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DEEPER INSIGHT INTO PATHOPHYSIOLOGY AND PHARMACO THERAPY OF ULCERATIVE COLITIS

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ABSTRACT

Ulcerative colitis is a chronic inflammatory disease of the rectum and colon. Results from many studies in people and animals of intestinal inflammation suggest that ulcerative colitis results from environmental factors triggering a loss of tolerance for normal intestinal flora in genetically susceptible individuals. Ulcerative colitis (UC) is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent and severity of colon involvement are variable. In its most limited form it may be restricted to the distal rectum, while in its most extended form the entire colon is involved. UC belongs to the inflammatory bowel diseases (IBD), which is a general term for a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract. UC is usually associated with recurrent attacks with complete remission of symptoms in the interim. The leading initial symptom of UC is diarrhea with blood and mucus, sometimes with pain. Fever and weight loss are less frequent. Extra intestinal symptoms can be an initial manifestation or can occur later in the course of the disease. Eighty percent of the patients have only proctitis or proctosigmoiditis, and only 20% have extensive colitis. However, in about 50% of patients with initial proctosigmoiditis, proximal extension occurs later, and in some patients the opposite takes place. Depending of the stage of the disease, endoscopy reveals reddening of the mucosa, increased vulnerability, mucosal bleeding, irregular ulcers, pseudopolyps, granularity, and loss of vascular architecture. Several drugs interacting with various points along the immune and inflammatory cascades are currently available for the treatment of UC. Corticosteroids, aminosalicylates, immunomodulators are the mainstay of medical treatment.

KEYWORDS: inflammatory, medical treatment, Bowel Disease, ulcerative colitis, aminosalicylates.

INTRODUCTION

Ulcerative colitis (UC) and Crohn disease are the principal constituents of the gastrointestinal inflammatory condition group known as Inflammatory Bowel Disease (IBD).[1] Ulcerative colitis is a worldwide, chronic, idiopathic, inflammatory disease of the rectal and colonic mucosa. The past decade has seen advances in our knowledge of the role of environmental factors, in particular enteric microflora, as well as genetic and immune factors in the pathogenesis of ulcerative colitis. Although progress hasbeen made in the overall management of the disease, no innovative treatment has been developed.[2] Chronic IBD may be divided into two major groups, ulcerative colitis (UC) and Crohn's disease (CD), clinically characterized by recurrent inflammatory involvement of intestinal segments with several manifestations often resulting in an unpredictable course. Ulcerative colitis is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent and severity of colon involvement are variable.[3] Primary sclerosing cholangitis and Ulcerative colitis are caused by progressive inflammation of the bile duct and large intestine respec-tively. The existence of any plausible association between Primary sclerosing cholangitis and Ulcerative colitis remains highly elusive. Little is known about the incidence and prevalence of primary sclerosing cholangitis and Ulcerative colitis remains highly elusive. Little is known about the incidence and prevalence of primary scle-rosing cholangitis with concomitant Ulcerative colitis in the Indian subcontinent. We report a case of Primary sclerosing cholangitis with long standing Ulcerative colitis which later also developed Pri-mary biliary cirrhosis[4] ulcerative colitis is a chronic disease characterized by diffuse mucosal inflammation of the colon. Ulcerative colitis always involves the rectum (i.e., proctitis), and it may extend proximally in a contiguous pattern to involve the sigmoid colon (i.e., proctosigmoiditis), the descending colon (i.e., left-sided colitis), or the entire colon (i.e., pancolitis).This article reviews the diagnosis and treatment of ulcerative colitis from a primary care perspective.[5] In ulcerative colitis, inflammation is restricted exclusively to the colon, or large bowel. During an acute disease flare the capacity of the colon to absorb water is usually severely reduced, which serves to further worsen the diarrhea. Because in ulcerative colitis only the colon is affected by the inflammatory process, nutritional deficiencies and associated symptoms are less common than with Crohn’s disease. Also, unlike Crohn’s disease, the inflammation in ulcerative colitis is limited to the mucosal layer. A common symptom is the occurrence of

bloody diarrhea with admixtures of mucus.[6] Ulcerative Colitis (UC) is a disease in which the lining of the colon (the large intestine) becomes inflamed. The immune system mistakenly targets the lining of the colon, causing inflammation, ulceration, bleeding and diarrhea. The inflammation almost always affects the rectum and lower part of the colon, but it can also effect the entire colon Although ulcerative colitis cannot be cured, it can usually be controlled. Most people are able to live active and productive lives. Control of the disease includes long-term medical treatment and regular monitoring for complications.

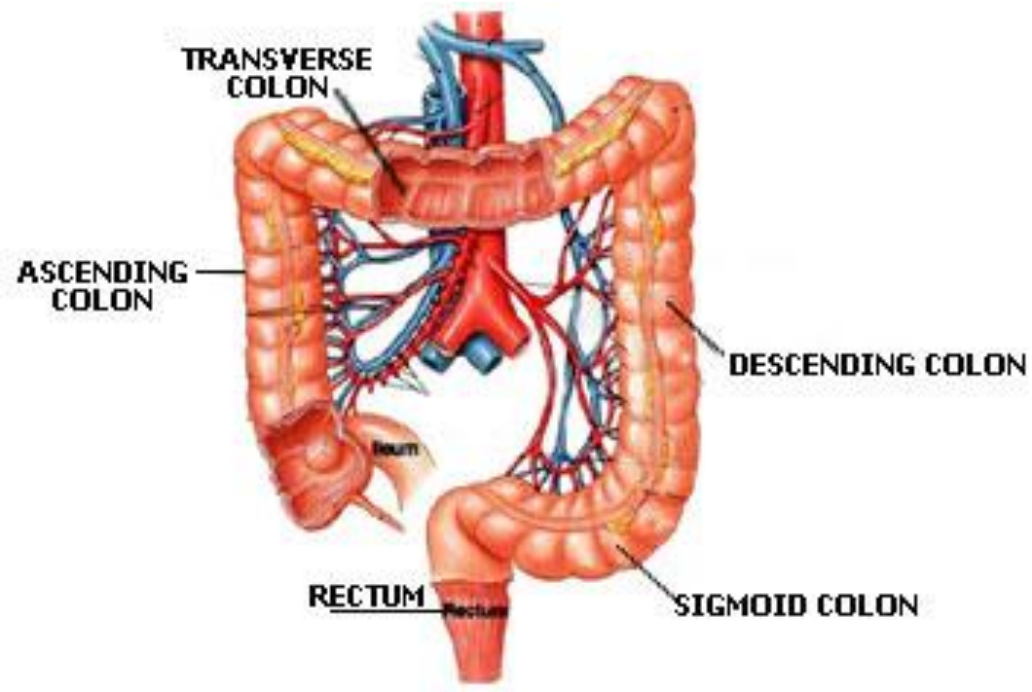

Fig1 :Structure of The Colon and Rectum.

Pathology

Macroscopic Features

1. mild inflammation
2. moderate disease
3. long-standing disease
4. fulminant disease

Etiology and Pathogenesis

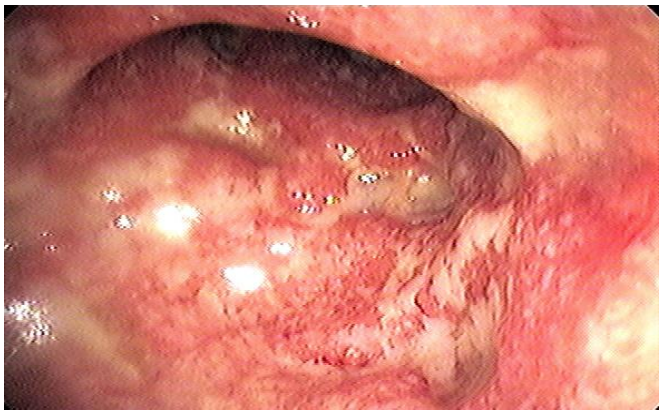

Fig 2: Structure of Ulcer Colitis.

What is Ulcerative Colitis?

UC is a painful and debilitating type of inflammatory bowel disease (IBD) that affects more than a half million Americans.[6] UC causes chronic inflammation of the colon, and patients with UC are at increased risk for colon cancer. There is currently no cure for UC (other than surgical removal of the colon) and long-term remission with current treatments is limited. New treatments for UC patients are urgently needed.[7]

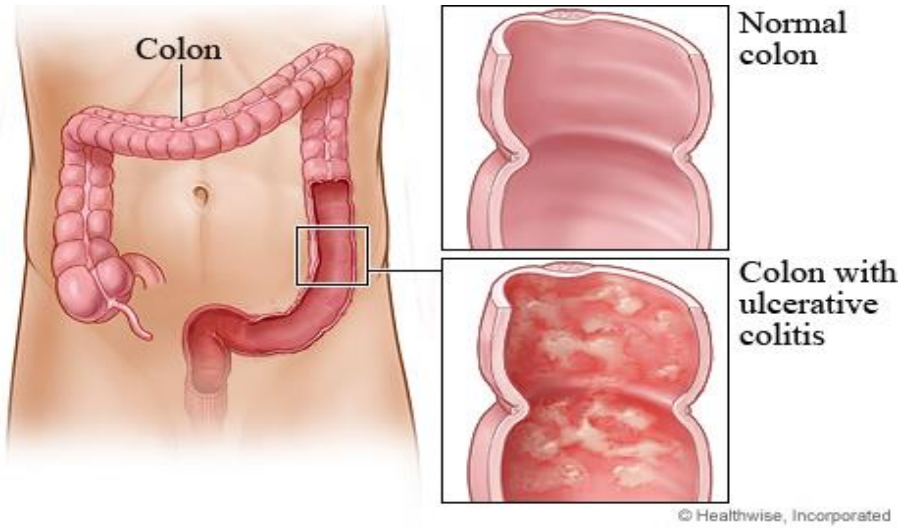

Fig 3: Structure of Normal and Ulcer with Ulcerative Colitis.

Common Vocabulary with Ulcerative Colitis

1. Ulcerative proctitis refers to disease limited to the rectum , Distal colitis or proctosigmoiditis is used when the inflammatory process extends into the mid-sigmoid colon.

2. Left sided colitis refers to disease that extends to but not beyond the splenic flexure (the sharp bend in the intestines where the transverse colon joins the descending colon, located under the spleen).
3. Extensive colitis is defined as disease that extends beyond the splenic flexure but not as far as the cecum (the beginning of the colon).
4. Pancolitis is used when the inflammatory process extends to the cecum.[8,9]

Types of Ulcerative Colitis and Their Associated Symptoms

The symptoms of ulcerative colitis will vary depending on the extent of inflammation and the location of the disease within the large intestine. Accordingly, it is very important for you to know which part of your intestine is affected. Listed below are some of the most common types of ulcerative colitis.

Ulcerative Proctitis

Bowel inflammation is limited to the rectum. Because of its limited extent (usually less than six inches of the rectum), ulcerative proctitis tends to be a milder form of ulcerative colitis. Symptoms include rectal bleeding, urgency, and rectal pain.

Proctosigmoiditis

Colitis affecting the rectum and sigmoid colon (the lower segment of colon located right above the rectum). Symptoms include bloody diarrhea, cramps, and tenesmus (straining to have a bowel movement). Moderate pain on the lower left side of the abdomen may occur in active disease.

Left-Sided Colitis

Continuous inflammation that begins at the rectum and extends as far as the splenic flexure (a bend in the colon near the spleen in the upper left abdomen). Symptoms include loss of appetite, weight loss, bloody diarrhea, and severe pain on the left side of the abdomen.

Pan-ulcerative (total) or Pancolitis

Affects the entire colon. Symptoms include loss of appetite, bloody diarrhea, severe abdominal pain, and weight loss.

Colorectal Cancer and Ulcerative Colitis

Overall, people with ulcerative colitis have an increased risk of colorectal cancer, although the degree of risk varies from one person to another. The risk of colorectal cancer is related to the duration and extent of ulcerative colitis.

Pancolitis

This group has the greatest risk. The risk begins to increase about 8 to 10 years after the symptoms of ulcerative colitis first appear. There is a 5 to 10 percent risk of cancer after 20 years and a 12 to 20 percent risk after 30 years of ulcerative colitis.

Left-Sided Colitis

In people with left-sided colitis, the risk of colorectal cancer begins to increase about 15 to 20 years after the symptoms of ulcerative colitis first appear.

Proctitis and Proctosigmoiditis

The risk of colorectal cancer is not significantly increased in people with proctitis and proctosigmoiditis. The risk of colon cancer is also increased in patients with coexisting primary sclerosing cholangitis (PSC).[10, 11, 12, 13]

Surveillance Recommendations

Colorectal cancer usually develops from precancerous changes (dysplasia) of the colonic lining, which can be detected with regular screening tests such as colonoscopy. In general, colonoscopy is recommended 8 to 10 years after symptoms appear in people with pancolitis, and starting 12 years after symptoms appear in people with left-sided colitis. Thereafter, colonoscopy should be repeated every year thereafter. If advanced precancerous changes or cancer are discovered, surgical removal of the colon (colectomy) is usually recommended.

Sign/Symptom	Ulcerative Colitis	Crohn's Disease
Area of intestinal tract affected	Any part of inner most lining of colon, continuous with no "patches" of normal tissue	Lower ileum most common but can flare up anywhere, including the colon; "patches" of normal tissue between affected areas; can affect entire intestinal wall
Diarrhea	Typically four episodes per day	Typically four episodes per day
Abdominal pain/cramping	Mild tenderness, lower abdominal cramping	Moderate to severe abdominal tenderness in right lower quadrant
Blood in stool	Present; amount depends on disease severity	Present; amount depends on disease severity
Fatigue	Result of excessive blood loss and anemia	Result of excessive blood loss, anemia, and poor nutrient absorption
Fever	Low-grade in severe cases	Low-grade in severe cases
Physical examination	Rectal exam may show peri-anal irritation, fissures, hemorrhoids, fistulas, and abscesses	Peritoneal irritation, abdominal or pelvic mass
Weight loss/anorexia	Weight loss in more severe cases	Weight loss and anorexia common due to poor digestion and intestinal absorption
Appetite	Often decreased during periods of disease exacerbation	Often decreased during periods of disease exacerbation
Risk of colon cancer	Increased	Increased

Fig4: Comparision between symptoms of ulcerative colitis and crohn's disease.

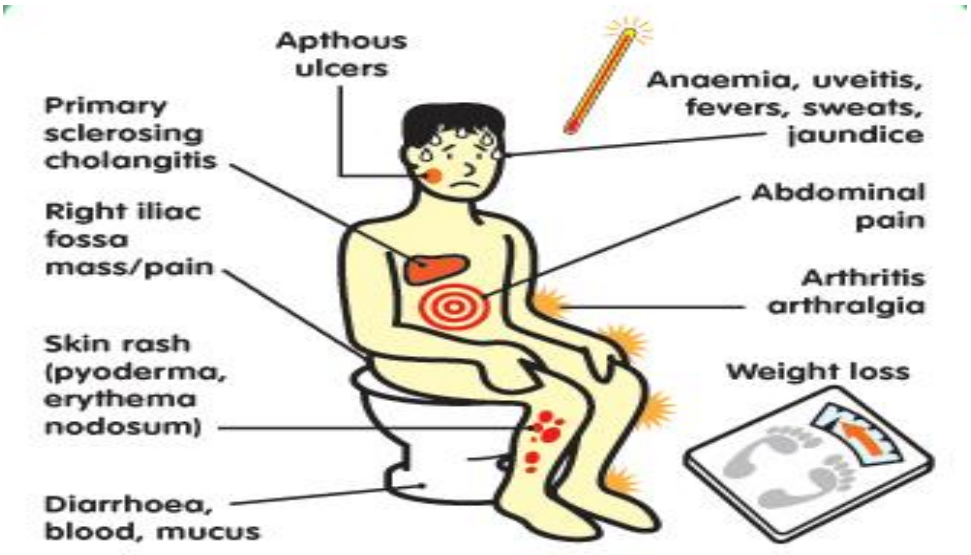

Fig5: Symptoms of Ulcer Colitis.

How do Crohn's Disease and Ulcerative Colitis Affect the Digestion?

Crohn's Disease

Crohn's disease can affect any segment of the digestive tract from the mouth to the anus. The most common site of inflammation in this disorder, however, is the final segment of the small bowel (the terminal ileum) and the immediately following first part of the colon, or large intestine. Disease affecting the small bowel in patients with Crohn's disease may result in the inadequate absorption of nutrients. The consequences include weight loss or deficiencies of individual or many nutrients. Patients, especially those who have undergone surgery on the terminal ileum, may require regular, life-long replacement injections of vitamin B12, usually at intervals of two to three months. If vitamin B12 deficiency persists, patients develop pernicious anemia, a dangerous condition in which the number of red blood cells is reduced.[14, 15,17]

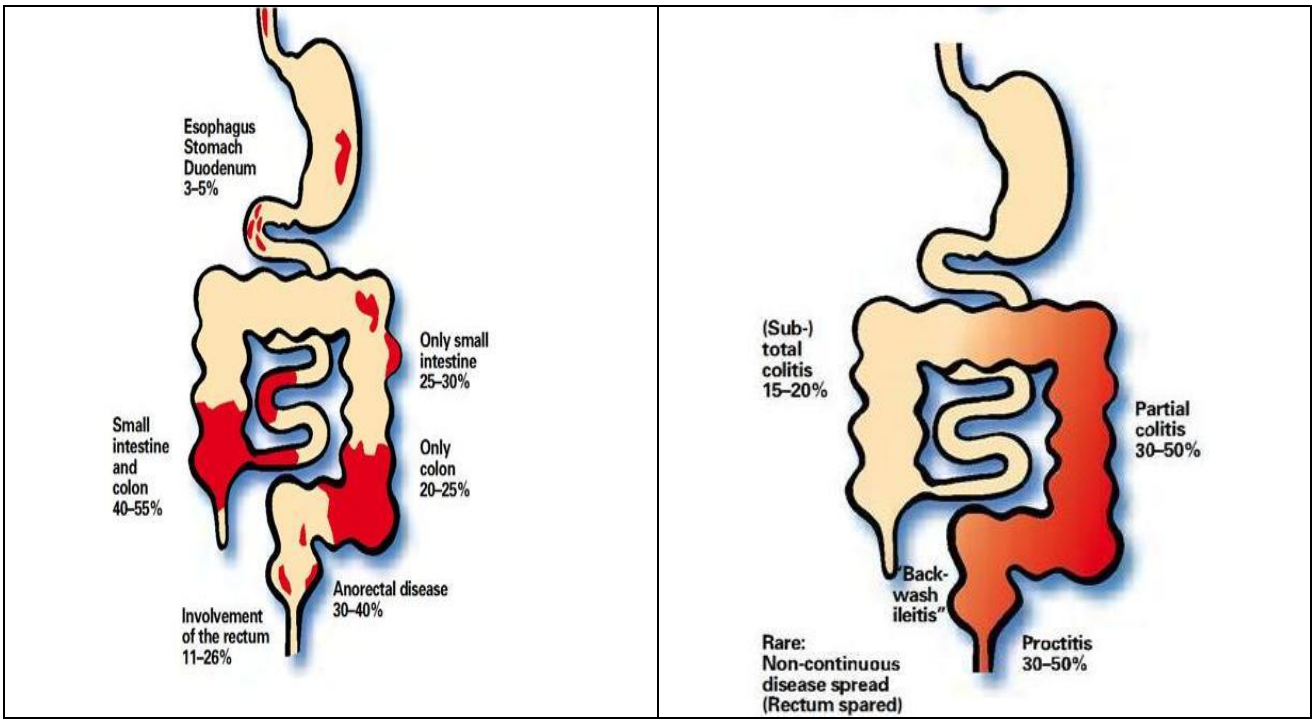

Fig 6: Localization and frequency of inflammation in Crohn's disease and ulcerative colitis.

Ulcerative Colitis

In ulcerative colitis, inflammation is restricted exclusively to the colon, or large bowel. During an acute disease flare the capacity of the colon to absorb water is usually severely reduced, which serves to further worsen the diarrhea. Because in ulcerative colitis only the colon is affected by the inflammatory process, nutritional deficiencies and associated

symptoms are less common than with Crohn's disease. Also, unlike Crohn's disease, the inflammation in ulcerative colitis is limited to the mucosal layer. A common symptom is the occurrence of bloody diarrhea with admixtures of mucus (figure 2).

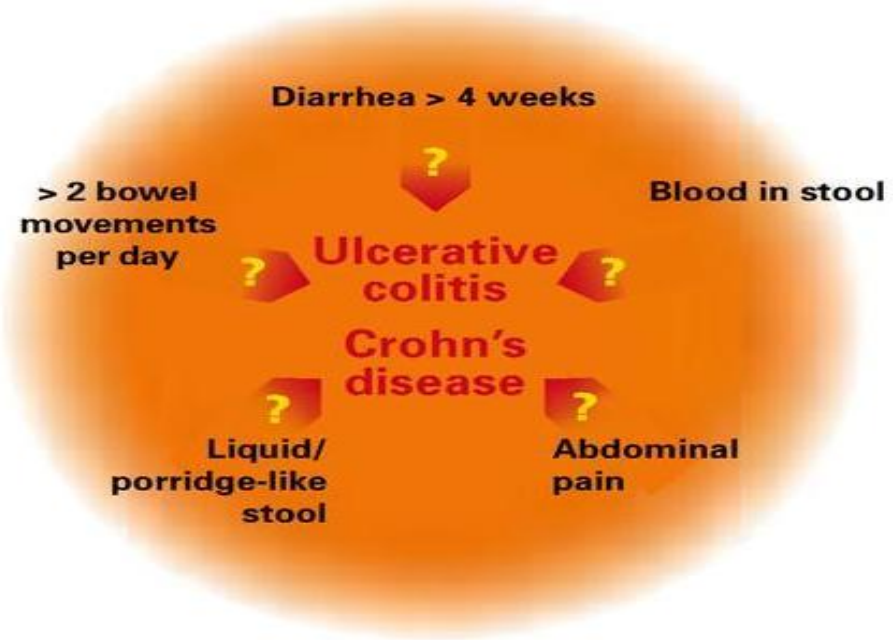

Fig 7: Symptoms that suggest inflammatory bowel diseases.

Can the Wrong Diet Trigger IBD?

Patients often ask whether individual nutritional or dietary factors are responsible for the development of inflammatory bowel diseases (IBD). The suspicion of a correlation is supported by the reported increase in the rate of IBD since the 1950's in Western industrialized nations. Factors that have been discussed in relation to this increased frequency of IBD since the end of World War II include the increased consumption of refined carbohydrates and chemically processed fats (trans fatty acids), the reduced consumption of dietary fiber, allergic reactions to baker's yeast, the replacement of human milk in the diet of infants and exposure to Mycobacterium avium paratuberculosis in inadequately pasteurized cow's milk. Current investigations are focusing on whether foods containing sulfur or sulfurated additives are responsible for the inflammatory changed in ulcerative colitis. Convincing evidence for a possible role for nutritional or dietary factors in the development of either Crohn's disease or ulcerative colitis, despite the increasing number of cases and changed style of life and nutrition in modern industrial nations, has yet to be discovered (figure 3). Only in the case of breast-feeding has there been clear evidence that this may protect against the development of IBD.

Fig 8: Inflammatory bowel diseases and nutrition: unsubstantiated correlations.

Nutritional deficiencies in IBD: How do they occur and what can I do?

During the course of their illness, a large number of patients with IBD experience either a general malnutrition or deficiencies of individual nutrients (table 1). Many IBD patients, especially those with Crohn's disease, are underweight and/or suffer from anemia. Low body weight and malnutrion, however, are associated with an increased risk for inflammatory flares and everything should be done to prevent them. Attention should be paid to a balanced diet and, when necessary, to nutrition therapy. Malnutrition and nutrient deficiencies in patients with IBD can be due to a wide range of causes. Potential causes for the development of malnutrition in inflammatory bowel diseases include.

1. Reduced dietary intake
2. Reduced absorption of nutrients in the small bowel (malabsorption) due to functional disturbances
3. Increased bowel movements in cases of diarrhea with associated nutrient loss

Nutrient	Crohn's disease		Ulcerative colitis	
	Inpatient	Outpatient	Inpatient	Outpatient
Weight loss	65–75	54	18–62	43
Hypalbuminemia ("Albumin deficiency")	25–80	0	25–50	n.s.
Anemia (various types)	60–80	54	66	n.s.
– Iron	25–50	37–53	81	n.s.
– Folate (folic acid)	56–62	10	30–41	n.s.
– Vitamin B_{12}	48	3–4	5	n.s.
Vitamin A	11–50	n.s.	93	n.s.
Vitamin D	23–75	n.s.	35	n.s.
Calcium	13	n.s.	n.s.	n.s.
Magnesium	14–33	n.s.	n.s.	n.s.
Potassium	6–20	n.s.	n.s.	n.s.
Zinc	40	1	n.s.	n.s.

n.s. = not studied

Fig9: Frequency (In %) Of Nutrient Deficiency or Nutrient Deficiency Associated Findings In In- And Outpatients with IBD.

Epidemiology

Ulcerative colitis affects approximately 250,000 to 500,000 persons in the United States, with an annual incidence of two to seven per 100,000 persons. The overall incidence of the disease has remained constant over the past five decades.[18] The financial cost is nearly $500 million annually, and the disease accounts for 250,000 physician visits and 20,000 hospitalizations per year.[10] The onset of ulcerative colitis is most common between 15 and 40 years of age, with a second peak in incidence between 50 and 80 years. The disease affects men and women at similar rates. The precise etiology of ulcerative colitis is not well understood. A current hypothesis suggests that primary dysregulation of the mucosal immune system leads to an excessive immunologic response to normal microflora.[19] Cigarette smokers have a 40 percent lower risk of developing ulcerative colitis than do nonsmokers; however, compared

with those who have never smoked, former smokers are approximately 1.7 times more likely to develop the disease.[20] No consistent link between diet and the development of ulcerative colitis has been found. Although an association between the use of nonsteroidal anti-inflammatory drugs and the development of ulcerative colitis has been suggested, 6 careful epidemiologic studies have failed to confirm that this association is causal.[20]

Extraintestinal Manifestations

1. dermatologic - erythema nodosum, pyoderma gangrenosum
2. rheumatologic - peripheral arthritis, ankylosing spondylitis
3. ocular - conjunctivitis, uveitis/iritis, episcleritis
4. hepatobiliary - steatosis, PSC
5. urologic - calculi, ureteral obstruction, fistulas
6. metabolic bone disorders - low bone mass

Ulcerative Colitis Treatment

Proctitis and Proctosigmoiditis

Proctitis or proctosigmoiditis are usually treated with one or more medications that are given as an enema (for proctitis or proctosigmoiditis) or a suppository or foam for proctitis. Suppositories and foam only reach the rectum or lower sigmoid colon, while enemas can reach as high as the splenic flexure. Some patients also require treatment with oral medications such as sulfasalazine (Azulfidine) and an 5-aminosalicylate (5- ASA) or related drugs (eg, Pentasa, Asacol, Colazal, Lialda, and Dipentum). In some cases, a steroid treatment (eg, Cortenema) is required. These treatments usually produce improvement after three weeks, lead to remission in up to 90 percent of people, and provide prolonged remission in up to 70 percent of people.

5-Asa Agents: Reducing Inflammation

5-Aminosalicylic acid (5-ASA) compounds, also known as aminosalicylates are the cornerstone of medical therapy for active ulcerative colitis. The 5-ASA in oral formulations needs to be protected from being absorbed in the upper gastrointestinal tract so that it can be delivered to the lower gastrointestinal tract where it has been shown to be highly effective for the treatment of UC.[21]Currently, oral 5-ASA derivatives have been considered to be initial monotherapy in mild to moderate disease of UC.[22] There are numerous preparations and dosing regimens available, such as sulfasalazine, mesalazine, olsalazine and balsazazide, which are the most commonly prescribed anti-inflammatory drugs in IBD. The precise

mechanism of action of 5-ASA is not known, but is likely due to a local anti-inflammatory effect from the luminal site in the diseased parts of gut. 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.[23] 5-ASA has been shown to have a topical mechanism of action in the treatment of UC . 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.[24,25,26]

Absorption of 5-ASA is followed by extensive metabolism to the major inactive N-acetyl-5-aminosalicylate (Nacetyl- 5-ASA) by the N-acetyl-transferase 1 enzyme in intestinal epithelial cells and the liver. Oral or rectal administration of 5-ASA the released active agent is taken up by intestinal epithelial cells in the small and large bowel. Absorbed 5-ASA and intestinally inactivated N-Ac-5-ASA are partly secreted back into the intestinal lumen.[24] Evidences have shown that 5-ASA could affect on eicosanoid metabolism and inhibit prostanglandin production in intestinal mucosa. It may interfere with the production of arachidonic acid by affecting the thromboxane and lipoxygenase synthesis pathway, function as “scavengers” of free oxygen radicals and inhibitors of reactive oxygen metabolite production. Moreover, 5-ASA may play a role in regulating mucosal lymphocyte and macrophage activities and inhibiting proinflammatory cytokine production such as IL-1 and IL-2.[26,27,28]

Sulfasalazine

Sulfasalazine is one of the oldest drugs used to treat UC. Common side effects associated with its use include headaches, skin rash, nausea, and reversible infertility in men; these side effects occur in over 10 percent of patients. Less common side-effects include hives, itching, pancreatitis, hepatitis and a low white or red blood cell count. Sulfasalazine possesses both anti-inflammatory (5-ASA) and antibacterial (sulfapyridine) properties. Taken orally, the drug is delivered intact into the right colon and subsequently is degraded by coliform bacteria into 5-ASA, the active moiety and sulfapyridine, which helps transport 5-ASA to target areas.4 A major drawback to its use, however, is that the most effective doses also tend to be associated with intolerable toxicity; nearly one out of every three sulfasalazine-treated

patients will develop adverse reactions. Common adverse effects include nausea, headache, vomiting, dyspepsia and anorexia, while less frequent, but more serious adverse effects include agranulocytosis, megaloblastic or hemolytic anemia, pancreatitis and sperm abnormalities. Patients with sulfa allergies should avoid sulfasalazine. Folic acid supplementation is recommended because sulfasalazine inhibits folate absorption. 5-aminosalicylate medications are generally tolerated better than sulfasalazine. As a result, they can be given in higher doses, which is often more effective. The most common side effects are headache, malaise, gas, and cramps. Hair loss and skin rash are less common. Rare side-effects include pericarditis, myocarditis, hypersensitivity pneumonitis, allergic reactions, pancreatitis, kidney problems, decreased blood counts, and hepatitis.[29,30,31]

Newer Aminosalicylates

Newer aminosalicylates deliver 5-ASA to the distal bowel without the sulfapyridine, thus allowing us to administer higher doses of the medication while limiting adverse effects and systemic toxicity. In equimolar doses, the oral 5-ASA preparations are equivalent in efficacy to sulfasalazine and their safety profile is similar or superior to that of placebo.5 Orally ingested 5-ASA alone undergoes rapid absorption in the jejunum and is therefore of limited efficacy in patients with colonic disease. Two main types of delayed release formulations have been developed to overcome this deficiency. The most commonly used aminosalicylate, is Meselamine, 5-ASA enveloped in a coating that dissolves at pH of 7 in the distal ileum and colon. In last few years, several trials have demonstrated that 5-ASA therapy can prevent the development of dysplasia and cancer in patients with long standing ulcerative colitis.[32,33,34]

Glucocorticoids (steroids)

Steroids may be the most difficult medication to tolerate since there are many side effects. Increased appetite, weight gain, acne, fluid retention, trembling, mood swings, and difficulty sleeping are common. Other side effects occur in patients who take steroids for long periods of time, particularly if high doses are used. These include diabetes, thinning of the skin, easy bruising, a “cushingoid” appearance (widening of the face and a hump in the back), thinning of the bones, body hair growth, cataracts, high blood pressure, stomach ulcers, avascular necrosis (a serious joint problem), and infections. Because of the risk of these side effects, most patients are tapered off of steroids as soon as possible.[35,36]

Treatment of Refractory Ulcerative Colitis

Refractory ulcerative colitis occurs when a person's disease does not respond or responds poorly to the medical treatments used to treat the disease. Patients who depend upon steroids to control their symptoms are usually referred to as having refractory disease.

6-mercaptopurine and Azathioprine

Azathioprine and its metabolite (6-mercaptopurine) have been used to treat refractory ulcerative colitis for many years. These drugs lessen symptoms in 60 to 70 percent of people and help to maintain remission and decrease the need for steroids. These treatments may require three to six months to produce their maximal effect. Patients taking these drugs need to be closely monitored for side effects, which can include a decrease in the white blood cell count, inflammation of the pancreas, and, less commonly,hepatitis (inflammation of the liver). Long-term use of these drugs has been associated with an increased risk of infections and possibly certain types of tumors.[36,37]

Aza and 6-Mp

The immune modulating thiopurines 6-MP and its prodrug AZA have proven efficacy in active IBD and in the maintenance of an induced clinical remission. Purine analogues AZA and 6-MP are chemically related immunomodulators, AZA is nonenzymatically converted to 6-MP.[42] AZA and its metabolite 6-MP are purine base analogs which inhibit biosynthesis and incorporation of purine nucleotides in cells during mitosis. AZA and 6-MP have been used to treat refractory UC for many years. These drugs lessen symptoms in 60%-70% of patients and also help to maintain remission and decrease the need for steroids. Both drugs may require three to six months to produce their maximal effect. AZA and 6-MP are used for long-term treatment in steroiddependent cases or for patients who do not respond to 5- ASA or corticosteroids. Optimal dosage for AZA is around 2.5 mg/kg body weight and induction of remission by these drugs may take 6-7 months. Intramuscularly applied methotrexate (MTX) is the second choice, while its efficacy starts earlier than that of AZA. Studies assessing oral lowdose MTX treatment are lacking. The risk of malignancy using immunosuppressive drugs as AZA is low and furthermore, especially AZA and 6-MP can be used rather safely during pregnancy. When initiating therapy with either AZA or 6-MP, measurement of complete blood count with differential is advocated at least every other week as long as doses of medications are being adjusted. The immunosuppressive properties of AZA/6-MP are mediated by the intracellular metabolism of 6-MP into its active metabolites,

6-thioguanine nucleotides (6TGN) and 6- methylmercaptopurine (6-MMP). Preliminary studies have suggested that the red blood cell concentration of 6TGN (RBC 6TGN) is a potential guide to therapy. The aims of the study were to evaluate the RBC 6TGN concentrations in adult patients with CD under long-term AZA/6-MP therapy and to correlate it with response to treatment and hematological parameters. Because of high relapse rate, it has been recently proposed to start with AZA or 6-MP as maintenance therapy for virtually all patients responding to cyclosporine. Prednisone tapering begins after 10-15 days and, after the patients are off-steroids, cyclosporine is stopped over the next month and the patient is maintained on.

AZA or 6-MP.[36, 37, 38, 39]

Antimicrobials: Decreasing Intestinal Flora Density

The role of antibiotics in the treatment of severe active UC is controversial. Several trials have failed to demonstrate a role of antibiotics (metronidazole or ciprofloxacin i.v.) as adjunctive therapy to corticosteroid in active UC. Rifaximin 400 mg bid significantly reduces the number of daily movement and the blood in stools compared to placebo in steroid-refractory severe active UC patients. Ciprofloxacin and metronidazole usually are administered on an empiric basis in patients with severe UC in addition to steroids. Also, these are used for the treatment of pouchitis after colectomy and ileoanal anastomosis. The dose of ciprofloxacin is 500 mg p.o. bid or 400 mg i.v. bid. The dose of metronidazole is 15 mg/kg (or 1g for 70-kg adult) i.v. over 1 h, while for the maintenance the dose is kept at infuse 7.5 mg/kg (or 500 mg for 70-kg adult) over 1 h q6-8h, not to exceed 4 g/d. A short course of intravenous ciprofloxacin is not effective as an adjunctive treatment to corticosteroids in severe UC. Whilst rifaximin does not permanently alter the colonic microbiota, resistant *Bifidobacterium* species have been found after 3 intermittent courses in patients with UC. Furthermore, ciprofloxacin has been shown to be effective when used in combination with standard treatment in patients with resistant disease.[40, 41, and 42]

Cyclosporine

Cyclosporine is a potent immunosuppressive which has a rapid onset of action (more rapid than AZA or 6-MP). Many open studies confirm that intravenous cyclosporine in a short-term data, at a dose of 2-4 mg/kg per day induces clinical improvement in more than 75% of the patients suffering from severe ulcerative colitis. Intravenous cyclosporine often demonstrates clinical efficacy within one week of the onset of treatment.23 Oral maintenance with

cyclosporine is not very popular because of its toxicity and long-term failure rate. One of the immunomodulators (AZA or 6-MP) is usually started concurrently with initiation of treatment with cyclosporine with the hope that AZA or 6-MP will be effective within three to six months and hence cyclosporine is rarely continued for more than 3-6 months. Measurement of blood pressure, full blood count, renal function and cyclosporine serum levels are advisable at 0, 1 and 2 weeks and then every month. Measurement of serum cholesterol and magnesium are appropriate before starting therapy because the risk of convulsions increases in patients with low cholesterol or magnesium. The other minor side effects include tremor, paresthesia, malaise, headache and abnormal liver functions. Major complications include renal impairment and infections. Prophylaxis against Pneumocystis carinii pneumonia is advised in all patients on cyclosporine. Cyclosporine enemas are not effective in left-sided ulcerative colitis.[43,44,45,46]

Treatment of Proctosigmoiditis and Leftsided Colitis

Topical (rectal) treatments like 5-ASA enemas are superior to oral preparations in the treatment and maintenance of remission of proctosigmoiditis and left-sided colitis.33 Topical corticosteroid enemas or foams are effective as active therapy, but not in remission. The topical therapyb generally has a quicker response time and a less frequent dosing schedule. Meta-analysis has clearly demonstrated that 5-ASA enema is superior to topical corticosteroids in the management of distal ulcerative colitis.34 For proctosigmoiditis, the standard recommendation is to begin treatment with 4 gm 5-ASA enema every night.35 The response is usually seen within four to six weeks. If the patient does not respond, additional morning 5-ASA or hydrocortisone enema can be considered. Once the patient goes into remission, frequency of enema should be tapered to every night or even on alternate nights. For patients who do not respond to or tolerate rectal preparation, an oral 5-ASA medication should be used. Combination therapy consisting of rectal, as well as oral 5-ASA preparation has been found to be more effective than either alone.36 Oral therapy with sulfasalazine, mesalamine, olsalazine or balsalazide is beneficial in achieving and maintaining the remission.[47,48,49]

Infliximab

Infliximab (Remicade®) is a powerful medication that has been used to treat Crohn's disease and rheumatoid arthritis, and is now used to treat refractory ulcerative colitis. Infliximab works differently than other treatments for UC. It is in a class of medications known as

biologic response modifiers, which work by interfering with pathways involved in inflammation. Infliximab must be given into a vein in a doctor's office or clinic, which takes one to three hours to complete. Infliximab may be used alone or in combination with other treatments. Because of their cost (generally more than $15,000 per year in the United States) and the potential risk of side effects, biologic response agents are generally reserved for patients with severe ulcerative colitis who have not responded to steroids, who prefer to avoid surgical removal of the colon.[50, 51]

Diet and Ulcerative Colitis

There are no specific foods that cause ulcerative colitis or help to maintain remission. A well balanced, nutritious diet can help maintain health and a normal body weight. However, many people can identify foods that worsen symptoms, and it is reasonable to avoid these foods. Table 2 lists foods and beverages that may worsen symptoms in some people. People who restrict their diet for any reason should take a daily multivitamin.[52, 53]

Vitamins and Medications

It is reasonable to take a multivitamin daily. As mentioned above, people who take sulfasalazine should take a folic acid supplement. Pain medications that contain nonsteroidal antiinflammatory drugs (NSAIDS), such as ibuprofen (Advil®, Motrin®) and naproxen (Aleve®), are not usually recommended since they can worsen symptoms or cause a flare. Acetaminophen (Tylenol®) should not cause a problem.[54, 55]

Lactose Intolerance

Lactose intolerance occurs when a person is not able to digest the sugar (lactose) contained in milk products. Symptoms of lactose intolerance occur after eating or drinking something that contains lactose, which may include diarrhea, cramps, or gas.

Ulcerative Colitis Nutrition Therapy

1. Eat small meals or snacks every 3 or 4 hours.
2. When you have symptoms, stick to the foods in the Recommended Foods chart. These
3. Foods are lower in fiber. When diarrhea decreases, you may have small amounts of whole grain foods and higher-fiber fruits and vegetables. Try them one at a time. If you have abdominal pain or diarrhea, then stop eating the new food. You can try it again at a later date.
4. Drink enough fluids to prevent dehydration. Aim for at least 8 cups of fluid each day.

5. Eat foods that have added probiotics and prebiotics. Ask your registered dietitian for
6. Good choices.
7. Use a multivitamin. You may need more of some vitamins and minerals than you do
8. When you are healthy.[55, 56,57]

CONCLUSION

The goal of therapy in inflammatory bowel disease is to induce and maintain remission in order to realize the best quality of life. Ulcerative colitis is a chronic inflammatory condition of the colon that does not shorten a patient's life span but can cause significant morbidity and lead to considerable expense. Before establishing the diagnosis of ulcerative colitis, a physician must carefully consider other inflammatory intestinal processes that resemble the disease. The goals of therapy are to suppress all inflammatory symptoms, both intestinal and extraintestinal, and then to choose the least toxic but most effective maintenance treatment to prevent flares. Over the long term, screening for neoplastic and cholestatic complications as well as complications of medical therapy take on greater importance.In ulcerative colitis disease activity is almost always associated with presence of diarrhea or bloody stool and can be easily accessed by sigmoidoscopy. The principal goals of maintenance therapy are avoiding disease progression and relapse and obviating corticosteroids and surgery. Consistent adherence to the maintenance therapy is very important and should be emphasized at each follow up consult. Ulcerative colitis is often a lifelong, multifaceted disorder that extends beyond disease related symptoms.

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