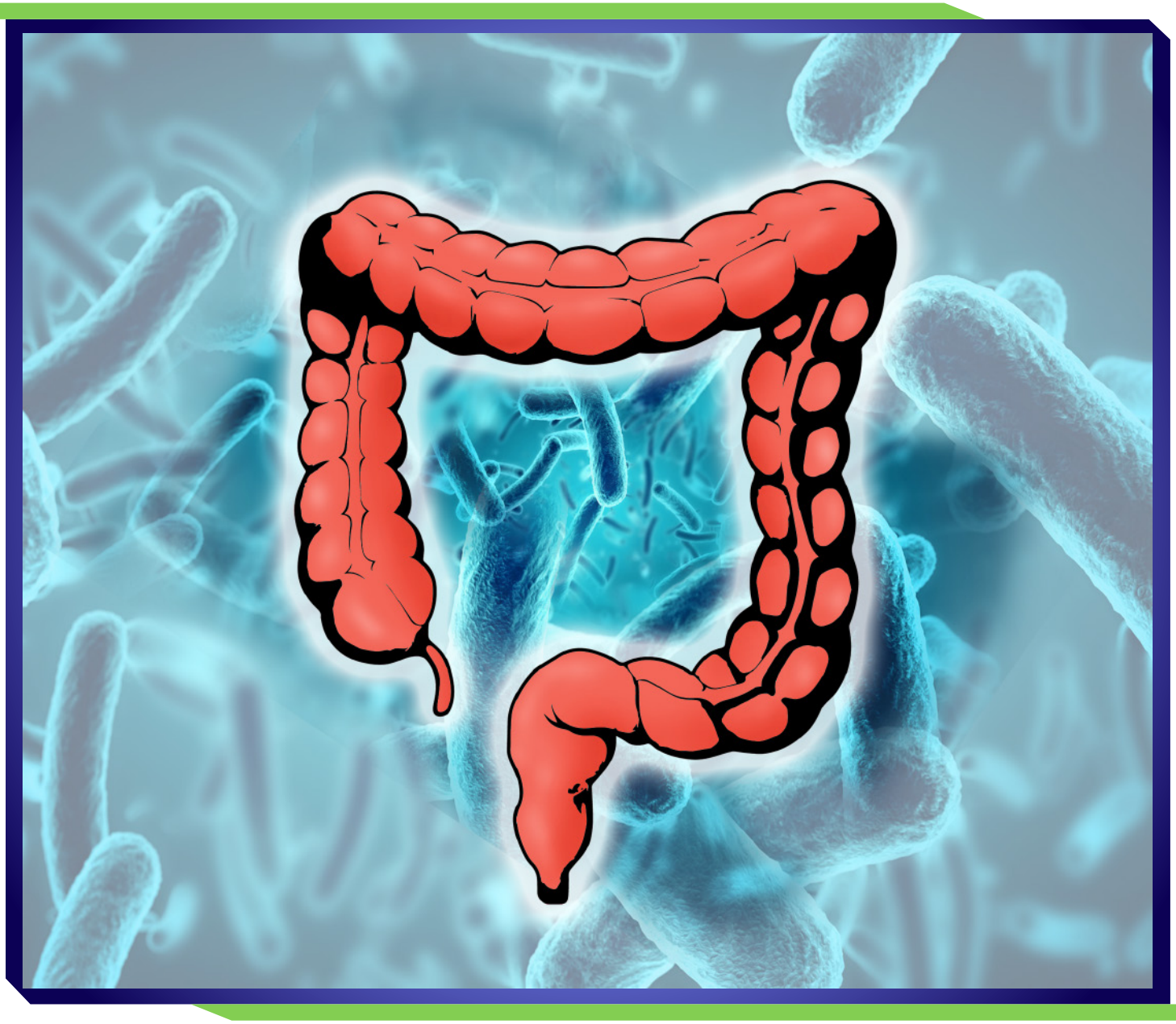
ULCERATIVE COLITIS:
Determining Ideal Targets for Treatment



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ANCC Accredited NCPD Hours: 2.1hrs

Target Audience: RN/APRN

Need Assessment

The need for precision medicine in ulcerative colitis will be greater than ever, as clinicians will have to choose which drug to use and which molecular pathway to target. An increased understanding of pharmacogenomics, biomarkers, and clinical features that identify subpopulations of patients who will best respond to specific medications will be needed to tailor therapy to individual patients. Other future research directions include combining biological therapies and head-to-head trials to determine the most optimal therapies and how to best position new medications.

Objectives

- Discuss the risk factors for ulcerative colitis
- Describe the pathophysiology of ulcerative colitis
- Identify the causes for mucosal inflammation in ulcerative colitis
- Discuss the clinical presentation and differential diagnosis in ulcerative colitis
- Describe the mainstay therapy in ulcerative colitis

Goal

The goal of this article is to examine the current high-quality disease management guidelines for Ulcerative Colitis, to ensure that investigation.

Introduction

Ulcerative colitis is a chronic inflammatory disease affecting the colon (as shown in fig.1). The pathogenesis is multifactorial (as shown in fig.2), involving genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors.

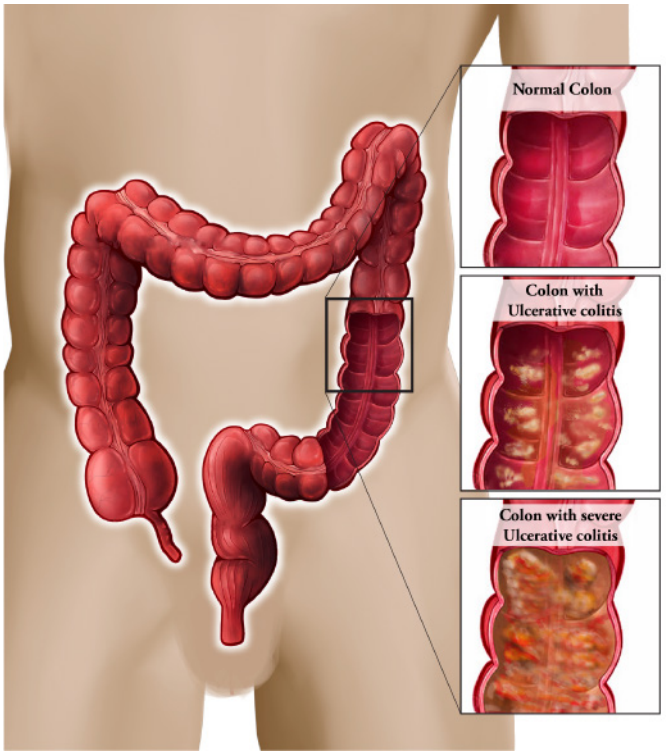

Figure 1 : Changes in colon with ulcerative colitis

Patients with ulcerative colitis have mucosal inflammation starting in the rectum that can extend continuously to proximal segments of the colon.

Ulcerative colitis usually presents with bloody diarrhoea and is diagnosed by colonoscopy and histological findings. ***The aim of management is to induce and then maintain remission, defined as resolution of symptoms and endoscopic healing.*** Treatments for ulcerative colitis include 5-aminosalicylic acid drugs, steroids, and immunosuppressants. Some patients can require colectomy for medically refractory disease or to treat colonic neoplasia. The therapeutic options for ulcerative colitis is expanding, and the number of drugs with new targets will rapidly increase in coming years. [1, Rank 5]

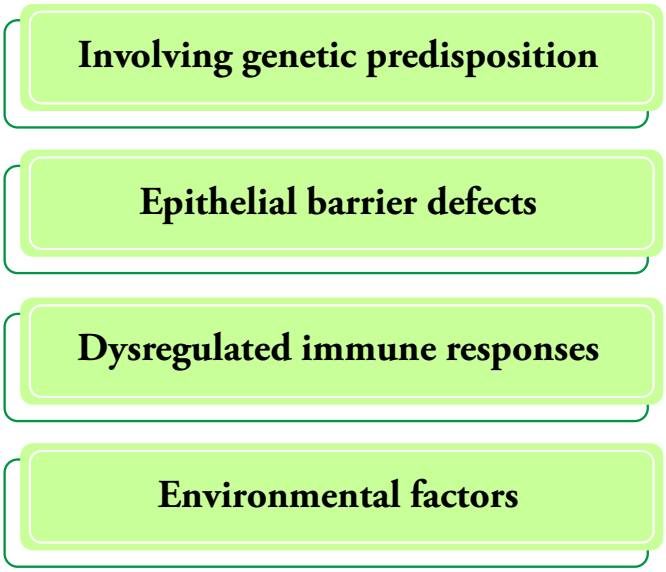

Figure 2: Pathogenisis of ulcerative colitis

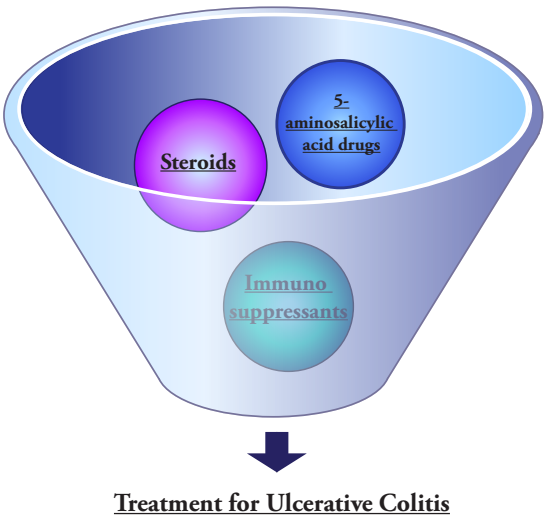

Figure 3: Treatments for ulcerative colitis

Risk Factors for Ulcerative Colitis

Many patients with ulcerative colitis have a family history of inflammatory bowel disease. First-degree relatives have four times the risk of developing the disease. Some populations have higher rates of ulcerative colitis than other ethnicities. Genome-wide association studies have identified 200 risk loci for inflammatory bowel disease to date, with most genes contributing to both ulcerative colitis and Crohn's disease phenotypes. Examples of loci associated with increased ulcerative colitis susceptibility include ***human leukocyte antigen and genes associated with barrier function, such as HNF4A and CDH1.*** However, genetics only explain 7.5% of disease variance, have little predictive capacity for phenotype, and currently are of limited clinical use.

The rising incidence of ulcerative colitis worldwide suggests the importance of environmental factors in its development. Former cigarette smoking is one of the strongest risk factors associated with ulcerative colitis, while active smokers are less likely to develop ulcerative colitis compared with former and non-smokers and have a milder disease course. ***Appendectomy appears to confer a protective effect against developing ulcerative colitis, especially when done for acute appendicitis in young patients.***

Patients newly diagnosed with ulcerative colitis are more likely than matched controls to have a history of gastroenteritis. Drugs, such as oral contraceptives, hormone replacement therapy, and non-steroidal anti-inflammatory drugs, have all been associated with an increased risk of ulcerative colitis, while antibiotic exposure has not. Breastfeeding appears to

Figure 4: Risk factors of Ulcerative colitis

decrease the risk of ulcerative colitis, while urban living can increase the risk. Certain ulcerative colitis risk factors that are significant in developed countries might not have the same effect in developing Asian or Middle Eastern populations. For example, smoking might not have as strong an effect, appendectomy does not appear to decrease risk, and antibiotics have been found to be protective when comparing developed countries with developing Asian or Middle Eastern countries. [2, Rank 3]

Pathophysiology of Ulcerative Colitis

Although existing literature often describes the pathogenesis of ulcerative colitis alongside that of Crohn's disease, important differences exist. Colonic epithelial cells (colonocytes), and mucous barrier and epithelial barrier defects are strongly implicated in the pathogenesis of ulcerative colitis(as shown in fig.5).

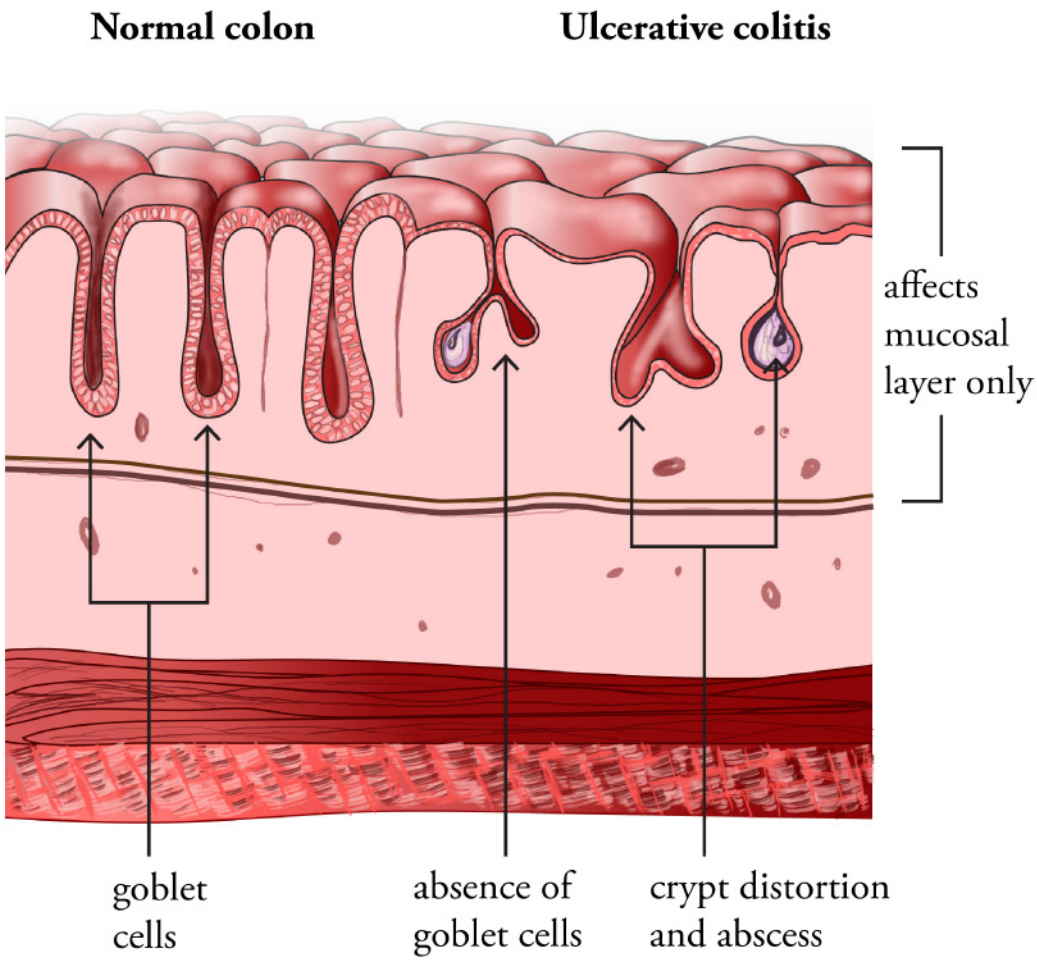

Figure 5: pathophysiology of Ulcerative colitis

The expression of peroxisome proliferator-activated receptor gamma (PPAR-γ), is reduced in the colonocytes of patients with ulcerative colitis. Existing PPAR-γ agonists are restricted by cardiac and metabolic toxicity. However, novel 5-aminosalicylic acid (5-ASA) analogues with greater PPAR-γ agonistic activity are being developed. Autoantibodies against colonocyte-associated tropomyosins have been described in ulcerative colitis, but conclusive evidence classifying ulcerative colitis as an autoantibody-mediated disease is scarce. Colonocyte-associated defects within XBP1, a key component of the endoplasmic reticulum stress response pathway, have been reported in ulcerative colitis. [4, Rank 4]

The contention that barrier function defects are the primary drivers of disease is supported by the fact that patients with active ulcerative colitis have depleted colonic goblet cells and a permeable mucus barrier.

Causes for Mucosal Inflammation in Ulcerative Colitis

Activated neutrophils accumulate in the blood and colonic tissue of patients with active ulcerative colitis compared with normal volunteers. Dendritic cells in patients with ulcerative colitis have enhanced expression of costimulatory molecules and are likely to be first responders in the setting of a breach in barrier integrity.

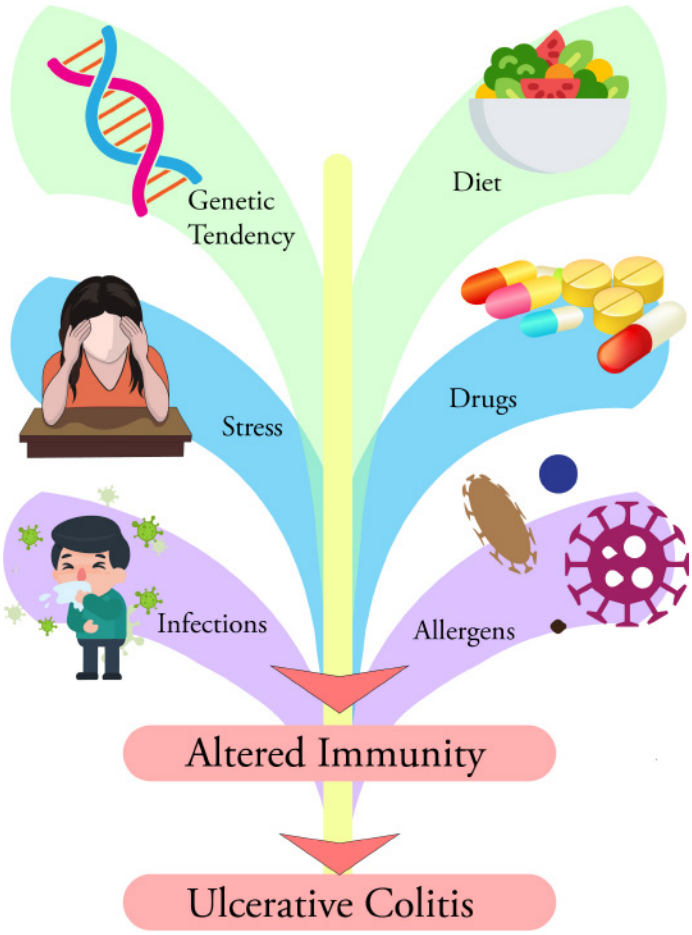

Figure 6: Immunity and Ulcerative colitis

Although elevated IgM, IgA, and IgG concentrations are reported in inflammatory bowel disease, there is a disproportionate increase in IgG1 antibodies in patients with ulcerative colitis. It is not known whether B cells are drivers of disease pathogenesis or merely responsive to barrier disruption.

Current evidence implicates both innate and adaptive cellular immunity as key to disease pathogenesis. Earlier evidence suggested that ulcerative colitis is a

modified T-helper-2 (Th2) disease, while Crohn's disease is Th1 driven. Extending the T-helper Th1/Th2 paradigm for Crohn's disease versus ulcerative colitis, data from 2014 show that a novel population of CD4-positive Th cells, which produce interleukin-9 (IL-9), are identified by the transcription factor PU.1 and contribute to the development of ulcerative colitis . IL-9 produced by Th9 cells inhibits cellular proliferation and repair. They have a negative effect on intestinal barrier function. Additionally, IL-9 modestly but significantly increases tissue concentrations of tumour necrosis factor-α (TNF-α) . [6, Rank 4]

Clinical Presentation and Differential Diagnosis of Ulcerative Colitis

Ulcerative colitis is a chronic disease affecting the colonic mucosa that most commonly presents with blood in the stool and diarrhoea. Up to 15% of patients can initially present with severe disease. Symptoms(as shown in fig.7) can include urgency, incontinence, fatigue, increased frequency of bowel movements, mucus discharge, nocturnal defecations, and abdominal discomfort (cramps), although abdominal pain tends to be less of a hallmark feature than in Crohn's disease. Fevers and weight loss can also be present in severe disease. Ulcerative colitis is classified by the extent of colonic involvement.

Figure 7: symptoms of Ulcerative colitis

Clinical presentation might vary on the basis of disease extent. Patients with proctitis might predominantly have urgency and tenesmus (sensation of incomplete evacuation), while in pancolitis, bloody diarrhoea and abdominal pain might be more prominent. Up to 10% of patients with proctitis or left-sided colitis can suffer from paradoxical constipation. ***Physical examination might reveal signs of anaemia,***

abdominal tenderness, and blood on rectal exam. Abdominal distention and tympany on percussion might indicate colonic dilatation, requiring prompt radiological assessment. Patients with ulcerative colitis might have anal fissures or skin tags due to irritation from diarrhoea, but the presence of anal or perianal fistulas should raise suspicion for Crohn's disease. Clostridium difficile is an important precipitant of flares and is associated with an increased risk of surgery and mortality, and should be ruled out at diagnosis and flare-ups. [9, Rank 3]

Extraintestinal manifestations can occur in about a third of patients with ulcerative colitis, and up to a quarter might have extraintestinal manifestations before inflammatory bowel disease diagnosis. Peripheral arthritis appears to be the most common extraintestinal manifestation. Primary sclerosing cholangitis and pyoderma gangrenosum are more common in ulcerative colitis than in Crohn's disease. The risk of venous thromboembolism in patients with inflammatory bowel disease is increased three to four times, and is greater when the patient is admitted with a flare or being treated with corticosteroids. Clinicians should have a high index of suspicion for venous thromboembolism, and hospitalised patients with ulcerative colitis should be prescribed venous thromboembolism prophylaxis. [10, Rank 5]

> **" Ulcerative colitis is a chronic inflammatory disease affecting the colon Ulcerative colitis usually presents with bloody diarrhoea and is diagnosed by colonoscopy and histological findings Some patients can require colectomy for medically refractory disease or to treat colonic neoplasia "**

Mild to Moderate Disease Activity in Ulcerative Colitis

UC is a chronic inflammatory bowel disease with onset most frequently in young adulthood. Most patients with UC have a mild-to-moderate course characterized by periods of activity or remission. Over 90% of patients with UC are treated with 5-aminosalicylates (5-ASA) shortly after disease diagnosis, and most who achieve clinical remission with these medications continue them for maintenance of remission. The minority of patients with UC require immunomodulators or biologic therapies for disease control.

The severity of UC is generally classified as mild-to-moderate or moderate-to-severe. The definition of mild-to-moderate disease activity in UC varies in clinical practice and the medical literature. For this guideline and the accompanying technical

review, mild-moderate UC was defined as patients with fewer than 4–6 bowel movements per day, mild-moderate rectal bleeding, absence of constitutional symptoms, low overall inflammatory burden, and absence of features suggestive of high inflammatory activity based upon Truelove and Witt's criteria and the Mayo Clinic score. Although disease activity exists on a spectrum, patients in the mild-moderate category who have more frequent bowel movements, more prominent rectal bleeding, or greater overall inflammatory burden should be considered to have moderate disease.

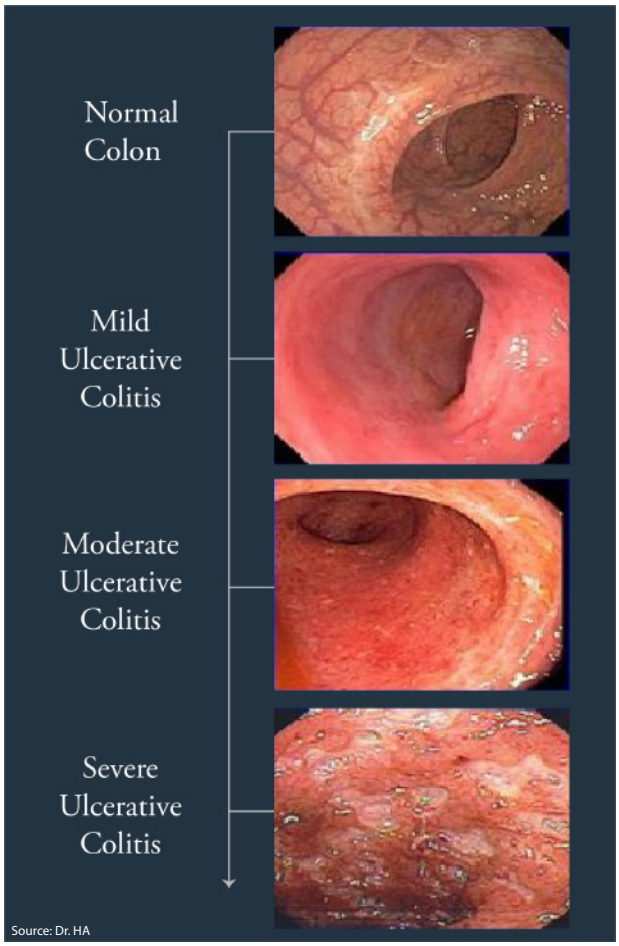

Figure 8: different types of ulcerative colitis

Patients with mild-moderate disease activity generally are at low risk of requiring colectomy. However, certain disease features, even in patients who present initially with mild-moderate disease activity, may predict an aggressive disease course. These include age less than 40 years at diagnosis, extensive disease, severe endoscopic activity (presence of deep ulcers), extra-intestinal manifestations, and elevated inflammatory markers.

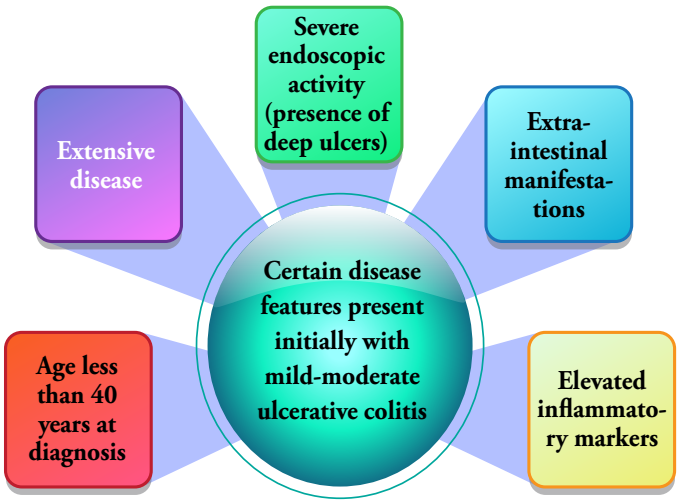

Figure 9: Certain disease features present initially with mild-moderate ulcerative colitis

Clinicians should be aware of these high-risk features to identify patients would may benefit from more aggressive initial therapy or who might need more rapid intensification of therapy if symptoms are not adequately controlled. In addition, clinicians should avoid repeated courses of corticosteroids, even in those with mild-moderate disease, and consider escalation of therapy in patients who frequently need corticosteroids for disease control. [12, Rank 5]

Mainstay Therapy for Ulcerative Colitis

The mainstay of therapy for mild-moderate UC is the 5-ASA class of medications, including sulfasalazine, mesalamine, and diazo-bonded 5-ASA. Sulfasalazine, the oldest medication in this class, consists of 5-ASA bonded to sulfapyridine. Sulfasalazine is converted to the sulfapyridine and 5-ASA moieties by colonic bacteria. The 5-ASA moiety is believed to be the active compound for treatment of UC, while sulfapyridine is thought to contribute to adverse effects.

Mesalamine is available in a variety of formulations designed to deliver the active compound to different parts of the small and/or large intestine. Diazo-bonded 5-ASAs, including balsalazide and olsalazine, are prodrugs converted to 5-ASA by colonic bacteria. Systemic exposure to 5-ASA is similar for all oral mesalamine preparations and diazo-bonded 5-ASAs. Therapeutic efficacy and safety are also similar with different 5-ASA formulations. Therefore, comparability of the different commercial formulations of mesalamine at equivalent doses was assumed for purposes of this guideline.

Patients with UC may have variable anatomic extent of their disease. Conventionally, patients are defined as having extensive disease if inflammation extends proximal to the splenic flexure, left-sided disease if inflammation extends proximal to the rectum but not past the splenic flexure (or <50 cm from the anus), and proctitis if inflammation is limited to the rectum (or <15–20 cm from the anus). Both disease severity and anatomic extent are important in choosing appropriate treatment. [11, Rank 3]

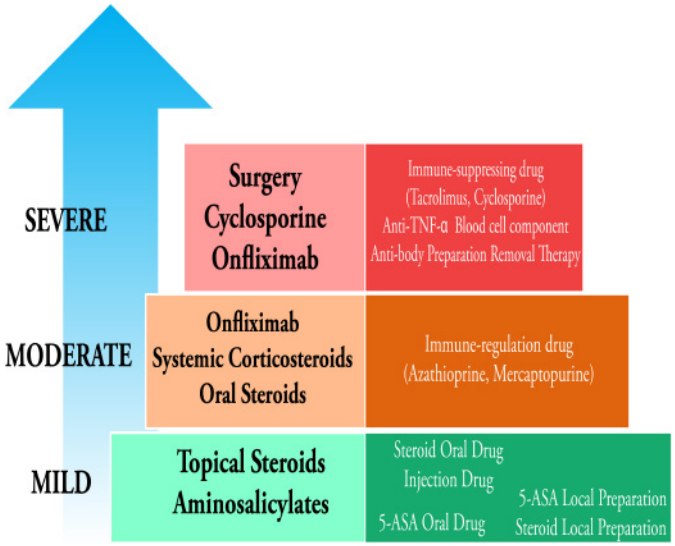

Figure 10: Drug therapy in ulcerative colitis

Combined Oral & Rectal Therapy

Combined oral and rectal therapy may allow a higher effective dose of 5-ASA to be delivered to the involved area of the colon. The strategy of combining oral and topical therapy allows optimization of 5-ASA regimens to achieve higher rates of induction and maintenance of remission, potentially avoid-

ing escalation of therapy to corticosteroids or immunosuppression. A potential drawback to a combined strategy is low patient acceptance of topical therapy and suboptimal adherence. Patients may prefer to try oral therapy first, with addition of rectal therapy in the event of inadequate response. Although trials did not compare optimized combination therapy with oral and rectal 5-ASA vs. corticosteroids and/or immunosuppressive therapy in the subset of patients with persistent mild-moderate disease activity, combination therapy may be able to salvage some patients with inadequate response to oral 5-ASA, and may be more acceptable to patients who wish to avoid corticosteroids or immunosuppression.

The overall evidence for this recommendation was rated as moderate quality. The event rates in both the induction and maintenance trials were low, leading to imprecision. In the maintenance studies, the oral mesalamine groups received low-dose mesalamine, but the oral and rectal treatment groups received over 2 grams of mesalamine in total, leading to indirectness because of differences in the total doses of medications received.

The American Gastroenterologist Assosciation suggests using combined high-dose oral mesalamine with rectal 5-ASA in patients with suboptimal response to standard-dose mesalamine or diazo-bonded 5-ASA or in patients with moderate disease activity, as defined above. High-dose oral mesalamine may have a modest benefit over standard-dose for induction of remission, and is similar for maintenance of remission. Escalating to high-dose over standard-dose mesalamine may thus have a modest benefit for achieving and maintaining remission. As discussed in recommendation 2, addition of rectal therapy may provide some additional benefit over oral therapy alone, although some patients prefer to avoid rectal therapy. Optimization of 5-ASA therapy by using high-dose oral therapy combined with rectal therapy may allow some patients to avoid corticosteroids or immunosuppression.

If patients are experiencing progressively worsening symptoms and increasing disease severity (for example, extra-intestinal manifestations or constitutional symptoms such as weight loss or fevers), escalation to high-dose oral mesalamine with rectal therapy may not be effective. These patients should be considered for use of systemic corticosteroids, biologic therapies and/or immunomodulators to induce disease remission. Continuing 5-ASA-based therapy in these patients may delay more effective therapy and place patients at risk for worsening disease and complications. [14, Rank 5]

The guideline first discusses appropriate therapy for patients with extensive disease, with additional specific recommen-

dations for patients with proctosigmoiditis or isolated proctitis. The guideline also covers less conventional therapies including probiotics, curcumin, and fecal microbiota transplantation. While this guideline is intended to assist in management of patients with mild-to-moderate UC, some patients will not respond adequately to the therapies, and may need to escalate therapy to systemic corticosteroids, immunomodulators, and/or biologic therapies for induction and maintenance of remission. The use of biologic therapies and/or immunomodulators is not specifically addressed in this guideline.

Estimates of the effects of different medications are presented as the 'risk for failure' to induce or maintain remission. Therefore, a relative risk (RR) less than one indicates that the agent under evaluation is more effective than the comparison medication or placebo for inducing or maintaining remission; a RR greater than one indicates that the agent under evaluation is less effective. [13, Rank 3]

> **"Clostridium difficile is an important precipitant of flares and is associated with an increased risk of surgery and mortality, and should be ruled out at diagnosis and flare-ups."**

Managing Side-effects of Medications for Ulcerative Colitis

Medication like Sulfasalazine is often poorly tolerated due to side effects such as headache, nausea, diarrhea, and rash. Patients often need to start at lower-dose sulfasalazine with gradual dose escalation as tolerated. In addition, sulfasalazine interferes with folic acid metabolism, and patients are recommended to take folate supplementation. Rare but serious cutaneous side effects, allergic reactions, hepatitis, and hematologic toxicity are also possible. Because of these side effects, laboratory monitoring of complete blood counts and liver function tests is needed. Overall, sulfasalazine may be more difficult to incorporate routinely into clinical practice because of its adverse effects and need for laboratory monitoring. However, sulfasalazine is commonly prescribed for rheumatologic disorders including spondyloarthropathies, rheumatoid arthritis and psoriatic arthritis. Patients with concomitant arthritic symptoms may benefit from its use.

Overall, standard-dose mesalamine and diazo-bonded 5-ASA are effective for both induction and maintenance of remission. There may be a small benefit for high-dose mesalamine over standard-dose mesalamine for induction of remission, but

not necessarily maintenance. Balsalazide is the better tolerated diazo-bonded 5-ASA, with similar effectiveness to standard-dose mesalamine for induction and better efficacy for maintenance. Therefore, either standard-dose mesalamine or balsalazide are appropriate for treatment of extensive mild-to-moderate UC. Sulfasalazine is potentially an acceptable alternative in patients who can tolerate it or in patients with prominent arthritic symptoms. [15, Rank 4]

Dosage of Medications for Ulcerative Colitis

The American Gastroenterologist Assosciation suggests using standard-dose oral mesalamine or diazo-bonded 5-ASA over budesonide preparations for induction of remission. Budesonide is a high potency corticosteroid with low systemic activity due to first pass metabolism by the liver. Two oral preparations of budesonide are currently available. Budesonide MMX is designed for release throughout the colon and is approved by the FDA for treatment of UC, while controlled ileal release (CIR) budesonide is primarily released in the distal ileum and right colon and has not been specifically approved for UC. Evidence for use of CIR-budesonide was derived from a 4-arm RCT comparing different doses of budesonide MMX to placebo, in which CIR-budesonide was used as an active comparator. There are few long-term efficacies or safety data for use of budesonide for maintenance of remission, and therefore budesonide is unsuitable for maintenance therapy given the potential for corticosteroid-related adverse effects.

The quality of evidence for budesonide MMX vs. placebo was moderate, and was rated down for imprecision due to low event rates. Evidence for CIR-budesonide vs. placebo and for budesonide MMX vs. mesalamine was rated as low quality due to imprecision and high risk of bias in the available studies. Evidence comparing CIR-budesonide to mesalamine was rated as moderate and was rated down due to low event rates. [17, Rank 3]

Studies of topical mesalamines for UC have used varying definitions of left-sided disease. Some have defined left-sided disease as inflammation extending up to the splenic flexure, while others have used a definition of inflammation extending <50cm from the anus. However, enema preparations are unlikely to reach proximal to the sigmoid colon. Patients with inflammation extending into the descending colon may more appropriately be treated with combined oral and topical therapy.

Clinicians recognize that many

patients prefer oral over topical therapy, and that adherence to rectal therapy may be inadequate. An additional limitation of rectal therapy is that patients with active disease may have difficulty retaining enemas adequately due to discomfort and urgency. Given these limitations and the uncertainty in the effect estimates, patients with mild-moderate ulcerative proctitis or proctosigmoiditis who place higher value on convenience of oral medication administration may reasonably choose oral 5-ASA over rectal therapy. Some patients with left-sided UC may choose to use combined oral and rectal therapy. [18, Rank 3]

Overall, rectal 5-ASA is superior to rectal corticosteroids for induction of remission, and both are superior to placebo. Given potential safety concerns with long-term rectal corticosteroids and superiority of rectal 5-ASA for inducing remission, topical 5-ASAs are preferred. In general, rectal 5-ASA and corticosteroids are both well tolerated. However, some patients, particularly those with active disease, experience discomfort with enemas or are unable to retain them adequately. Patients may prefer corticosteroid foam preparations over enemas because of ease of delivery, better tolerability and improved retention. Foam and enema preparations of the same medication have similar efficacy. Thus, patients on rectal therapy who place a higher value on ease and tolerance of medication administration may reasonably choose corticosteroid foam preparations over mesalamine enemas.

The American Gastroenterologist Assosciation suggests using rectal corticosteroid therapy in patients with ulcerative proctitis who are refractory to or intolerant of mesalamine suppositories. Although there are no RCTs of corticosteroid suppositories in this population, indirect evidence from patients with ulcerative proctosigmoiditis suggests a benefit of rectal corticosteroids, as noted above. Additionally, some patients with prominent proctitis symptoms may tolerate a foam preparation with less discomfort and improved retention compared to a suppository. Therefore, a trial of a rectal corticosteroid is reasonable for patients with inadequate response or tolerance to mesalamine suppositories. Patients with refractory symptoms could also be considered for oral 5-ASAs or systemic corticosteroids. [16, Rank 4]

“ Naive lymphocytes are imprinted during activation with specific trafficking programmes. Dendritic cells play a central part in this process by integrating environmental cues and inducing expression of specific integrins and chemokine receptors ”

Methods for Management of Patients who Fail to Achieve Clinical Remission

Patients may fail to achieve clinical remission despite optimized use of 5-ASA therapy as outlined in the preceding recommendations. Management of these patients requires escalation of therapy, most commonly consideration of a course of corticosteroids to achieve disease control. Some patients with high-risk features as outlined in the introduction may also need earlier consideration of corticosteroids. Second-generation corticosteroids and oral prednisone appear to be equally effective for induction of remission in this situation, although in one study comparing prednisolone to fluticasone, symptoms improved more rapidly with prednisolone.

Second-generation corticosteroids appear to have fewer corticosteroid-related side effects, but are significantly more costly than oral prednisone. Therefore, the choice between budesonide MMX and oral prednisone primarily involves trading-off costs and potential for adverse events. Patients who place higher value on avoidance of side effects and lower value on avoiding costs can reasonably choose budesonide MMX in this situation. Lastly, patients who require repeated or prolonged corticosteroid courses should be considered for escalation to biologic therapies and/or immunomodulators. [20, Rank 4]

> **"Although elevated IgM, IgA, and IgG concentrations are reported in inflammatory bowel disease, there is a disproportionate increase in IgG1 antibodies in patients with ulcerative colitis"**

Although probiotics are popular amongst patients with UC, their benefit for either inducing or maintaining remission is unclear. In general, probiotics are well-tolerated with low rates of adverse effects. However, if they are used instead of other proven therapy, patients are at risk for progressive symptoms and disease complications. Thus, given their lack of proven efficacy, probiotics should not be used instead of therapies known to be effective. The effectiveness of probiotics added on to proven therapies such as oral or rectal 5-ASA is unknown.

The identified RCTs were inconsistent in studying several different probiotic formulations and with heterogeneous results. Additional research in this area is needed to identify patient populations for whom probiotics might be beneficial, to identify specific bacterial strains with the

greatest therapeutic potential, and to determine appropriate doses. [19, Rank 3]

Curcumin has immunomodulatory, pro-apoptotic, and anti-angiogenic properties that have sparked interest in its use for immune-mediated diseases. Because of curcumin's taste and color, it is difficult to develop true placebos for RCTs, and studies of its efficacy are at risk of bias due to inadequate blinding. Curcumin is generally well tolerated without significant harmful effects. The potential risk of using curcumin is delaying more effective therapy with potential for symptom progression. Larger well-designed studies of curcumin are needed to define its role in patients who do or do not respond to proven therapy such as oral or topical 5-ASA and to evaluate its effectiveness for maintenance. [22, Rank 2]

The current evidence supports use of standard-dose mesalamine or diazo-bonded 5-ASAs for induction and maintenance of remission in patients with extensive mild-moderate UC. Use of combined oral and rectal 5-ASA in patients with extensive disease may improve rates of induction of remission, as may escalation to high-dose oral with rectal 5-ASA in patients with suboptimal response to standard-dose therapy. Those with moderate symptoms may benefit from early use of combined oral and rectal 5-ASA. Patients with proctosigmoiditis or proctitis can be treated with topical mesalamines rather than oral 5-ASA. Those patients with suboptimal response or intolerance to rectal mesalamine may opt to use rectal corticosteroids enemas or foams. Patients with inadequate response to optimized 5-ASA require escalation of therapy to oral prednisone or budesonide. [21, Rank 5]

Evolving Targets in Treatment of Ulcerative Colitis

Clinical Targets

Patient reported outcomes such as resolution of rectal bleeding and bowel habit normalization, should be a therapeutic target for UC. However, including objective inflammation measures as clinical study endpoints is important because the use of patient reported outcomes alone has resulted in high remission rates for placebo. Furthermore, a small but consistent proportion of patients with endoscopic and histological remission may continue to report symptoms of unknown etiology. Noninflammatory mechanisms, such as small intestinal bacterial overgrowth, bile acid diarrhea, changes in motility or permeability, neurologic abnormalities, dysbiosis, or chronic fibrotic changes, may be possible causes.

Conversely, around a quarter of patients who are clinically asymptomatic

have endoscopically active disease. Interestingly, patients report a higher symptom burden than their healthcare providers using the same index; thus, the data collection method may be important to consider. Although simple surveys and/or mobile applications could improve symptom reporting by patients, these findings altogether point to the shortcomings of using solely clinical endpoints or patient reported outcomes to reliably assess disease status. Given the US Food and Drug Administration's recognition of patient reported outcomes as a clinical target, stool frequency and rectal bleeding remain important, although tools to monitor and quantify these measures need to be refined. Ultimately, evidence suggests that symptoms should be supplemented with objective targets. [20, Rank 4]

Quality of Life Measures

The restoration of a patient's quality of life (QoL) is mostly considered to be the ultimate goal. There are inherent challenges in using QoL endpoints, such as the lack of standardized instruments and the subjective nature of QoL. Two prospective studies using different instruments reported high-to-moderate correlation between QoL scores and clinical drug response over a short time. The disease-specific Inflammatory Bowel Disease Questionnaire measure was dose-responsive and had a linear correlation with Mayo scores (endoscopic score of disease activity). Therefore, although evidence of active disease association with reduced QoL continues to accumulate, consensus on QoL instruments across IBD studies remains a challenge.

> **"Extraintestinal manifestations can occur in about a third of patients with ulcerative colitis, and up to a quarter might have extraintestinal manifestations before inflammatory bowel disease diagnosis"**

Some clinicians have suggested that an objective disability index may be a valuable long-term target as well. The IBD disability index was developed according to World Health Organization disability classifications. The instrument has since been validated, opening the door for measuring disability in clinical trials. In studies investigating factors associated with disability, active disease, poor drug adherence, and corticosteroid treatment (vs biological treatment) were associated with increased disability, supporting the utility of the IBD disability index.

Fatigue is commonly reported in

patients with IBD and is associated with active disease; chronic fatigue has recently been shown to be more prevalent in patients with IBD than in a reference population. Fatigue has been associated with poor QoL using both general and IBD-specific instruments, emphasizing the importance of this patient reported outcomes domain. However, validation of objective measures of fatigue is needed before incorporating it as a target in UC. [23, Rank 3]

Endoscopic Targets

Endoscopic mucosal healing measurement is foundational to the indexes of disease severity and extent. The most often used endoscopic disease activity metrics are the UC Endoscopic Index of Severity (UCEIS) and the Mayo Clinic indexes (Mayo score). Despite extensive research, these indexes are not fully validated and can be subject to interobserver disagreement. The UCEIS has shown less intra- and inter-reader variability than the Mayo score. Since that time, studies have shown that UCEIS has a better correlation with disease severity and treatment responsiveness than the Mayo score and is more sensitive to detect deep ulcers becoming smaller and shallower, which the Mayo score overlooks. Recent Mayo score variations may surpass the original by incorporating the extent of inflammation along the colon while attempting to preserve the score's ease of use.

Several studies preferred the Mayo score for real-world endoscopic healing evaluations, but emerging evidence supports UCEIS. For settings where the Mayo score is still preferred, centralization can improve interobserver agreement for the endoscopic components, and a recent study suggested that training can improve consistency in community settings.

When the recommendations were developed, targets for the Mayo and UCEIS indexes were under debate, with a score of 1 considered the minimum target for both. Recent evidence suggests that more stringent endoscopic goals are associated with better outcomes and lower relapse risk.

Procedure type can also influence endoscopic assessments. Sigmoidoscopy is

> **" The mainstay of therapy for mild-moderate UC is the 5-ASA class of medications, including sulfasalazine, mesalamine, and diazo-bonded 5-ASA. Medication like Sulfasalazine is often poorly tolerated due to side effects such as headache, nausea, diarrhea, and rash. "**

the standard technique in clinical trials, whereas colonoscopy is typically performed in clinical practice to confirm UC diagnosis and assess disease. A recent study demonstrated that sigmoidoscopy can evaluate distal colon inflammation with accuracy comparable with colonoscopy, particularly in patients with active disease.

Novel endoscopic imaging techniques (e.g., computed virtual chromoendoscopy, confocal laser endomicroscopy) may improve diagnostic accuracy for assessing endoscopic healing in UC. For example, confocal laser endomicroscopy can evaluate mucosal permeability that correlates with disease severity and treatment response. However, these imaging techniques require specialized training, and their utility in routine clinical care is still unclear. [25, Rank 5]

Histological Targets

In UC, histological remission, defined as microscopic normalization of colonic mucosa, is distinct from endoscopic remission, which entails the resolution of endoscopically visible disease activity. Of several histology indexes available, the Nancy index and the Robarts Histopathology Index (RHI) have been the most studied indexes. In a prospective observational study, 87.1% of patients with histological remission at initial assessment remained in clinical remission after 1 year. In addition, histological remission in patients with UC was a strong predictor of steroid-free remission and clinical recurrence after 3 years of follow-up and was associated with lower hospitalization and corticosteroid use rates over a median follow-up period of 6 years. In a retrospective study, histological normalization was associated with increased odds of relapse-free survival compared with endoscopic healing or histological quiescence. Together, these data suggest that histologic remission can predict long-term outcomes.

Thus, including histological endpoints as treatment targets should enter into consideration. However, a uniform validated histology index is still needed because some researchers used the Nancy score, whereas the other studies used different indexes. [27, Rank 4]

Validation of histologic indexes could broaden the use of this mucosal healing measure beyond its current limited application. The RHI was developed by selecting histopathological descriptors that had intra- and inter-reader reliability across the Geboes score, modified Riley score, and a visual analog scale. RHI incorporates the level of chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in the epithelium, and any erosion or ulcera-

tion present in the mucosal tissue.

Similarly, the Nancy index scores ulceration, acute inflammatory cell infiltrate (i.e., neutrophils), and chronic inflammatory infiltrate (i.e., lymphocytes, plasmacytes). These 2 indexes correlate with clinical remission and disease activity, as well as with the Mayo endoscopic score and fecal calprotectin (Fecal calprotectin) concentrations. These indexes provide an opportunity for wider adoption of simplified or reliable histological scoring systems; however, further research is needed to validate their relationship with long-term outcomes, to establish clinically meaningful cutoff points, and to explore the feasibility and reliability of their practical adoption among community pathologists.

In the future, molecular studies may complement tissue exams for histological evaluation in UC. In this regard, intramucosal calprotectin was found to be associated with histological, endoscopic, and clinical remission. [29, Rank 3]

Imaging Targets

Imaging modalities are an attractive monitoring alternative compared with the invasive current procedures but are not yet considered sufficient to evaluate mucosal healing in UC, novel methods notwithstanding. A magnetic resonance enterography disease index (magnetic resonance (MR) index of activity) was found to be viable to assess mucosal healing in a small cohort of patients with Crohn's disease (CD). One study demonstrated that diffusion-weighted magnetic resonance imaging (MRI) using an MRI-specific index (Nancy score) accurately defined mucosal healing (endoscopically determined) in a small cohort of patients with UC. Similarly, MR colonography was found to have a high accuracy for the diagnosis of disease activity and severity in UC. Further research to validate imaging modalities, indexes, and correlations with long-term disease outcomes are needed.

Ultrasound, a noninvasive radiation-free imaging modality used to evaluate the extent of disease activity (i.e., mucosal alterations, transmural involvement), was shown to have sensitivity and specificity similar to that of MRI and computed tomography for the diagnosis of IBD. Several studies had investigated the ability of contrast-enhanced ultrasound to distinguish between quiescent and active disease via vascular activity. A systematic review on the utility of ultrasound for disease monitoring found that several UC ultrasound indexes have been developed, but they generally assessed bowel wall thickness, Doppler signal, wall layer stratification, compressibility, fatty wrapping, and strain pat-

tern. The researchers concluded that indexes have been developed with suboptimal methodology, thus development and validation of a new index are warranted [30, Rank 3]

Biomarkers as Targets

Although endoscopic and histological assessments are direct disease measures, they are invasive and costly, and thus non-invasive biomarkers of mucosal healing, treatment response, and/or disease flares are desirable. There was insufficient evidence supporting the use of biomarkers as surrogate endpoints for treatment optimization. However, data on the clinical utility of biomarkers, particularly Fecal calprotectin, have been accumulating. Regular Fecal calprotectin monitoring, with treatment escalation in patients with increased levels was associated with a reduced rate of relapse, albeit non-statistically significant. In addition, mesalamine dose escalation reduced calprotectin levels to <100 μg/g, and relapse occurred sooner in patients with calprotectin level >200 μg/g.

New longitudinal observational studies found that escalating Fecal calprotectin concentrations may predict relapse in patients with inactive UC as early as 3 months before the presentation of symptoms. Whether Fecal calprotectin concentration changes can be used as surrogates of treatment response is still under investigation. Studies have reported that Fecal calprotectin concentration reductions may be predictive of endoscopic and histological response to induction therapy and clinical remission.

Low Fecal calprotectin concentrations also correlate with the absence of mucosal inflammation or structural abnormalities. In addition, reductions in Fecal calprotectin during treatment have been found to be dose-responsive. A meta-analysis defined an optimum cutoff point for Fecal calprotectin as 50 μg/g, but various concentration thresholds have been used across correlative studies. Thus, standardization and validation of a single Fecal calprotectin cut-off point is needed to characterize its specificity and sensitivity as a biomarker ready for clinical practice. Because clinical data increasingly support Fecal calprotectin as a UC biomarker, the optimal therapeutic target needs to be determined via well-designed disease-modification trials. [33, Rank 3]

Studies are underway to identify and characterize additional promising fecal biomarkers such as leucine-rich α-2 glycoprotein, prostaglandin E-major urinary metabolite, hemoglobin concentration, M2-pyruvate kinase, lactoferrin, and high mobility group box 1.

There are conflicting data on the utility of serological biomarkers as predictors of disease activity. C-reactive protein (CRP) and erythrocyte sedimentation rate were found to have low accuracy in detecting endoscopic activity in patients with UC. A post hoc analysis of a prospective clinical trial showed that CRP levels failed to discriminate between patients in clinical remission, with endoscopic inflammation and with mucosal healing. In pediatric patients with UC, neither marker was found to be useful in predicting clinical, endoscopic, or histological UC disease activity. [31, Rank 2]

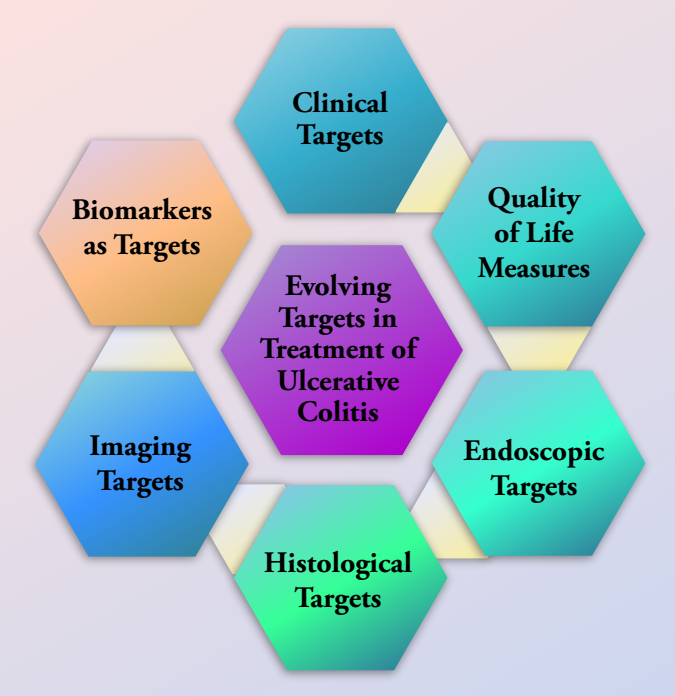

Figure 11: Evolving Targets in Treatment of Ulcerative Colitis

Evolving Targets in Treatment of Ulcerative Colitis

The treatment approaches in UC may require greater healthcare utilization, wider use of invasive procedures, and treatment escalation in the face of apparent symptomatic resolution, which raises potential barriers to implementation from patients, payers, and clinicians. Moreover, although the consensus provided therapeutic goals, practical algorithms to reach these goals are needed. Thus, integration of management into real-world UC clinical settings requires evidence generation to demonstrate its benefits and to validate therapeutic algorithms

Demonstrating that the treatment approach can modify the disease course and prevent disability and long-term complications is critical to justify the added costs and healthcare utilization. Even in CD, where the CALM trial demonstrated that a tight control algorithm could improve clinical and endoscopic outcomes, long-term follow-up was necessary to evaluate the impact on disease course and support a paradigm shift in management. Another study along similar lines is currently underway.

For UC, researchers propose an algorithm for incorporating T2T approaches into clinical care. However, this or any other algorithm would require prospective clini-

cal studies to demonstrate its impact on disease outcomes and QoL. [32, Rank 4]

Evaluation of Endoscopic Healing in Ulcerative Colitis

Regarding the evaluation of endoscopic healing, the immaturity of the evidence connecting the pursuit of endoscopic targets to improved long-term outcomes represents a barrier for practical acceptance. This review captures the dichotomy between 2 disease score methods, either Mayo or UCEIS can be used. In our opinion, UCEIS is the preferable score, although Mayo may be more familiar and therefore more feasible in clinical practice (for both, the target would be a score of 0). An important initial step to address current gaps, however, would be to aim for consistency in the routine adoption and recording of a disease score in patient reports, perhaps starting with Mayo, if that is the most feasible, but aspiring to eventually incorporate UCEIS as standard practice.

The incorporation of histologic scores lags behind endoscopic scores. Although it may be advisable to start considering how histologic evaluation could be integrated into routine practice, histologic score targets are not recommended for current practice because of the lack of prospective interventional studies demonstrating benefit of solely histologically guided therapy decisions. Given the limited number of current UC therapies, abandoning a medication in a patient with endoscopic remission and histologic inflammation only is not advisable until prospective data become available.

Because endoscopic scoring cannot be centralized in practice as it is in clinical trials, gaps in training represent another barrier to the effective adoption of endoscopic or histologic assessments. Educational initiatives or practice-centric programs guided by experts have proven useful in improving inter-reader reproducibility, but this is an area still in search of optimal solutions. [34, Rank 4]

Given the invasiveness and cost of the monitoring procedures required, there is a need for data-driven evidence on the utility

> **“ Drugs, such as oral contraceptives, hormone replacement therapy, and non-steroidal anti-inflammatory drugs, have all been associated with an increased risk of ulcerative colitis, while antibiotic exposure has not. Breastfeeding appears to decrease the risk of ulcerative colitis ”**

of noninvasive monitoring methods in predicting UC relapse to reduce healthcare and patient burden. At present, Fecal calprotectin remains the most developed noninvasive means, and evidence suggests that it can be incorporated in the clinic for disease monitoring. A well-validated Fecal calprotectin threshold that would indicate mucosal healing remains under investigation because clinical trials so far have used variable thresholds (13.9–261 μg/g) and correlative measures (e.g., reference data, definition of relapse).

Regarding practical application of Fecal calprotectin testing, researches propose that in current practice, a cutoff point of < 100 μg/g could be a target indicative of low disease activity. In practice, Fecal calprotectin should be measured close to the time of an endoscopic assessment to "benchmark" the Fecal calprotectin level to the individual patient. Furthermore, studies on home-based testing allowing patient self-measurement have reported good correlation with the classic enzyme-linked immunosorbent assay, which may help realize frequent Fecal calprotectin monitoring with less patient burden. Imaging modalities offer a noninvasive method of monitoring disease activity for patients at higher risk for endoscopic disease and of tracking structural changes resulting from chronic inflammation that may be contributing to long-term complications. However, more research is required to investigate the specificity, sensitivity, and reliability of these tools.

Regarding patient reported outcomes, 2 clear criteria have emerged as critically relevant for UC (rectal bleeding and stool frequency), but other QoL domains have been poorly studied (e.g., fatigue, disability) and are not consolidated into a single instrument. The increasing interest in patient reported outcomes by regulators for drug development in IBD could and should propel the validation of tools following regulatory guidelines. [36, Rank 4]

Patient Perspective of Management of Ulcerative Colitis

Patient considerations could be key to the success of personalized management approaches because motivated patients would be expected to remain adherent and compliant with protocols, even during times of disease remission and symptom resolution. Physicians should discuss specific goals that patients may have and patient concurrence with the treatment target. Patient adherence to a management approach will require their acceptance of dose escalation if the goal is deeper level healing or remission (histological or molecular/biomarker).

Personalized regimens should consider disease severity and a patient's tolerance of aggressive treatment and possibly repeated procedures and testing, as well as the risk factors for complications, relapse, and side effects. Ideally, patient education would also foster the incorporation of lifestyle changes (dietary recommendations, etc.), which may have limited intrinsic efficacy but could contribute to symptom improvement. [37, Rank 4]

Ultimately, the overarching aim of a treatment approach in UC is to meaningfully modify the disease course, restoring QoL and preventing major long-term functional impairment and disability. Therefore, measuring how management strategies deliver against specific goals under each perspective will be critical to validate this clinical paradigm and propel its wider adoption. ***Undoubtedly, such validation will require studies that are ambitious in scope (encompassing measures of clinical status, surgery rates, resource utilization, cost-effectiveness, patient function, QoL, and patient reported outcomes), large in size, and lengthy in duration.*** Real-world cohorts may offer a good platform for such studies, although the challenges of conceptualizing comparative schemas (i.e., what would the reference controls for such a study be, and would historic data be valid) and reaching investigator consensus in the definition of suitable treatment targets and outcome measures should not be underestimated. Alternatively, large prospective clinical trials investigating the benefit of a management approach in UC, similar to that of CALM or REACT2 in CD, could help clinicians understand the value and feasibility of meeting targets with current therapies and monitoring tools. [38, Rank 3]

Selection of Therapy

Every effort should always be made to ensure there is shared therapeutic decision making between physicians and patients. ***There are many factors to consider when discussing therapeutic options with patients diagnosed with UC, including both disease-related (e.g., disease extent, inflammation severity) and patient-related factors (e.g., preferences, cost, comorbidities).*** Unfortunately, we are not yet in an era where we can reliably predict individuals' responses to specific medical therapies, for example, based on individual serum or tissue analyses.

The most important disease-related factors to consider include endoscopic/histologic and clinical disease severity as well as disease extent. Disease extent is defined as proctitis if inflammation is limited to the rectum, <15–20 cm from the anus. During their disease course, approximately 30% of

adult patients with limited disease will have evidence of proximal extension based on endoscopy/histology or radiology. If mucosal involvement extends proximally from the rectum up to the splenic flexure (<50 cm from the anus) or past the splenic flexure, the disease is reclassified as either left-sided or extensive/pancolitis, respectively. Limited proctitis occurs in 30–60% of adult patients with UC and manifests as hematochezia and tenesmus, left-sided colitis in 16–45% as proctitis plus diarrhea and abdominal cramping, and extensive colitis in 15–35% as left-sided colitis plus constitutional symptoms, fatigue, and fever.

In all patients, triggering factors such as infection (e.g., Clostridiodes difficile, cytomegalovirus) should be evaluated for and managed appropriately. Appropriate treatment of infection should be initiated in conjunction with UC treatment in symptomatic patients with positive stool studies. These patients should be closely monitored after initiation of UC treatment as they may have a suboptimal response due to concomitant infection. [39, Rank 4]

Goals of Therapy in Ulcerative Colitis

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee defined the treat to target (T2T) approach in UC, which represented a paradigm shift away from treating primarily to clinical resolution of symptoms toward a more rigorous target of additionally treating to endoscopic/histologic remission, or so-called "mucosal healing". Indeed, this shift was based on evidence demonstrating that mucosal healing is associated with long-term clinical remission, corticosteroid-free clinical remission, and avoidance of colectomy. Adequate control of inflammatory burden over time also reduces the risk of colorectal neoplasia. ***Accordingly, the target for UC therapy is clinical remission defined as the resolution of rectal bleeding and diarrhea, and endoscopic remission defined as a Mayo endoscopic subscore of 0 or 1.***

Historically, ***medical therapy for UC was limited to corticosteroids.*** Excitingly, over just the past 1–2 decades, the medical therapeutic armamentarium now approved for the management of UC has exploded, and continues to expand. Clinical and endoscopic remission in UC may be achieved with several classes of medication including mesalamine, immunomodulators, corticosteroids, biologics and, most recently, small molecules. The choice of therapy depends on multiple factors such as disease severity and extent, patient preference and expectations, medication formulation, and route of administration. Optimal management of UC requires an ongo-

ing, close collaboration between patient and physician with shared decision making and informed consent. [38, Rank 3]

Mild to Moderate Ulcerative Colitis

Mild-moderate UC is defined clinically as <4–6 bowel movements per day with mild-moderate rectal bleeding in the absence of constitutional signs or symptoms such as fever and tachycardia, and laboratory abnormalities including elevated inflammatory markers and anemia. Mild-moderate UC is defined endoscopically as mucosal erythema, decreased or absent vascularization, friability, and erosions.

Mesalamines are the first-line therapy for induction of remission in mild-moderate UC. There are different formulations of mesalamines, including oral, suppository, or liquid enema. Selection among mesalamine formulations for treatment of mild-moderate UC depends primarily on disease extent. Indeed, based on a meta-analysis of 17 studies evaluating 2925 patients with mild-moderate UC on mesalamine therapy, there was no significant difference in the efficacy or safety of different mesalamine formulations.

Proctitis is managed with mesalamine suppository 1 g/day to target the involved rectum. Suppositories should be self-administered at bedtime and retained for 1–3 h for maximal benefit. Left-sided UC is managed with oral mesalamine 2–3 g/day and topical mesalamine 4 g/day enema formulation, which will reach the splenic flexure with appropriate use. Enemas should be administered at bedtime and retained overnight for approximately eight hours. Extensive mild-moderate UC is managed with oral mesalamine 2–3 g/day and topical mesalamine in either enema 4 g/day or suppository 1 g/day formulation.

Clinical response is typically high, with 40–70% of patients expected to respond within 14 days; however, it can take up to eight weeks to achieve clinical and endoscopic remission. In patients with prominent arthritic symptoms, sulfasalazine is an acceptable alternative to mesalamine, though often poorly tolerated due to side effects such as headache, nausea, diarrhea, and rash [43, Rank 4]

Second-line Therapies

Second-line therapies for patients with mild-moderate UC who do not respond to mesalamine are corticosteroids. Systemic corticosteroids and budesonide-multimatrix (MMX) are both effective in induction of remission; however, the latter formulation has the important bene-

fit of minimal systemic absorption due to high first-pass hepatic metabolism and, thus, more favorable side effect profile. In a placebo-controlled randomized clinical trial (RCT) of 510 patients with mild-moderate UC and inadequate response to mesalamine, 13% of patients randomized to budesonide-MMX reached the primary endpoint of combined endoscopic and clinical remission at eight weeks compared to 7.5% of patients randomized to placebo. Patients typically demonstrate clinical response within seven to 10 days.

Budesonide-MMX is dosed as 9 mg daily for six to 10 weeks for induction of remission. In patients who respond, the dose is tapered to 9 mg every other day for two weeks followed by discontinuation, for a total of eight to 12 weeks of therapy. If patients do not show initial response to budesonide-MMX, then systemic corticosteroids, namely prednisone, is an option to induce remission. Prednisone is started at 40 mg per day and clinical response should be expected within 1–2 weeks.

After two weeks, the dose should be tapered by 5–10 mg per week. Rectal steroids are available in suppository and liquid or foam enema formulations and are effective in induction of remission with a relative risk of 0.73 when compared to placebo. Corticosteroids in any formulation are not indicated for maintenance of remission due to side effects of therapy, which are most pronounced with systemic corticosteroids and include mood disturbance, hyperglycemia, weight gain, acne, insomnia, avascular necrosis, and skin atrophy, among others.

Rectal mesalamine is superior to rectal corticosteroids for induction of remission. In a meta-analysis of 13 trials comparing rectal mesalamine and rectal corticosteroids, topical mesalamine (enema formulation 1–4 g/day or suppository formulation 1 g/day) was superior to topical corticosteroids for inducing remission. Given this, in addition to the potential safety concerns with long-term rectal corticosteroids, rectal mesalamine is preferred for mild-moderate UC. However, patients may prefer corticosteroid foam enemas to mesalamine liquid enemas because of ease of delivery and retention.

Patients who achieve remission with mesalamine therapy should continue on the same medication. Steroids are not appropriate for maintenance of remission due to adverse effects and lack of long-term efficacy. [41, Rank 4]

Moderate to Severe Ulcerative Colitis

Moderate-severe UC is clinically defined as 4–6 bowel movements per day with moderate-severe rectal bleeding in the absence of constitutional signs or symptoms. Moderate-severe UC is defined endoscopically as marked mucosal erythema,

absent vascularization, friability, granularity, spontaneous bleeding, and ulcerations. The agents currently approved for the induction and maintenance of remission of moderate-severe UC include the biologics infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab, in addition to the small-molecule Janus kinase (JAK) inhibitor tofacitinib. Generally speaking, prior to starting these agents and immunomodulators, all patients should have appropriate pre-initiation safety labs and vaccinations, although the latter are sometimes not possible due to acute presentation, as well as ongoing interval surveillance of healthcare maintenance needs. [43, Rank 4]

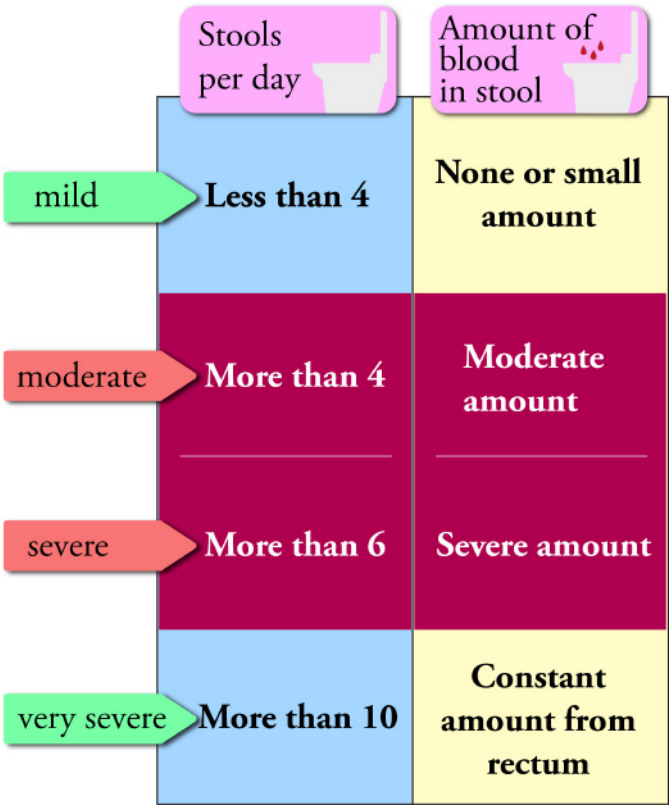

Figure 12: comparison of clinical features of different stages of ulcerative colitis

Monoclonal Antibodies for the Treatment for Ulcerative Colitis

Infliximab, adalimumab, and golimumab are monoclonal antibodies that target tumor necrosis factor (TNF)-alpha, an inflammatory cytokine that mediates intestinal tract inflammation and is increased in patients with active UC. In a meta-analysis of six studies including 1823 patients with moderate-severe UC, patients treated with anti-TNF agents were 2.5-fold more likely to achieve clinical remission compared to patients treated with placebo; no single agent was clinically superior to the others. The expected time to clinical response after initiation of these agents ranged from one to eight weeks.

Infliximab is administered intravenously, while adalimumab and golimumab are administered subcutaneously. Schedules for induction and maintenance vary according to the agent, and might also be altered based on disease trajectory and response. Biosimilars are near-identical copies of biologic agents that are equivalent to originator agents in efficacy and safety. Biosimilars of infliximab and adalimumab have been approved for the management of moderate-severe UC and are increasingly being used due to their significantly reduced cost. Therapeutic drug monitoring is beyond the scope of this article, but is

increasingly incorporated into clinical practice with the most robust data available for infliximab. [45, Rank 4]

The combination of infliximab and azathioprine is superior in the achievement of corticosteroid-free remission than infliximab or azathioprine monotherapy alone. In a trial of patients with moderate-severe UC previously naïve to TNF inhibitors, patients who received infliximab and azathioprine experienced higher rates of corticosteroid-free clinical remission at 16 weeks compared with patients who received either infliximab or azathioprine alone. The decision of combination therapy, however, must consider patient- and disease-related factors, a full discussion of which is beyond the scope of this review. Notably, there is no incremental benefit in continuing mesalamine therapy in patients with moderate-severe UC who are escalated to anti-TNF therapy. [46, Rank 3]

Vedolizumab is a humanized monoclonal antibody that recognizes the α4β7 cell surface glycoprotein expressed on circulating B and T lymphocytes and selectively blocks gut lymphocyte trafficking Vedolizumab is administered intravenously in an induction and then maintenance phase, with patients typically demonstrating clinical response within six weeks of the first dose. In the only head-to-head trial of biologic agents in patients with moderate-severe UC, vedolizumab was superior to adalimumab with respect to clinical remission and endoscopic improvement. Vedolizumab has a more favorable side effect profile compared to the anti-TNF inhibitors given its gut selectivity, and is not significantly associated with an increased risk of serious infection or malignancy.

> **"Genome-wide association studies have identified 200 risk loci for inflammatory bowel disease to date, with most genes contributing to both ulcerative colitis and Crohn's disease phenotypes."**

Ustekinumab, a monoclonal antibody directed against the p40 subunit of interleukin-12 and interleukin-23, is the newest biologic approved for moderate-severe UC. In a randomized, placebo-controlled trial of patients with moderate-severe UC, patients treated with ustekinumab had significantly higher rates of clinical remission and endoscopic improvement at week eight compared to placebo. Although the induction dose is administered intravenously as a one-time dose, the subsequent maintenance doses are administered subcutaneously, and might be more appealing for some patients. Clinical response is expected

within three to six weeks of induction. Similar to vedolizumab, ustekinumab offers a favorable infectious safety profile compared to the anti-TNF agents. The rates of serious adverse events in randomized clinical trials were equivalent in the ustekinumab and placebo groups. [47, Rank 5]

Tofacitinib is a small-molecule JAK inhibitor that modulates interleukin signaling, blocks the downstream effects of proinflammatory cytokines, and is approved for patients with moderate-severe UC who have failed or cannot tolerate TNF inhibitors. Tofacitinib is an oral medication with a rapid onset of action; clinical response to induction dosing is typically experienced within three days. Depending on disease and patient factors, induction dose ranges from 5 mg twice daily to 10 mg twice daily.

In two randomized, placebo-controlled trials of patients with moderate-severe UC, patients treated with tofacitinib 10 mg orally twice daily had higher rates of clinical and endoscopic remission at week eight compared to placebo. Tofacitinib is associated with an increased risk of herpes zoster virus reactivation in patients with UC, thromboembolic events, and elevated lipid profiles. The increased risk of thrombotic events is associated with the 10 mg, twice daily dosage, typically used for patients with UC refractory to anti-TNF agents. Individual thrombosis risk assessment should be performed for patients with UC with a history of thromboembolic disease or cardiovascular disease before tofacitinib is considered. [48, Rank 3]

Treatment with Cyclosporine

Cyclosporine directly inhibits calcineurin, a component of cytokine gene transcription, and downregulates IL-2, IL-3, IL-4, and TNF-alpha. In a randomized, placebo-controlled trial of 11 patients with ASUC, 82% of patients treated with cyclosporine had clinical response within seven days. ***Cyclosporine is administered as a continuous intravenous infusion for hospitalized patients with ASUC with close monitoring of levels every two days to achieve target concentrations.***

Clinical response is typically seen within two to three days, and colectomy rates have been shown to be less in patients treated with cyclosporine. Patients who have improvement of stool frequency to <6 bowel movements per day and resolution of hematochezia may be converted from intravenous to oral cyclosporine to be continued for three months. Cyclosporine, while itself not appropriate for maintenance therapy, is an effective bridge to an alternative medication that is approved for UC maintenance. For example, cyclosporine in the acute hos-

> "Dysbiosis is seen in patients with ulcerative colitis, although to a lesser degree than in patients with Crohn's disease. Decreased biodiversity, with a lower proportion of Firmicutes and increased Gamma-proteobacteria and Enterobacteriaceae, has been reported in patients with ulterative colitis. Additionally, patients with the disease have increased sulphite-reducing. Deltaproteobacteria in the colon"

pitalized setting as a bridge to vedolizumab in the outpatient setting is one therapeutic approach. [49, Rank 5]

Opioid Medications Use in UC Disease

Opioid medications have analgesic and anti-motility properties. They are more likely to be prescribed to UC patients than to matched controls. ***Risk factors*** for use include ***female gender, multiple surgeries, severity of pain, higher clinical disease activity, a history of depression or anxiety and polypharmacy, particularly with neuropsychiatric drugs. Patients with sustained poor quality of life have a higher risk of subsequent opioid use and a decreased time to first opioid prescription. Use of narcotics, correlate with corticosteroid use in UC.***

A study showed that opioid prescribing was highest in the first month following UC diagnosis where 11% of patients received this class of drug. Prescription was more common in females and in Crohn's disease relative to UC. Patients with UC were more likely to become heavy opioid users (defined as a dose exceeding 50 mg of morphine or equivalent per day for at least 30 consecutive days) than age-matched controls. Use of narcotics in both Crohn's disease and UC is associated with increased prevalence of depressive symptoms, a higher risk of serious infection in IBD and increased mortality. Historical studies show an association of opioid prescription with development of toxic megacolon in fulminant colitis. [29, Rank 5]

Future Directions

As more is learned about intestinal inflammation, new tools and treatment targets may emerge. Endomicroscopy studies have developed more detailed mucosal healing criteria (including crypt numbers, crypt lumen deformity, crypt lumen leakage, and vascular leakage). Further studies

could determine the predictive value of endomicroscopic mucosal changes regarding clinical outcomes.

The search for biomarkers is also evolving, with a recent study identifying 4 gene transcripts responsive to antitumor necrosis factor therapy and correlated with endoscopic disease activity; these molecular markers pinpoint changes in disease activity more accurately than CRP, erythrocyte sedimentation rate, and platelet count. Further research is needed to shed light on the underlying causes and etiology of persistent symptoms in patients with endoscopic remission. To that end, the development of a functional UC bowel damage index beyond endoscopy or histology scoring would provide a major research and management tool.

The management paradigm, widely accepted in rheumatoid arthritis, is an emerging approach in IBD. This approach is currently more established in the treatment of CD, but growing evidence supports its usefulness in UC. Given the new evidence, the management recommendations could be updated for both CD and UC. In the near future, we might need to look beyond the mucosa and recognize fibrosis and molecular healing as components of UC. All these factors may hold the key to avoiding long-term functional deficits and disability in UC.

Finally, the implementation of management strategies in routine practice remains challenging and requires a shift. ***Successful management implementation will require patient and physician education and communication (to create true personalized treatment plans and goals), renewed efforts in evidence generation to validate reliable and preferably noninvasive endpoints that predict favorable long-term outcomes, and establishment of the superior risk-benefit and cost-effectiveness profile of a successful management strategy over the current paradigms.*** [40, Rank 4]

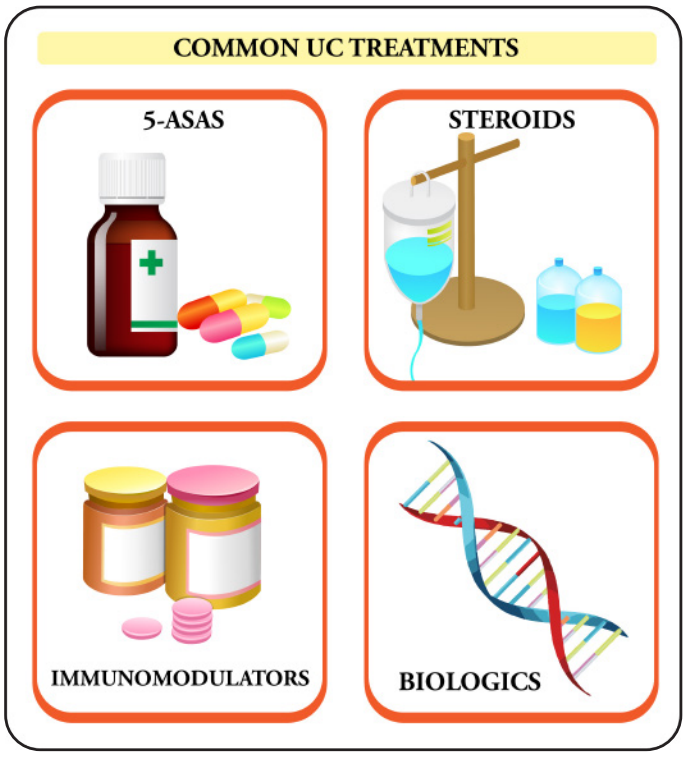

Figure 13: common treatments of ulcerative colitis

Conclusion

Appropriate treatment options for patients with ulcerative colitis vary according to disease severity. The positioning of biologics and small molecules depends on patients' disease extent and severity, previous medication exposure, and preference. Medication risks and therapeutic benefits should be incorporated in patient discussions to ensure informed decision making. Recent developments highlighted include new imaging techniques; increasing numbers of new drugs; changes in the way these drugs are used with accelerated treatment and reduction in prolonged use of older therapies with greater toxicity; the increasing importance of infection screening at diagnosis; changes in therapeutic goals (such as mucosal healing) and advances in therapeutic monitoring. This makes Ulcerative Colitis treatment ever more complex and highlights the importance of multidisciplinary working, and finding more effective ways to deliver services. [50, Rank 5]

***Important information for post-test is highlighted in red letters, boxes and diagrams.**

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