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## Ulcerative Colitis

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### 1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease that primarily affects the colonic mucosa; it is most commonly diagnosed in patients aged 15-35 years, although the condition can affect patients of any age and of either sex. Its exact etiology remains uncertain. The annual incidence of ulcerative colitis in western countries is estimated to be 6-8 cases per 100,000 individuals, with the prevalence reaching 70-150 cases per 100,000 individuals. The disease course is generally relapsing-remitting, with patients experiencing few or no gastrointestinal symptoms between symptomatic relapses.

As medical options increase, decisions about the sequence and timing of therapy and surgery in particular become more difficult. Consequently a therapeutic strategy is necessary, keeping an eye on the direction of travel to avoid going round in circles from one incompletely effective therapy to another. Patients live with a considerable symptom burden despite medical treatment in the hope that a cure for ulcerative colitis will emerge. This article reviews the new advances in ulcerative colitis, epidemiology, pathogenesis, diagnosis, new therapeutic goals, as well as therapy that occurred in the past year.

### 2. Epidemiology

The prevalence of ulcerative colitis (UC) rapidly increased in western countries in the second half of the twentieth century and is becoming more common in the rest of the world as different countries adopt a Western lifestyle.<sup>(1)</sup> There are many similarities between Asian and Western populations, even significant differences do exist. These differences in genetic and environmental influences represent an important opportunity to understand the influences that lead to the development of UC.<sup>(2)</sup> UC tends to be a disease of young adulthood.<sup>(3)</sup> There are slightly more women affected than men. Cigarette smoking is protective in ulcerative colitis, an effect that has yet to be satisfactorily explained. It is well known that smoking reduces the severity of disease in ulcerative colitis, reducing the number of hospitalizations and need for steroids or surgery. By contrast, smoking increases the severity of Crohn's disease, increasing the number of exacerbations and the need for steroids.<sup>(4)</sup> Additionally, early appendectomy (before age 20) has resulted in a lower risk of ulcerative colitis.<sup>(5,6)</sup> Accurate descriptive epidemiology is needed now more than ever, so that it can be applied to the various populations with inflammatory bowel disease (IBD) such that further genetic and clinical studies can be conducted.

### 3. Genetics in ulcerative colitis

It is well known that IBD is a disease that has appeared over the last century and that its incidence varies markedly with geographic location, urbanization, and industrial development. Such data clearly highlight the presumptive importance of environmental factors in modulating disease evolution in IBD. However, a variety of other epidemiologic data also highlight the intimate role played by genetic factors in IBD pathogenesis. For instance, marked ethnic and racial differences in disease prevalence have been noted, particularly in Ashkenazi Jews. Furthermore, twin studies have demonstrated a much higher rate of disease concordance in monozygotic compared with dizygotic twins, particularly in Crohn's disease. However, it should also be highlighted that over 60% of monozygotic twins are not concordant for IBD. Thus, genetic susceptibility alone, while important, is clearly not sufficient for the development of disease.

The greatest identifiable risk factor for the development of IBD is having a first-degree family member affected by the disease. Affected first-degree relatives are more frequently identified in patients with Crohn's disease (9% to 15%) than in those with ulcerative colitis (6% to 9%), and appear to be more common in patients with earlier disease onset and in those of Jewish descent. Siblings of an affected individual are at highest risk. The risk of disease in the offspring of patients is very difficult to calculate accurately due to the paucity of data. Offspring of couples who are both affected by IBD (either Crohn's disease, ulcerative colitis, or "mixed" [ie, 1 parent with Crohn's disease and the other with ulcerative colitis]) appear to have about a 30% chance of developing disease by 30 years of age. If only a single parent has IBD, then the risk appears to be much less: approximately 9% if the parent has Crohn's disease, and about 6% if the parent has ulcerative colitis.

The substantial heterogeneity seen in IBD suggests that it does not encompass only 2, but many inflammatory disorders. Various epidemiologic data support this concept. Multiply-affected families show surprising concordance for disease phenotype, including age of onset, disease location, and extra-intestinal manifestations. Longitudinal studies examining changes in Crohn's disease phenotype over time demonstrate the stability of disease location, but the progression of disease behavior following diagnosis. The current genetic model for IBD attempts to encompass these observations. It is generally believed that there may be a number of "susceptibility genes" that confer a general predisposition to IBD. Other "modifier genes," although they don't initiate disease, then act to influence specific phenotypic characteristics such as disease behavior, complications, and treatment response, among others. Both "susceptibility" and "modification" may be further influenced by interaction with environmental factors.

### 4. Mechanisms of disease and pathogenesis

Chronic intestinal inflammation in UC results from the interactions of genetic, immunologic, microbial and environmental factors.<sup>(7)</sup> It is proposed that IBD results from the failure to appropriately downregulate nonspecific inflammation initiated by an environmental trigger, such as an acute, self-limited infection or NSAID use.<sup>(8)</sup> Normal hosts quickly clear infections of invasive enteric bacteria, downregulate innate immune responses and heal the injured mucosa without stimulating effector T-cell responses.<sup>(9)</sup> By contrast, genetically susceptible hosts who are unable to clear an invading pathogen and/or generate tolerogenic immune response to commensal microbial agents—by mounting appropriate innate

immunity, downregulating immune responses or healing the mucosal barrier—subsequently activate pathogenic T-cell responses to commensal bacteria and proceed to chronic, relapsing intestinal inflammation. Resistance to T-cell apoptosis, lack of response to downregulatory signals and continuous exposure to luminal antigens and adjuvants help sustain this inflammatory response.<sup>(10)</sup>

Many environmental factors can influence mucosal immune responses and enteric bacteria composition, including diet, smoking, stress, altered microenvironment and NSAID exposure.<sup>(11)</sup> Although it postulated that self-limited, nonspecific infections can initiate the onset of chronic inflammation and reactivate quiescent disease, it is possible that a persistent pathogen could cause disease in individuals unable to clear infections, or that the commensal bacteria of some patients could acquire virulence factors (e.g. toxins, adherence and/or invasion properties) that might cause chronic intestinal inflammation.<sup>(12)</sup>

## 5. Diagnosis of ulcerative colitis

**Endoscopy;** Colonoscopy is more sensitive than radiographic studies in detecting early changes associated with UC, and represents the primary modality to obtain tissue for histologic evaluation. Clinicians should be cognizant that even if the colonic mucosa appears macroscopically normal, there may be histologic changes diagnostic of UC. Therefore, it is of paramount importance that biopsies be procured, even from tissue that appears endoscopically normal. Histology represents the most sensitive measure of disease extent and activity. In 10% of all patients, colonoscopy with biopsy is unable to differentiate between Crohn's colitis and ulcerative colitis.<sup>(13)</sup>

In early-stage edema, confluent erythema with rectal involvement is typical. As the disease progresses, granularity and contact bleeding is appreciated endoscopically. With progression of disease to the late stages, discrete ulcerations with pus/exudate and loss of haustral folds is characteristic. The presence of aphthoid ulcerations is not seen in patients with ulcerative colitis. Chronic inflammation frequently leads to diffuse mucosal atrophy, leaving behind hypertrophic areas of swollen, edematous tissue and areas of granulation that assume a polypoid configuration. These areas, known as pseudopolyps, have no malignant potential and occur in both ulcerative colitis and Crohn's disease.<sup>(14)</sup> Histologically, ulcerative colitis has alterations of crypt architecture including crypt architectural distortion. Paneth cells are commonly found in normal individuals, proximal to the hepatic flexure; however, in patients with ulcerative colitis, it is not uncommon to discern their presence distal to the hepatic flexure suggestive of prior crypt destruction and subsequent regeneration. It is most common to find these features distally. It is also common to find basal plasma cells and many basal lymphoid cells, indicating the presence of chronicity.<sup>(19)</sup> Basal plasma cells are, however, not specific for ulcerative colitis and may be seen in other chronic disorders, such as collagenous colitis and Crohn's disease and, rarely, in infectious colitis. Other minor features of ulcerative colitis include hyperplasia of argentaffin cells, mucosal vascular congestion with edema, and focal hemorrhage. Depletion of goblet cell mucin is a characteristic and consistent finding in acute ulcerative colitis, and except where dysplasia is present, is another reliable indicator of disease activity.<sup>(15)</sup>

**Radiographic Studies;** Radiographic imaging for evaluation of patients with ulcerative colitis also remains a standard and helps to differentiate ulcerative colitis from Crohn's disease. The presence of mucosal granularity is the earliest radiographically detectable evidence of disease in ulcerative colitis. The granular pattern is thought to result from

abnormalities associated with edema and hyperemia. <sup>(16)</sup> Early ulcer formation in ulcerative colitis appears as fine speckled barium collections superimposed on a granular-appearing mucosa. Other associated findings may be present, including haustral fold thickening, colonic shortening, polyps and pseudopolyps, strictures, dysplasia, colorectal cancer, and toxic dilation for various disease stages. <sup>(17)</sup>

**Serologic Testing;** Combined serologic testing has also been proposed to help differentiate between ulcerative colitis and Crohn's disease in cases of indeterminate colitis. At this time, there is insufficient evidence to demonstrate that perinuclear anti-neutrophilic cytoplasmic antibody (pANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) testing alone is completely reliable in reaching a definitive diagnosis. <sup>(18)</sup> The presence of ANCA, pANCA, ASCA, anti-OmpC (outer membrane porin from Escherichia coli), and anti-CBir1 (anti-CBir1 flagellin) markers appears to be associated with ulcerative colitis and Crohn's disease. <sup>(19,20)</sup> More markers and combined serologic testing represent a promising step forward for diagnosis.

## 6. Backwash Ileitis in ulcerative colitis

Involvement of the distal ileum in ulcerative colitis (UC) is termed backwash ileitis (BWI). Most authors agree that BWI has a similar morphologic pattern of mucosal inflammation and injury to UC and does not have the features typical of CD. <sup>(21)</sup> Features that favor a diagnosis of CD rather than chronic UC with BWI, are an extensive length of involved small bowel, involvement of the jejunum, proximally located regions of active ileitis separated by skip regions of uninvolved cecum or distal ileum, greater inflammatory activity and mucosal injury in the ileum than the cecum, transmural ileal inflammation with granulomas and neural hyperplasia, and mucous gland (so-called pyloric gland) metaplasia of the ileal mucosa. <sup>(22)</sup> In endoscopic biopsy specimens, features that suggest a diagnosis of CD include mucous gland metaplasia or the constellation of focal lamina propria edema with crypt disarray and no to mild active inflammation that involves a small region of a tissue fragment surrounded by normal small bowel mucosa. Mild BWI consists of active inflammation and edema that is located predominantly in villus tips without significant lamina propria focal edema or crypt disarray. In BWI, mild ileal mucosal injury is found in association with moderate or markedly active cecal colitis. Focal ileal erosions with mild active inflammation seen in association with mildly active cecal colitis should be considered CD. <sup>(23)</sup>

## 7. Indeterminate colitis

Although some patients who are initially labelled as having indeterminate colitis eventually have classic features of ulcerative colitis or Crohn's disease, others who remain indeterminate may have a unique phenotype. If a unique phenotype exists, novel diagnostic tests are needed to positively identify this group, instead of relying on current tests that can only exclude ulcerative colitis and Crohn's disease. Until indeterminate colitis becomes a diagnosis based on positive test results, data regarding the epidemiology, response to therapy and cancer risk will likely remain difficult to interpret. <sup>(24,25)</sup> At present time serological tests can not diagnose or predict the course of indeterminate colitis. The serological tests would not be diagnostic for indeterminate colitis until there exists at least one test that positively identifies the subgroup of indeterminate colitis. <sup>(26)</sup>



## 8. Treatment of ulcerative colitis

Clinical trials on ulcerative colitis have all used different endpoints to define response and remission. Some outcomes that matter to patients, such as hospitalization, time off work, surgery and mortality, are difficult to measure, but are only now being captured in large trials. Other outcomes (steroid-free remission, speed of response, time to relapse) also matter to patients, are readily understood, easily measured and more informative than composite indices. Surrogate markers for determining improved outcomes, such as fewer hospital visits, or surgery, include mucosal healing.

## 9. 5-Aminosalicylic Acid (5-ASA)

When free 5-ASA is administered orally, it is nearly completely systemically absorbed from the proximal small intestine and then extensively metabolized to N-acetyl-5-ASA in intestinal epithelial cells and the liver; it is then excreted in the urine.<sup>(27)</sup> 5-ASA has been shown to have a topical mechanism of action in the treatment of ulcerative colitis.<sup>(28)</sup> Therefore, strategies to "protect" orally administered 5-ASA from absorption until it reaches the colon have been developed. These strategies include the use of prodrugs; delayed-release formulations; controlled-release formulations; and, more recently, sophisticated formulations that combine both delayed-release and sustained-release mechanisms.

**Prodrug Formulations;** The first strategy employed to protect 5-ASA until it reaches the colon was to design prodrugs that release active drug in the colon by the bacterial enzyme azo reductase. Three such drugs were developed: sulfasalazine, olsalazine, and balsalazide. The oldest of these agents, sulfasalazine, consists of 5-ASA linked to sulfapyridine by an azo bond. Olsalazine comprises 2 molecules of 5-ASA linked by an azo bond as a dimer, and balsalazide consists of 5-ASA linked by an azo bond to 4-amino-benzoyl-beta-alanine. Sulfasalazine is formulated as a 500-mg tablet containing 200 mg of 5-ASA. Sulfasalazine is administered orally 4 times daily to minimize side effects associated with the sulfapyridine moiety. Olsalazine is formulated as a 250-mg capsule and is administered orally twice daily. Balsalazide is formulated as a 750-mg tablet that contains 262 mg of 5-ASA. Balsalazide is administered orally 3 times daily. A capsule formulation of balsalazide is currently under development.<sup>(29)</sup>

**Delayed-Release Formulations;** The second strategy employed to protect 5-ASA until it reaches the colon was to coat the drug with polymers that release at pH 6 or pH 7, thus delaying release of active drug until it reaches the small bowel or the cecum. Four such oral drugs were developed: Asacol (Ohio), Salofalk (Germany), Mesasal (Canada), and Claversal (Germany). Asacol is a delayed-release tablet formulation of 5-ASA that is coated with a polymer called Eudragit-S, which releases drug in the terminal ileum and colon at pH  $\geq 7.0$ . Salofalk, Mesasal, and Claversal are delayed-release tablet formulations that are coated with a polymer called Eudragit-L, which releases drug in the distal jejunum and proximal ileum. Asacol is formulated as a 400-mg tablet and as an investigational 800-mg tablet (currently available only in Canada); it is administered orally 2-3 times daily. Salofalk, Mesasal, and Claversal are formulated as 250- and 500-mg tablets and are administered orally 3-4 times daily.<sup>(30)</sup>

**Controlled-Release Formulations;** The third strategy employed to protect 5-ASA until it reaches the colon was to formulate the 5-ASA as ethylcellulose-coated microgranules that gradually release beginning in the duodenum and continuing throughout the jejunum, the

ileum, and the colon to the rectum. <sup>(31)</sup> Only 1 controlled-release drug was developed: Pentasa (Pennsylvania). After the ethylcellulose-coated microgranules release the drug throughout the small intestine and colon. <sup>(32)</sup> Pentasa is formulated as 250-mg and 500-mg tablets, 250-mg and 500-mg capsules, and 1000-mg sachets; this agent is administered orally 1 g once or twice daily for induction of remission and treatment of mild-to-moderate active ulcerative colitis.

**Delayed- and Sustained-Release Formulations;** The fourth strategy employed to protect 5-ASA until it reaches the colon was the use of a sophisticated formulation that coats pellets or matrices containing 5-ASA with polymers that release at pH 6 or pH 7, thus delaying release of pellets or matrices until they reach the small bowel or the cecum. The pellets or matrices contain 5-ASA that gradually releases, beginning in the distal small bowel and continuing throughout the colon to the rectum. Two such drugs have been developed: mesalamine pellets (Salofalk GranuStix; Germany) and mesalamine with MMX technology (Lialda in the United States and as Mezavant in Europe).

Mesalamine pellets have an outer coating of the Eudragit-L polymer and an additional retarding polymer in the pellet core. The entire mesalamine pellet dose passes unaltered to the distal jejunum and proximal ileum. After the Eudragit-L polymer disintegrates at pH 6.0 in the distal jejunum and proximal ileum and the 5-ASA is then released from the pellet core. <sup>(33)</sup> Mesalamine pellets are formulated as 500-mg sachets and are administered orally 1-3 times daily.

MMX technology has a pH-sensitive film which delays the release of 5-ASA until the tablet reaches the terminal ileum. Intestinal fluids are thought to interact with hydrophilic excipients causing the tablet to form a viscous gel, which slows diffusion of 5-ASA into the colonic lumen. It is supposed that other lipophilic excipients reduce the rate of dissolution and extend the process of delivery of 5-ASA. It is clear that it works, for both inducing and maintaining remission in single or twice daily doses. <sup>(34-36)</sup>

### **Once-daily mesalamine**

Once-daily oral formulations of 5-aminosalicylic acid (5-ASA) are likely to be preferred if they offer comparable efficacy and improved adherence. This premise appears correct with Pentasa showed a better remission rate at 1 year in the single daily dose group. Questionnaires confirmed significantly greater compliance and acceptability in the once-daily group. Same results with mesalamine MMX and Salofalk <sup>(37,38)</sup> the effect is likely to be generic rather than compound specific.

### **High-dose 5-aminosalicylic acid**

The benefit of mesalamine 4.8 over 2.4 g/day is limited to symptom improvement rather than remission in mild or moderately active colitis, as confirmed in the large ASCEND I trial and a systematic review. <sup>(39,40)</sup>

### **Induction and maintenance of remission with 5-aminosalicylic acid therapy**

The efficacy of oral and rectal formulations of 5-aminosalicylate acid (5-ASA) has been demonstrated in clinical trials as both induction and maintenance agents for mildly to moderately active ulcerative colitis. Two large meta-analyses showed that 5-ASAs were significantly more effective than placebo for induction of remission, and within the limits of this analysis, there was no significant difference between the efficacy of sulfasalazine and the other 5-ASA therapies. <sup>(41)</sup>

At present, there are no published maintenance-of-remission studies involving mesalamine pellets or MMX mesalamine in patients with active ulcerative colitis.

As with other chronic diseases requiring maintenance therapy, compliance with the prescribed medical regimen is a challenge. Although compliance in clinical trials, which involve a highly selected and motivated patient group, is greater than 80%, much lower rates were seen in community-based, "real-world" studies (40% to 60%).<sup>(42)</sup> Noncompliance results in an increased risk for disease relapse, a diminished quality of life, and a possible increase in the risk for colorectal cancer.<sup>(43)</sup> Therefore, successful management of patients with ulcerative colitis requires treatment strategies that encourage and confirm compliance with the prescribed therapeutic plan.

## 10. Combination oral and topical 5-ASA therapy

A fundamental principle of 5-ASA therapy is delivery of the drug to the site of disease. Several studies, including a meta-analysis, confirmed the efficacy of 5-ASA in an enema formulation in both inducing and maintaining remission in left-sided ulcerative colitis (defined as distal to the splenic flexure).<sup>(44,45)</sup> The addition of topical 5-ASA to oral therapy increases mucosal levels of mesalamine by 3-fold in the descending colon and over 20-fold in the rectum.<sup>(51)</sup> Moreover, it has been demonstrated repeatedly that the combination of 5-ASA in oral and enema formulations is superior to either therapy alone in inducing and maintaining remission of extensive colitis.<sup>(46)</sup>

## 11. Corticosteroids

Systemic corticosteroids are often given to ulcerative colitis patients with moderately to severely active disease. Over 5 years study, those patients who had achieved complete response with steroid treatment had less need for immunosuppression, fewer hospitalizations, and a longer time interval to relapse in comparison with the group not received steroids. However, colectomy rates were similar among all patient groups. Therefore, the study authors suggested that more aggressive therapy, probably with immunosuppressants, is required for patients who do not completely respond to their first corticosteroid course.<sup>(47)</sup>

The impact of prednisone on bone density, independent of disease activity, has been the subject of debate, as clinicians have reported osteoporosis in corticosteroid-naïve UC patients, and found normal bone densities in some patients on long-term steroids.

The most serious complication associated with corticosteroid therapy in UC is avascular necrosis (osteonecrosis). A search of a large database identified 94 patients with IBD and avascular necrosis; these subjects were matched to IBD controls without avascular necrosis. Important to note was that 6 patients with avascular necrosis had never been exposed to corticosteroids. Likely risk factors for avascular necrosis included systemic steroid exposure, IBD severity, parenteral nutrition, estrogen exposure, and cigarette smoking in ulcerative colitis patients. Although some of these risk factors are modifiable, above all, corticosteroid therapy must be minimized in IBD patients.<sup>(48,49)</sup>

Dexamethasone encapsulated into the patient's own erythrocytes and infused back into the patient may offer a way to deliver adequate steroid therapy to tissues while minimizing the adverse effects often associated with steroid use. Autologous erythrocytes can be used as drug carriers, owing to the capability of their membrane to be opened and resealed in



appropriate conditions. An ideal drug to be encapsulated into erythrocytes is dexamethasone 21-phosphate (Dex 21-P), a biologically inactive compound. In this randomized clinical trial involving 40 patients with mildly to moderately active ulcerative colitis, subjects received either dexamethasone encapsulated into erythrocytes at entry and at day 14; prednisolone 0.5 mg/kg with tapering; or sham infusions of dexamethasone encapsulated into erythrocytes. At 8 weeks, remission was achieved in 85% of patients who received the erythrocyte-mediated delivery of dexamethasone, in 80% of prednisolone-treated patients, and in 20% of sham-treated patients ( $P < .01$ ). No patient treated with encapsulated dexamethasone experienced steroid-related side effects, as compared with 80% of the prednisolone-treated group. The study authors concluded that very low doses of dexamethasone delivered via encapsulated erythrocytes may be as effective as prednisolone but without the steroid-related side effects. <sup>(50,51)</sup>

Steroid resistance remains a major clinical challenge, but emerging knowledge of the pathogenesis of IBD is enabling the development of new agents to overcome this resistance. Many difficult questions remain to be answered, such as whether steroid resistance is an inherent property of an individual or if it is acquired. The demonstration of steroid resistance in the lymphocytes of healthy individuals would suggest that it is an inherent property of an individual that is only of relevance in the presence of inflammatory disease.<sup>(52)</sup> However, the observation that some individuals become less responsive to steroids over time makes this hypothesis more difficult to support. The clonal nature of lymphocyte proliferation raises the possibility that steroid treatment gradually depletes activated steroid-sensitive lymphocytes leaving behind a highly steroid-resistant population over time. May be, combination treatment with existing treatments, such as is employed in the treatment of TB or even malignancy will offer the answer to preventing the development of steroid-resistant lymphocyte clones. Steroid-resistant UC remains a difficult condition to treat. We must consider when designing future trials whether response to treatment is an adequate end point. Patients need to be in steroid-free remission, and this is what we should aspire to achieve. <sup>(53)</sup>

## 12. Azathioprine/6-Mercaptopurine

Thiopurines are widely used in the treatment of inflammatory bowel disease (IBD). However, in clinical practice, azathioprine (AZA) or mercaptopurine (MP) are not effective in one-third of patients and up to one-fifth of patients discontinue thiopurine therapy because of adverse events. <sup>(54)</sup> Dosing recommendations for the thiopurine analogs have traditionally been based on the patient's weight and the impact on hematologic and hepatic parameters. More recently, measurement of the levels of the 2 primary metabolites, 6-thioguanine (6-TGN; thought to be a marker of drug efficacy), and 6-methylmercaptopurine (6-MMP; associated with hepatotoxicity in some instances), as well as the activity of the thiopurine methyltransferase (TPMT) enzyme, has been purported to provide a more accurate prediction of patient response to therapy and of appropriate dosing. <sup>(55)</sup>

In patients refractory to thiopurines who have high TPMT activity and preferentially metabolize the agents to produce the 6-MMP metabolite instead of the 6-TGN metabolite. The addition of low-dose allopurinol (100 mg or less daily) along with a greatly reduced dose of the purine analog (often 25-50 mg) not only resulted in treatment success, but also in a reversal of the 6-TGN:6-MMP nucleotide ratio to favor production of the 6-TGN nucleotide. The 6-mercaptopurine dose ranged from 0.35 mg/kg to 0.61 mg/kg, although

the study authors suggested lowering the dose to 25 mg daily for 4 weeks prior to initiating the allopurinol. Due to the risk for serious hematologic consequences, further research recommended be done prior to the adoption of this combination of therapies in clinical practice. <sup>(56)</sup>

Intolerance to 6-mercaptopurine does not necessarily mean that the same patient will be unable to be treated with azathioprine, although severe hematologic reactions and pancreatitis resulting from treatment with one of the agents usually precludes challenge with the other. A previous study suggested that patients with an intolerance to azathioprine could subsequently receive 6-mercaptopurine. <sup>(57)</sup> A practical option for patients who cannot tolerate thiopurines (both azathioprine and 6-mercaptopurine) is to try mycophenolate mofetil. In a case series of 70 patients, 24% achieved steroid-free remission for almost 3 years. <sup>(58)</sup>

### 13. Calcineurin inhibitors (Cyclosporine/Tacrolimus)

Clinical improvement usually occur within 1-4 weeks of treatment with calcineurin inhibitors and duration of therapy is 3-6 months. <sup>(59)</sup>

Cyclosporine has demonstrated efficacy in the treatment of severe steroid-refractory ulcerative colitis, but questions persist as to the long-term outcomes of those patients treated with the "salvage" agent. In a study of 75 patients, 79% avoided colectomy during their hospitalization; 56% were well at 6 months; and 45% were still well at a mean of 14.7 years later. Higher rates were seen among the 69 patients in the latter subset, with 80% initially avoiding colectomy, 73% well at 6 months, and 54% still well at a mean of 8.6 years later. <sup>(60-62)</sup>

Tacrolimus showed better results than cyclosporine as it has powerful immunosuppressant, 10 to 20 times greater than cyclosporine and it has consistent absorption even in the presence of gastrointestinal disease. Its intravenous dose 0.01-0.02 mg/kg/day and 0.1-0.2mg/kg/day orally. <sup>(63)</sup>

Prophylaxis against *Pneumocystis carinii* pneumonia is strongly recommended when using the calcineurin inhibitors. <sup>(64)</sup>

### 14. Anti-tumour necrosis factor therapy for ulcerative colitis

Infliximab therapy for ulcerative colitis showed modest steroid-free remission rate (21% at 6 months in the combined active ulcerative colitis trials ACT 1 and ACT 2). Nevertheless, subsequent analysis showed an associated reduction in colectomy, <sup>(65)</sup> but whether this benefit is maintained remains unclear. Outside of clinical trial settings, outpatient case series have reported colectomy rates of up to 50% after a median follow up of 13 months, <sup>(66)</sup> but lower rates in less refractory patients. Older patients and those who are perinuclear antineutrophil cytoplasmic antibody (p-ANCA) positive may respond less well. <sup>(67)</sup> A single series of 10 patients with ulcerative colitis who had lost response to infliximab were given adalimumab (160/80) in a 4-week open-label trial. Four patients improved, six did not respond, and of these, two went onto colectomy. <sup>(68)</sup> Phase III studies of adalimumab for ulcerative colitis are in progress. Infliximab for acute severe colitis is best considered separately, as is the question of whether to continue immunomodulators. The "real-world" experience with infliximab in ulcerative colitis seems to recapitulate efficacy results seen in the large clinical trials. <sup>(69)</sup>

## 15. Long-lasting clinical remission in patients with ulcerative colitis

The induction of an effective and long-lasting clinical remission, including tissue mucosal healing, is of the utmost importance in reducing the need for surgery and in lessening the incidence of dysplasia and cancer. Maintenance therapy should begin only after a patient has achieved a favorable clinical response to induction therapy. <sup>(70)</sup>

The US FDA has set the stage in adopting stringent criteria for clinical remission, including tissue healing with symptomatic improvement, for future clinical trials investigating the efficacy of medical therapies in patients with ulcerative colitis. This renewed standardization of controlled clinical trials will lead to the development of more effective therapies that improve patient outcome while potentially avoiding complications of long-standing ulcerative colitis. <sup>(71)</sup>

## 16. Acute severe ulcerative colitis

Intravenous corticosteroids remain the mainstay for acute severe colitis. In case of steroid refractory severe ulcerative colitis, the choice for rescue therapy in 2008 is between infliximab and calcineurin inhibitors (cyclosporine A or tacrolimus).<sup>(72)</sup> Controlled trials are needed, because case series report 20-75% coming to colectomy after infliximab for intravenous-steroid resistant ulcerative colitis.<sup>(73)</sup> Safety is a key factor, especially if surgery becomes necessary. While it is generally accepted that elective surgery in the presence of infliximab is safe, the same may not apply to emergency colectomy for acute severe colitis. Combination therapy in an attempt to avoid colectomy cannot be recommended. <sup>(74)</sup> The message should be to use objective indices that predict outcome at an early stage (on the third day of intravenous steroid treatment). A new index for patients with acute severe colitis has been developed and validated which depend on C-reactive protein and stool frequency. <sup>(75)</sup>

## 17. Surgery for ulcerative

Colectomy is an integral component of an overall therapeutic strategy. Patients with an ileal pouch anal anastomosis (IPAA) have a quality of life similar to patients with ulcerative colitis in remission or mild disease, although it depends on the measure used. <sup>(76)</sup> Complications of IPAA have been reviewed, but a common dilemma is the impact of pelvic surgery on fecundity and pregnancy on pouch function. Infertility rate was 12% before and 26% after IPAA among 945 patients in seven studies. No significant difference was seen in pouch function after vaginal delivery, but elective caesarean section for patients with a pouch tends to be favoured after discussion with the obstetrician and patient. <sup>(77)</sup>

## 18. Pouchitis

Pouchitis, a non-specific, idiopathic inflammation of the ileal reservoir, has become the most frequent long-term complication following pouch surgery for UC. The reported incidence of pouchitis is largely variable because of differences in nature and duration of the follow-up and, particularly, because a myriad of diagnostic criteria have been used to define this syndrome. Most patients who develop acute pouchitis do so within the first year, but some may suffer their first attack some years following surgery. <sup>(78)</sup>

Metronidazole appears to be an effective therapy for active chronic pouchitis. Bismuth carbomer foam enemas may not be an effective therapy for chronic active pouchitis. Oral probiotic therapy with VSL - 3 appears to be an effective therapy for maintaining remission in patients with chronic pouchitis in remission. There is no evidence of a difference in the maintenance of symptomatic remission in patients with chronic pouchitis treated with glutamine versus butyrate suppositories, and it is unknown whether glutamine and butyrate are equally effective or ineffective. Additional randomized, double - blind, placebo - controlled, dose - ranging clinical trials are needed to determine the efficacy of empiric medical therapies currently being used in patients with pouchitis. <sup>(79-81)</sup>

## 19. Novel therapies

Although conventional therapy accounts for the management of at least 90% of patients with ulcerative colitis, it is often new treatment that attracts attention. Therapeutic targets other than tumour necrosis factor (TNF) are sorely needed, since conventional therapy, however well used, is reaching its limits.<sup>(82)</sup>

Visilizumab; This anti-CD3 monoclonal antibody binding to activated T cells to induce apoptosis showed real promise as rescue therapy for intravenous steroid-resistant ulcerative colitis. The phase 1 dose-ranging study has been reported, but sadly the phase III study was suspended in 2007 when interim analysis showed no benefit.<sup>(83)</sup>

Phosphodiesterase 4 Inhibitor; Phosphodiesterase 4 is a key enzyme in cell homeostasis and inflammation, and its inhibition has been useful in rheumatoid arthritis and other diseases. A phase II study of tetomilast (OPC-6535) in 186 patients with active ulcerative colitis showed potential benefit in those with more active disease, but did not reach significance for remission or overall response.<sup>(84)</sup>

Phosphatidylcholine; Insufficient phosphatidylcholine in colonic mucus fits with current concepts of a primary defect in barrier function. Significantly more patients given phosphatidylcholine 2 g/day were able to stop steroids compared with placebo.<sup>(85)</sup>

Other Agents; Interferon- $\beta$  still seeks a role for treating ulcerative colitis, although a case report describes the onset of the condition during treatment with interferon- $\beta$  for multiple sclerosis. A similar disparity applies to rituximab, an anti-CD20-antibody that might inhibit B-cell-mediated destruction of epithelial cells. It is undergoing pilot studies in ulcerative colitis, but a case report describes disease exacerbation. Abatacept prevents T-cell activation by inhibiting costimulation through CD28 and worked in two animal models of colitis; it is undergoing clinical trials at present.<sup>(86)</sup>

## 20. IV Iron therapy for anaemia in ulcerative colitis

In most studies testing oral iron, 100–200 mg of ferrous salts (fumarate or sulphate) were administered. As only small amounts of iron are absorbed (10–30 mg) the majority of ingested iron passes along within the bowel content. <sup>(87)</sup> At sites of ulcers, the iron-rich luminal matter may increase the formation of hydroxyl radicals (by catalysing the Fenton reaction:  $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^\bullet + \text{OH}^-$ ). The hydroxyl radical is the primary oxidizing species; it can be used to oxidize and break apart organic molecules and thereby may enhance tissue damage and disease activity of the underlying IBD. As this hypothesis is difficult to test in patients, it has been subject of several studies using animal model of IBD. <sup>(88)</sup> Many publications that tested the effect of iron on intestinal disease activity, oxidative



stress or the degree of mucosal inflammation in rodent models of IBD. Although the experimental setting, the iron dose and the readout are quite diverse, these studies unanimously support the hypothesis of iron-induced hydroxyl radical generation in the inflamed tissue leading to worsening of intestinal inflammation and increased colon carcinogenesis.<sup>(89)</sup>

From eight studies that tested oral iron in IBD, intolerance was a common finding leading to discontinuation in up to 21%. Two studies using ferric iron reported fewer side effects despite good effectiveness. Some case-control studies saw similar intolerance to non-IBD patients in others the frequency and spectrum of side effects (increase in diarrhoea vs. constipation) was considerably different. A 15-year-old girl developed typical symptoms of UC after treatment of anaemia with ferrous sulphate. Recently, some worsening of proctosigmoiditis was demonstrated by rigid sigmoidoscopy.<sup>(90)</sup>

Intravenous iron therapy for IBD-associated anaemia has been suggested in the 1970s, but clinical trials have not been performed until the early 1990s. Studies during the last 10 years showed that IV iron polymaltose or iron sucrose appear effective and safe. Iron sucrose may be administered undiluted as a 100 mg slow intravenous injection over 2 to 5 minutes or as an infusion of 100 mg, diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes per session for a total cumulative dose of 1000 mg within the 14 day period. There is limited experience with administration of an infusion of 500 mg iron sucrose diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5 to 4 hours on day 1 and day 14. Hypotension may occurred in up to 10% of patients treated.

Patients receiving regular parenteral iron therapy require monitoring of hematologic parameters and iron indices (Hb, Hct, transferrin saturation, and ferritin).

Sufficient IV iron should be administered to maintain transferrin saturation between 20% and 50%. Iron therapy should be withheld in patients with transferrin saturation  $\geq 50\%$ . Since transferrin saturation values increase rapidly after IV administration of iron sucrose, serum iron values may be reliably obtained 48 hours after IV iron sucrose dosing.<sup>(91,92)</sup>

## 21. Colorectal cancer in ulcerative colitis

There is no doubt that patients with ulcerative colitis have an increased risk for colorectal cancer, and that colorectal cancer remains an important cause of death in IBD patients. It is interesting to note that worldwide, ulcerative colitis related colorectal cancer rates seem to be diminishing, possibly due to the benefits of cancer surveillance programs, chemopreventive efforts, or to a changing risk-factor profile. Cancer surveillance colonoscopy programs have been in place for IBD patients for at least 30 years. Perhaps the efforts of gastroenterologists have been successful in decreasing cancer rates over that time period. It is encouraging to see that many patients with advanced neoplasia (high-grade dysplasia or cancer) have had earlier examinations where low-grade dysplasia was detected. Inflammation appears to be an important biological risk factor for the development of CRC. Clinically, duration and anatomic extent of colonic inflammation are the most important risk factors for CRC in chronic ulcerative colitis. Chronic inflammation increases oxidative stress; promotes repeated cycles of injury, regeneration, and repair; and accelerates the accumulation of oncogenic mutations. Over time, accumulation of these mutations may result in dysplasia, an unequivocal neoplastic change in the colon. With additional key mutations, dysplasia can transform into invasive colorectal cancer.<sup>(93)</sup> Other established risk factors include primary sclerosing cholangitis (PSC) (increases the relative risk of CRC 4.8-



fold compared with just chronic ulcerative colitis alone) and a family history of CRC (increases the risk of CRC 2.5-9.2 fold compared with chronic ulcerative colitis alone).<sup>(94)</sup> Other risk factors such as backwash ileitis and young age at diagnosis (in some studies) have been described; however, the clinical role of these factors remains to be determined.<sup>(95)</sup> Smoking reduces the risk of CRC in chronic ulcerative colitis by 50%, but increases the risk of CRC in Crohn's disease 4-fold.<sup>(96)</sup> Pseudopolyps also increase the risk of CRC in chronic ulcerative colitis, by 2.5-fold, perhaps either as a historical marker of more severe inflammation or because pseudopolyps may obscure the sensitivity of surveillance colonoscopy.<sup>(97)</sup>

The ultimate protective factor against the development of CRC in chronic ulcerative colitis is proctocolectomy for all patients, beginning 8-10 years after the onset of disease. The currently recommended strategy for preventing CRC in this setting is to perform regular surveillance colonoscopy in all patients beginning at 8-10 years after the onset of disease, with proctocolectomy reserved for those patients with histologic evidence of dysplasia on mucosal biopsies. A colectomy at the time of low-grade dysplasia detection would have prevented advanced neoplasia from developing.<sup>(98)</sup>

## 22. Chemoprevention

**5-ASA agents;** have been suggested to have chemopreventive properties because of their structural and partial functional relationship with aspirin. A 2005 meta-analysis of 9 observational studies identified a significant risk reduction associated with 5-ASA therapy, with the OR for dysplasia and colorectal cancer combined (ie, combined endpoint) at 51% in patients with ulcerative colitis. Although the existing evidence for the protective association between 5-ASA use and colorectal cancer or dysplasia is promising but inconclusive, the potential benefit is based on good clinical rationale, and given the excellent safety profile of this class of drugs, will likely encourage compliance with long-term prescribed therapy.<sup>(99)</sup>

**Steroids, aspirin, NSAIDs.** There are several studies that suggest steroids, aspirin, and NSAIDs may reduce the risk of CRC in chronic ulcerative colitis. Although the long-term use of these therapies is not routinely encouraged in this patient population, these data are helpful in suggesting that a common anti-inflammatory or anticancer mechanism shared with 5-ASA may be important.<sup>(100)</sup>

**Immunomodulators;** data regarding the effects of these agents on CRC risk are mixed. The reason for these observed differences may relate to differences in the molecular properties of immunomodulators compared with other anti-inflammatory therapies, differences in the reduction in inflammation or mucosal healing achieved with each medication, or differences in the neoplasia risk of the underlying population taking each medication.<sup>(101)</sup>

**Ursodeoxycholic acid.** The strongest for chemoprevention is for ursodeoxycholic acid in PSC-chronic ulcerative colitis patients reducing the risk of CRC by 80%. Ursodeoxycholic acid is an antioxidant that reduces the colonic concentration of the secondary bile acid deoxycholic acid, a carcinogen.<sup>(102)</sup>

**Folate.** In the setting of sporadic CRC, low folate levels have been associated with an increased risk of developing colorectal adenomas and carcinomas. Patients with IBD are at risk for low folate levels due to reduced intestinal absorption because of competitive inhibition from sulfasalazine use and because of folate loss due to active disease. Several case-control studies show a nonstatistical trend that patients with chronic ulcerative colitis who consume folate tend to have a reduced risk of CRC. Despite lack of definitive clinical

evidence, many experts recommend folate supplementation in patients with long-standing chronic ulcerative colitis, on the basis of biological rationale and safety. <sup>(103,104)</sup>

5-ASA Formulation	Clinical Response	Induction Remission	Maintenance Remission	Mucosal Healing
Delayed and sustained release	+	+	+	+
Delayed release	+	-	+	-
Olsalazine	-	-	+	-
Balsalazide	+	-	-	-

Table 1. Proven efficacy of 5-ASA therapy in patients with ulcerative colitis

### 23. Pregnancy with ulcerative colitis

Fertility is affected in postsurgical ulcerative colitis. There are no increases in adverse outcomes with quiescent ulcerative colitis. Active disease at conception increases the risk for adverse outcomes. The majority of medications for ulcerative colitis are safe in pregnancy and breastfeeding as shown in table 2 and table 3. <sup>(105-109)</sup>

Category B Medications	Category C, D Medications	Contraindicated
Oral, topical mesalamine	Corticosteroids	Methotrexate
Sulfasalazine, olsalazine, balsalazide	Azathioprine	Thalidomide
Infliximab	6- mercaptopurine	
Ciprofloxacin, metronidazole (after first trimester)	Cyclosporine	
Loperamide	Diphenoxylate + atropine	

Table 2. Safety of IBD Medications During Pregnancy

Safe to Use When Indicated	Limited No Data	Contraindicated
Oral, topical mesalamine	Infliximab	Methotrexate
Sulfasalazine, olsalazine, balsalazide	Azathioprine	Thalidomide
Low doses of steroids (< 20 mg)	6- mercaptopurine	Cyclosporine

Table 3. Safety of IBD Medications During Breastfeeding

The indications for surgery during pregnancy are identical to those for nonpregnant patients, including obstruction, perforation, abscess, and hemorrhage. Although the obstetric indications for caesarean section do not differ in women with IBD, women with IBD undergo elective caesarean sections more frequently than do women in the normal population. <sup>(110)</sup>

## 24. Quality of living for patients with ulcerative colitis

Ulcerative colitis negatively affects physical and psychosocial well-being. Quality of Living is diminished in many patients with ulcerative colitis; strategies for improvement of Quality of Living must therefore be included in any therapeutic plan and there must be a multifaceted approach to improve Quality of Living.<sup>(111)</sup>

Disease activity seems to be the principal factor affecting Quality of Living. Identifying other potential factors that have a negative impact on Quality of Living is vital in order to achieve therapeutic success. Although drug therapy for ulcerative colitis is effective in achieving and maintaining remission, medication nonadherence remains a considerable obstacle, especially in quiescent disease. Patient-physician communication is crucial for successful management of patients with ulcerative colitis. Ultimately, choosing a therapy that is convenient, effective, and safe will help improve adherence, maintain remission, and potentially decrease the need for surgery or development of colorectal cancer.<sup>(112,113)</sup>

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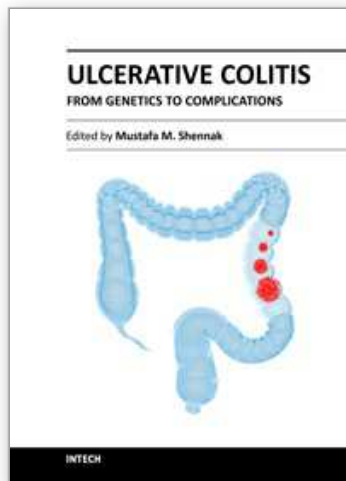
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## **Ulcerative Colitis from Genetics to Complications**

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Ulcerative Colitis (UC) is a rapidly evolving medical field, and will continue to be very exciting in the next few decades. Although the underlying cause of this disease is still unknown, results in research dealing with various issues related to this disease are published every day. Chapters included in this book review the most recent literature on related advancements in regard to this chronic disease, which is controllable but not curable. Aspects like epidemiology, pathophysiology, genetics, incriminated etiologies, clinical aspects, complications, and disease management, including advancements in the diagnostic and therapeutic options, were documented by well known clinicians, researchers, and world wide authorities in their fields. This book on UC will be a valuable addition to each doctor's library interested in this subject, or for physicians dealing with patients suffering from this disease. Authors have also included figures and diagrams to depict their point, and to easily reach the minds of the readers in the simplest way.

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