REVIEW ARTICLE

MEDICAL PROGRESS

Ulcerative Colitis

Silvio Danese, M.D., and Claudio Fiocchi, M.D.

Ulcerative colitis was first described in the mid-1800s,[1] whereas Crohn's disease was first reported later, in 1932, as "regional ileitis."[2] Because Crohn's disease can involve the colon and shares clinical manifestations with ulcerative colitis, these entities have often been conflated and diagnosed as inflammatory bowel disease, although they are clearly distinct pathophysiological entities. Ulcerative colitis is the most common form of inflammatory bowel disease worldwide. In contrast to Crohn's disease, ulcerative colitis is a disease of the mucosa that is less prone to complications and can be cured by means of colectomy, and in many patients, its course is mild.[3] The literature on the pathogenesis and treatment of so-called inflammatory bowel disease has tended to focus on Crohn's disease,[4-7] and few articles expressly discuss ulcerative colitis.[8,9] Here we review our current understanding of the pathophysiology, diagnosis, and treatment of ulcerative colitis to date; we also compare ulcerative colitis with Crohn's disease and refer to both as inflammatory bowel disease according to the context.

From the Department of Gastroenterology, Istituto Clinico Humanitas, Milan (S.D.); and the Department of Gastroenterology and Hepatology, Digestive Disease Institute, and Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland (C.F.). Address reprint requests to Dr. Fiocchi at the Cleveland Clinic Foundation, Lerner Research Institute, Department of Pathobiology/NC22, 9500 Euclid Ave., Cleveland, OH 44195.

N Engl J Med 2011;365:1713-25.
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PATHOGENESIS

EPIDEMIOLOGIC FEATURES

Ulcerative colitis and Crohn's disease are disorders of modern society, and their frequency in developed countries has been increasing since the mid-20th century. When inflammatory bowel disease is identified in a new population, ulcerative colitis invariably precedes Crohn's disease and has a higher incidence. The incidence of ulcerative colitis is 1.2 to 20.3 cases per 100,000 persons per year, and its prevalence is 7.6 to 246.0 cases per 100,000 per year, as compared with an incidence of 0.03 to 15.6 cases and a prevalence of 3.6 to 214.0 cases per 100,000 per year for Crohn's disease.[10] Among children, however, ulcerative colitis is less prevalent than Crohn's disease.[11] The highest incidence and prevalence of inflammatory bowel disease are seen in the populations of Northern Europe and North America and the lowest in continental Asia, where ulcerative colitis is by far the most common form of inflammatory bowel disease.[12] A westernized environment and lifestyle is linked to the appearance of inflammatory bowel disease, which is associated with smoking, diets high in fat and sugar, medication use, stress, and high socioeconomic status.[13] Inflammatory bowel disease has also been associated with appendectomy.[13] Of these factors, only cigarette smoking and appendectomy are reproducibly linked to ulcerative colitis. Smoking is associated with milder disease, fewer hospitalizations, and a reduced need for medications.[14] Removal of an inflamed appendix in early life is associated with a decreased incidence of ulcerative colitis,[15] whereas the opposite is true for Crohn's disease.

GENETIC FEATURES

The discovery that *NOD2* variants are associated with susceptibility to Crohn's disease opened a new era in the study of the genetic basis of inflammatory bowel disease.[16,17]

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In studies of twins, there is stronger concordance with Crohn's disease than with ulcerative colitis, and the identification of a large number of susceptibility loci for Crohn's disease in early genome-wide association studies suggested that genetic influences play a greater role in Crohn's disease than in ulcerative colitis.[18] A meta-analysis of six such studies recently confirmed the presence of 47 loci associated with ulcerative colitis, of which 19 are specific for ulcerative colitis and 28 are shared with Crohn's disease.[19] Several pathways potentially associated with ulcerative colitis were identified in the meta-analysis and in individual studies based on validated loci or chromosomal regions.[20] Risk loci for *ECM1*, *HNF4A*, *CDH1*, and *LAMB1* implicate dysfunction of the epithelial barrier; an association with *DAP* suggests a link to apoptosis and autophagy; and associations with *PRDM1*, *IRF5*, and *NKX2-3* suggest defects in transcriptional regulation. In addition, multiple genes in the interleukin-23 signaling pathway overlap in ulcerative colitis and Crohn's disease (e.g., *IL23R*, *JAK2*, *STAT3*, *IL12B*, and *PTPN2*). Several risk loci linked to other immune system–mediated diseases are associated with ulcerative colitis, particularly *HLA-DR* and genes involved in helper T-cell types 1 and 17 (Th1 and Th17) differentiation, such as *IL10*, *IL7R*, *IL23R*, and *IFN-γ*. Altogether, genetic studies indicate that both specific and nonspecific gene variants are associated with ulcerative colitis, and the two forms of inflammatory bowel disease share disease pathways. Ulcerative colitis appears to be as genetically heterogeneous as Crohn's disease, but given the large number of implicated genes and the small additive effect of each, genetic screening is not currently indicated to assess the risk of ulcerative colitis.

MICROBIOLOGIC FEATURES

Health depends on a beneficial host–microbe interaction. This is certainly true for intestinal health, particularly in the colon, which harbors a greater and more diverse number of microorganisms than any other organ.[21] The gut immune system is generally tolerant of this microbial load, and a breakdown in tolerance is postulated to be central to the pathogenesis of inflammatory bowel disease.[22] Although loss of tolerance to the gut microbiota is demonstrable in animal models of inflammatory bowel disease, there is only limited evidence for this finding in patients with Crohn's disease and none in those with ulcerative colitis.

It has also been postulated that alterations in the composition of the gut microbiota, defects in mucosal immunity, or the two factors combined could lead to ulcerative colitis; however, supportive evidence is sparse. A key issue is the characterization of the gut microbiota in the normal intestine and in the intestine in patients with inflammatory bowel disease. This issue awaits answers from the Human Microbiome Project, which aims to define the composition of the intestinal microbiota in conditions of health and disease.[23] There is a consensus that the density of microbiota is greater in patients with ulcerative colitis or Crohn's disease than in healthy control subjects, but whether there are reproducible, disease-specific alterations is unclear.[24] The fact that antibiotic therapy has no clinical effect on ulcerative colitis argues against an important role of bacteria in this disease, whereas antibiotics do provide some benefit in luminal Crohn's disease.[25] Although serum antibacterial antibodies are present in patients with ulcerative colitis, they are much more common and are found in higher titers in patients with Crohn's disease. Furthermore, the range of antibodies against bacterial antigens (anti-I2, anti-OmpC, and anti-CBir1 antibodies) and fungal antigens (anti–*Saccharomyces cerevisiae* antibodies [ASCA]) is broader in Crohn's disease, whereas the only ulcerative colitis–associated antibody is perinuclear antineutrophil cytoplasmic antibody (pANCA), which recognizes nuclear antigens that may cross-react with bacterial antigens.[26]

MUCOSAL IMMUNE RESPONSE

Intestinal homeostasis requires a controlled innate immune response to the microbiota, which is recognized by toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)–like receptors on epithelial and immune cells.[27] This recognition process contributes to tolerance, but when the process is dysregulated, inflammation ensues. At present, there is no clear evidence of specific, innate immune defects in ulcerative colitis; an increased expression of TLR2 and TLR4 by colonocytes[28] is probably secondary to inflammation. In contrast, in Crohn's disease, abnormalities of innate immunity are linked to variants of the NOD2, ATG16L1, and IRGM genes, the products of which normally mediate microbial recognition.[16,17,29,30] The production of proinflammatory cytokines, such as interleukin-1β, interleukin-6, tumor necrosis factor α (TNF-α), and

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tumor necrosis factor–like ligand 1 (TL1A), is universally increased in patients with inflammatory bowel disease but does not allow one to discriminate between ulcerative colitis and Crohn's disease.

Abnormalities in humoral and cellular adaptive immunity occur in ulcerative colitis. Elevated IgM, IgA, and IgG levels are common in inflammatory bowel disease, but there is a disproportionate increase in IgG1 antibodies in ulcerative colitis.[31] Abnormalities of adaptive immunity that differentiate ulcerative colitis from Crohn's disease are defined by mucosal CD4+ T cells, which were initially divided into two lineages: Th1 and type 2 helper T cells (Th2). Crohn's disease is a Th1-like condition, on the basis of evidence of increased production of interferon-γ.[32] In contrast, ulcerative colitis represents an atypical Th2 response, as indicated by the presence of nonclassical natural killer T cells in the colon that secrete abundant interleukin-13, which mediates epithelial-cell cytotoxicity, apoptosis, and epithelial-barrier dysfunction.[33,34] Interleukin-5–producing Th2-polarized T cells are also present in ulcerative colitis. The balance between Th1 and Th2 has been used to differentiate between ulcerative colitis and Crohn's disease. However, additional helper-cell lineages have recently been delineated, including Th17 cells that produce the proinflammatory cytokine interleukin-17, the levels of which are increased in the mucosa of patients with inflammatory bowel disease.[35] However, defects in T-cell regulatory function have not been reported in ulcerative colitis.[36]

EPITHELIAL CELLS AND AUTOIMMUNITY

Because inflammation in ulcerative colitis typically does not extend into the small intestine and occurs in proximity to the epithelium, colonocytes are implicated in the pathogenesis of this disease. It has been proposed that the epithelium is diffusely abnormal, irrespective of inflammation.[37] Other reported abnormalities in ulcerative colitis include an epithelial-barrier defect and impaired expression of peroxisome proliferator–activated receptor γ (PPAR-γ), a nuclear receptor that regulates inflammatory genes.[38] In both ulcerative colitis and Crohn's disease, epithelial cells have a decreased ability to activate suppressor CD8+ T cells, but this abnormality is probably secondary to other immune events.[39] Variants of the XPB1 gene, the product of which is a component of the stress response of the endoplasmic reticulum in epithelial cells, have been linked to inflammatory bowel disease, reinforcing the concept that colonocytes are involved in its pathogenesis.[40]

Autoimmunity may play a role in ulcerative colitis. In addition to pANCA, this disease is characterized by circulating IgG1 antibodies against a colonic epithelial antigen that is shared with the skin, eye, joints, and biliary epithelium[41]; since these are the sites of extraintestinal manifestations in ulcerative colitis, it is possible that cross-reacting antibodies against the colon cause organ-specific damage. Tropomyosin 5, a structural protein, is the putative target autoantigen of the IgG1 antibodies,[42] but evidence of classical antibody-mediated autoimmunity in ulcerative colitis is still lacking. Figure 1 summarizes our current understanding of the pathogenesis of ulcerative colitis.

CLINICAL MANIFESTATIONS

SYMPTOMS, CLINICAL COURSE, AND ASSESSMENT OF DISEASE ACTIVITY

Bloody diarrhea with or without mucus is the hallmark of ulcerative colitis. The onset is typically gradual, often followed by periods of spontaneous remission and subsequent relapses. Active disease is manifested as mucosal inflammation commencing in the rectum (proctitis) and in some cases spreading to the rest of the colon (Fig. 1A in the Supplementary Appendix, available with the full text of this article at NEJM.org). Although proctitis is frequently associated with fecal urgency and the passage of fresh blood, constipation may paradoxically occur. Proctosigmoiditis, left-sided colitis, extensive colitis, or pancolitis (Fig. 1B in the Supplementary Appendix) may lead to diarrhea, frequent evacuations of blood and mucus, urgency or tenesmus, abdominal pain, fever, malaise, and weight loss, depending on the extent and severity of the disease.[43] A small area of inflammation surrounding the appendiceal orifice (cecal patch) can be identified in patients with left-sided ulcerative colitis and in those with proctitis or proctosigmoiditis[44] (Fig. 1C in the Supplementary Appendix), but this finding is not specific. The prognosis for patients with ulcerative colitis is generally good during the first decade after diagnosis, with a low rate of colectomy; over time, remission occurs in most patients.[3] Assessment of the clinical activity of ulcerative colitis

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helps the clinician choose diagnostic tests and make therapeutic decisions. Various indexes of disease activity have been developed on the basis of clinical, laboratory, and endoscopic findings, but they are used primarily in clinical trials.[45]

COMPLICATIONS

Acute complications, such as severe bleeding and toxic megacolon (Fig. 1D in the Supplementary Appendix), may occur in patients with extensive or severe inflammation; other problems, such as epithelial dysplasia or cancer, may emerge during the chronic phase (Fig. 1E in the Supplementary Appendix). On the basis of data from referral centers, the cumulative risk of colorectal cancer among patients with chronic ulcerative colitis may reach 20 to 30% at 30 years,[46] but the incidence rate is much lower in population-based series (approximately 2%).[47] Risk factors for cancer include a long duration of disease, regardless of clinical activity; extensive involvement; a young age at onset; severe inflammation; the presence of primary sclerosing cholangitis; and a family history of colorectal cancer. Although surveillance colonoscopy is recommended for patients at risk, there is no clear evidence that such surveillance increases survival.[48] Extraintestinal manifestations involving various organs and systems (e.g., joints, skin, liver, eye, mouth, and coagulation) that either precede the onset of symptoms or appear and evolve in parallel with intestinal manifestations occur in 10 to 30% of patients with ulcerative colitis (Table 1).

Figure 1 (facing page). Current Concepts Concerning the Pathogenesis of Ulcerative Colitis.

Glycolipids from epithelial cells, bacteria, or both induce the up-regulation of interleukin-13 receptor $\alpha 2$ (IL-13 $\alpha 2$) on mucosal natural killer T cells; autocrine interleukin-13 (IL-13) activates these cells, which expand in number and create a positive feedback loop that enhances interleukin-13–mediated natural killer T-cell cytotoxicity, causing epithelial-barrier dysfunction. This leads to enhanced absorption of bacterial products and the generation of antibacterial antibodies; damage to epithelial cells induces the production of anti-tropomyosin antibodies by B cells, while nuclear proteins from neutrophils induce the production of perinuclear antineutrophilic cytoplasmic antibodies (pANCA). In addition to type 1 and type 17 helper T cells (Th1 and Th17), an increased number of type 2 helper T cells (Th2) produce interleukin-13, which induces epithelial-barrier dysfunction, resulting in increased permeability, and interleukin-5 (IL-5), which may contribute to eosinophil recruitment and activation. Increased absorption of bacterial products stimulates dendritic cells and macrophages, resulting in the production of proinflammatory cytokines and chemokines. Interleukin-1β–activated epithelial cells secrete epithelial neutrophil-activating peptide 78 (ENA-78) and interleukin-8, which recruit neutrophils, as well as monocyte chemoattractant protein 1 (MCP-1), which attracts and activates macrophages, and RANTES (regulated upon activation, normal T cell expressed and secreted), which attracts and recruits effector helper T cells. Genetic variants associated with ulcerative colitis, reduced expression of peroxisome proliferator–activated receptor γ (PPAR-γ) by colonocytes, mucus abnormalities, and abnormalities of regulatory T cells (Treg) may also contribute to selective autoimmune and immune-mediated events in the pathogenesis of ulcerative colitis. IL-1 denotes interleukin-1, IL-6 interleukin-6, TL1A tumor necrosis factor–like ligand 1, and TNF-α tumor necrosis factor α.

DIAGNOSIS

An accurate diagnosis of ulcerative colitis involves defining the extent and severity of inflammation, and this information provides the basis for selecting the most appropriate treatment and for predicting the patient's prognosis. Both endoscopy and biopsy are required to determine specific histologic characteristics; radiologic and ultrasonographic examinations are not critical but may be useful.[43] All these investigations aid in differentiating ulcerative colitis from other conditions that have similar presentations (Table 2).

ENDOSCOPIC STUDIES

Colonoscopy shows a uniformly inflamed mucosa that starts at the anorectal verge and extends proximally, with an abrupt or a gradual transition from affected to normal mucosa. In mild ulcerative colitis, the mucosa has a granular, erythematous appearance, with friability and loss of the vascular pattern. In moderate disease, erosions or microulcerations are evident, whereas in severe ulcerative colitis, shallow ulcerations with spontaneous bleeding are generally seen (Fig. 2A, 2B, and 2C in the Supplementary Appendix). In pancolitis, inflammation stops at the ileocecal valve, with occasional limited involvement of the distal ileum, a condition known as backwash ileitis.[49] Colonoscopy helps to differentiate ulcerative colitis from Crohn's disease, which is typically characterized by rectal sparing, aphthous ulcers, skip lesions

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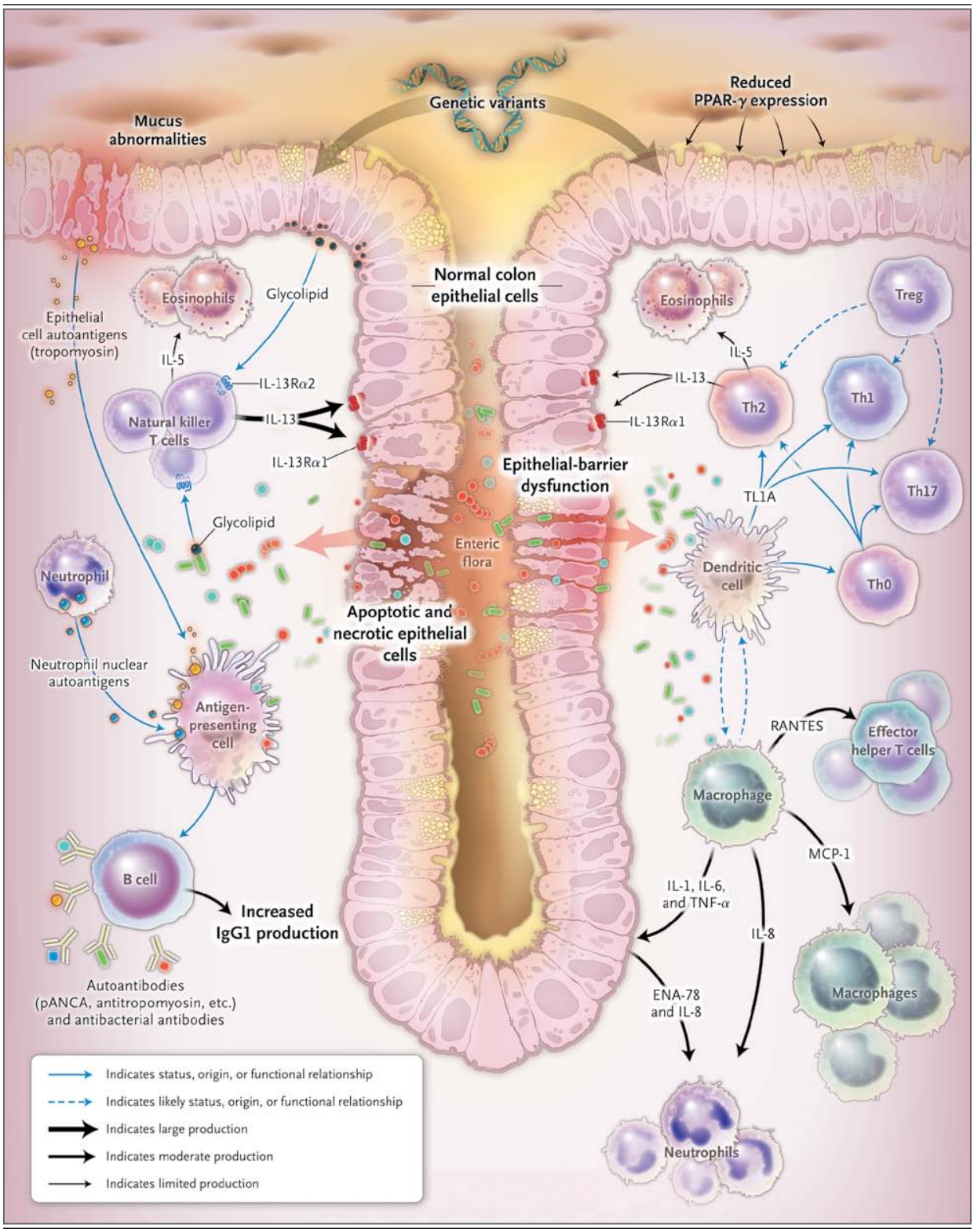

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Table 1. Complications in Ulcerative Colitis.

Complication	Comments
Intestinal involvement	
Bleeding	Common; becomes severe in approximately 10% of patients; frequent cause of iron-deficiency anemia
Toxic or fulminant colitis	Usually develops in extensive colitis with severe inflammation; may cause paralytic ileus with abdominal distention; perforation is possible
Toxic megacolon	Severe colonic distention (6 cm or more) accompanied by fever, pain, tenderness, and intense leukocytosis; perforation may occur, with high risk of death; can be caused by endoscopy in patients with severe or fulminant colitis
Stricture	Uncommon; when present, investigation to rule out cancer must be aggressive
Dysplasia or colorectal cancer	A concern in any patient with disease of more than 8 years' duration, particularly in those with extensive colitis and pancolitis; may be multifocal and arise in flat lesions
Extraintestinal involvement	
Musculoskeletal system complications	Peripheral arthritis: most commonly migratory, nondestructive arthritis of large joints, which usually parallels disease activity; axial arthritis: ankylosing spondylitis and sacroiliitis (often HLA-B27–positive), which is usually independent of disease activity; osteoporosis, osteopenia, osteonecrosis, fractures
Skin complications	Erythema nodosum, pyoderma gangrenosum, oral ulcers
Hepatobiliary system complications	Primary sclerosing cholangitis (risk of cholangiocarcinoma), fatty infiltration, autoimmune liver disease
Ocular conditions	Most common in the anterior chamber: episcleritis, scleritis, uveitis, iritis, conjunctivitis
Hematopoietic system complications	Anemia of chronic diseases, iron-deficiency anemia, anemia of mixed origin
Coagulation system complications	Clotting abnormalities, abnormal fibrinolysis, thrombocytosis, endothelial abnormalities; thromboembolic events, particularly in peripheral veins

(areas of inflammation alternating with normal mucosa), a cobblestone pattern, and longitudinal, irregular ulcers.

In patients with cycles of inflammation and healing and in those with chronic, unremitting inflammation, colonoscopy may reveal pseudopolyps or mucosal bridging (Fig. 2D and 2E in the Supplementary Appendix). If a stricture is detected, multiple biopsies are mandatory to rule out malignant disease; biopsies are also required for surveillance of dysplasia in patients who have the disease for longer than 8 years. Although there is no clear evidence that surveillance prolongs survival,[50] biopsy specimens should be taken from all colonic segments, regardless of whether they are inflamed, with a particular focus on irregular mucosa, polypoid lesions, and any raised, dysplasia-associated lesion or mass[51] (Fig. 2F in the Supplementary Appendix). Newer endoscopic techniques that are gaining acceptance, such as chromoendoscopy, narrow-band imaging, and autofluorescence imaging, may better delineate suspicious mucosal patterns and improve the detection of dysplasia (Fig. 2G in the Supplementary Appendix).[45,52,53]

HISTOLOGIC EVALUATION

In ulcerative colitis, inflammation is characteristically restricted to the mucosal layer, with infiltrates varying in density and composition during active disease or stages of remission (Fig. 3A and 3B in the Supplementary Appendix). Infiltrates consist primarily of lymphocytes, plasma cells, and granulocytes; the last are being particularly prominent during acute flare-ups and accumulate in crypt abscesses[54] (Fig. 3C in the Supplementary Appendix). Other typical features include goblet-cell depletion, distorted crypt architecture, diminished crypt density, and ulcerations. However, epithelioid granulomas, which are typical of Crohn's disease, are not present. Looking for epithelial dysplasia is critical, given the risk of can-

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Table 2. Most Common Differential Diagnosis in Ulcerative Colitis.

Diagnosis	Diagnostic Clues
Infectious colitis	History of travel, food poisoning, infectious outbreak, or immunosuppression; acute diarrhea, aphthoid ulcers, erosions, bleeding; positive serologic test
Parasitic infestation	History of foreign travel, visit to endemic areas; recurrent diarrhea after travel
Crohn's colitis	Skip lesions, transmural inflammation, patchy infiltrates, mucosal cobblestoning, presence of granulomas, fistulas, perianal disease
Indeterminate colitis	Compatible with inflammatory bowel disease, but routine diagnostic examination fails to meet criteria for ulcerative colitis or Crohn's disease
Diverticulitis	History of chronic left-lower-quadrant pain, known diverticulosis, detection of diverticula; localized inflammation
Microscopic colitis	
Lymphocytic colitis	Watery diarrhea, inflammation with increased number of intraepithelial lymphocytes
Collagenous colitis	Similar to lymphocytic colitis but with presence of subepithelial collagen layer
Acute self-limited colitis	Temporally limited; prominent neutrophilic infiltration, minimal architectural distortion
Eosinophilic colitis	History of allergies; heavy eosinophilic infiltrates in the mucosa
Radiation colitis	History of abdominal or pelvic irradiation; eosinophilic infiltrates, epithelial atypia, fibrosis, capillary telangiectasia
Diversion colitis	History of surgically excluded bowel loop; prominent lymphoid hyperplasia
Medications (e.g., nonsteroidal anti-inflammatory drugs, chemotherapy)	History of medication use; nonspecific mucosal inflammation or mucosal erosions resembling ischemic changes
Pseudomembranous colitis	History of antibiotic use or recent hospitalization; scattered, patchy, mushroomlike exudates in the mucosa; stools positive for *Clostridium difficile* toxins
Ischemic colitis	Older age, history of ischemic episodes; mucosal fibrosis, crypt atrophy
Graft-versus-host disease	History of allogeneic bone marrow or organ transplantation, crypt-cell apoptosis
Solitary rectal ulcer	Chronic inflammation with architectural distortion, fibrosis, and muscle-cell hyperplasia
Enema-induced colitis	History of bowel cleansing; mild neutrophilic infiltration of the epithelial layer

cer in patients with long-standing ulcerative colitis; however, dysplasia can occur at any stage without indicating malignant transformation (Fig. 3D in the Supplementary Appendix). There are no exact criteria for the diagnosis of ulcerative colitis, but in most cases, the presence of two or three of the aforementioned histologic features will suffice.[55] The severity of inflammation on histologic examination and the severity of disease on endoscopic examination may not coincide; for instance, histologic findings may indicate severe disease even in a patient with endoscopically quiescent disease.

LABORATORY TESTS

Although not diagnostic, laboratory measurements are helpful in assessing and monitoring disease activity and in differentiating ulcerative colitis from other forms of colitis. Blood counts and measurements of the erythrocyte sedimentation rate and the level of fecal lactoferrin or calprotectin help determine the severity of the inflammation. Stool

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cultures for *Clostridium difficile*, campylobacter species, and *Escherichia coli* 0157:H7 are recommended to rule out an infectious cause or complication. Patients with severe, refractory disease should be assessed for cytomegalovirus infection by means of histologic, immunochemical, serologic, culture, or DNA testing.[56] A positive test for ASCA or pANCA is not diagnostic, given the limited sensitivity and specificity of the tests; when they are performed in combination, however, the results may help differentiate among ulcerative colitis, Crohn's disease, and indeterminate colitis.[57] This last condition affects approximately 10% of patients, who have colitis with features of both Crohn's disease and ulcerative colitis.

THERAPY

MEDICAL THERAPY

According to current consensus-based guidelines, the choice of treatment for patients with ulcerative colitis should take into consideration the level of clinical activity (mild, moderate, or severe) combined with the extent of disease (proctitis, left-sided disease, extensive disease, or pancolitis), the course of the disease during follow-up, and patients' preferences.[43,58,59]

Induction of Remission

Sulfasalazine and 5-aminosalicylates (mesalamine, olsalazine, and balsalazide), given orally, rectally (by means of suppository or enema), or both, represent first-line treatment for ulcerative colitis, with an expected remission rate of about 50%.[60] Mild-to-moderate proctitis can be treated with mesalamine suppositories (1 g per day) or enemas (2 to 4 g per day); clinical remission occurs in most patients within 2 weeks, with repeated treatments as needed. If this fails, 5-aminosalicylate enemas (2 to 4 g per day) or glucocorticoid enemas (hydrocortisone at a dose of 100 mg per day, or new preparations such as budesonide or beclomethasone) are a next step.[61-63] Patients who do not have a response to rectally administered agents may be given oral glucocorticoids (up to 40 mg of prednisone or its equivalent).

Mild-to-moderate left-sided colitis to extensive ulcerative colitis is initially best treated with a combination of rectal and oral 5-aminosalicylate (up to 4.8 g per day).[64] Escalating doses of oral 5-aminosalicylate generally produce the best clinical response,[65] and a once-daily dose of 5-aminosalicylate (2 g per day) or newer, controlled-release formulations, such as multimatrix 5-aminosalicylate (2.4 g per day) are reported to be as effective and to promote adherence to treatment.[66,67] Patients with mild-to-moderate ulcerative colitis that is refractory to rectal therapies and to oral 5-aminosalicylate are candidates for oral glucocorticoids or immunosuppressive agents (azathioprine or 6-mercaptopurine); those who do not have a response to maximal doses of 5-aminosalicylate or oral glucocorticoids should be given intravenous glucocorticoids.[59] For patients who continue to require glucocorticoid therapy and for those who do not have a response to it, a good therapeutic option appears to be infliximab, a monoclonal antibody against TNF-α, administered at a dose of 5 mg per kilogram of body weight at 0, 2, and 6 weeks.[68] Infliximab in combination with azathioprine (2.5 mg per kilogram) was reported to be superior to infliximab or azathioprine monotherapy for inducing glucocorticoid-free remission in patients with moderate-to-severe ulcerative colitis.[69]

Many specialists suggest that patients with extensive, severe disease receive a 5-day to 7-day course of intravenous glucocorticoids[59]; if the disease is unresponsive, then intravenous cyclosporine (2 mg per kilogram) or infliximab is usually the next step. Although cyclosporine can be effective, it generally delays rather than prevents subsequent colectomy[70]; furthermore, infliximab is increasingly used as an alternative treatment for patients with refractory disease, given its effectiveness and better short-term safety profile as compared with other therapies.[71,72] Several schema have been proposed for determining whether colectomy should be performed in patients with unresponsive disease; these schema incorporate stool frequency; levels of C-reactive protein, albumin, and fecal calprotectin; and radiologic and endoscopic findings.[73] Composite indexes appear to be the most reliable means of assessment; for example, the Oxford index recommends that colectomy be considered if the C-reactive protein level is above 45 mg per milliliter and if the patient has 3 to 8 stools per day and more than 8 stools per day on day 3 after the initiation of treatment with intravenous glucocorticoids or cyclosporine.[73]

Maintenance of Remission

After remission has been achieved, the goal is to maintain the symptom-free status, which can be accomplished with various medications, with the exception of glucocorticoids, which have no place

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in maintenance therapy, given the marked side effects associated with their long-term use. Both oral and rectal 5-aminosalicylate have greater efficacy than placebo for maintenance of remission in patients with distal disease.[74,75] Thiopurines (e.g., azathioprine at a dose of 2.5 mg per kilogram or 6-mercaptopurine at a dose of 1.5 mg per kilogram) are recommended when 5-aminosalicylate is ineffective or not tolerated or when the patient is glucocorticoid-dependent, although it may take several months before their maximal effectiveness is reached. In a meta-analysis,[76] azathioprine was superior to placebo, and adverse events, including acute pancreatitis and bone marrow suppression, occurred in more than 10% of patients. In a randomized trial involving glucocorticoid-dependent patients, the proportion of patients with glucocorticoid-free remission was significantly higher with azathioprine than with 5-aminosalicylate (53% vs. 21%).[77] Thiopurines, which are widely used, are associated with an increased but low risk of lymphoproliferative disorders (<1 case per 1000 patient-years).[78] For patients who do not have a response to immunosuppressive therapy or cannot tolerate it, anti–TNF-α agents are gradually being adopted; higher rates of remission and improvement on endoscopy, as well as lower rates of colectomy, are reported when infliximab trough levels are detectable in the circulation.[79]

Unlike Crohn's disease, ulcerative colitis may respond to probiotic therapy. For example, *Escherichia coli* strain Nissle 1917 (200 mg per day) is not less effective than 5-aminosalicylate (1.5 g per day) for maintaining remission,[80] and the probiotic VSL#3 (3600 billion colony-forming units per day for 8 weeks) in conjunction with 5-aminosalicylate can help induce remission in mild-to-moderate ulcerative colitis.[81]

SURGICAL TREATMENT

Reported colectomy rates among patients with ulcerative colitis range from less than 5% to more than 20%.[82,83] Surgery can be curative in such patients, but it is not curative in patients in Crohn's disease. The expanding use of anti–TNF-α agents has not decreased the need for colectomy for patients with ulcerative colitis.[84] There are multiple indications for surgery, including the failure of medical therapy, intractable fulminant colitis, toxic megacolon, perforation, uncontrollable bleeding, intolerable side effects of medications, strictures that are not amenable to endoscopic alleviation, unresectable high-grade or multifocal dysplasia, dysplasia-associated lesions or masses, cancer, and growth retardation in children.[85] There are also multiple surgical options. Traditional proctocolectomy with ileostomy is curative and technically straightforward; however, possible complications include small-bowel obstruction, fistulas, persistent pain, sexual and bladder dysfunction, and infertility.[86,87] Total proctocolectomy with ileal pouch–anal anastomosis (IPAA) is currently the procedure of choice for most patients who require elective surgery, since it has the distinct advantage of preserving anal-sphincter function. This approach is associated with an acceptable morbidity rate (19 to 27%), extremely low mortality (0.2 to 0.4%), and good postoperative quality of life.[88] Continent ileostomy is an alternative procedure for patients with ulcerative colitis who are ineligible for or have declined IPAA or who have not been helped by it.[85] A pouch with a nipple valve is surgically created from the ileum and connected to the skin of the lower abdomen. This procedure allows stools to be retained and drained as necessary with a catheter. Any residual colonic mucosa can become cancerous, with the mandate for long-term endoscopic surveillance.

Pouchitis, the most common and most clinically important long-term complication of IPAA, is a nonspecific inflammation probably caused by an immune response to the newly established microbiota in the ileal pouch (dysbiosis).[89] The incidence of pouchitis can be as high as 40%; in 10 to 20% of cases, pouchitis becomes chronic. Symptoms include increased stool frequency, urgency, incontinence, seepage, and abdominal and perianal discomfort. Treatment consists primarily of antibiotics (metronidazole, ciprofloxacin, or rifaximin), and probiotics can be effective for preventing recurrence.[90] Pouch failure, a condition requiring pouch excision or permanent diversion, occurs in 8 to 10% of patients.[89]

FUTURE CHALLENGES AND NOVEL THERAPIES

Ulcerative colitis is generally easy to diagnose, and conventional step-up therapy is adequate for managing mild-to-moderate disease activity. Nevertheless, various important challenges remain. Several questions regarding the pathogenesis of ulcerative colitis remain to be answered. Why is inflammation restricted to the mucosal layer? Are colonic epithelial cells specific targets of an im-

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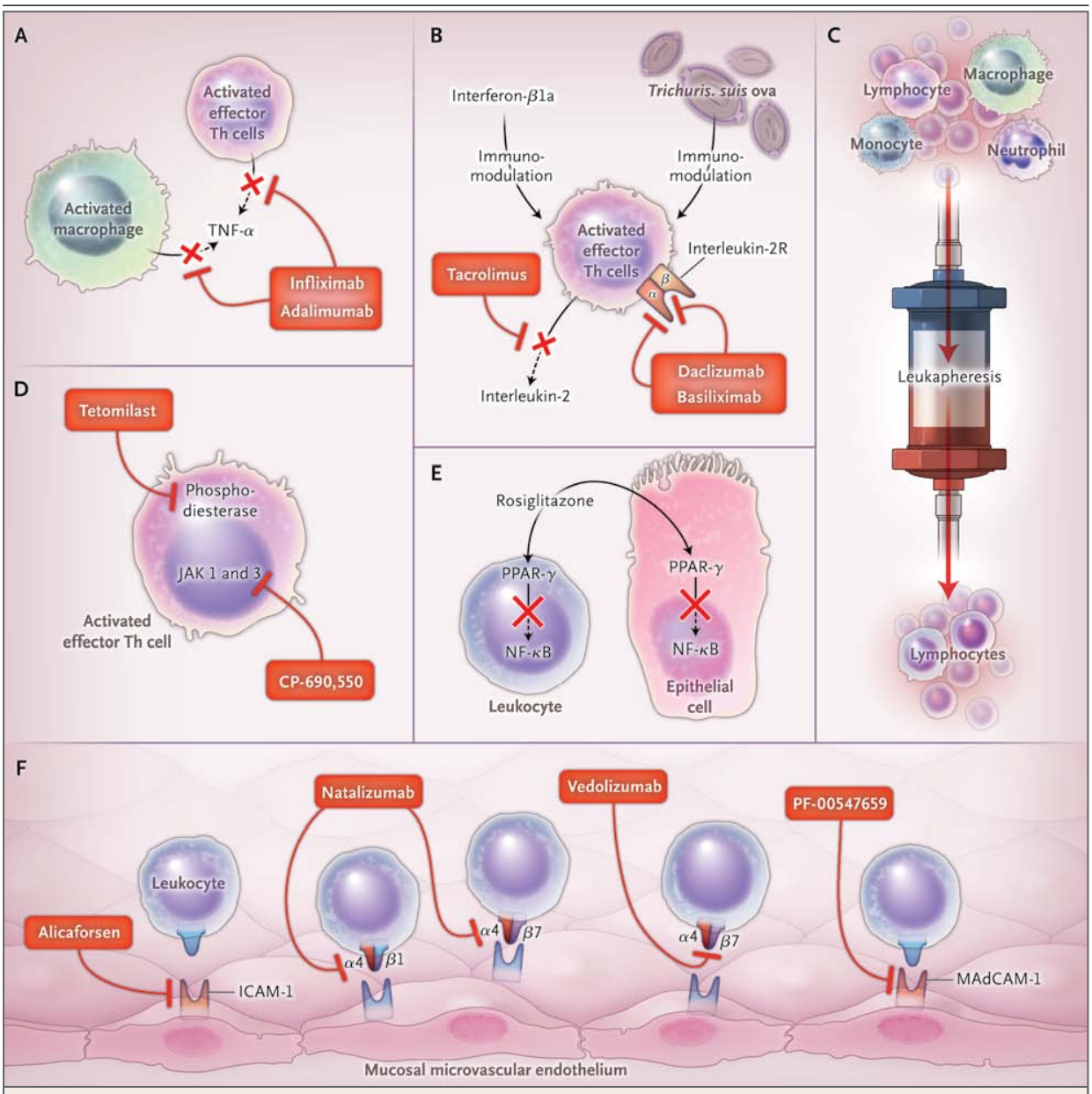

Figure 2. Agents for Which Evidence of Therapeutic Efficacy in Ulcerative Colitis is Established or Preliminary.
Shown are biologic and other novel agents, their target cells, and their mechanisms of action. ICAM-1 denotes intercellular adhesion molecule 1, JAK Janus kinase, MAdCAM-1 mucosal addressin-cell adhesion molecule 1, NF-κB nuclear factor κB, PPAR-γ peroxisome proliferator–activated receptor γ, and TNF-α tumor necrosis factor α. (Detailed descriptions of the mechanisms of action and classes of agents, as well as key references, can be found in Table 3 in the Supplementary Appendix.)

mune response? How does the luminal microbiota relate to the inflammatory response? Why does pouchitis develop in patients with an IPAA?

The monitoring and detection of dysplasia in patients with long-standing ulcerative colitis and residual mucosa after resection remain crucial, given the potential for malignant transformation. Although repeated colonoscopy with multiple biopsies is the routine approach, reliable molecular biomarkers are needed to distinguish cases

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that progress to cancer from those that do not.[91] Mucosal healing appears to be an important end point of therapeutic efficacy, correlating with a reduced relapse rate and perhaps a reduced risk of cancer, but the definition, standardization, and validation of this end point are incomplete.[92]

Many patients with ulcerative colitis still receive suboptimal doses of medications (particularly the aminosalicylates), continue to take glucocorticoids for exceedingly long intervals, or switch to biologic agents before immunosuppressive therapy has been optimized. In many cases, colectomy is a reasonable option, yet patients and clinicians alike remain reluctant to accept it because of personal preferences or in spite of problems with medications, even though protracted salvage therapy can do more harm than good, particularly in regard to quality of life and the risk of neoplasia.

The timing for the use of biologic agents in patients with ulcerative colitis is being evaluated — for example, in ongoing trials to assess the efficacy of alternative anti–TNF-α and other biologic agents[93] (Fig. 2, and Table 1 in the Supplementary Appendix). Adalimumab, a different anti-TNF-α antibody, is reported to induce remission,[94] and antibodies such as MLN0002 and PF-00547659, which prevent homing of leukocytes to the gut, have shown preliminary efficacy in active ulcerative colitis.[95,96] Because interleukin-13 appears to be an effector cytokine in ulcerative colitis, the development of interleukin-13–blocking agents seems justified, a conclusion supported by a recent study showing that the administration of interferon beta-1a in patients with ulcerative colitis inhibits interleukin-13 production.[97] Reports of exacerbation of ulcerative colitis in patients given rituximab to deplete B cells suggest that caution is crucial in evaluating new therapies.[98] Whether it is feasible to modify the natural history of ulcerative colitis by such measures as stem-cell therapy or combined immunosuppressive therapies early in the course of the disease is a question that remains to be answered.

Dr. Danese reports receiving fees for board membership from Merck Sharp & Dohme, consulting fees from Schering Plough, AstraZeneca, Abbott Laboratories, and Takeda Millennium, and lecture fees, including fees for service on speakers' bureaus, from UCB Pharma, Ferring, and Merck Sharp & Dohme; and Dr. Fiocchi, receiving lecture fees, including fees for service on speakers' bureaus, from Merck Sharp & Dohme and Broad Medical Research Program. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Jean-Paul Achkar, Mary Bronner, Jeffry Katz, Helmut Neumann, Markus Neurath, Julian Panes, Asit Parikh, Laurent Peyrin-Biroulet, Bo Shen, Michael Sivak, Warren Strober, Scott Strong, Gert van Assche, and Severine Vermeire for providing comments on the figures and expert suggestions.

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