	Inductive Therapies	
Sulfasalazine	Improvement or remission at 3-6 g/day	38% to 62%
5-ASA (mesalamine)	Improvement or remission at 1.5-4 g/day, with increased efficacy at higher doses	43% to 64%
Antibiotics	Metronidazole 10-20 mg/kg/day	67% to 95%
	Ciprofloxacin 1 g/day	
Corticosteroids	Response to oral prednisone 0.25-0.75 mg/kg/day, IV methylprednisolone at 40-60 mg/day, budesonide 9 mg/day	53% to 78%
AZA/6-MP	Improvement or reduction in daily steroid doses with 6-MP 1.5 mg/kg/day or AZA 2-3 mg/kg/day for active bowel disease or fistulas	36% to 91%
Methotrexate	Clinical improvement or reduction in daily steroid dosage with 15 mg/wk oral or 25 mg/wk IM/SC methotrexate for active bowel disease or fistulas	39% to 54%
Cyclosporine*	Response in patients with chronically active CD treated with oral cyclosporine 5-7.5 mg/kg/day; uncontrolled trials demonstrate higher response rate for patients with severe CD and refractory fistulas who receive IV cyclosporine 4 mg/kg/day	35% to 59%
Infliximab	Clinical improvement at 4 wk after single 5-mg/kg infusion in chronic active CD; also effective for fistulas	81%
Placebo	Partial or complete remission in 12 placebo-controlled trials	8% to 50%
	Maintenance of Medically Induced Remission	
5-ASA	Relapse-free rates at 12-24 mo at dosages of 1.5-3 g/day	47% to 69%
AZA/6-MP	Remission at 6 mo-2 y with AZA at dosages of 2-2.5 mg/kg/day (as measured by prevention of relapse, maintenance of well-being, or ability to taper steroids)	54% to 100%
Methotrexate	Remission rate at 40 wk with methotrexate 15 mg/kg/wk	65%
Placebo	Maintenance of remission at 12-24 mo	35% to 64%
	Maintenance of Surgically Induced Remission	
5-ASA	Maintenance of remission at 3 mo-3 y at dosages of 1.5-3 g/day	44% to 75%
AZA/6-MP	Maintenance of remission at 2 y with 6-MP at 50 mg/day	47%
Metronidazole	Prevention of clinical recurrence at 2-3 y after resection at dosages of 10-20 mg/kg/day; reduction of severe endoscopic lesions noted as early as 3 mo	70% to 74%
Placebo	Remission at 3 mo-6 y	15% to 73%

*Reserved for patients unresponsive to parenteral corticosteroids or those with severe perianal or fistulizing disease.

Adapted with permission from Stein RB, Hanauer SB. *Gastroenterol Clin North Am.* 1999;28:297-321.

The efficacy of sulfasalazine, olsalazine, and balsalazide for inducing remission is less clear, presumably because colonic bacteria are necessary to cleave the compound and release the active 5-ASA moiety. Thus, their utility is limited primarily to patients with colonic disease.[49,81]

Antibiotics

The antibiotics metronidazole and ciprofloxacin are used to induce remission in mild to moderate CD and to treat perianal manifestations. Current efficacy data for metronidazole are not particularly robust. Sutherland and colleagues evaluated the efficacy of 10 and 20 mg/kg metronidazole compared with placebo for 105 patients. Although active treatment was associated with significant improvement in disease activity, there were no differences in remission rates between metronidazole- and placebo-treated patients.[82] This trial included comparable numbers of men and women, and there were noted no sex-related differences in safety or efficacy. Bernstein and colleagues showed that metronidazole treatment improves the perianal manifestations of CD. In a small, open-label trial with 21 patients (5 men, 16 women) with chronic, unremitting CD, metronidazole at 20 mg/kg/day was associated with dramatically decreased drainage, erythema, and induration. Complete healing was achieved by 48% of patients, and 24% of patients attained advanced healing.[83] No differences were reported between men and women. The most common side effects of metronidazole include nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, and abdominal cramping. Use of metronidazole causes an unpleasant, metallic taste. Serious adverse events include peripheral neuropathy and convulsive seizures.[84] Ciprofloxacin also has been used as inductive therapy, with results comparable to those with mesalamine.[85] A retrospective chart study, an open-label trial, and a randomized, controlled trial provide evidence that ciprofloxacin is effective alone or in combination with metronidazole.[86-88]

Induction of Remission: Moderate to Severe Disease

Corticosteroids

Corticosteroid treatment often is used for patients with moderate to severe disease if 5-ASA treatment at maximal doses is not effective. The efficacy of corticosteroid treatment was shown in both the National Cooperative Crohn's Disease Study and the European Cooperative Crohn's Disease Study, in which response to prednisone or methylprednisolone treatment was significantly better than to placebo.[49,81,89] Budesonide, a relatively new corticosteroid indicated for inducing remission in mild to moderate CD involving the ileocecal area, has lower systemic bioavailability than do older steroids.[90] Two randomized, double-blind, short-term studies evaluated its efficacy in CD. One study compared 3 dosages of budesonide with placebo over an 8-week treatment period. At 8 weeks, 33% of patients receiving 3 mg/day, 51% receiving 9 mg/day, and 43% receiving 15 mg/day had achieved remission, compared with 20% of placebo-treated patients.[91] Subgroup analysis did not reveal any relationship between effect of treatment and any variable tested, including sex. The second study was a randomized, blinded comparison of budesonide and prednisolone in patients with active ileal or ileocecal CD.[90] At 10 weeks, 53% of budesonide-treated patients and 66% of prednisolone-treated patients had achieved remission. Although there was a significant difference in treatment benefit favoring prednisolone, there were fewer short-term side effects associated with budesonide.[90] Although budesonide may have a more favorable short-term side-effect profile, long-term safety data are

not yet available, and concerns exist regarding the potential for bone loss and cataract formation. The recommended duration of treatment is 8 weeks.[92]

Despite their efficacy in inductive therapy, benefits of corticosteroids are offset by short- and long-term side effects. Further, approximately one fifth of patients become steroid resistant and one third become steroid dependent.[93] Munkholm and colleagues prospectively studied a cohort of 196 patients with CD during their first course of steroid treatment. Of all complete and partial responders, 55% experienced a prolonged response, and 45% relapsed or could not be withdrawn from treatment within 1 year.[94] Similar outcomes were identified in Olmsted County.[95] Data such as these have prompted most experts to make all efforts to avoid the use of corticosteroids for active CD.

AZA and 6-MP

The immunomodulators AZA and 6-MP are used in inductive therapy. A recent meta-analysis of 7 studies found that, compared with placebo, AZA or 6-MP had an odds ratio (OR) of response of 3.09 (95% confidence interval [CI], 2.45 to 3.91) in patients with active CD.[96] Importantly, in the studies that reported data on steroid use, 65% of patients who received AZA or 6-MP consumed fewer steroids. 6-MP also has been shown to have a favorable effect on fistulae.[97]

Methotrexate

Methotrexate is an immunomodulator whose anti-inflammatory properties include inhibition of IL-1 production and induction of apoptosis in T-cell subpopulations.[49] Feagan and colleagues evaluated 25 mg/week of methotrexate or placebo in a randomized, double-blind, 16-week trial with 141 patients with active CD. All patients also received 20 mg/day of prednisone, which was tapered during the treatment period. After 16 weeks, 39.4% of methotrexate- and 19.1% of placebo-treated patients had achieved remission ($P = .025$). Patients in the methotrexate group received significantly less prednisone than did placebo-treated patients ($P = .026$).[98] Additional analyses were performed that examined the relationship of outcome with factors such as age, sex, and site of disease, but they yielded no significant associations with the primary efficacy outcome.

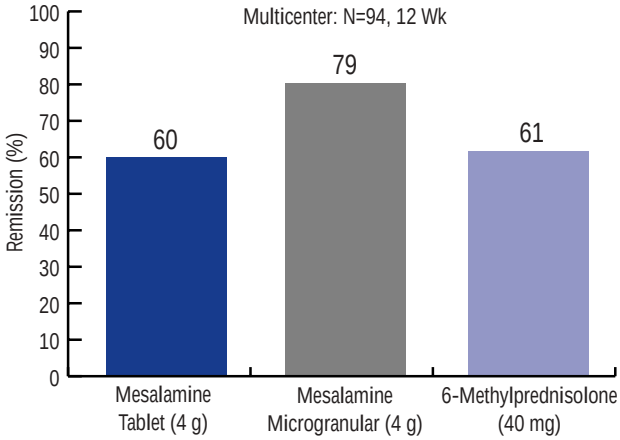
The disadvantages of methotrexate treatment are its side effects, which necessitate careful monitoring of patients, and the numerous contraindications to therapy. Patients require monthly monitoring of serum aminotransferase and albumin concentrations, and liver biopsies must be performed on those with persistent enzyme elevations or hypoalbuminemia. Additional risks include hypersensitivity pneumonitis, bone marrow depression, and teratogenicity.[98]

Infliximab

Infliximab is a chimeric monoclonal antibody that is targeted to TNF-α, a proinflammatory cytokine. It is the first biologic agent to be approved by the Food and Drug Administration (FDA) for use in CD. Its efficacy was evaluated in a 12-week, double-blind, placebo-controlled trial with 108 patients with moderate to severe, treatment-resistant CD.[99] Patients were randomized to receive a single IV infusion of infliximab 5 mg/kg, 10 mg/kg, or 20 mg/kg or placebo. At 4 weeks, 81% of patients receiving 5 mg/kg, 50% receiving 10 mg/kg, and 64% receiving 20 mg/kg had achieved clinical response, compared with 17% of placebo-treated patients. Overall, 33% of infliximab- and 4% of placebo-treated patients attained remission.[99] Forty-seven percent of patients in this trial were male and 53% were female. No effects of sex on treatment were reported. A second study reported positive effects of infliximab on fistula healing.[100] Approximately half of all infliximab-treated patients, who received 5-mg/kg doses of infliximab at 0, 2, and 6 weeks, achieved complete response, with all fistulae closed.[100] When data were adjusted for sex or prior resection, regression analysis continued to yield significant benefits of treatment ($P = .001$).[100]

Figure 6

Induction Therapy in CD With Prednisone vs Mesalamine Tablets or Microgranular Formulation



Adapted with permission from Prantera C, et al. *Gastroenterology.* 1999;116:521-526.

Expanded use of infliximab has resulted in heightened concerns over its safety. Serious opportunistic infections, including TB, histoplasmosis, listeriosis, and pneumocystosis, have been reported in clinical studies and postmarketing surveillance. Of the 84 cases of TB reported through June 2001, 14 patients have died.[101] The FDA has since received additional reports, for a total of 117 cases of infliximab-associated TB as of November 30, 2001.[102] Accordingly, the package labeling has been revised to include a Boxed Warning to alert physicians that TB and other opportunistic infections have been observed with treatment. In addition, infliximab should not be administered to patients with congestive heart failure, as it has been found to worsen this condition.[103,104] Along with other anti-TNF-α therapies, it has been implicated as a risk factor in demyelinating central nervous system lesions and should be avoided by patients with multiple sclerosis.[105]

Another concern is the development of human antichimeric antibodies (HACA) to infliximab. This antibody response is associated with hypersensitivity reactions that can occur at various times after infusion and include symptoms such as urticaria, dyspnea, hypotension, fever, rash, headache, sore throat, myalgia, polyarthralgia, hand and face edema, and/or dysphagia.[104] Further, HACA formation often leads to loss of drug efficacy.[106] Until more is learned about the long-term safety of infliximab, it seems prudent to restrict its use to patients with refractory CD.

Cyclosporine

Cyclosporine has been evaluated in several large, randomized studies. In one study, 71 patients with active, chronic CD that was

resistant to corticosteroids or who could not tolerate them were randomized to cyclosporine or placebo.[107] Response to treatment was rapid (2 weeks). At 3 months, 59% of cyclosporine- and 32% of placebo-treated patients had clinical improvement.[107] Three subsequent trials, however, did not show a benefit of cyclosporine treatment,[108] probably because of lower doses that were used. IV cyclosporine has been shown to be effective in treating refractory fistula.[109] The major advantages of IV cyclosporine are its efficacy and the speed of response. A disadvantage is the potential for recurrence after cessation of therapy.

Induction of Remission: Severe or Fulminant Disease

Patients with severe or fulminant disease require hospitalization.[31] Medical treatment options include IV corticosteroids, infliximab, antibiotics, and IV cyclosporine or tacrolimus.[110,111]

Maintenance of Remission

Before we begin an overview of medications, it should be restated that corticosteroids should not be used for maintenance therapy.[31] A recent randomized, double-blind study of budesonide, a newly available corticosteroid, has confirmed that corticosteroids are ineffective for maintaining remission in CD.[112]

Mesalamine

Several meta-analyses have reviewed the efficacy of 5-ASAs in the maintenance of remission in CD. In an analysis of 5 clinical trials, benefits conferred by mesalamine treatment were significantly superior to those with placebo or no treatment. The overall relapse-free rates with mesalamine treatment were 91% at 6 months, 84% at 12 months, and 72% at 24 months.[113] A more recent meta-analysis assessed the efficacy of mesalamine in prevention of relapse after either medically-induced or surgically induced remission.[114] This analysis concluded that mesalamine significantly reduced the risk of relapse after surgery, but not when remission was medically-induced and particularly not after remission was induced by steroids.[114,115] The most recent study of mesalamine in the maintenance of medically-induced remission did not show a statistically significant effect of mesalamine on relapse rate.[116]

The use of mesalamine in maintenance of CD remission is currently a matter of debate. The varying results of these studies can be explained by the different study designs, different dosages used, duration of treatment, patient subpopulations, and pharmacokinetics of the mesalamine preparations that were used. Although it is known that the efficacy of mesalamine is dose-related, the dose potential of mesalamine for maintenance of remission has not been explored fully.

AZA and 6-MP

Six placebo-controlled trials have evaluated the efficacy of AZA for maintenance therapy. A meta-analysis of these studies revealed an overall OR of response of 2.27 (CI, 1.76 to 2.93). A total of 67% of AZA-treated patients responded to treatment in comparison with 53% of placebo-treated patients.[96] In the 2 studies that reported steroid data, AZA had a steroid-sparing effect.[96] A preliminary report evaluating 6-MP maintenance therapy for children demonstrated that combined 6-MP/prednisone treatment was significantly superior to prednisone monotherapy. Further, at 12 months, prednisone use was significantly lower in the combined-therapy group.[117]

Methotrexate

Feagan and colleagues conducted a double-blind, placebo-controlled, multicenter study to evaluate methotrexate as maintenance therapy for 76 patients who had achieved methotrexate-induced remission.[118] At week 40, a significantly higher percentage (65%) of methotrexate-treated patients were in remission, than in the placebo-treated (39%; $P = .04$) group. Kaplan-Meier estimates of the time to relapse in the 2 groups is shown in Figure 7.[118]

Metronidazole

Metronidazole for maintenance of surgically-induced remission was evaluated in a double-blind, placebo-controlled trial.[119] Sixty patients received either high-dose metronidazole or placebo for 3 months. At 1 year, metronidazole significantly reduced the recurrence rate compared with placebo (4% vs 25%, respectively). At 2 and 3 years, however, differences in recurrence rates were not significant.[119] Therefore, though metronidazole delayed symptomatic recurrence of CD, the response diminished over time.

Surgical Options

UC

Approximately 30% of patients with UC will undergo colectomy.[120] Surgical removal of the entire colonic and rectal mucosa in UC is curative. Surgery is an absolute requirement when there is massive hemorrhage, perforation, or carcinoma.[47] Additional indications for surgery are severe colitis with or without toxic megacolon unresponsive to medical therapy and medical intractability despite optimal use of both inductive and remittive treatments.[47,120] Great care must be taken to preserve reproductive function in women who undergo surgery for IBD. In rare cases, surgery is performed to control extraintestinal manifestations (EIMs), and it is sometimes required for children with growth retardation.[47,121]

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the procedure of choice in the surgical treatment of UC. This operation is attractive to patients because it avoids a permanent ileostomy and removes the disease while preserving anorectal function. The surgical technique involves excision of the cecum, colon, and proximal rectum; stripping of the distal rectal and proximal anal mucosa; construction of a J-shaped ileal pouch; and IPAA. This procedure is most often performed in 2 stages.[122] Stapled operations are perhaps the most common method of anastomosis of the pouch to the anal canal, providing early continence superior to that with the hand-sewn technique.[123] Some experts suggest that using anti-adhesion gels or lifting the ovaries away from the surgical field and placing them where there is less chance of adhesion may help preserve ovarian function, although this has not yet been evaluated formally in women undergoing IPAA. Recent evidence suggests subfertility in women undergoing proctocolectomy and IPAA.[124]

Fazio and colleagues assessed the long-term outcomes of restorative proctocolectomy and IPAA based on 11 years' experience with more than 1000 patients.[125] Functional results and QOL were good to excellent for 93% of patients whose data were complete.[125] Overall, restorative proctocolectomy with IPAA appeared safe. Although there was an appreciable rate of early and late complications, overall functional results were generally good, and patient satisfaction was high.[125]

Crohn's Disease

The recurrent nature of CD is a deterrent to surgery. The small intestine is regarded as a nonrenewable resource. Once segments of small bowel are removed and some intestinal adaptation occurs, a relatively stable state is reached, but there is a resultant spectrum of disability ranging from no perceptible effect to short-bowel syndrome. Nonetheless, surgery almost always is necessary at some point in the lifetime of patients afflicted with CD, and resections can rapidly restore QOL for patients with medically refractory CD. Researchers at the Cleveland Clinic found that 90% of patients with ileocolitis and 70% with ileal or colonic disease require surgery within 10 years of diagnosis.[126] Because nearly half of patients will experience recurrence,[121] patients with extensive small-bowel disease are vulnerable to disability from foreshortening of intestinal length.

Surgical resection, strictureplasty, or drainage of abscesses is indicated to treat intractable hemorrhage, perforation, persisting or recurrent obstruction, abscess, or fulminant disease unresponsive to medical treatment.[31] Several types of operations are used: intestinal resection with or without anastomosis, bypass procedure (internal or external), or strictureplasty. In general, resection of diseased intestinal segments is preferred over bypass procedures.[126] Bowel–especially small-bowel–conservation is highly desirable, and strictureplasties represent an important advance in small-bowel preservation for patients with multiple short-segment strictures.

Summary

Surgery in IBD should not be viewed as a failure of treatment or as the "option of last resort." The objective of any treatment is to improve well-being and confer a better QOL. If these aims cannot be achieved with safe and effective medical treatment, then surgery may provide the best option for restoring health and improving QOL and well-being.

Evolving and Future Treatments

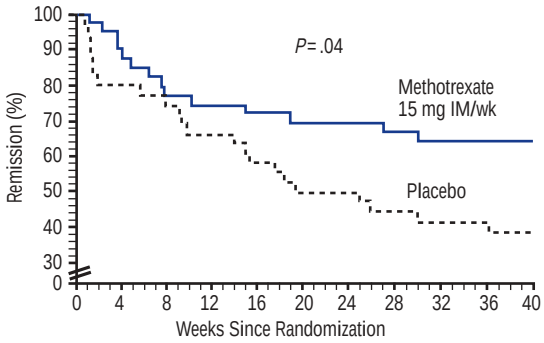
Scientific and clinical research have not only provided new insights into the underlying causes of IBD but have revealed new targets for therapy. At present, there are numerous agents in various phases of clinical testing. Most of them are biologic therapies that selectively target key molecules or processes that are implicated in IBD pathogenesis. A brief overview is provided here.

The promising new agents fall into several categories, listed in Table 5, page 12. A number of them are similar to infliximab, targeting TNF-α. A second category consists of agents that inhibit the adhesion (and thus migration) of leukocytes to areas of inflammation. A third class of molecules aim at restoring immunologic homeostasis by inhibiting Th1 cell functions. A fourth category comprises growth factors, including epidermal growth factor. A final category of miscellaneous agents includes molecules such as IFN-γ, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), growth hormone (GH), IL-11, tacrolimus, medroxyprogesterone acetate, nicotine, and probiotic therapies.

Although the vast majority of reports on these agents are in abstract form, several full reports have been published recently. One investigated CDP571, a more humanized anti-TNF-α monoclonal antibody, for the treatment of active CD in 169 patients with moderate to severe disease.[127] While an overall benefit of treatment was observed, not all endpoints were statistically

Figure 7

Efficacy of Methotrexate for Maintenance of Remission in CD



significant. The treatment appears to be safe, but further clinical testing is needed to define its efficacy better.[127] A second study assessed the activity of a humanized monoclonal antibody to α4 integrin (natalizumab) in 30 patients with active CD. At 2 weeks, 39% of natalizumab-treated patients and 8% of placebo-treated patients had attained remission. Further trials with this agent, particularly using higher doses, are needed.[128] A preliminary study has been published on the use of GH for CD. Thirty-seven adults with active CD were randomized to GH or placebo. At 4 months, GH-treated patients had significantly lower scores on the Crohn's Disease Activity Index than did placebo-treated patients, suggesting that GH treatment may confer clinical benefit.[129]

Lowry and coworkers reported their clinical experience with combined therapy consisting of tacrolimus and AZA or 6-MP for 11 patients with treatment-refractory CD perianal fistulae.[130] All 11 patients experienced clinical improvement with tacrolimus therapy. Seven (63.6%) had a complete response and 4 (36.3%) had a partial response.[130] These preliminary data suggest that combination therapy that includes tacrolimus may play a role for patients with treatment-refractory perianal CD.

Several randomized trials have assessed the effect of nicotine on active UC and on maintenance of remission. Overall, benefits of nicotine patches were relatively modest in active UC,[131,132] and transdermal nicotine alone was no better than placebo in the maintenance of remission.[133]

Probiotic therapy is based on the hypothesis that the intestinal flora may contribute directly to the pathogenesis of UC, and therapeutic colonization with nonpathogenic strains of *Escherichia coli* may improve the clinical course. One study evaluated oral bacteriotherapy as maintenance treatment for patients with chronic pouchitis. A probiotic preparation (VSL#3) was compared with placebo for 40 patients in remission.[134] Within 9 months, 15% of patients receiving VSL#3 and 100% of placebo-treated patients had relapsed.[134] The results of this study suggest that probiotic therapy may have a role in UC, although further studies are needed to confirm these results.

Finally, future research in IBD will help elucidate the various disease types and responses to treatments seen with different

Table 5

Potential Future Therapies for IBD

Category	Specific Agents in Clinical Trials
Anti-TNF-α	• CDP571 (a fully humanized monoclonal antibody to TNF-α) • Etanercept • Onercept (a soluble p55 TNF receptor) • CNI-1493 (a MAP-kinase that inhibits activation of TNF-α gene expression) • Thalidomide
Antileukocyte Adhesion Therapies	• Natalizumab (anti-α4 integrin antibody) • LDP-02 (anti-α4β7 integrin antibody) • Isis 2302 (antisense oligonucleotide that inhibits ICAM-1)
Inhibitors of T_h1 Cell Function	• Anti-IL-12 • Anti-IFN-γ • Anti-IL-2 receptor (daclizumab, basaliximab) • Anti-CD4
Growth Factors	• Epidermal growth factor • KGF-1 • KGF-2 (repifermin, a homolog of KGF-1)
Miscellaneous Agents	• IFN-β • G-CSF (filgrastim) • GM-CSF (sargramostim) • GH (somatropin) • IL-11 • Tacrolimus • 6-Thioguanine • Medroxyprogesterone acetate • Nicotine and nicotine agonists • Tacrolimus • Probiotic therapy (VSL #3, *Escherichia coli* Nissle 1917)

IBD = inflammatory bowel disease; TNF = tumor necrosis factor; MAP = mitogen-activated protein; ICAM = intracellular adhesion molecule; IL = interleukin; IFN = interferon; KGF = keratinocyte growth factor; G-CSF = granulocyte colony stimulating factor; GM-CSF = granulocyte-macrophage colony stimulating factor; GH = growth hormone.

patient populations. Genetic discoveries pave the way for further understanding as well. Differences in IBD between men and women are an important issue, but it is an area in which, unfortunately, our knowledge base is far from complete. Sex differences have historically been underresearched, primarily because, until recently, women were often not included in clinical trials. The rationale given for their exclusion was that it was for the protection of possibly pregnant women; in addition, it was believed that women's hormonal cycling might somehow skew results.[135] However, a study from the FDA reported that women have been participating in clinical trials at nearly the same rate as men in recent years, and the evaluation of sex differences in efficacy, safety, and pharmacokinetic parameters of drugs used to treat IBD is expected to be a focus of future investigations.

IBD Management–Adherence Challenges

Adherence to therapy is a critical issue in IBD, particularly because the chronic nature of these illnesses often necessitates an indefinite duration of therapy. Although adherence is necessary for patients to gain optimal benefits from their prescribed treatment regimens, there is considerable evidence that patient adherence often is poor. In one recent study, the adherence rate of patients taking maintenance therapy for quiescent UC was only 40%.[136] The following section will define patterns of nonadherence, the factors that affect adherence to IBD medication, and strategies that can be used to ensure that continued therapy and continued benefits are realized. For the physician, it is important to realize that adherence connotes a 2-way relationship rather than a physician mandate. Good communication between physician and patient is a key aspect in addressing the adherence challenges in IBD.

Patterns of Nonadherence

Nonadherence can be due to failure to fill a prescription, under- or over-consumption of medication, alteration of the dosage regimen, or incorrect administration of medication.[137] Although taking every dose of prescribed medication is ideal, the possibility that doses may be missed should be discussed with the patient. Patients should learn, for example, what to do if they miss a dose or when to double a subsequent dose.[137] Patients may sometimes inappropriately alter the dosing regimen because they find it difficult to take prescribed medications at work or school. For these patients, a more convenient regimen may increase adherence. Incorrect administration of treatment is a potential problem with topical therapy. Patients may find it embarrassing to discuss rectal administration with their physicians or pharmacists, yet the inappropriate administration of enemas may render topical therapies ineffective.[137] Finally, up to 15% of patients may never fill the prescriptions provided by their physicians, despite instructions or dialogue.[137]

IBD Concerns Differ By Sex

Knowing the concerns of patients with IBD enables physicians to provide an individualized approach to treatment. Indeed, sensitivity to these concerns may do much to maximize adherence. A recently published study examined the influence of sex on illness-related concerns.[138] Whereas many IBD concerns were shared independent of sex, women were more concerned than men regarding 4 illness-related aspects: having children, attractiveness, feelings about their bodies, and feeling alone.[138] Attention to the normal concerns of all patients with IBD, and special consideration to the concerns of women, can have a positive impact on many aspects of patient care.

Factors Affecting Adherence to IBD Medication

Illness-Related Factors

Illness-related factors such as severity, extent, and duration of disease may impact the patient's perception that therapy is needed. If the patient has a high frequency, duration, or intensity of flare-ups or has severe complications, there is a greater likelihood that the patient will take medication. Conversely, patients with few IBD flares are more likely to discontinue maintenance therapy, and less extensive disease is significantly associated with nonadherence.[136]

Treatment-Related Factors

Treatment-related factors include the convenience (number of pills and dosing regimen) and formulation (pill size and mode of delivery). The efficacy and side-effect profiles of prescribed treatments are important also. Of the 5-ASA compounds, for instance, sulfasalazine is associated with side effects (including anorexia, headache, nausea, vomiting, gastric distress, and oligospermia) due to toxicity of the sulfapyridine moiety.[49,50] The adverse effects of this agent are dose related—a characteristic that limits the ability to titrate doses for maximum effect. In the case of mesalamine, however, doses can be increased without a risk of side effects. The optimal maintenance dose for efficacy is usually the same as the inductive dose, and side effects are minimal during maintenance. Steroids, immunomodulators, and biologic therapies are associated with a range of short- and long-term side effects that must be considered before therapy is initiated. An optimal balance between safety and efficacy, with careful attention to the patient's individual needs, will promote adherence. The cost of treatment and reimbursement issues may impact the patient's ability to procure treatment. These factors have become more significant with the advent of more expensive biologic therapies.

One factor that may affect treatment adherence positively is the evidence that continued long-term use of 5-ASAs has a protective effect on the development of colorectal cancer (CRC).[139,140] This adherence-related benefit of 5-ASA treatment may motivate many patients to continue their treatment regimens.

Patient-Related Factors

Among the patient-related factors that undermine adherence is the failure of patients to discuss major concerns with their physicians. A study by Bell and colleagues probed the characteristics of patients who did not voice their concerns.[141] These patients were more likely to be younger, less educated, unmarried, and less trusting of their physicians. In addition, they were found to be less satisfied with their overall care.[141] These findings highlight the need for physicians to establish relationships with patients that promote productive, open communication.

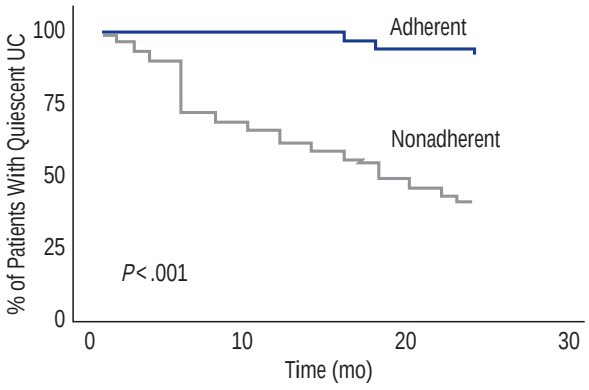
Inadequate education is a second patient-related factor that affects adherence. Based on responses to a questionnaire that explored levels of knowledge, only 30% of patients thought that they had adequate knowledge of their own disease.[142] Additional patient-related factors are 1) lack of skills or knowledge necessary to follow the treatment regimen, 2) refusal to believe that treatment will help or that benefits will outweigh side effects, and 3) circumstances (including financial need, sickness, child-care problems, transportation difficulties, or employment) interfering with treatment.[143] Several studies have identified patient characteristics that are associated with nonadherence. A chief characteristic is male sex.[136,144] Why women are more adherent to therapy is not yet clearly understood.

The Consequences of Nonadherence

A recent study established that medication adherence is associated with improved outcomes in IBD. Kane and Hanauer conducted a prospective study in a cohort of 98 patients taking a maintenance regimen of mesalamine (Asacol®) for quiescent UC.[144] Adherence was defined as consumption of 75% or more of the prescribed supply of medication. At 6 months, 12% of patients had clinical recurrence, all of whom were noncompliant with therapy.

Figure 8

Consequences of Nonadherence to IBD Maintenance Therapy



Kane SV, Hanauer SB. *Gastroenterology.* 2000;118(suppl 4):A886. Abstract 4900.

At 12 months, another 19 patients, 15 of whom were nonadherent, had experienced recurrence. Eighty-seven percent of patients with clinical recurrence within 12 months were nonadherent compared with 26% of patients remaining in remission (Figure 8).

Keys to Optimizing Adherence

There are several keys to optimizing adherence. The first is individualization of therapy, based on the patient's disease and therapeutic history, response to previous medications, track record of adhering to therapies as prescribed, and cost considerations. A second is education of the patient and family regarding the disease and the need for continued treatment. A third key is a productive patient-physician partnership that fosters open communication. Such a partnership enables the physician to provide emotional and psychological support. Support also is available through the Crohn's & Colitis Foundation of America (www.ccfa.org), whose stated mission is to "cure and prevent CD and UC through research, and to improve the QOL of children and adults affected by these digestive diseases through education and support." Following these measures to optimize adherence will help achieve the ultimate goal: the patient's commitment to the therapeutic objective.

Extraintestinal Manifestations of IBD

UC and CD are associated with numerous chronic inflammatory disorders in organ systems distant from the gut. They can appear in virtually any system in the body, including musculoskeletal; skin and mucous membranes; dermatologic; ocular; bronchopulmonary; cardiac; hematologic, renal and genitourinary; pancreatic; hepatobiliary; endocrine and metabolic; and neurologic.[145] Some herald an attack (eg, the dermatologic manifestations erythema nodosum and pyoderma gangrenosum are associated with active bowel disease). Others, such as ankylosing spondylitis, primary

sclerosing cholangitis (PSC), and uveitis, are either episodic or progressive independent of intestinal disease activity. Common EIMs are listed in Table 6.

Table 6

Extraintestinal Manifestations of IBD

- Skin
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Metastatic CD
- Musculoskeletal
  - Peripheral arthritis
  - Rheumatoid arthritis
  - Ankylosing spondylitis, sacroiliitis
- Ocular
  - Iritis, uveitis, episcleritis
- Hepatobiliary
  - Gallstones
  - Sclerosing cholangitis, cholangiocarcinoma
- Renal
  - Kidney stones
  - Amyloidosis
- Other manifestations
  - Aphthous stomatitis
  - Hypercoagulable state
  - Anemia

Pathophysiologic Links Between IBD and EIMs

The most intriguing—and as yet unanswered—questions in this area are: What are the pathogenic links between IBD and EIMs? Is colitis an "intestinal manifestation" of systemic immune dysfunction? Does response (or lack of response) to treatment provide clues to the pathogenesis of EIMs? Does aggressive management of colitis, or use of immunomodulators, change the natural history of EIMs? Does response to biologic agents offer clues to the interaction between the gut and various organ systems?

Our current understanding of EIMs is rather rudimentary. It is theorized that some of the most prominent EIMs are extraintestinal responses to events that originate in the intestine. The cells that are generated during the dysregulated inflammatory response in the gut are believed to enter the systemic circulation and home to distant sites within the body, where they stimulate a chronic inflammatory state.[145]

Epidemiology

A recent population-based study reported the prevalence of EIMs and their relationship to disease diagnosis and gender. Bernstein and colleagues assessed the presence of PSC, ankylosing spondylitis, iritis/uveitis, pyoderma gangrenosum, and erythema nodosum in 4,454 subjects with known diagnoses of IBD for at least 10 years. Arthritis was not assessed.[146] The 10-year prevalence rates based on at least 5 health-system contacts for CD and UC in relation to sex are shown in Figure 9. A total of 6.2% of patients with IBD had 1 of the 5 major EIMs studied in this report, but only 0.3% of patients had multiple EIMs. Iritis/uveitis was the most common EIM, occurring in 2.2% of women and 1.1% of men. Iritis/uveitis was particularly more common in women with UC (3.8%). PSC was most common in men with UC (3%). Ankylosing spondylitis was more common in men, particularly those with CD (2.7%). Pyoderma gangrenosum was more common in CD and equally so among males and females (1.2%). Erythema nodosum also was present in equal proportion in UC and CD but was more common in women (1.9%) than in men.[146] The differences in prevalence between UC and CD are intriguing, as are the differences related to sex. The reasons for these variations are presently unknown.

The EIMs of IBD encompass a vast, heterogeneous group of diseases that are often quite difficult to treat. Their relative rarity precludes controlled trials of medical therapies. Despite this, investigators in the field of IBD are encouraged to report the response of EIMs to tested medications to further the goal of finding effective treatment. Scientific and clinical research into these diseases should incorporate the expertise of many disciplines, including rheumatology, ophthalmology, dermatology, and gastroenterology. Finally, some experts suggest that for certain EIMs that are known to respond to such agents, biologic therapies combined with immunomodulators should be used earlier in the course of treatment.[147]

Complications of IBD: Cancer

The risk of CRC is increased for patients with UC. Increased risk is associated with duration, age, extent of disease, and a concurrent diagnosis of PSC.[148,149] Patients with CD have an increased risk of colon cancer, although there have been few population-based studies.[150] The risk of colon cancer in CD is reported to increase with early diagnosis (before age 30) and greater extent of disease.[150,151]

A recently published 14-year population-based study has provided new data and additional insights into the incidence of cancer in IBD. Bernstein and colleagues assessed cancer incidence in patients with IBD in comparison with a non-IBD population that was matched for age, gender, and geographic location.[152] They found a higher incidence rate ratio (IRR) of colon cancer for both CD (2.64; 95% CI, 1.69–4.12) and UC (2.75; 95% CI, 1.91–3.97). This higher risk was more prominent among men than women. There was a higher IRR of rectal cancer only among patients with UC (1.90; 95% CI, 1.05–3.43), and a higher IRR of small-intestine cancer only in patients with CD (17.4; 95% CI, 4.16–72.9). These data corroborated previous findings regarding a greater risk of colon cancer and rectal cancer in both UC and CD in a North American population.[148,150]

CRC Prevention

Two studies have provided evidence that long-term therapy with 5-ASAs confers protection against CRC. In one study, CRC occurred in 3% of patients on long-term sulfasalazine or mesalamine therapy and in 31% whose treatment was stopped or who were nonadherent to therapy.[139] A second study found that regular therapy with mesalamine, at least 1.2 g/day, reduced the risk of cancer by 81%.[140]

Risk of Other Cancers

There have been a number of reports suggesting that IBD is associated with an increased risk of extracolonic malignancies. Bernstein et al found a higher IRR of extraintestinal tumors only for the liver and biliary tract in CD patients (5.22; 95% CI, 0.96–28.5) and UC patients (3.96; 95% CI, 1.05–14.9).[152] There was a greater risk of developing lymphoma in males with CD. The incidence rates of breast, prostate, and respiratory carcinomas were not significantly different for patients with IBD from those in the general population.[152]

Dysplasia Surveillance

The incidence of colon cancer raises sufficient concern to make practitioners consider dysplasia surveillance a potential means of identifying precancerous lesions or cancers at an early, curable stage. Dysplasia can be a harbinger of cancer development or an indication that cancer is already present. Endoscopic surveillance with biopsies searching for dysplasia, though far from a perfect method, is the most widely available clinical tool.[153] It is endorsed as the standard of care for patients with UC, and a recent study with selected patients with CD suggests that it should be considered strongly for patients with chronic extensive Crohn's colitis.[154]

Recommendations for endoscopic dysplasia surveillance are as follows: for patients with UC, a finding of definite dysplasia, regardless of grade, can be associated with the presence of cancer and should mandate a colectomy.[155] In contrast, if the initial endoscopy findings are negative, after 8 years, surveillance should be performed every 1 to 3 years until disease duration reaches 20 years. After this point, the frequency of surveillance should be increased to once per year. Patients with UC should be made aware of the risk of CRC so that they can address changes in their usual pattern of disease and so that they can participate in decisions regarding surveillance issues.

Complications of IBD: Osteoporosis

Osteoporosis and its complications—fractures of the hip, spine, wrist, and other skeletal sites—are a significant public health problem in the United States. An estimated 1.5 million fractures due to osteoporosis occur each year.[156] Although attention has largely focused on postmenopausal women and elderly persons of both sexes, who constitute the largest at-risk groups, osteoporosis is a common clinical problem in IBD. The prevalence of osteoporosis in IBD is reported to be approximately 20% to 30%.[157]

Causes of Osteoporosis in IBD

Patients with IBD face both general risk factors for osteoporosis and ones specific to IBD (Table 7).[59] Osteoporosis may be caused by drugs that are used to treat IBD, including corticosteroids, cyclosporine, and methotrexate. Inflammatory cytokines themselves can affect bone-remodeling processes that result in increased bone resorption. Some patients may become malnourished or may malabsorb certain nutrients, specifically vitamin D and calcium. Vitamin D deficiency occurs in 30% to 60% of patients with CD.[59] Another factor is hypogonadism, which is reported to occur in 25% of female patients and 10% of male patients with IBD.[158]

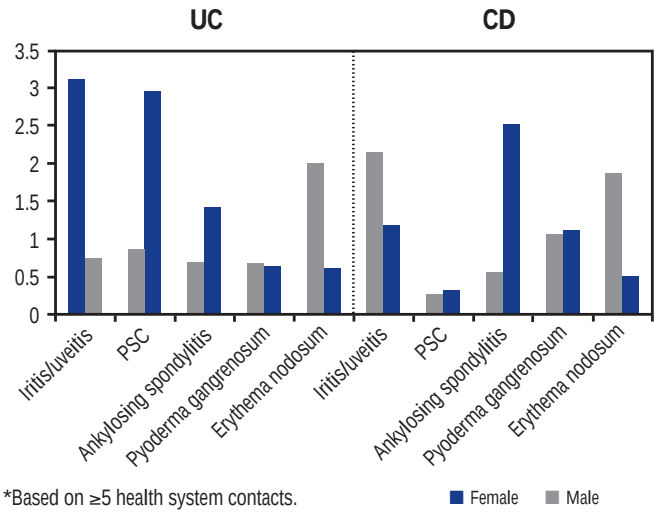
Corticosteroid-Induced Bone Loss

Glucocorticoids are the most common cause of drug-related osteoporosis, which occurs through actions that lead to increased osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation.[159] Bone loss occurs rapidly upon initiation of corticosteroid therapy and is most rapid in the first 6 months of drug use. Skeletal effects are both dose and duration dependent.[159] Daily prednisone doses of 7.5 mg or more often result in significant bone loss and increased fracture risk.[160]

The American College of Rheumatology Task Force on Osteoporosis Guidelines has published recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis.[159] These may be useful for patients with IBD, because treatment approaches for IBD patients and those with rheumatoid arthritis often are similar. Treatment guidelines are accessible from the American College of Rheumatology web site (www.rheumatology.org). Patients should begin osteoporosis prophylaxis at the initiation of corticosteroid therapy. Bone mineral density measurement should be obtained at this time to determine the patient's risk for osteoporosis independent of treatment and to provide a baseline measurement for monitoring changes in bone mass.[159] All attempts should be made to taper steroids as soon as a clinical response is achieved. This will not only potentially minimize the long-term risks of osteoporosis for patients with IBD; but is also consistent with

Figure 9

Ten-Year Prevalence Rates of EIMs in UC and CD, By Sex*



Bernstein CN, et al. *Am J Gastroenterol.* 2001;96:1116-1122.

Table 7

Causes of Osteoporosis in IBD

General risk factors

- Advancing age
- Female gender
- Premature loss of gonadal function (ovarian or testicular)
- White or Asian race
- Family history of osteoporosis
- Small bone structure with thin body habitus
- Physical inactivity
- Low calcium intake
- Cigarette smoking
- Excessive alcohol use
- Nulliparity

IBD-related risk factors

- Drugs (cyclosporine, methotrexate, corticosteroids)
- Inflammatory cytokines (IL-6, IL-1, TNF-α)
- Vitamin D deficiency
- Calcium malabsorption
- Hypogonadism

Adapted with permission from The American College of Gastroenterology, (American Journal of Gastroenterology), 1999;94:878-883.

clinical data that demonstrate that corticosteroids are ineffective for maintenance therapy.

Monitoring, Preventing, and Treating Osteoporosis in Patients With IBD

With the advances in bone mineral density measurement techniques and an improved understanding of risk factors for osteoporosis, it is now possible to identify patients at high risk for fracture. It has been estimated that, for each standard deviation decrease in femoral neck bone density, there is a 2.6-fold increase in the age-adjusted risk of hip fracture.[156] The optimal timing of bone densitometry and patient-selection criteria for screening have not yet been established in IBD. Although it seems prudent to screen all patients early, when intervention would have the greatest impact, this may not be the most cost-effective strategy. Therefore, one could consider limiting screening to certain high-risk groups. It is clear that bone health must be considered for women, children, and older patients.

Prevention of bone loss is preferable to rebuilding of bone mass. Routine measures to reduce the risk of osteoporosis should be initiated. A discussion of therapeutic options may be found in the National Osteoporosis Foundation's Osteoporosis Clinical Guidelines. Several different antiresorptive drugs are currently approved for the prevention and/or treatment of osteoporosis, including hormone replacement therapy, raloxifene, calcitonin, and 2 bisphosphonates—alendronate and risedronate. All of these drugs lower the risk of vertebral fractures, but only the bisphosphonates are known to lower the risk of hip fracture. Risedronate has been demonstrated to prevent bone loss and lower vertebral fracture risk for patients taking glucocorticoids.[161]

Summary

An active approach is needed for the prevention and treatment of osteoporosis in patients with IBD. It is important that physicians recognize that their patients—particularly those receiving corticosteroid therapy—are at increased risk for osteoporosis. Osteoporotic fracture is a devastating event that, with careful identification and treatment, can be avoided.

Patient-Care Issues

Special Considerations for Men and Women: Conception and Reproduction

IBD has its peak onset primarily during the second and third decades of life, during a woman's peak reproductive years. For women, issues related to having children may be of particular concern.[138] Overall, outcomes for women desiring pregnancy are good and are enhanced by well-controlled disease.

Fertility

The fertility of women with UC appears to be normal. In one case series, 81% of women had conceived. If women who were voluntarily childless were excluded from the analysis, 92% of all women were fertile.[162] A case-controlled study including 177 women with CD and 84 with UC also concluded that IBD was not associated with reduced fecundity.[163] Overall, fertility is unaffected in women with UC or inactive CD, but it may be decreased in women with active CD. In addition, fertility has been shown to be lower in women who undergo IPAA.[124,164] Male fertility is normal, although sulfasalazine treatment causes reversible oligospermia and reduces semen quality.[51,165]

Pregnancy

The effect of pregnancy on IBD has been evaluated in terms of disease activity. Among patients with inactive UC, about one third will relapse during the 12 months of gestation and puerperium, a rate similar to that of nonpregnant patients for the same period. Of patients with active UC at the time of conception, approximately 45% will get worse, 25% will improve, and 25% will remain the same. Of women with inactive CD, about 25% will have relapses during pregnancy and puerperium, a rate similar to that for nonpregnant CD patients. Among pregnant patients with active CD, CD will improve for one third, remain unchanged for one third, and deteriorate for one third.[166]

IBD poses no threat to the fetus. A review of 24 published studies on the effects of IBD on pregnancy is presented in Table 8. In 82 pregnancies, CD and UC had no major effect on outcome.[167] Although birth weight was marginally lower than in controls, there were no statistically significant effects on duration of pregnancy, mode of delivery, hypertension, and/or proteinuria.[168] A more recent prospective, case-controlled study of 30 pregnancies in patients with either UC or CD similarly found that disease did not influence the outcome of pregnancy.[169] Overall, pregnancy for patients with IBD is safe, particularly if disease is in remission.

Medical Therapy During Pregnancy

Maintenance of remission and treatment of relapse are continuing therapeutic goals during pregnancy. Mesalamine, the first-line treatment, is safe to use in pregnancy. Its safety was assessed in a trial with 165 women, most of whom (72%) took mesalamine throughout pregnancy. Mesalamine was not associated with more malformations (0.8%) than a control group (3.8%). There were no significant differences between groups in maternal obstetric history, rates of live births, miscarriages, pregnancy terminations, ectopic pregnancies, delivery method, or fetal distress.[170] As with nonpregnant patients, the inductive dose of mesalamine should be maintained during pregnancy to prevent relapse.

Sulfasalazine is safe in pregnancy, although frequent side effects may hamper its use.[166] It interferes with folic acid metabolism, so folic acid supplementation is required during pregnancy.[171] Because sulfasalazine causes oligospermia and poor sperm motility, men should change to another 5-ASA medication prior to attempts to conceive with their partners.

The effects of ciprofloxacin in pregnancy were reported in a study involving 103 women, of whom 87 were being treated during the first trimester. There were 63 normal births, 18 therapeutic abortions, 10 spontaneous abortions, 8 congenital abnormalities, and 4 fetal deaths in utero.[172] Although the report notes that ciprofloxacin has been used frequently in pregnancy without causing adverse events, these data suggest that it should be used with caution. Metronidazole readily crosses the placental barrier, and it is a carcinogen in mice after long-term use.[173] Nevertheless, when its safety in pregnancy was assessed by a meta-analysis of 1083 women, metronidazole did not appear to be associated with increased teratogenic risk.[173] However, because of conflicting evidence and lack of long-term data, metronidazole is contraindicated during the first trimester.[84,174]

Corticosteroids are associated with increased spontaneous abortion, cleft palate, and stillbirth in mice but have rarely shown teratogenicity in humans. When congenital abnormalities were reported, they were relatively mild, and there has been no evidence of increased frequency.[166] It has been suggested that more extensive treatment involving combinations of oral corticosteroids, topical corticosteroids, and sulfasalazine poses greater risks to the fetus.[162]

The use of immunosuppressive drugs is not contraindicated in pregnancy. Most information on the use of these agents comes from the area of transplantation. Animal studies have shown that agents such as AZA, cyclosporine, and tacrolimus are not carcinogenic. Although some agents are teratogenic (AZA, prednisone, tacrolimus) and mutagenic (AZA) in animals, such effects have not been noted in human infants.[175] The finding that higher doses produce more negative consequences in animals suggests that low doses should be used by pregnant women, especially if immunosuppressants are used in combination.[175]

AZA and 6-MP appear to be relatively safe in pregnancy. AZA was assessed in a small retrospective study involving 14 patients. No congenital abnormalities or subsequent health problems were noted.[176] The safety of 6-MP was evaluated in a case-controlled study with 155 women. Its use was not associated with increased prematurity, spontaneous abortion, congenital abnormalities, childhood infections, or neoplasia.[177] On the other hand, methotrexate is contraindicated during pregnancy. The FDA has designated it a category X drug, meaning that its use is associated with fetal abnormalities in animals or human babies, with the potential risks of the drug outweighing its benefits. Due to a lack of data, infliximab treatment should be stopped before conception until further information on its effects during pregnancy is known.

Childbirth

Preterm birth (< 37 weeks) occurs more frequently for women with IBD. Baird and coworkers reported a 2- to 3-fold increase in preterm births.[163] Among women with CD, the OR is 3.1 (95% CI, 1.8–5.4). In women with UC, the OR is 2.7 (95% CI, 1.4–5.3).[163] There is no convincing evidence that vaginal delivery is harmful, and it should be considered for all women without active perineal disease.

Breast-feeding

Some IBD medications are safe to use while breast-feeding when indicated. Mesalamine, sulfasalazine, and corticosteroids appear to be safe, as does topical mesalamine. There are few available data on the use of AZA/6-MP, metronidazole, or ciprofloxacin. Methotrexate and cyclosporine are contraindicated for nursing mothers.[174]

Special Considerations for Men and Women: Psychosocial Issues

Health-Related Concerns in IBD

Comprehensive assessment of patient health includes the psychosocial aspects of illness. Patients with IBD have identified a number of problems that impact their QOL, including frequent, loose bowel movements, abdominal pain, poor sleep patterns, avoidance of social activities if no toilets are nearby, anger at being ill, and frustration with the chronic nature of the disease.[178] Drossman and colleagues used an IBD-specific questionnaire to measure the worries and concerns of patients with IBD.[179] Four indices of disease that most concerned patients were identified as those relating to the impact of their disease; sexual intimacy; complications; and body stigma. A higher level of concern was found among women, patients with greater disease severity, and those with lower educational status. A recently published study provided further insight into the influence of sex on illness-related concerns.[138] Women were significantly more likely to report a higher severity of IBD symptoms and a higher level of overall concern about IBD than men, particularly regarding having children, attractiveness, feelings about their bodies, and feeling alone.[138]

Table 8

Effect of UC and CD on Pregnancy*

	UC	CD
Number of pregnancies	1155	388
Normal births	83.3%	83.1%
Congenital abnormalities	1.1%	1.2%
Spontaneous abortions	9.1%	10.9%
Stillbirths	1.9%	2.4%

*UC results represent 18 literature reports and CD results represent 6 reports.

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QOL

Patients with IBD have impaired health-related QOL which is related to disease extent in UC, severity of disease (in both UC and CD), and treatment efficacy. Several non–disease-related factors also are important. Unemployment, a lower level of education, an important life event in the previous 12 months, prior use of steroids, female sex, and prior use of immunosuppressive agents have been shown to predict poorer health-related QOL. These factors may be useful in identifying patients who might benefit from intensive psychosocial interventions.[180] Though most patients with IBD can function and are relatively active, many require intermittent intense support and care. The presence of a strong social support network and positive coping strategies is also important. Support for patients also is available through the Crohn's & Colitis Foundation of America. Optimal care should therefore include psychosocial supportive interventions for patients who need them.

Surgery

Surgery for IBD is often viewed as signifying "failure" by both patients and their physicians. Instead, surgery should be viewed as an important part of patient care that, in combination with medical therapy, will lead to optimal results for health and QOL. A study by Fazio and colleagues that assessed long-term functional outcome and QOL after stapled ileal-pouch surgery indicated that long-term QOL was excellent and the level of continence was satisfactory.[181] There appear to be important differences in the attitudes toward surgery of women and men with IBD. Women are more concerned with its effects on body image, sexual intimacy, and childbearing. Women often report more severe symptoms than men, perhaps because of the greater incidence of coexisting irritable bowel syndrome in women and possible worsening of symptoms with the menstrual cycle. Women may also have more problems with continence, both before and after surgery, secondary to prior obstetrical injury to the anal sphincter. Both men and women frequently experience a sense of isolation and helplessness. Preoperative teaching and contact with other patients may significantly reduce anxiety, lead to realistic expectations, and improve outcome.

Special Considerations for Children and Adolescents

The diagnosis and management of IBD in children and adolescents pose unique clinical challenges. There are many common clinical

features and therapeutic options irrespective of the patient's age. However, IBD often occurs at a particularly vulnerable period of childhood and adolescence, with potentially adverse effects on growth, QOL, and psychosocial functioning. Unique problems include growth failure and pubertal delay.

Diagnostic Dilemmas

Approximately 10% to 15% of all school-aged children consult physicians for recurrent abdominal pain. In its milder forms, the nonspecific symptoms of IBD may easily be mistaken for recurrent abdominal pain or another functional bowel disorder, thus delaying the correct diagnosis. This is particularly true for CD, in which anorexia, growth failure, arthralgias, or fever may be present in the absence of any GI symptoms. In contrast, in most cases of UC, hematochezia generally leads to rapid consultation and a diagnostic colonoscopy.

There is a clinical need for accurate, noninvasive screening tests for IBD. The high negative predictive value of the serologic assays in excluding IBD could obviate unnecessary, more invasive and costly testing. Recent data regarding pediatric patients suggest that pANCA and ASCA testing can be useful for diagnosing IBD in patients with nonspecific symptoms and normal physical exams.[182] The incorporation of noninvasive testing into a diagnostic strategy may facilitate clinical decision making when the diagnosis is initially uncertain. At this point, the relatively low sensitivity of pANCA and ASCA testing should not preclude the diagnosis in children with chronic diarrhea, bleeding, abdominal pain, weight loss, or growth retardation.

Pediatric patients with CD often manifest few GI symptoms yet are commonly found to have anorexia and growth failure. In these children, noninvasive techniques to demonstrate subclinical inflammation would be of great benefit. Active CD is associated with neovascularization, believed to occur in response to increased angiogenesis-growth factor release. Spalinger and colleagues used pulsed color Doppler abdominal sonography to estimate intestinal wall vessel density as a function of disease activity. Affected bowel loops were found to be thicker in children with CD, and vessel density was more frequently moderate or high in active than in quiescent CD.[183] This technique is simple to perform, is noninvasive, and has the potential advantage of being used to monitor the course of disease.

Nutritional Issues

Impaired nutritional status is often underestimated or overlooked in IBD, particularly in patients with CD, of whom one third may display growth failure.[184] The available data support the use of enteral nutritional treatment to induce remission in patients with CD.[184] The major advantages of such an approach are the virtual absence of side effects, avoidance of steroid therapies that stunt growth, and nutritional repletion.[184] Elemental diets have been used successfully by steroid-dependent and even steroid-resistant patients. Cyclical nutritional therapy has been shown to increase growth velocity, improve disease activity, and reduce corticosteroid requirements of children with CD.[185,186] This approach is not appropriate for all patients with CD. The response is generally disappointing when patients have extensive or distal colonic involvement or when the CD is associated with severe anorectal disease.

Medical Management

Medical therapy for IBD is similar for children, adolescents, and adults. The most common medications used for children are 5-ASAs. A pediatric study examined the occurrence and tolerance of side effects during treatment with mesalamine and sulfasalazine. The results demonstrated that whereas the majority of patients were maintained in remission with either drug, patients reported a preference for mesalamine based on ease and frequency of administration.[187] It should be noted that mesalamine treatment is safe and well tolerated by children, despite dosages that are relatively higher on a g/kg/day basis than those taken by adults. A second study compared the safety and efficacy of olsalazine and sulfasalazine. Side effects were frequent in both groups. After 3 months, 39% of patients taking olsalazine were asymptomatic or clinically improved compared with 79% taking sulfasalazine. Ten patients on olsalazine and 1 on sulfasalazine required prednisone because of lack of response or worsening colitis.[188]

Some IBD medications have significantly different side effects in children. Prednisone causes a significant slowing of linear growth. For most patients with IBD, the negative effects of prednisone on height are added to the negative effects of malnutrition. Long-term administration of prednisone can result in significant delays of height gain.

AZA and 6-MP are effective immunosuppressive drugs for the long-term management of IBD. A recent randomized, placebo-controlled trial with 55 children with active CD showed that 6-MP significantly decreased the need for prednisone and improved maintenance of remission.[117] This study supports the use of AZA or 6-MP in pediatric patients with moderate to severe CD. Despite the therapeutic advantages of AZA and 6-MP, concerns regarding drug-related toxicity and delayed onset of action have restricted their use in IBD.[117]

Psychosocial Issues

IBD presents a major, lifelong health threat to children, challenging the psychological resources of both patients and families. IBD frequently interferes with physical activities, limits social interactions, disrupts education, impairs growth, and delays puberty. Children with IBD have been reported to have significantly impaired QOL.[189] These children need sympathetic management, and efforts should be concentrated on improving their daily psychosocial functioning so that their lives are as normal as possible.[190] This can best be achieved through medical control of disease activity, attainment of normal growth and development through nutritional interventions, and provision of psychosocial support when needed.

Special Considerations for Elderly Patients

Although most cases of IBD develop during the second and third decades of life, the onset of IBD may not occur until after the age of 60.[191] There is a clear bimodal distribution in the pattern of onset, with a second peak occurring in the fifth and sixth decades of life (Figure 1, page 1).[3] The clinical manifestations and course in the elderly are similar to those in younger patients, although in UC there is a trend toward more distal disease, and in CD, colonic involvement is more common than small-bowel disease.[192,193] In addition, though mortality rates are generally similar to those of age-matched controls, a subset of patients with UC can have a severe initial attack that may be associated with a high fatality rate.[191] Features of IBD in the elderly are presented in Table 9.

Medical options are similar to those for younger patients, although the care of elderly patients is made more challenging by the high frequency of concomitant medical problems. This highlights

the need for therapies, such as mesalamine, that are safe. Glucocorticoid therapy should be avoided because of the increased risk of osteoporosis and other steroid-related complications.[191] The indications for surgery and the choice of operations for elderly patients are similar to those for younger patients. Poor sphincter tone resulting in higher rates of fecal incontinence make IPAA a less attractive option for elderly patients with UC.[191]

Conclusion

Comprehensive care for patients with IBD represents a complex clinical challenge that requires the skilled integration of both the art and science of medicine. It is obvious that optimal strategies for patients across the lifespan require that physicians take many factors into account, including those that may be special priorities for men, women, or children. Although significant progress has been made in determining the best approaches, there is a clear need for more research in many areas. Therefore, though this review represents the current state of the art in IBD, it is anticipated that as our knowledge of this disease area grows, our approaches to management will evolve also.

Table 9

Features of IBD in the Elderly

UC	CD
• Slight male predominance	• Slight female predominance
• Severe initial attacks	• Delays in diagnosis
• High mortality rates with severe attacks	• More frequent colonic and less frequent ileal involvement
• More frequent distal disease	• More frequent distal colonic involvement, with good response to medical therapy
• Possibly lower rates of relapse and extension	• Low recurrence rates
• Low risk of colorectal cancer	• Low mortality rates, particularly with distal colonic involvement
• Good long-term prognosis	

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UNAPPROVED/INVESTIGATIONAL USE

Generic Name	Trade Name	Approved Use (if any)	Unapproved/ Investigational Use
Alendronate	Fosamax®	Treatment and prevention of osteoporosis in post-menopausal women, prevention of glucorticoid-induced osteoporosis in women and men, and Paget's disease	N/A
Azathioprine (derivative of 6-mercaptopurine)	Imuran®	Rheumatoid arthritis and renal transplantation	Crohn's disease and ulcerative colitis
Budesonide	Pulmicort Turbuhaler®, Rhinocort® Entocort™	Asthma and allergic rhinitis Crohn's disease	N/A
CDP-571 (anti-TNF-α monoclonal antibody)	N/A	N/A	Crohn's disease and ulcerative colitis
Ciprofloxacin	Cipro®	Various aerobic bacterial infections	Crohn's disease
Cyclosporine	Sandimmune®, Neoral®	Allogeneic transplantation, rheumatoid arthritis, and psoriasis	Crohn's disease and ulcerative colitis
5-Aminosalicylate mesalamine olsalazine sodium balsalazide disodium	Asacol®, Pentasa,® Rowasa,® Canasa® Dipentum® Colazal™	Ulcerative colitis	Crohn's disease
Glucocorticoids (hydrocortisone, prednisone, and prednisolone)	Various	Ulcerative colitis and numerous other indications	N/A
Growth Hormone	Various	Growth failure and endogenous growth hormone deficiency	Crohn's disease
Infliximab (anti-TNF-α monoclonal antibody)	Remicade®	Moderately to severely active Crohn's disease refractory to conventional treatments, fistulizing Crohn's disease, and rheumatoid arthritis	Ulcerative colitis and other inflammatory disorders
Methotrexate	Various	Neoplastic disease, psoriasis, and rheumatoid arthritis	Crohn's disease
6-Mercaptopurine	Purinethol®	Leukemia	Crohn's disease and ulcerative colitis
Metronidazole	Flagyl®	Trichomoniasis *(Trichomonas vaginalis),* amebiasis, and anaerobic bacterial infections	Crohn's disease
Natalizumab (α–4 integrin inhibitor)	Antegren®	N/A	Crohn's disease
Risedronate	Actonel®	Treatment prevention of osteoporosis in post-menopausal women, treatment prevention of glucorticoid-induced osteoporosis in women and men, and Paget's disease	N/A
Sulfasalazine	Azulfidine®	Ulcerative colitis	Crohn's disease
Tacrolimus	Prograf® Protopic®	Allogeneic transplantation Atopic dermatitis	Primary sclerosing cholangitis, Crohn's disease, and ulcerative colitis

TNF=tumor necrosis factor; N/A=not available

All correspondence concerning the contents of this publication should be directed to:
The Editor, *CLINICIAN*®
SynerMed Communications
Dept 102
405 Trimmer Road
PO Box 458
Califon, New Jersey 07830

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THE STATE OF THE ART IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE
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1. Which of the following factors are believed to be associated with an increased risk of inflammatory bowel disease (IBD)?
   a. Mutations in one or more genes
   b. Breastfeeding
   c. Appendectomy before the age of 20
   d. Use of corticosteroids

2. Which of the following statements best describes the current theory regarding the etiology of IBD?
   a. IBD is an autoimmune disease directed against self-antigens that mimic those that are found on pathogenic enteric bacteria.
   b. Mutations in the NOD2 gene are the cause of Crohn's disease.
   c. In a genetically susceptible individual, environmental factors trigger a dysregulated immune response characterized by aberrant T-cell activation and production of inflammatory cytokines.
   d. In a genetically susceptible individual, environmental factors trigger a dysregulated immune response and the production of autoantibodies that ultimately result in clinical signs and symptoms of disease.

3. Which of the following has been shown to decrease the risk of colon cancer in patients with IBD?
   a. Appendectomy before the age of 20
   b. The use of tobacco in patients with ulcerative colitis
   c. Induction therapy with corticosteroids
   d. Long-term adherence to mesalamine therapy

4. Which of the following statements is not true for both ulcerative colitis and Crohn's disease?
   a. Infliximab is used to induce remission.
   b. The peak onset is bimodal, with most cases developing during the second and third decades of life and a second peak in the fifth decade.
   c. Aminosalicylates are first-line treatment for induction and maintenance of remission.
   d. The risk of colon cancer is increased.

5. Choose the statement that does not describe the efficacy and safety of oral mesalamine.
   a. While there is no dose-response for efficacy, more frequent dosing is associated with increased efficacy.
   b. Increasing the dose of mesalamine is associated with an increased rate of side effects.
   c. There is a dose response for efficacy but not for side effects.
   d. The induction dose should equal the maintenance dose.

6. What is the role of corticosteroid therapy in the maintenance of remission in ulcerative colitis and Crohn's disease?
   a. Corticosteroids should not be used for maintenance therapy.
   b. Corticosteroids are recommended for maintenance of remission for patients with moderate to severe disease who do not respond to first-line therapy.
   c. While corticosteroids are effective for maintenance of remission, they should be tapered in order to avoid long-term side effects such as osteoporosis.
   d. While older agents are ineffective, budesonide, a newly available corticosteroid, has been shown to be effective in maintaining remission in IBD.

7. Which of the following factors negatively affects adherence to IBD therapy?
   a. Less extensive disease
   b. Inadequate patient education
   c. Male gender
   d. b and c
   e. All of the above

8. Which of the following is not an IBD-related risk for osteoporosis?
   a. Long-term aminosalicylate therapy
   b. Corticosteroid use
   c. Presence of inflammatory cytokine
   d. Vitamin D deficiency

9. Which of the following has been identified as an illness-related concern that is unique to women?
   a. Being a burden
   b. Having children
   c. Inability to work
   d. Having to avoid social activities if a toilet is not nearby

10. Which of the following is true regarding the presentation and clinical course of new-onset IBD in elderly patients?
    a. Nonspecific symptoms of IBD in elderly patients may easily be mistaken for recurrent abdominal pain or another functional bowel disorder.
    b. Clinical manifestations and course are similar to those seen in the younger population, although in CD there is a trend toward more distal disease and in UC colonic involvement is more common than small-bowel disease.
    c. Clinical manifestations and course are similar to those seen in the younger population, although in UC there is a trend toward more distal disease and in CD colonic involvement is more common than small-bowel disease.
    d. New-onset IBD is rare in the elderly.

Please record your Posttest answers on the other side.

THE STATE OF THE ART IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE
CLINICIAN® Monograph

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