“CLINICAL PROFILE OF PATIENTS WITH ULCERATIVE COLITIS”- ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL & MRC, BELGAUM

By

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In Partial Fulfillment
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Under the Guidance of

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DECLARATION

I hereby declare that this dissertation entitled **"CLINICAL PROFILE OF PATIENTS WITH ULCERATIVE COLITIS - ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL & MRC, BELGAUM"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. REKHA. S. PATIL** $_{MD}$ Professor, Department of Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 10.

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LIST OF ABBREVIATIONS USED

5-ASA	-	5 aminosalicylates
6- MP	-	6- Mercaptopurine
ACTH	-	adrenocoricotropic hormone
ASCA	-	Anti-Saccharomyces cerevisiae antibody
CD	-	Crohn's Disease
DALM	-	Dysplasia associated lesion or mass
EIM	-	Extra intestinal manifestations
HLA	-	Human Leucocyte Antigen
i.v.	-	Intravenous
IBD	-	Inflammatory bowel disease
IEL	-	Intraepithelial lymphocytes
Ig	-	Immunoglobulin
IL	-	Interleukin
IPAA	-	Ileal pouch- anal anastomosis
MDR	-	Multi Drug Resistance
NS	-	Not significant
NSAIDs	-	Non Steroidal anti-inflammatory drugs
OC pill	-	Oral Contraceptive pill
pANCA	-	Peri- nuclear antineutrophil antibody
PINES	-	Paracrine, immune, neural and endocrine
S	-	Significant
Th	-	T Helper cell
TNF	-	Tumor Necrosis Factor
UC	-	Ulcerative Colitis
VS	-	Very significant

ABSTRACT

Background and Objectives

The two major forms of inflammatory bowel disease are Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease can affect any part of GIT and UC affects only large bowel. Both these conditions are not associated with increased mortality. The objectives of the present study were to assess the clinical profile of ulcerative colitis.

Methods

The present One year cross sectional study was conducted in the Department of General Medicine on 35 patients of UC admitted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum between the period of January 2008 to December 2008. Patients underwent thorough clinical examination according to predesinged and pretested proforma, colonoscopy and biopsy which were supported by relevant investigations. All patients in the study underwent endoscopy. Assessment of clinical disease activity in patients of UC was done by Truelove and Witts index.

Results

Present study revealed peak incidence in age group of 21 to 40 years. Male:Female ratio was 1.91:1 revealing higher male predominance. Diarrhea (100%) with passage of blood in stools (97.14%) and pain in abdomen (68.57%) were common presenting complaints. Extraintestinal manifestations are seen in moderate to severe disease group in about 25.71% of patients, arthritis is most

common extraintestinal manifestation. Ulcerative colitis was more common in non smokers. Nearly two third of the patients have left sided disease or pancolitis.

Conclusion

There is significant correlation between clinical severity and histopathological grading. There is significant correlation between endoscopic grading and histopathological grading. There is no correlation of endoscopic grading (Baron's criteria) with clinical severity (Truelove Witts). The disease causes substantial morbidity and health care cost.

Key words

Baron's criteria; Truelove Witts; Ulcerative colitis;

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INTRODUCTION

Inflammatory bowel Disease (IBD) characterizes those conditions characterized by tendency for chronic or relapsing immune activation within gastrointestinal tract (GIT). The two major forms of IBDs are Crohn's disease (CD) and Ulcerative Colitis (UC). Crohn's disease can affect any part of GIT and UC affects only large bowel. Both these conditions are not associated with increased mortality, however are associated with increased morbidity and decrease in quality of life. They pursue a protracted relapsing and remitting course usually extending over years. These diseases can lead to substantially higher direct and indirect health care costs.

These two major forms of IBD have many similar clinical, radiological, epidemiological, and histopathological (HP) characteristics suggesting that underlying causation may be similar. Indeed, occasionally they cannot be distinguished on clinical grounds between UC and CD, yet both of them are distinct syndromes, with divergent treatment and prognosis.

The incidence and prevalence of UC varies widely between different populations and from country to country. In West, incidence of UC is stable at 10 per 100000. Reports from East Asia has documented emergence of IBD, especially UC, but incidence are still low as compared to the West. The prevalence in our country is 44.3 per 1 lakh population (2004). In India over last two decades UC has emerged from 'rare disease' to a "frequently seen disease".[1]

Even after many years of research, when it was first described in symposium at Royal Society of Medicine in 1909, studies have failed to objectively ascertain the etiology of the disease. Many hypotheses have been put forward but all of them have been the subjective ones. What all data and information we have today, is from the studies and work abroad, where social life, customs, habits and environment are quite different from ours.

Many studies have been published describing various aspects of the disease from Europe and the United States over the past 50 years. However, more data is required from India to study the disease course. The earlier studies reported from India suggested a low incidence and a milder pattern of the disease. Subsequent reports in the late nineties have reported increased incidence of UC, reflecting either increased awareness, availability of better facilities for diagnosis, or truly an increased incidence of the disease.[1]

In India, most patients belong to a lower socioeconomic group. In western series, the upper class is more often affected. There is no Indian data regarding urban and rural prevalence. Publications from the west indicate that, smoking decreases the risk and severity of disease by 40%. We have a little data from India in this regard. Extraintestinal involvement is little studied in India.[1]

In view of the above context the present study was undertaken to access the magnitude and clinical profile of UC in a tertiary care medical center.

OBJECTIVES

The objectives of the present study were to assess the clinical profile of ulcerative colitis.

REVIEW OF LITERATURE

Ulcerative colitis

Ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract that affects the large bowel and is a major disorder under the broad group of inflammatory bowel diseases (IBDs).

"An inflammatory disease of unknown origin, characterized clinically by recurrent attacks of bloody diarrhea, and pathologically by a diffuse inflammation of the wall of the large bowel. The inflammatory changes spread proximally from the rectum; and are confined to (or most severe in) the colonic and rectal mucosa".[2]

From this it will be apparent that the customary name by which this disease is known 'ulcerative colitis'- is a thoroughly bad one, as ulceration is not a 'sine qua non' of the disease, and the disease usually involves colonic and rectal mucosa. Undoubtedly idiopathic diffuse mucosal proctocolitis would be a more accurate descriptive term. Unfortunately the terminology appertaining to various forms of colitis is already buried under the verbal debris of several centuries; and the term 'ulcerative colitis' possesses the twin merits of admirable brevity and wide usage, this is the term which will be adopted in the following description of the disease.[3]

Historical background

In all probability, we will never know who first described ulcerative colitis; although the disease was first referred to the name of Sir Samuel Wilks in 1859. Prior to that, as far back as Roman times, various forms of non-contagious diarrhea were described freely in the literature by physicians such as Aretaeus (A.D. 300) and Soranus (A.D. 117). It has been suggested that, in 1745 Prince Charles, the Young Pretender to the throne, suffered from ulcerative colitis and cured himself by adopting a milk-free diet.[2,4]

Physicians were unaware until the later part of 19th century that UC differed from dysentery. Sir William Wilks gets the credit for describing the first case of UC when he wrote to Medical Times & Gazzette in 1859, describing the postmortem he performed on young women who died after three week's illness.[5] He described it has 'Idiopathic Dysentery (Colitis)'. Wilks performed thousands of autopsies at Guy's hospital in London, and it is possible to trace, in successive editions of his Lectures, the evolution of his classification of inflammation of the bowel.[6] In the first edition, in 1859, he distinguished between enteritis, tuberculosis, caecitis, typhlitis, colitis and epidemic dysentery. He with Walter Moxon in 1875 isolated UC from various form of dysentery.[7] Sir William Allchin in 1885 commented upon trifling amount of pain associated with UC.[8] Pitt and Durhan described a case of girl in 1885 with history of diarrhea for five years. They were the ones who described pseudopolyps. The term "ulcerative colitis" was coined in 1888 by Hale-White. They wrote a useful article describing 29 cases.[9]

Clarity came in the early 1900s from a surgeon, Lockhart-Mummery, at St. Mark's (the London rectal hospital). He stated quite simply, "The most important advance in our knowledge of these cases has been due to the invention of the electric sigmoidoscope".[10] Among his 36 patients Lockhart-Mummery saw definite inflammation in 24 and found a tumor in 7. In 4, he saw excess gelatinous mucus on a thick edematous, but still shiny, mucosa; he called the condition "chronic hypertrophic catarrh". His sigmoidoscopic distinction between this chronic hypertrophic catarrh and true colitis led him to emphasize that colitis was not a neurosis, but a disease with visible structural lesions. In 1907, he used the term "sigmoiditis" to indicate that with a sigmoidoscope he could be sure only that the colitis involved the rectosigmoid, and he could not know whether the whole colon was involved.[11]

In 1909, Hawkins described the chronic and relapsing nature of the disease course, and the "stealthy hemorrhage" onset of distal disease in which bleeding often occurred in the presence of constipation. In that same year, Sir Arthur Hurst gave a more complete description of UC, including its sigmoidoscopic appearances and differentiation from bacillary dysentery.[12] Its etiology remained controversial, however, and an infectious or psychosomatic origin was considered the primary cause.

In 1939, R.N. Chopra, P.N. Ray and associates first described such a disease in India in the Indian Medical Journal, where they recorded 120 cases from the School of Indian Tropical Medicine in Calcutta.[13]

The first half of 19th century was still bad time for patients with UC. The true medical treatment was euphuism and could hardly justify even term supportive as nothing was known about electrolytes, malnutrition, antibiotics or corticosteroids. Surgeons were called to perform illeostomy. With the development of Koenig's bag, the operations were performed earlier and frequently. It was Dennis in 1945 who emphasized the need for total colectomy with permanent illeostomy.

Dr. Sidney Truelove and colleagues studied the medical aspect and listed complications, course and prognosis in 1950. Wells in 1952, showed the term 'segmental colitis' a term used by both Hurst and Crohn was 'colonic form of Crohn's disease' (CD).[14] In 1959, Brooke separated the two forms of diffuse colitis by pointing out granulomatous rather than ulcerative nature of underlying inflammatory process in CD.[15]

Sulfasalazine came into existence through the inspiration of Swedish Dr. Nanha Schwartz.[16] Truelove et al compared sulfasalazine with steroids in 1962 and showed that both were equally effective and stated, whether steroids maintained remission was doubtful.[17]

The 1970's, three very important studies appeared. In 1971, KN Jalan et al described details of this disease in 300 cases.[18] Similar studies were published by Dr. B.D. Pimparkar from Bombay and Dr. B.K. Jha of the All India Defence Services.[19,20] Dr Khosla reported the prevalence in a hospital-based study. In a report of 10 cases, Prof. S.N. Khosla described epidemiological aspects not addressed by previous authors.[21] Two important studies have emerged from our

own center: those of Dr. Kochar et al and Dr. Sethi et al. Dr. Ajit Sood from Ludhiana has reported a nice study of 145 cases.[22,23]

Synonyms

- Idiopathic Proctocolitis
- Proctosigmoiditis
- Colitis Gravidum
- Thromoboulcerative colitis

Epidemiology

The incidence and prevalence of UC varies with geographic location and ethnicity. Rigorous epidemiologic studies have been limited by several potential issues. The diagnosis of UC may be difficult due to its variation in clinical manifestations, and in some regions, the common occurrence of infectious colitis can mimic UC.

In general, there has been a distinct north-south gradient in risk. The areas with the highest rates of reported incidence and prevalence of UC include North America, England, northern Europe, and Australia. In North America, the incidence ranges from 6.0 to 14.3 cases per 100,000 person-years and the prevalence ranges from 37 to 246 cases per 100,000 persons.[24] In Europe, the incidence ranges from 1.5 to 20.3 cases per 100,000 person-years and the prevalence ranges from 21 to 243 cases per 100,000 persons. The disease has been considered more common in northern Europe, although recent studies suggest that the incidence of UC in southern Europe is comparable to that in

northern Europe.[25] In contrast, studies have reported significantly lower annual incidence rates of 0.6 to 6 per 100,000 persons in other parts of the world, including Asia, Africa, and Latin America.[24]

UC in Asia generally is less common than in the Western countries. The prevalence and annual incidence rate for UC in Japan have remained relatively stable at about 5.5 cases per 100,000 persons and 0.36 to 0.5 cases per 100,000 persons, respectively; this stability is in contrast with the rising incidence of Crohn's disease in the Japanese population.[26] Limited data also suggest similar findings in the Chinese and Korean populations. The prevalence of UC in India has been reported to be substantially lower than that among Europeans. Increasing incidence has been reported in North India.[27]

Demographic features

Age of onset

UC may present at all ages, although diagnosis before the age of 5 years or after 75 years is uncommon. The peak incidence of UC occurs in the 2nd and 3rd decades of life. Studies have reported a second, smaller peak in the elderly, between the ages of 60 and 70 years. This second peak is less pronounced than that for Crohn's disease.

Gender distribution

Most studies have not shown any gender difference in the occurrence of UC and a male-to-female ratio of nearly 1:1 applies to all age groups. Few studies have shown mild male predominance in high and low incidence areas.

Ethinic & Racial differences

Several studies suggest that incidence of IBD among African Americans is approaching that of Whites. In contrast to the limited data on the indigenous South Asians, several studies have demonstrated that South Asian immigrants in England are more likely to have UC than are European natives.[27,28, 29] Israeli studies suggest a higher prevalence of UC among Jews from Europe & America compared to those of Asia and Africa.[30] This changing epidemiology with immigrant population from low-risk to high-risk geographic regions supports the concept of environmental influence on disease development.

Etiology and pathogenesis

The etiology of UC is presently unknown but is likely multifactorial. The currently held paradigm involves the complex interaction of three elements: genetic susceptibility, host immunity, and environmental factors. Dysregulation of the enteric immune response in genetically predisposed individuals leads to the development of acute and chronic inflammation and the pathologic feature of mucosal damage. The specific inciting antigens for the inflammatory process have yet to be identified, but several sources have been suggested, including pathogenic and commensal microorganisms, metabolic byproducts of these agents, and normal epithelial structures.

Genetics

The familial incidences of UC vary widely among different studies, but about 10% to 20% of patients have at least one another affected family member.

[31] This familial association generally occurs in first-degree relatives. The relative risk of the same disease in a sibling of an individual with UC has been estimated between 7 and 17 based on North American and European studies. Parents, offspring, and second-degree relatives appear to be at a lower risk for developing UC than are first-degree relatives. Data from the United States suggest a preponderance of parent-sibling combinations, but in the United Kingdom, the disease is shared more commonly by siblings. The lifetime risk of developing disease is threefold higher among first-degree relatives of Jewish patients compared with relatives of non-Jewish patients.[30] This familial association contrasts with the low incidence of UC among spouses of patients with IBD in most series. Although reports of IBD in both husband and wife are rare, a study of 30 conjugal instances of IBD found a higher frequency of husband-wife pairs, both of whom developed disease after cohabitation, thus suggesting a shared environmental exposure.[32]

Studies on the clinical characteristics of familial disease also have shown that the onset of disease in a child is noted at a much earlier age than in the affected parent, but there is a high degree of concordance between affected siblings for age of onset. This observation of the younger age of onset in the offspring of an affected patient may have genetic basis, such as inheritance from parents of a greater number of putative susceptibility genes, or may be due just to earlier recognition by parents and physicians. For all affected first-degree relatives within a family, there is a high concordance for type of disease (UC vs. CD), extent of disease, and occurrence of extraintestinal manifestation.[33]

It is likely that multiple genes are involved and that different genes may confer susceptibility, disease specificity, and phenotype. Linkage studies have suggested that there are susceptibility genes for UC on chromosomes 2, 3, 6, 7, and 12.[34,35] The IBD2 locus on chromosome 12 appears to have the strongest linkage demonstrated in studies. The recently identified *NOD2*/*CARD15* gene mutations located on chromosome 16 associated with Crohn's disease have not been associated with UC. Similar to Crohn's disease, a recent study has linked the C3435T polymorphism for the human multidrug resistance 1 (*MDR1*) gene to susceptibility for UC. [36]

There also are genes that appear to influence disease behavior independently of susceptibility genes. The best studied of these are the human leukocyte antigen (HLA) alleles. One allele of HLA-DR2 (*DRB1*1502*) appears to be involved in disease susceptibility in Japanese and Jewish populations. Several centers have reported an association between severe disease and a rare allele of HLA-DR1 (*DRB1*0103*). In some studies, the HLA-DR3, DQ2 haplotype is associated with extensive colitis, especially among women. Among the Jewish population, the peri-nuclear antineutrophil antibody (pANCA) is a marker for the *DRB*1502* allele of HLA-DR2, but in non-Jewish whites, this antibody is associated with the HLA-DR3 DQ2-tumor necrosis factor (TNF)-α_2 haplotype.

Environmental risk factors

No specific infective organism, however, has been isolated consistently from patients with UC, and therefore, it is unlikely that the disease is caused by a

single common infectious agent. Studies have shown reduced numbers of anaerobic bacteria and *Lactobacillus* spp. both in experimental colitis and in patients with active UC but not quiescent disease.[37]

Perinatal Infection in mothers may influence the expression of IBD. It has been proposed that paramyxovirual perinatal or childhood infection might result in persistant infection resulting in chronic granulomatous vasculitis.

Cigarette smoking

Since the first widely publicized report of an inverse association between UC and smoking, many studies have confirmed this unusual finding. The odds ratio for development of UC in smokers is less than 1.[38] The mechanism of action of this unusual association remains uncertain. Suggested mechanisms include increase and normalized mucus production as protective factor and inhibition of immune response. Nicotine increases colonic mucus production and decreases eicosanoid levels. It decreases prostaglandin E2 levels, decreases natural killer cells and impairs neutrophil adherence and movement due to inhibition if IL-8. Smoking also reduces rectal blood flow, which decreases the number of inflammatory mediators reaching mucosal surface.

However former cigarette smokers have increased risks of developing UC then people who have never smoked. One study suggested that former smoker remains greatest risk for developing UC in first 3 years of life after stopping smoking where as others found risk to be remain high beyond 10 years.[39]

Passive smoking has also been associated with increased UC risk. Passive smoking exposure at birth was significantly associated with development of UC.[40]

Appendectomy

Studies have consistently demonstrated a negative association between appendectomy and subsequent development of UC.[41, 42] The mechanisms for this protective effect of appendectomy on UC are unknown. It is possible that removal of appendiceal-associated lymphoid tissues may abrogate certain pathologic alterations in mucosal immune responses and therefore prevent the onset of UC. Alternatively, the absence of those lymphoid tissues merely may characterize an immune response distinct from UC. The former hypothesis is suggested by a population based study that found a lower incidence rate of UC after appendectomy, compared with that before appendectomy.[43]

Oral contraceptives and breast feeding

In a British population-based study, there was a slight increase in UC among contraceptive users, but the association became insignificant after adjusting for social class and smoking habits. A subsequent meta-analysis also failed to show a significant association, with a pooled relative risk of 1.29 for developing UC with oral contraceptive use.[44] Breast-feeding has been suggested to be protective against the development of UC; however, this protective benefit is weak and not shown by other studies.[45]

Diet

Wheat, maize, cow's milk, refined sugar, fruit and vegetables, alcohol, food additives (silicon dioxide), and toothpaste were mentioned as risk factors for UC in different studies. None, however, has been shown conclusively to be associated with UC. Early reports implicated food allergy, especially milk allergy, as a potential etiology of UC. A subsequent study also found a positive relationship between allergy to cow's milk in infants and later development of UC.[46] Clinical observations further argue against dietary allergy as a potential cause of UC, including the lack of response to bowel rest during a severe attack of disease, and anecdotal case reports that bowel diversion with an ileostomy was not effective in treating active UC. At present, there is little evidence that milk or any other food plays a primary role in the etiology of UC.

Miscellaneous factors

UC is more prevalent in high socioeconomic groups. NSAIDS have found to worsen UC. Seasonal variation has been reported, disease activity peaking in December.

Pathogenesis of diarrhea in UC

Diarrhea in UC is complex; rather than being produced by a single pathophysiologic mechanism. It is caused by several mechanisms that may include the effect of substances released by enteric endocrine cells, and cytokines released by local and remote immunologically reactive cells; the activity of the

enteric nervous system, and peripherally released peptides and hormones (paracrine, immune, neural, and endocrine systems)

There is dysregulation of the PINES in UC.[47] Diarrhea in patients with UC results from more than just exudation into the lumen because of destruction of the mucosa. Intact enterocytes are barraged by multiple secretagogues released by immune cells in the intestine and by bacterial toxins that may influence enterocyte function. Although initial models of diarrhea in UC suggested that altered fluid transport is driven by chloride secretion, subsequent studies have demonstrated that the diarrhea in UC is mediated by an anti-absorptive effect associated with down-regulation of sodium channels and pumps. The pathophysiology of diarrhea in UC is even more complex if the role of luminal bacteria is considered. Bacterial proteins, such as flagellin, may stimulate the production of cytokines, such as interleukin (IL)-8, that further attract inflammatory cells. Cytokines and immune cells also may influence enterocyte secretory and absorptive pathways directly. Conversely, epithelial cells may secrete cytokines that enhance neutrophil function, such as IL-6[48]

Immunopathogenesis

The physiologic state of the intestine is one of constant low-grade inflammation in response to environmental stimuli such as bacterial products or endogenous factors. Breaches in this well-regulated mucosal immune system lead to the chronic uncontrolled mucosal inflammation observed in UC. In this regard, immunologic mechanisms in the pathogenesis of UC involve both humoral and cell-mediated responses.

Humoral Immunity

Histologic examination of the inflamed colon indicates a marked increase in the number of plasma cells. The largest proportional increase occurs in IgG synthesis, which has the highest pathogenic potential among antibody classes. The increase in IgG synthesis in UC is most pronounced in the IgG_1 and IgG_3 subclasses, in contrast to Crohn's disease, in which the increase in IgG_2 synthesis is more prominent.[49,50] This disparity in the local IgG subclass response likely reflects differences in antigenic stimuli or host immunoregulatory responses between the two groups of IBD patients. Many of these antibodies are thought to be epiphenomena because the serum antibody titers do not correlate with clinical parameters. Nevertheless, the known cross-reaction between enterobacterial antigens and colonic epithelial epitopes may be an important triggering event, even though, later in the course of the disease, the serum antibody titer to either the bacterial or the colonic antigen may be unimportant.

The concept that UC is an autoimmune disease is supported by its increased association with other autoimmune disorders, including thyroid disease, diabetes, and pernicious anemia. Patients with UC have varying levels of autoantibodies to lymphocytes, ribonucleic acid, smooth muscle, gastric parietal cell, and thyroid antibodies; these are neither tissue nor disease specific. Antibodies to epithelial cell-associated components, which specifically recognize intestinal antigen, also have been described. The best characterized intestinal autoantigen is an epithelial antigen of 40-kd size found in normal colonic epithelium. This autoantigen is recognized by IgG eluted from the inflamed colonic mucosa of patients with UC and is a component of the tropomyosin

family of cytoskeletal proteins. This autoantibody has the potential to activate complement in vivo, but direct evidence of antibody-induced cytotoxicity has not been observed. The antibody response to this 40-kd protein appears to be unique to UC and is not found in Crohn's disease or other inflammatory conditions. This autoantigen shares an epitope with antigens found in the skin, bile duct, eyes, and joints, sites frequently involved in the extraintestinal manifestations of UC. The precise pathogenic significance of this autoantibody in UC remains unclear at present.

An autoantibody that has received significant attention is pANCA.[51] This autoantibody is present in 60% to 85% of patients with UC.[52] It is synthesized within the lamina propria and is of the IgG_1 subclass. The antigen to which the pANCA is directed has not yet been determined with certainty. Just as with other autoantibodies found in patients with UC, the pathogenic relevance of pANCA in this disorder is unknown. In fact, the prevailing thought is that pANCA has no pathogenic role in UC but that it may serve as a potential marker of susceptibility and genetically distinct subsets of UC. The level of pANCA titer does not correlate with disease activity but may decline in patients with long-standing remission or in patients who have had colectomy for at least 10 years. Studies have suggested that pANCA may be associated with a more aggressive disease course and the development of pouchitis following ileal pouch-anal anastomosis (IPAA) in patients with UC.[53]

Cellular Immunity

The mucosal T cells can be divided into two anatomically different groups: lamina propria lymphocytes and intraepithelial lymphocytes (IELs). Immune cells within the lamina propria consist of a mixture of cell types, including T cells, B cells, macrophages, and dendritic cells. The most common immune cells are IgA-secreting plasma cells. Lamina propria lymphocytes express surface adhesion molecules, α4β7, that provide a homing signal for peripheral immune cells to the mucosal sites. Studies using nonspecific mitogens have found diminished suppressor activity during active disease only, but an antigen-induced suppressor assay has shown that patients with UC in remission exhibited suppressor defects to a range of mycobacterial and enterobacterial antigens.[54] This phenomenon of antigen-induced suppression was predominantly $CD8^+$ cell dependent and correlated with a poor response to skin testing with purified protein derivative; these defects were limited to the peripheral blood and not lamina propria lymphocytes.

In patients with UC, the absolute number of IELs is normal or reduced. Most of these cells are $CD8^+$ cells, and the function of IELs has not been well characterized. It has been suggested that they are cytotoxic and also may be active in suppressing local immune response. In patients with UC, the proportion of IELs using the γδ T cell receptor may increase. However, the function and significance of γδ T cells are unknown. Although T cell mediated immunity has attracted the most attention in the pathogenesis of UC, nonspecific cellular immunity also is altered. In patients with active disease, there is an overproduction of circulating monocytes as well as mucosal macrophages. The

inflamed mucosa of patients with UC also exhibits infiltration of substantial numbers of granulocytes.[55]

Epithelial Cells

Patients with UC have an increased turnover rate of colonic epithelium, and other abnormalities of epithelial cells include a reduced metabolism of short-chain fatty acids, especially butyrate, abnormal membrane permeability, and altered composition of glycoprotein mucus produced by the colonic epithelium. The role of epithelial cells in the pathogenesis of IBD is supported further by animal modes of colitis using disruption of colonic epithelium.

Consequences Of Immune Activation

Activation of macrophages, lymphocytes, and colonic epithelial cells leads to the release of a variety of cytokines and mediators that further amplify the immune and inflammatory response of UC and result in tissue damage. Based on the cytokines they produce, $CD4^+$ T cells have been divided into two major immune phenotypes: T helper 1 (Th1) and T helper 2 (Th2). The Th1 response is characterized by cell-mediated immunity and is associated with the production of interleukin (IL)-2 and interferon (IFN)-γ. The differentiation of T cells along a Th1 pathway is stimulated by IL-12 generated in response to exposure to infectious agents. The Th2 response is characterized by the production of cytokines IL-4, IL-5, and IL-10, which amplify the humoral immune response. Th1 and Th2 subsets reciprocally down-regulate each other through cytokine production. [56] Both Th1 and Th2 pathways can be regulated by unique regulatory T cells (Th3, T regulatory 1) subsets that produce IL-10 and transforming growth

factor-β and down-regulate inflammation. Macrophages in the inflamed colon in patients with active UC synthesize IL-1β, TNF, and IL-6, whereas lamina propria T cells probably produce IL-2 and IFN-γ. This immune response can be up-regulated further by presentation of antigen to $CD4^+$ lymphocytes by colonic epithelial cells that express HLA class II antigens. Release of these cytokines also may lead to other abnormalities seen in UC, such as increased epithelial cell permeability and collagen synthesis. Alteration of endothelium by a variety of cytokines may result in local ischemia. Increased expression of endothelial adhesion molecules in response to inflammatory mediators recruits circulating granulocytes and monocytes to the inflamed tissues, thus further perpetuating the inflammatory response. Elevated cytokine levels within the mucosa also stimulate the release of metalloproteinase from fibroblasts with subsequent matrix degradation. Mucosal concentrations of many mediators have been shown to be elevated in patients with active UC, including leukotrienes, thromboxane, platelet-activating factor, nitric oxide, and reactive oxygen metabolites. These mediators, which are mostly released from active macrophages and neutrophils, contribute to inflammation and mucosal injury, alter epithelial cell permeability, and interfere with iron transport, thereby further contributing to diarrhea. Diarrhea in UC also is caused by complement activation and the release of kinins and other inflammatory mediators from mast cells and eosinophils.

Pathology

Macroscopically

UC involves rectum and extends proximally to involve all part of colon. 40-50% of patients have disease limited to rectum.30-40% have disease extending beyond sigmoid but not involving whole colon. 20% have pancolitis.[57] Proximal spread occurs in continuity without areas of uninvolved mucosa. When whole colon is involved, the inflammation extends 1-2 cm into the terminal ileum which is known as black water ileitis.

The mucosa in UC appears hyperemic, edematous, and granular in mild disease. As disease progresses, the mucosa becomes hemorrhagic with visible punctate ulcers. These ulcers may enlarge and extend into the lamina propria. They often are irregular with overhanging edges or may be linear along the line of the teniae coli. Epithelial regeneration with recurrent attacks results in the formation of pseudopolyps, which is typical of long-standing UC but that also may be seen in acute disease. Another characteristic appearance of long-standing disease is atrophic and featureless colonic mucosa, associated with shortening and narrowing of the colon. Patients with severe disease may develop acute dilatation of the colon, and these cases are characterized by thin bowel wall and grossly ulcerated mucosa with only small fragments or islands of mucosa remaining. With perforation, a fibrinopurulent exudate may be seen on the serosal surface of the bowel.

Microscopic features

The early stage of UC is marked by edema of the lamina propria and congestion of capillaries and venules, often with extravasation of red blood cells. This is followed by an acute inflammatory cell infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages. There also may be increased numbers of eosinophils and mast cells. Neutrophilic infiltration of colonic crypts gives rise to cryptitis and ultimately to crypt abscess with neutrophilic accumulations in the crypt lumina. This acute inflammatory infiltration results in the characteristic histopathology of goblet cell mucin depletion, formation of exudates, and epithelial cell necrosis. None of these histologic findings, however, is specific for UC. Inflammation in UC characteristically is confined to the mucosa, in contrast to the transmural involvement of Crohn's disease. The inflammatory changes typically end at the luminal aspect of the muscularis mucosa. With increasing inflammation, however, the surface epithelial cells become flattened and eventually ulcerate. Deep ulceration may undermine the surrounding epithelium. Whereas this deeper involvement may be confused with Crohn's disease, it usually presents diffusely rather than with the fissuring pattern of transmural inflammation that characterizes Crohn's disease.

The healing phase of UC, the inflammatory infiltrate subsides and epithelial regeneration takes place. Epithelial cells undergoing regenerative changes become cuboidal with eccentric, large nuclei, and prominent nucleoli. These features may be confused with dysplasia. Thus, a diagnosis of dysplasia in UC should be made with caution in the presence of acute inflammation.

Accordingly, surveillance colonoscopy should be performed during a period of remission.

A classic histologic feature of chronic quiescent UC is crypt architectural distortion or actual dropout of glands. Architectural changes include branching or bifid glands, wide separation among glands, and shortened glands that do not extend down to the muscularis mucosa. Whereas architectural alteration is a prominent feature of chronic quiescent UC, the histologic abnormalities may revert to normal after mild flares in the early course of disease. Another characteristic feature of chronic quiescent UC is Paneth cell metaplasia, with the presence of Paneth cells beyond the hepatic flexure, where they typically are absent. Other nonspecific chronic changes seen in UC include neuronal hypertrophy and fibromuscular hyperplasia of the muscularis mucosa.

Most of these findings are not specific for UC. Features that reflect chronicity and thus argue against a diagnosis of infectious or acute self-limited colitis include distorted crypt architecture, crypt atrophy, increased intercrypt spacing to fewer than 6 crypts per millimeter, an irregular mucosal surface, basal lymphoid aggregates, and a chronic inflammatory infiltrate. Histologic severity of inflammation does not necessarily correlate with clinical disease activity in patients with UC and patients may be relatively symptom free, while histology reveals significant inflammation.

Clinical features of UC

Symptoms

UC usually affects the rectum and extends proximally in diffuse symmetric and contiguous pattern. Patient may develop proctitis, proctosigmoiditis, left sided colitis (inflammation up to splenic flexure), extensive colitis (extending beyond splenic flexure) and pancolitis. The location of inflammation tends to remain constant throughout the disease course in the patients and the combination of disease extent and disease severity influence disease presentation and prognosis.

The onset of UC typically is slow and insidious. Symptoms have usually been present for weeks or months by the time the patient seeks medical attention. The median interval between the onset of symptoms and diagnosis of UC is approximately nine months.[58]

Patients with UC may present with a variety of symptoms. Common symptoms include diarrhea, rectal bleeding, passage of mucus, tenesmus, urgency, and abdominal pain. In more severe cases, fever and weight loss may be prominent. The symptom complex tends to differ according to the extent of disease. Patients with proctitis often have local symptoms of tenesmus, urgency, mucus, and bleeding, whereas patients with extensive colitis may have more diarrhea, weight loss, fever, clinically significant blood loss, and abdominal pain. In general, the severity of the symptoms correlates with the severity of the disease; however, active disease may be found at endoscopy in patients who are otherwise asymptomatic.

Pain in abdomen is uncommon as disease is limited to mucosa where as pain receptors are present in serosa and peritoneum.

Patient with fulminant colitis have severe colitis, appear toxic and have continuous bloody diarrhea of greater than 10 bowel movements per day. They are febrile with temperature more than 101°F and have tachycardia, abdominal distention, signs of localized or generalized peritonitis, and leucocytosis,. Toxic megacolon is said to occur when there is radiologic evidence of colon dilatation to greater than six cm in an acutely ill patient. Fulminant colitis and toxic megacolon are clinical diagnoses. The endoscopic examination should be avoided in patients with severe or fulminant colitis, because of the risk of inducing megacolon or perforation.

Physical Examination

Patients with mild to moderate UC usually present with a normal physical examination along with left lower quadrant tenderness along with pallor related to iron deficiency anemia. More severely ill patient present with features of systemic toxicity (fever, tachycardia, and hypotension), dehydration, anemia and more localized abdominal tenderness. Severe disease is characterized by abdominal tenderness, possible colonic dilatation and fulminant disease by rebound tenderness and prostration. A quite ill patient may appear deceptively well as concomitant steroid therapy may mask peritoneal signs. Colonic perforation can occur in toxic megacolon but also in severe colitis without colonic dilatation. Life threatening hemorrhage is less. Colonic strictures in UC are rare and should arouse the suspicion of carcinoma. There may be findings

related to extraintestinal manifestations of UC or from complications of therapy in UC.

Assessment of disease activity in UC

Assessment of disease activity is important for prognostication and therapeutic decision making. Several instruments have been developed to allow standardized evaluation of disease activity for UC. Although none is accepted universally as standard, one of the most commonly used for this purpose is that of Truelove and Witts.[59] The Truelove and Witts classification is reliable and simple to use in clinical practice, although it is most applicable for patients with extensive colitis and may not adequately reflect disease severity in patients with limited colitis. Additionally, the Truelove and Witts classification does not take into account endoscopic findings in assessing the disease severity. Endoscopic findings do not always correlate with clinical symptoms, but such correlations generally are more consistent within individuals. Thus, although therapeutic decisions are based primarily on clinical status, it may be useful to follow sigmoidoscopic mucosal appearance over time in an individual patient if the clinical response to treatment is uncertain.

Table 1: Truelove and Witts Classification of Ulcerative Colitis

Variables	Mild disease	Severe disease
Stools (no. per day)	<4	> 6
Blood in stools	Intermittent	Frequent
Temperature	Normal	> 37.5
Pulse	Normal	> 90
Hemoglobin	Normal	< 75% normal
ESR (mm/hour)	< 30	> 30

Moderate disease is intermediate between mild and severe disease.

Extraintestinal manifestations

Extraintestinal manifestations may coincide with diagnosis of disease, predate or complicate long standing UC. They are more common in patients with increased severity of disease. Immunological mechanisms are likely responsible for this manifestations.

Table 2: Extraintestinal manifestations

System	Manifestations
Musculoskeletal	Peripheral arthropathy Ankylosing spondylitis Sacroiliitis Osteopenia Osteoporosis Osteomalacia Osteonecrosis
Dermatologic	Erythema nodosum Pyoderma gangrenosum Oral ulcerations Angular stomatitis Aphthous stomatitis Pyostomatitis vegetans Psoriasis Sweet's syndrome (acute febrile neutrophilic dermatosis)
Ophthalmologic	Uveitis/iritis Episcleritis Scleritis Conjunctivitis Retinal vascular disease
Hematologic	Iron deficiency anemia Autoimmune hemolytic anemia Anemia of chronic disease Leukocytosis or thrombocytosis Leukopenia or thrombocytopenia Hypercoagulable state Coagulation abnormalities

System	Manifestations
Hepatobiliary	Steatosis Primary sclerosing cholangitis Pericholangitis Cholangiocarcinoma Autoimmune hepatitis
Genito urinary	Nephrolithiasis Fistulas Obstructive uropathy Amylodosis Membranonephritis
CVS	Pleuropericarditis Endocarditis Myocarditis Cardiomyopathy
Pulmonary	Fibrosing Alveolitis Apical fibrosis Bronchitis Pulmonaryvasculitis Bronchietasis Bronchiolitis
Neurological	Neuropathy Vasculopaty Myopathy Meningitis CVT

Complications of UC

Only 15% of patients with UC present initially with catastrophic illness. Massive hemorrhage occurs in 1% of the patient. Toxic megacolon, defined as transverse colon with a diameter of 5-6 cm with loss of haustrations, occurs in 5% of severe attacks and can be triggered by electrolyte abnormality and

narcotics. About 50% of acute dilatations will be relieved by medical therapy only. Perforation is most dangerous of local complication and physical signs of peritonitis will not be obvious especially if patient is receiving glucocorticoids. The mortality rate for perforation complicating toxic megacolon is 15%.Obstruction caused by benign stricture formation occurs in 10% of patients, which should be surveyed for carcinoma.

Dysplasia and colorectal cancer in UC

Patients with UC have an increased risk of colorectal cancer. This risk is dependent on several factors, the most important being the duration and extent of the disease. Other risk factors include PSC, family history of colon cancer, age at diagnosis of disease, severity of inflammation, and possibly backwash ileitis.[60] The incidence of colon cancer in UC varies depending primarily on the duration and extent of the disease but has been estimated at approximately 7% to 10% at 20 years of disease and as high as 30% after 35 years of disease.[61] Thus, in general, the risk of CRC may be estimated to increase within the range of 0.5% to 1.0% per year after 8 to 10 years of disease in patients with extensive UC.

Although prophylactic colectomy can virtually eliminate the risk of colorectal cancer, patients often are unwilling to undergo surgery, particularly if there is no other indication for colectomy. Thus, colonoscopic surveillance programs have been developed in an effort to reduce the risk of colorectal cancer associated with UC. The primary goal of surveillance colonoscopy is to detect dysplasia, defined as unequivocal neoplastic epithelium, because currently it is the most important marker to detect concurrent or subsequent cancer. Dysplasia

can be classified histologically and endoscopically into several groups, each with different prognostic implications. Histologic assessment is classified as negative, indefinite, and positive for dysplasia. Two grades of dysplasia are recognized: low and high.[62] Endoscopically, dysplasia can be characterized as flat or raised based on the appearance of the surface of the dysplastic area. Flat dysplasia represents most of the dysplasia detected in patients with UC. Raised dysplasia is also termed *dysplasia-associated lesion or mass* (DALM) and can be found as a polypoid lesion, mass, plaque, or stricture.

The predictive value of low-grade dysplasia for the development of more advanced lesions varies among studies. In a systematic review of 10 studies in the literature, the risk of synchronous cancer at immediate colectomy was 19% (3 of 16) in patients with low-grade dysplasia.[63] In patients with newly diagnosed low-grade dysplasia after a previously normal surveillance colonoscopy, 16% later progressed to high-grade dysplasia, DALM, or cancer (8%), whereas 29% of patients with untreated low-grade dysplasia found at the initial surveillance colonoscopy progressed to high-grade dysplasia, DALM, or cancer (13%). In a single center study of 46 UC patients with flat low-grade dysplasia on surveillance colonoscopy, unexpected advanced neoplasia occurred in 4 (24%) of 17 patients who underwent immediate colectomy.[64]

Most authorities recommend annual to biannual colonoscopy with biopsies in patients with UC extending beyond proctitis who have disease for 8 to 10 years.[65] Examinations should be performed during periods of inactive disease so as not to allow inflammation and reactive change to obscure the picture. Four-quadrant biopsies should be obtained every 10 cm and from any potentially

dysplastic lesion. Thus, performing proper surveillance requires extensive biopsies. In fact, it has been estimated that at least 18 jumbo biopsies are required to achieve 95% probability of identifying dysplasia or cancer if it is present. Because the goal of surveillance colonoscopy is to detect dysplasia before cancer develops, a minimum of 64 biopsies are required to detect highest rate of dysplasia anywhere in the colon with 95% confidence.

Ulcerative colitis disease markers

Antineutrophilic cytoplasmic antibody (ANCA) was originally reported in IBD in 1980s. The IBD specific ANCA displays perinuclear highlighting (pANCA) on immunoflurence staining and is DNAse sensitive. The antigen to pANCA is directed is nuclear histone (h1). pANCA has shown to be prevalent in sera of approximately 60% of UC and 20% of CD.

Anti-Saccharomyces cerevisiae antibody (ASCA) is expressed in 10% of patients of UC and 60% of patients of CD and <5% non IBD patients.[66]

Classical Laboratory Markers

The routine tests like complete blood picture, ESR, CRP and serum albumin are very sensitive for inflammation but are less specific. Thrombocytosis is less found inUC compared to CD.

Fecal Markers

Sensitive assays for leucocytes in stool, such as fecal calprotectin and fecal lactoferrinis, are used to differentiate IBD from functional bowel

disorders.[67] They are not however specific as they are increased in infections, NSAIDs and bowel neoplasms.[68, 69]

Radiographic imaging for UC

Supine plain film of the abdomen

The presence of intraperitoneal air may be missed on plain abdominal films. In the presence of severe disease, the luminal margin of the colon (i.e., the interface between the colonic mucosa and the luminal gas) becomes edematous and irregular. Thickening of the colonic wall often is apparent on a plain film, and prognostic signs such as mucosal islands (islands of residual mucosa surrounded by extensive deep ulcerations), small bowel distention, and colonic dilatation can be detected. Plain films also are useful for detecting the presence of fecal material. Inflamed colon seldom contains feces, and no fecal material is present when the whole colon is involved. It is common, however, for a patient with left-sided disease to have proximal constipation. Thus, a plain film can give considerable information with respect to the extent of disease. The presence of marked colonic dilatation suggests fulminant colitis or toxic megacolon. A plain abdominal film also may detect unsuspected free air and is especially useful in following the daily progress of a patient on high-dose glucocorticoid therapy in whom such a complication may be masked.

Barium studies

The earliest radiologic change of UC seen on barium studies is fine mucosal granularity. The mucosal line becomes irregular and is not as sharp as

that of a normal colon. With increasing severity, the mucosal line becomes thickened and irregular, and superficial ulcers are well shown en face. Deep ulceration can appear as “collar-stud” or “collar-button” ulcers in tangent, which indicates that the ulceration has extended through the mucosa to the muscularis propria. Loss of haustrations occurs in patients with long-standing disease. Since lack of haustrations can be a normal appearance for the left colon, this sign is relevant for only the ascending and transverse colon. With long-standing disease, loss of haustration may lead to a featureless and tubular appearance of the colon. Other chronic changes are shortening of the colon and widening of the presacral space as seen on a lateral film of the rectum. Pseudopolyps may be present and often are filiform. In the presence of active changes, these pseudopolypoid changes can resemble a cobblestone pattern.

CT and MRI

The hallmark of UC is mural thickening. The mean wall thickness is 8mm. 70% patients reveal inhomogeneous enhancement of colonic wall with mural stratification. This enhancement results in classical target or double halo sign characterized by inner soft tissue ring comprising mucosa lamina propriae and muscularis mucosae; a central low density ring comprising muscularis propriae and serosa.MRI reveals mural thickening along with high signal intensity in muosa and submucosa on T1 and T2 weighted images.

Endoscopy

Indications

1. Necessity for correct diagnosis (both endoscopically and histologically)
2. Assessment of disease severity and extent.
3. Dilatation of strictures
4. Surveillance endoscopy in long standing chronic colonic disease.

The endoscopic features are not specific to differentiate ulcerative colitis form Crohn's disease but some features favour.

Variable	Ulcerative Colitis	Crohn's Disease
Distribution	Diffuse inflammation that extends proximally from the anorectal junction	Rectal sparing, frequent "skip" lesions
Inflammation	Diffuse erythema, early loss of vascular markings with mucosal granularity or friability	Focal and asymmetric, "cobblestoning"; granularity and friability less common
Ulceration	Small ulcers in a diffusely inflamed mucosa; deep, ragged ulcers in severe disease	Aphthoid ulcers, linear/serpiginous ulceration; intervening mucosa is often normal
Colonic lumen	Often narrowed in long-standing chronic disease; "tubular colon"; strictures are rare	Strictures are common

Assessment of disease activity

Baron's criteria macroscopically grades the severity of inflammatory changes using four item scale, with score ranging from 0-IV.[70] Today it is the most commonly used scale. Histopathological grading scale has also been developed.[71]

Table 3: Endoscopic assessment (Baron's criteria)

0	Normal mucosa
I	Loss of vascular pattern
II	Granular, nonfriable mucosa
III	Friability on rubbing
IV	Spontaneous bleeding, ulceration

Table 4: Histological assessment

0	Normal
I	No significant inflammation—possibly architectural changes of chronic disease and small foci of lymphocytes but no acute inflammation, crypt abscesses, or epithelial destruction.
II	Mild to moderate inflammation—edema, vascularity, increased acute and chronic inflammatory cells but intact epithelium.
III	Severe inflammation—heavy infiltrate of acute and chronic inflammatory cells, crypt abscesses, ulceration of surface epithelium, purulent exudate.

Management of UC

Medical therapy

The goals of medical therapy of UC are:

1. To induce remission
2. To maintain remission;
3. To maintain adequate nutrition;
4. To decrease disease and treatment related complications; and
5. To improve the quality of life.

The current management strategy focuses on using appropriate medical therapy and optimizing timing of surgery.

Current therapeutic strategies can be classified broadly based on disease activity into those that treat active disease (induction therapy) and those that prevent recurrence of disease once remission is achieved (maintenance therapy). The extent of disease in any given patient is an important consideration to help determine the route of administration of medication. Enema preparations may be used alone or in combination with systemic therapy for patients with left-sided disease or disease distal to splenic flexure. Proctitis or disease limited to the rectum may be treated with suppositories or foam preparations. Other important factors to consider are prior response to or side effects from a specific medication and patient compliance. These factors might favor or preclude the use of a specific agent.

Table 5: Induction Therapy for Ulcerative Colitis Depending on Disease Severity

Mild disease	Moderate disease	Severe disease
5 – aminosalicylates • (L1)Topical (distal colitis) • Oral (distal /extensive colitis) • Combination(/L1)	5 – aminosalicylates • (L1)Topical (distal colitis) • Oral (distal /extensive colitis) • Combination(/L1) **Glucocorticoids** • (L1)Topical (distal). • Oral (distal/extensive) • Azathioprine or 6-mercaptopurine	• IV glucocorticoids • IV cyclosporine • IV infliximab

Table 6: Maintenance Therapy for Ulcerative Colitis

Preparation	Type
5-Aminosalicylates	Topical (Distal) Oral (distal/extensive)
Azathioprine or 6-mercaptopurine	-

Given the chronic nature of UC, medications need to be both efficacious and well accepted by patients from the standpoints of safety and ease of administration. The mainstay of medical therapy focuses on regimens that alter host response to decrease mucosal inflammation. Therapies that target other aspects of the systemic inflammatory process or manipulate the enteric flora also have been developed to treat UC.

Sulfasalazine

Sulfasalazine is the first line of therapy and is effective for inducing remission in patients with mild-to-moderate UC.[72] At a dose of 3 to 6 g/day, sulfasalazine induces remission in 39% to 62% of patients with mild-to-moderate UC, about twice the remission rate of placebo-treated patients.[73]

Various formulations and controlled-release systems have been developed to deliver 5-ASA to specific sites of the gastrointestinal tract without the sulfapyridine moiety, which is thought to be responsible for most of the side effects. 5-ASA is released from olsalazine and balsalazide in the colon on cleavage of the azo bond via the bacterial enzyme azoreductase. Approximately 99% of the drug is delivered intact to the colon, and its metabolites are cleared rapidly in the urine. Two commonly used mesalamine preparations allow delivery of 5-ASA before the drug reaches the colon:

(1) Pentasa, which uses ethylcellulose-coated microgranules that release mesalamine from the duodenum throughout the small bowel and the colon (≈50% of 5-ASA is released in the small intestine, while the remainder is released in the colon): and

(2) Asacol, which is a Eudragit-S-coated mesalamine tablet that is released at a pH greater than 7, usually in the distal ileum and the colon (with Asacol, ≈15% to 30% of mesalamine is released into the small bowel). These oral 5-ASA derivatives and mesalamines have been shown to be superior to placebo for mildly to moderately active UC.

Balsalazide has been shown to have superior efficacy and more rapid response compared with other mesalamine agents.[74] In a randomized, controlled study, balsalazide 6.75 g daily, a dose equivalent to mesalamine 2.4 g daily, achieved higher rates of remission and better tolerance compared with pH-dependent mesalamine 2.4 g daily.It has been suggested that the greatest benefit of balsalazide is in patients with newly diagnosed left-sided UC. For this indication, mesalamine is not effective at doses lower than 2 g daily, and there is an increased response at doses of 4 to 4.8 g daily. This dose of Asacol is comparable to 12 g/day of sulfasalazine, which is impractical in clinical practice because of the high probability of intolerance. No controlled trial has evaluated the use of aminosalicylates for severely active UC, but they are generally thought not to be effective in severely active disease.

Once remission is achieved, sulfasalazine and other 5-aminosalicylates are effective in maintaining it. This benefit appears to be dose dependent for sulfasalazine with a dose of 2 g/day often employed to balance both efficacy and adverse side effects. Such a dose-dependent response, however, has not been found with the other 5-ASA preparations, and at doses of 1.5 to 4.8 g/day, remission can be maintained in more than 50% of patients.[73] In general, the same dose of mesalamine or 5-ASA derivative that achieves induction of remission is

recommended for maintenance therapy, though this recommendation has not been formally tested in a randomized, placebo-controlled fashion. Common side effects of sulfasalazine include fever, rash, nausea, vomiting, and headaches. Other less common but important side effects of sulfasalazine include hypersensitivity reactions, reversible sperm abnormalities, and impairment of folate absorption. Approximately 15% of patients on sulfasalazine develop significant side effects that require discontinuation of the medication. Up to 90% of patients who are intolerant to sulfasalazine, however, can tolerate mesalamine. Folate supplementation should be prescribed to patients receiving sulfasalazine. Olsalazine is associated with drug-induced diarrhea in up to 10% of patients, which often limits its use. It has been noted that if olsalazine is ingested with meals and continued despite the side effect of diarrhea, its incidence can be lessened substantially to 3%. In fact, a systematic review of oral 5-ASA for maintenance of remission in UC found olsalazine to be significantly inferior to sulfasalazine, and this reduced efficacy was related mostly to a significantly higher rate of withdrawals because of adverse events. Oral mesalamine preparations do not appear to have significant dose-dependent toxicity.

Glucocorticoids

At doses equivalent to 40 to 60 mg/day of prednisone, glucocorticoids are effective first-line therapy for moderate-to-severe flares of UC.[75] The use of doses higher than 60 mg/day is associated with increased side effects without appreciable clinical benefit and thus should be avoided. The addition of sulfasalazine to corticosteroids in moderately to severely active UC does not offer any incremental benefit. Although no study has directly compared the efficacy of

oral and parenteral glucocorticoids, the latter commonly are used in severe disease. No adequately designed controlled study has been performed to confirm the clinical impression that continuous infusion of parenteral glucocorticoids is superior to pulse therapy. Glucocorticoids have no maintenance benefits in patients with UC. Steroid-dependent patients, or individuals who are unable to taper off glucocorticoids without experiencing disease exacerbation, benefit from the addition of steroid-sparing agents. There has been no trial to date assessing mesalamine therapy and its efficacy to maintain remission induced with glucocorticoids. The long-term remission rate in patients who required parenteral glucocorticoids for severe UC is approximately 50%.[76] Immunomodulatory agents as discussed subsequently should be considered in patients who are steroid dependent, require two courses of glucocorticoids for induction of clinical response or remission within 1 year, or require parenteral glucocorticoids to induce remission.

Topical glucocorticoids in liquid and foam formulations are effective short-term therapy for active UC distal to the splenic flexure. Foam preparations often are tolerated better by patients and may be easier to retain than liquid preparations. As mentioned previously, topical glucocorticoids have been found to be less effective than topical mesalamine for inducing remission of distal UC; however, the combination of topical corticosteroids and topical mesalamine often is more efficacious than either alone in the short-term treatment of distal UC.

ACTH (40 units i.v., 8th hourly)

One double-blind, randomized, controlled trial suggested that intravenous ACTH was more effective than intravenous hydrocortisone for the treatment of severely active UC only in steroid-naive patients; this observation has not been confirmed.[77] Because most patients with severely active flares have been treated previously with glucocorticoids, ACTH rarely is used in clinical practice. A noteworthy complication of ACTH therapy is bilateral adrenal hemorrhage.

Immunomodulators

Azathioprine and 6-Mercaptopurine (6-MP): These two agents are purine analogs that interfere with nucleic acid metabolism and cell growth and exert cytotoxic effects on lymphoid cells.

Available data also suggest their benefit in steroid sparing and maintenance of remission in patients with UC. A study found that 6-MP therapy allowed reduction or cessation of glucocorticoids in 61% of patients with steroid-dependent UC.[78] As a maintenance agent; continued azathioprine therapy resulted in a 1-year relapse rate of 36% in patients with remission achieved by azathioprine compared with a relapse rate of 59% in patients who discontinued azathioprine following azathioprine-induced remission. The relapse rate has been reported to be as high as 87% in one retrospective review of 105 patients treated with 6-MP for chronic refractory UC, in which complete clinical remission was achieved in 65% of the patients.[79] Small, randomized, but open-label study, however, suggested that azathioprine monotherapy was at best comparable to high-dose sulfasalazine (6 g daily) as maintenance therapy following steroid-induced remission in patients with severely active UC.[80]

Given the controversies regarding the optimal doses for azathioprine and 6-MP therapy, there is no standard guideline regarding initial dosing and its subsequent adjustment. One approach is to start the medication at 50 mg daily and increase by 25 mg every 1 to 2 weeks while monitoring for cytopenia, a potential toxicity of therapy. Azathioprine and 6-MP therapy have a delayed onset of action. The mean time to clinical response with azathioprine or 6-MP therapy in patients with UC has been reported to be 3 to 4 months in uncontrolled studies, a figure that is similar to the 17 weeks response time to clinical benefit in placebo-controlled trials of azathioprine or 6-MP therapy for active Crohn's disease.[81] Intravenous loading of azathioprine at 40 mg/kg for 36 hours does not shorten the time required for a therapeutic response in patients with Crohn's disease. Such practice presumably would have the same results if attempted in patients with UC.

Cyclosporine

Cyclosporine A is a potent inhibitor of cell-mediated immunity. Its use in UC is primarily in patients with severe, steroid-refractory disease. In this study of 20 patients who did not respond to at least 7 days of intravenous hydrocortisone, 9 of the 11 patients receiving continuous intravenous infusion of cyclosporine at 4 mg/kg/day responded compared with none of the 9 patients receiving placebo therapy.[82] The response was rapid, at a mean of 7 days. After the therapy was converted to oral cyclosporine, 44% of those patients who responded initially required colectomy during the 6-month follow-up period.[83] The addition of azathioprine or 6-MP in patients who have responded to intravenous cyclosporine reduces the rate of relapse or colectomy.[84] Thus, cyclosporine can be considered a

bridge therapy to control active disease while waiting for elective surgery or the onset of action of azathioprine or 6-MP. Intravenous cyclosporine monotherapy may be equally as effective as intravenous glucocorticoids in patients with severely active UC, thus potentially minimizing toxicities of combination therapy. With the addition of azathioprine, long-term remission at 1 year may be more likely in patients who initially respond to intravenous cyclosporine monotherapy than in those who respond to intravenous corticosteroids.

Because most of the serious adverse effects of cyclosporine, which are discussed subsequently, are dose dependent, intravenous doses lower than 4 mg/kg that still can achieve efficacy would be desirable. One randomized, controlled trial has shown that a dose of 2 mg/kg is as effective as 4 mg/kg given intravenously in patients with severely active UC, judged by clinical response rates, time to response, and short-term colectomy rates. The mean plasma cyclosporine levels were 237 ng/mL in patients receiving the 2 mg/kg dose and 332 ng/mL in patients receiving the 4 mg/kg dose. As expected, the higher dose resulted in a higher incidence of hypertension, albeit not a statistically significant one. Thus, high-dose intravenous cyclosporine dose not appear to provide additional clinical benefit over low-dose therapy in the treatment of severe UC. Initiating therapy at 2 mg/kg may be reasonable, but regardless of the dose used, careful monitoring of plasma cyclosporine trough levels is necessary.

Antibiotics

Antibiotics have a limited role in the management of UC, and most controlled studies have not demonstrated their benefit either in active disease or

maintenance of remission. The most commonly used antibiotics in this setting are metronidazole and ciprofloxacin.[85] One randomized, controlled trial reported a modest benefit for the addition of ciprofloxacin for 6 months in patients with UC refractory to mesalamine and corticosteroids.[86] Recent data have been published on a poorly absorbed (<0.4%) antibiotic, Rifaximin, for treatment of steroid refractory UC and have demonstrated efficacy over placebo. At present the data showing efficacy of antibiotics for treatment of patients with UC are not as convincing as are the data for treatment of Crohn's disease. Thus, at present the primary role of antibiotics in the treatment of UC is in the management of its suppurative complications.

Probiotics

Probiotics are living organisms in foods and dietary supplements that beneficially affect the host by improving its intestinal microbial balance. For patients with mildly to moderately active UC, open-label pilot studies reported remission rates of 63% to 71% with *Saccharomyces boulardii* and VSL#3 [four strains of *Lactobacillus* (*Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subspecies *bulgaricus*, *Lactobacillus plantarium*, and *Lactobacillus casei*), three strains of *Bifidobacterium* (*Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium breve*), and one strain of *Streptococcus* (*Bifidobacterium salivarius* subspecies *thermophilus*)] respectively.[87, 88]

As a maintenance therapy, a specific strain of *E. coli*, Nissle 1917, was equally effective as low-dose mesalamine in preventing relapse in two randomized, controlled trials of 236 patients with UC in clinical remission.[89]

Alteration of the composition of the fecal flora by probiotic therapy has been shown in an uncontrolled study in which VSL#3 was administered to patients with quiescent UC. This probiotic maintenance therapy resulted in clinical relapses in 25% of the patients over 12 months, and the fecal concentrations of the nonpathogenic bacterial species contained in VSL#3 increased significantly throughout the entire duration of therapy, starting as early as 20 days after initiation of therapy.[90] Controlled trials comparing probiotic regimens to higher doses of mesalamine are necessary before routine use of probiotics as a maintenance therapy in patients with UC.

Nutritional Therapy

Short-chain fatty acids, especially butyrate, have been shown to be the main energy substrate for colonocytes. Butyrate metabolism accounts for approximately 70% of colonocyte oxygen utilization. The suggestion that there is an impairment of colonocyte oxidation of short-chain fatty acids in UC led to therapeutic investigations on this form of nutritional therapy. Indeed, placebo-controlled studies have found butyrate enemas to be beneficial in treating mildly active left-sided colitis.[91]

Fish oils containing eicosapentaenoic acid have been found to attenuate colitis in animal models of colitis, probably via protecting the integrity of colonic mucosa, suppressing the inflammatory response, or both. In a small, placebo-controlled, cross-over study of patients with mild-to-moderate UC, treatment with fish oil resulted in a 56% reduction in disease activity compared with a 4% reduction in controls ($P<0.05$).[92] This benefit has not been confirmed in other

studies, and a benefit in maintaining remission has not been observed. Furthermore, compliance is limited because of side effects and the odor of the fish oil preparation.

In contrast to Crohn's disease where bowel rest and total parenteral nutrition may improve disease, multiple studies have not found total parenteral nutrition with or without bowel rest to have any therapeutic advantage in patients with UC. Parenteral nutrition, however, may offer nutritional benefit in these patients.

Other therapies

Nicotine

Randomized, controlled trials have shown some benefit of transdermal nicotine in the treatment of active UC.[93] When administered at the highest tolerated dosage of 22 mg/day or less for 4 weeks in patients with mildly to moderately active UC, transdermal nicotine resulted in clinical improvement in 39% of patients compared with 9% of patients who received placebo therapy (P = 0.007).[94] As a single therapy, however, transdermal nicotine was not as effective as low-dose prednisolone.[95] Common side effects included nausea, lightheadedness, itching, and tremor. Topical nicotine therapy has fewer side effects and may be an alternative. Pilot studies have shown topical nicotine to be beneficial in patients with distal UC, but no large, randomized, controlled trial has been performed and transdermal nicotine has not been found to be effective as a maintenance therapy. Thus, based on the available data on clinical efficacy and

the overall poor patient tolerability, the use of nicotine cannot be considered part of standard armamentarium for treating UC.

Heparin

a group of sulfated glycosaminoglycans, has both anti-inflammatory and immunomodulatory properties in addition to its well-known anticoagulant activity. The exact mechanism whereby heparin may ameliorate UC remains uncertain. An anticoagulant benefit, however, may not be responsible, because similar efficacy has not been observed in patients with IBD when treated with warfarin. Based on reports of fortuitous improvement in patients with UC receiving heparin for treatment of deep venous thromboses, pilot studies have suggested that unfractionated heparin may be effective for inducing remission in patients with severe, refractory UC. Compared with glucocorticoids as a first-line therapy, however, small randomized, controlled trials have reported conflicting results.[96] Intravenous heparin therapy was associated with substantial bleeding complications. Low-molecular-weight heparin offers advantages over un-fractionated heparin in its route of administration, and preliminary studies suggested a benefit of low-molecular-weight heparin in the treatment of active UC. Unfortunately, this finding was not confirmed in a large, placebo-controlled trial of patients with mildly to moderately active UC receiving low-molecular-weight heparin for 6 weeks.[97]

Biologic therapy

Antitumor Necrosis Factor Antibody Therapy

TNF is a key proinflammatory cytokine that has been demonstrated to play a role in several disease states, including IBD. Elevated TNF concentrations have been found in inflamed intestine in patients with Crohn's disease and UC, and stool and mucosal concentrations of TNF in patients with IBD have been shown to correlate with clinical disease activity.

Infliximab is a chimeric monoclonal antibody of IgG_1 subclass, directed against human TNF-α. Recently presented preliminary results from two large multicenter, multicountry randomized, double-blind trials (ACTI and ACTII) showed efficacy of infliximab therapy in UC.[98, 99] In these two similarly designed trials, 728 patients with moderately to severely active UC who failed conventional therapy were randomized to placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at weeks 0, 2, and then every 8 weeks for one year. In the ACTI trial where all patients were either refractory to or intoler-ant of glucocorticoids and/or azathioprine and/or 6-mercaptopurine, clinical response was achieved at week 30 in 52% and 51% of patients receiving infliximab 5 mg/kg and 10 mg/kg, respectively. The rates of clinical remission at week 30 were 34% and 37% in the two respective groups. These results were significantly higher than the response and remission rates of 30% and 16%, respectively, in patients receiving placebo therapy. Treatment with infliximab was also shown to have steroid-sparing and mucosal healing properties. These data have led to the approval of infliximab by the Food and Drug Administration for patients with moderately to severely active UC who have had an inadequate response to conventional therapy.

Antiadhesion Molecule Therapy

These molecules are glycoproteins expressed on the surfaces of endothelial cells and lymphocytes. Adhesion molecules are important in cellular trafficking in IBD and other diseases, in which immune and inflammatory cells from the periphery are recruited into sites of inflammation. Among these, natalizumab is a humanized IgG_4 monoclonal antibody against lymphocyte adhesion molecules, α4 integrins. A pilot study of 10 patients with active UC suggested clinical benefit with a single infusion of 3 mg/kg of natalizumab.[100]

Other Biologic Therapies

IL-2 is one of the major cytokines produced by Th1 cells. Given the predominance of Th2-driven immune phenomena, two agents designed to block the binding of IL-2 to its receptor have been examined for potential efficacy in UC. Daclizumab, a humanized monoclonal antibody against the IL-2 receptor (CD25), has been suggested to be beneficial in patients with refractory UC in a small open-label pilot study. A potential clinical benefit also has been reported with basiliximab, a chimeric monoclonal antibody to the IL-2 receptor, in a small, uncontrolled study of patients with steroid-refractory UC.[101] Along the emphasis on T cell-mediated immune response in the pathogenesis of UC, a humanized monoclonal antibody to CD3, visilizumab, has shown promise in a pilot study in hospitalized patients with UC whose disease failed to respond to intravenous glucocorticoids.[102]

Cytapheresis

Active UC is characterized by activation and infiltration of leukocytes in the colonic mucosa. Since leukocyte-derived inflammatory cytokines play an important role in the initiation and perpetuation of the inflammatory process, reduction of peripheral blood levels of leukocytes has been proposed as a therapeutic option for treating the disease. Several methods of depleting peripheral blood leukocytes have been developed and have been shown to hold promise in the treatment of severely active UC in both controlled and uncontrolled studies.[103, 104] The primary benefit of these leukocyte apheresis therapies appears to be as adjunctive therapy, allowing steroid taper and possibly maintaining remission; however, leukocytapheresis is an intensive therapy and the practicalities of its use still need to be addressed. Use of leukocytapheresis in the treatment of UC should be reserved to the clinical trial setting until data from large-scale, randomized, controlled trials are available.

Nuclear Hormone Receptor Agonist

Peroxisome proliferator-activated receptor-gamma is a nuclear hormone receptor that is best known for its role in regulating metabolism and adipocyte differentiation. It also has been shown to have immunomodulatory and anti-inflammatory properties in multiple sites, including the colon. A pilot clinical trial has reported potential benefit of a ligand for this receptor, rosiglitazone, in the treatment of patients with mildly to moderately active UC, with a response rate of 54% and a remission rate 27% after 12 weeks of therapy.[105] A multicenter, randomized, controlled trial currently is ongoing to evaluate its efficacy in UC.

Surgical management

Nearly half of the patients with extensive chronic UC undergo surgery within first 10 years of their illness.

Indications for Surgery in Ulcerative Colitis:

1. Uncontrollable colonic hemorrhage
2. Toxic megacolon
3. Colonic perforation
4. Medically-refractory disease
5. Colonic dysplasia or carcinoma
6. Systemic complications
7. Intolerable or unacceptable side effects from medical therapy

Although single staged total proctocolectomy with ileostomy has been operation of choice, no operations maintain continence, while surgically removing involved rectal mucosa. The IPAA is the most frequent continence preserving surgery performed in which the ileum is fashioned to a pouch is sutured to the anus in end to end fashion. Controversy exists as to whether the retained transitional epithelium is at risk for developing dysplasia and carcinoma.[106]

METHODOLOGY

The present study was conducted in the Department of General Medicine on 35 patients of UC admitted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2008 to December 2008.

Source of Data

All diagnosed cases of UC admitted in wards of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Method of the Collection of the Data

Study Design

One year cross sectional study.

Place

The study was conducted at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Duration

The present study was conducted during the period of January 2008 to December 2008.

Sample size

The sample size of the study was 35.

Sampling Procedure

Based on hospital statistic a minimum of 30 patients was considered as sample size. However during the study period 35 proved cases of UC have been admitted and all these cases were included in this study.

Study Subjects

All patients coming to KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum with history suggestive of ulcerative colitis (for example abdominal pain and bloody diarrhea) were subjected to colonoscopy and biopsy. In proved cases, clinical profile, through history, examination, and relevant investigations was studied. Percentage distribution of different morbid conditions in the study was calculated.

Selection Criteria

Inclusion criteria:

1. Colonoscopy and biopsy proven cases of ulcerative colitis admitted in the wards of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period of one year.

***Exclusion criteria*:**

1. Crohns disease
2. Indeterminate Colitis
3. Infections
4. Ischemia

5. Malignant Conditions
6. Drug induced colitis

The ethical clearance had been obtained from the institutional committee authorised for the study. During the study period, all patients presenting with and fulfilling the inclusion criteria were included in the study after obtaining informed written consent (Annexure I). Patients underwent thorough clinical examination according to predesinged and pretested proforma (Annexure II), colonoscopy and biopsy which were supported by relevant investigations.

The patients underwent the following investigations:

1. CBC with peripheral smear
2. Platelet count
3. ESR
4. LFT
5. Stool routine and ova/cyst
6. Stool culture/sensitivity and occult blood
7. Colonoscopy & Biopsy
8. Special investigations as were required.

Procedure

All cases were analysed by age, gender, clinical symptoms, laboratory investigations, colonoscopic findings and histopathological features. Clinical

severity was assessed by Truewitt Love's criteria and endoscopic grading (Baron's criteria) was performed.

The study was conducted on basis of:

Clinical symptoms and signs

- Symptom duration
- Diarrhea
- Bloody stools
- Constipation
- Weight loss
- Fever
- Abdominal pain
- Extra intestinal (EI) symptoms like, joint pain, oral ulceration
- History of smoking and alcohol intake.

Laboratory investigations

- Hemoglobin (Hb): Patients were divided into three groups to compare with the clinical severity (Truelove Witts index): >11 gm%, 11%-8%, <8%.
- Serum Albumin: Patients were divided into three groups to compare with the clinical severity (Truelove Witts index): >3.5, 3-3.5, <3.5
- TC, DC and peripheral smear were taken.
- Colonoscopic evaluation was done in all patients and biopsy was taken from different sites.

- Other relevant investigations were performed.

Clinical disease activity indices

Assessment of clinical disease activity in patients of UC was done by Truelove and Witts index.

Colonoscopic features

All patients in the study underwent endoscopy. The following were assessed:

- Regions involved with patterns of involvement (continuous or patchy)
- Vascular pattern (Blurring or loss of normal vascular pattern)
- Erythema
- Mucosal edema, granularity or friability
- Mucosal erosion apthous, ulceration or deep ulcerations.
- Presence of pseudopolyps or cobblestone.

Endoscopic disease activity was assessed using Baron's criteria.

Histopathological assessment

Histopathological features used in evaluation of colonoscopic biopsy were the following:

- Crypt distortion
- Goblet cell destruction
- Crypt abscess

- Superficial erosion
- Deep ulcer
- Lymphoblastic infiltration
- Granuloma / Parasite / Lymphoma

Statistical analysis

Patients were divided into 3 grades based on histopathological findings. In this study, correlation of risk factors namely smoking and alcohol with clinical disease activity and lab parameters namely hemoglobin, albumin and blood group with clinical disease activity were studied using chi-square test.

Also, correlation between endoscopic and histopathological, endoscopic and clinical disease activity, histopathological and clinical disease activity was studied using chi- square test.

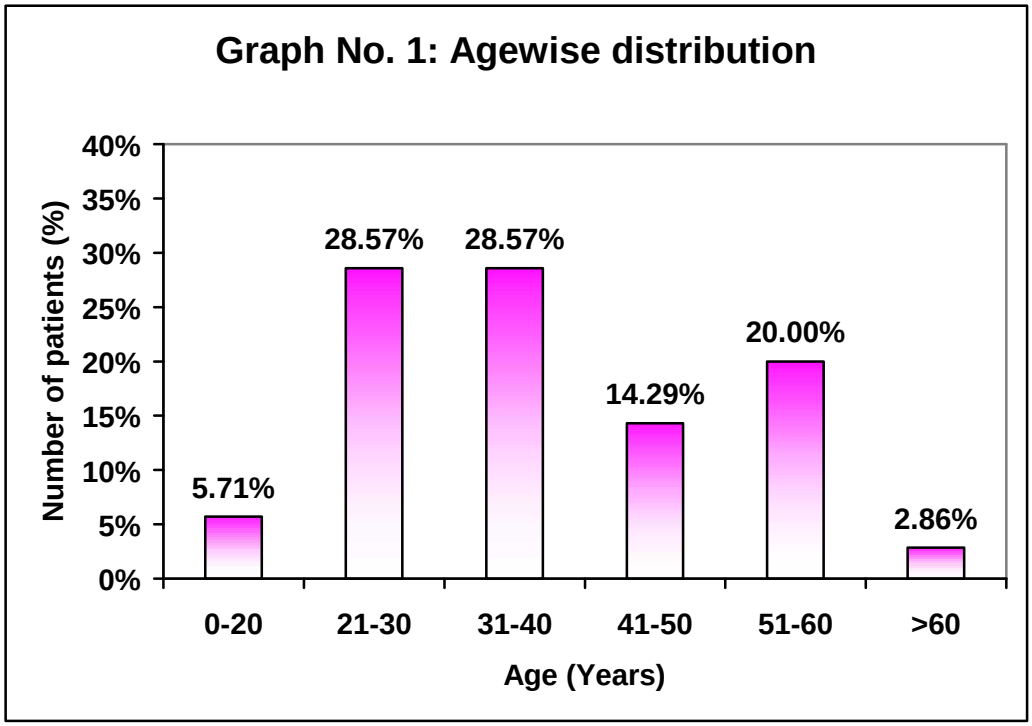
Percentage distribution of different morbid conditions in the study was calculated. Chi Square test with calculation of p value was done when there was comparison between two variables.

RESULTS

The present study was conducted in the Department of General Medicine on 35 patients of UC admitted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2008 to December 2008. This study comprised of total 35 cases of UC. The observations and findings made are as below.

Table 7: Age wise distribution

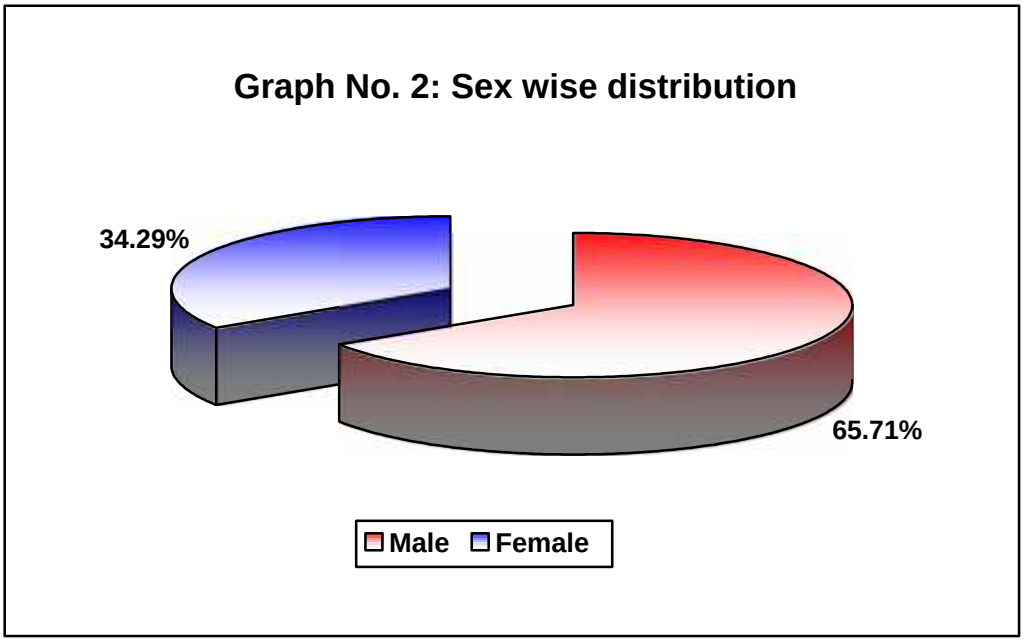
Age group (years)	Patients	
	Number	**Percentage**
0 – 20	02	5.71%
21 – 30	10	28.57%
31 – 40	10	28.57%
41 – 50	05	14.29%
51 – 60	07	20.00%
> 60	01	2.86%
Total	35	100%



Inference: Our study revealed peak incidence in age group of 21 to 40 years. The youngest patient was 16 years and oldest was 79 years. The mean age of the patients was 38.12 ± 13.12 years.

Table 8: Sex wise distribution

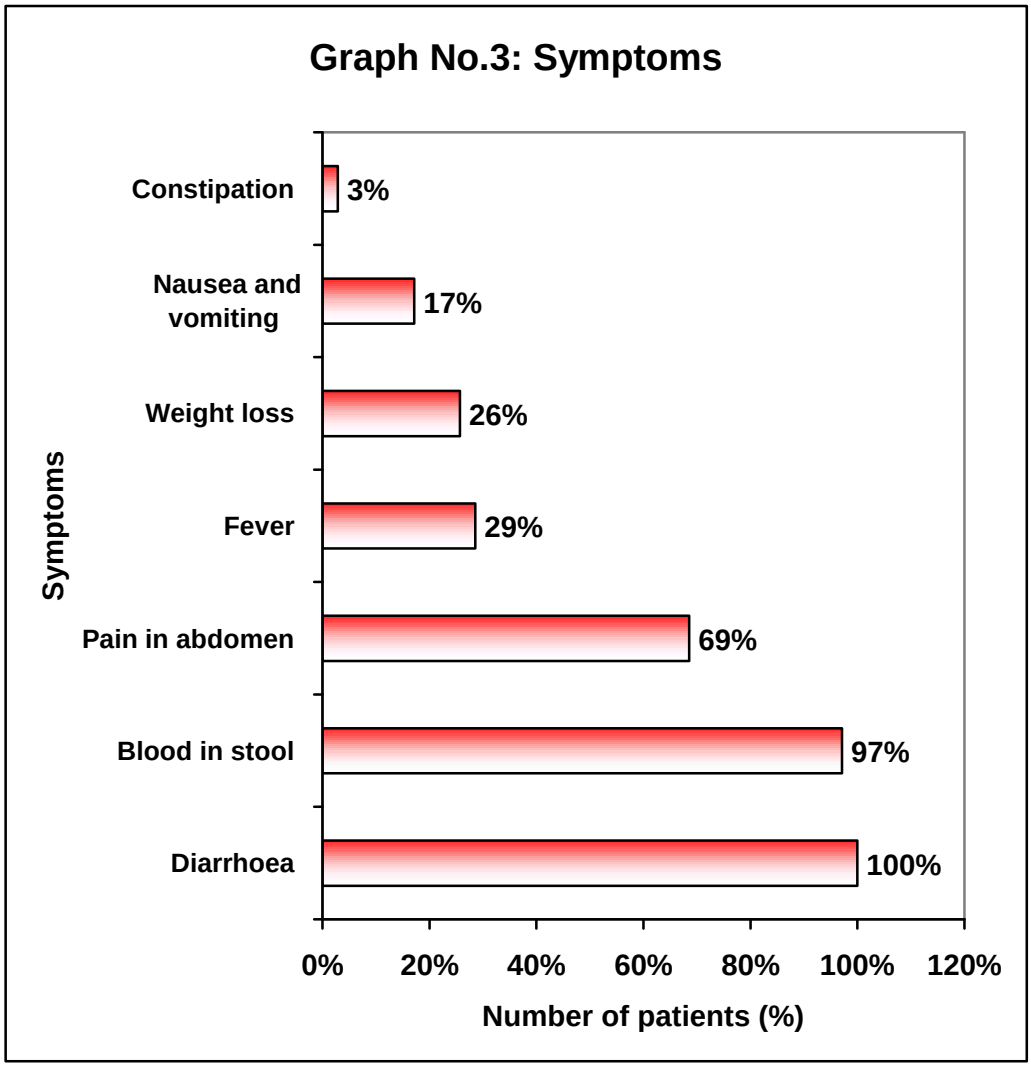
Age group (years)	Males		Female	
	Number	Number	Percentage	Percentage
Patients	23	65.71%	12	34.29%



Inference: Male:Female ratio was 1.91:1, revealing higher male predominance in our study. 65.71% (23) patients were male and 34.29% (12) patients were female.

Table 9: Symptoms

Symptoms	Patients	
	Number	**Percentage**
Diarrhea	35	100%
Blood in stool	34	97.14%
Pain in abdomen	24	68.57%
Fever	10	28.57%
Weight loss	09	25.71%
Nausea and vomiting	06	17.14%
Constipation	01	02.86%



Inference: Diarrhea (100%) with passage of blood in stools (97.14%) and pain in abdomen (68.57%) were common presenting complaints. Other symptoms like weight loss (25.71%), nausea and vomiting (17.14%) and constipation were less frequently encountered.

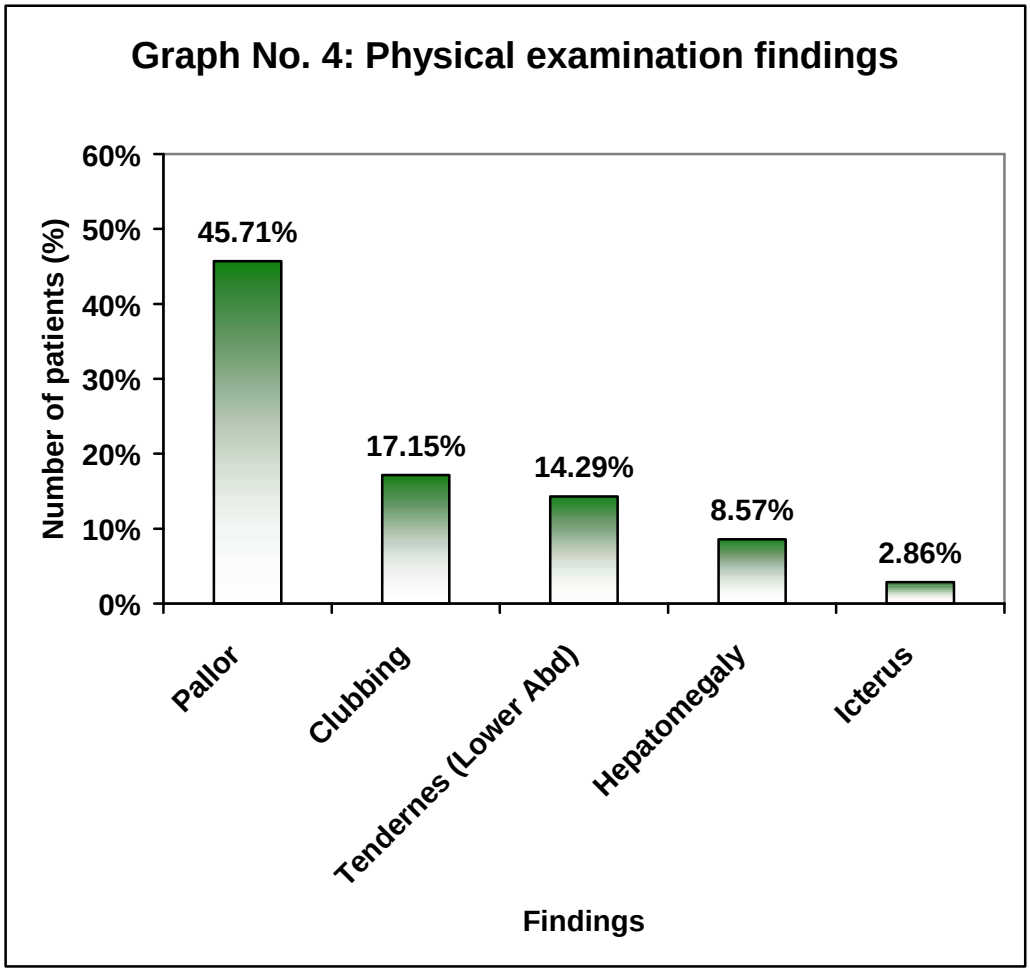
Table 10: Duration of presenting symptoms

Duration	Patients	
	Number	**Percentage**
0 – 5 months	12	34.29%
6 – 10 months	10	28.57%
11 – 15 months	06	17.15%
16 – 20 months	02	5.71%
21 – 25 months	03	8.57%
>25 months	02	5.71%

Inference: The mean symptom duration was 10.9 ± 11 months.

Table 11: Physical examination findings

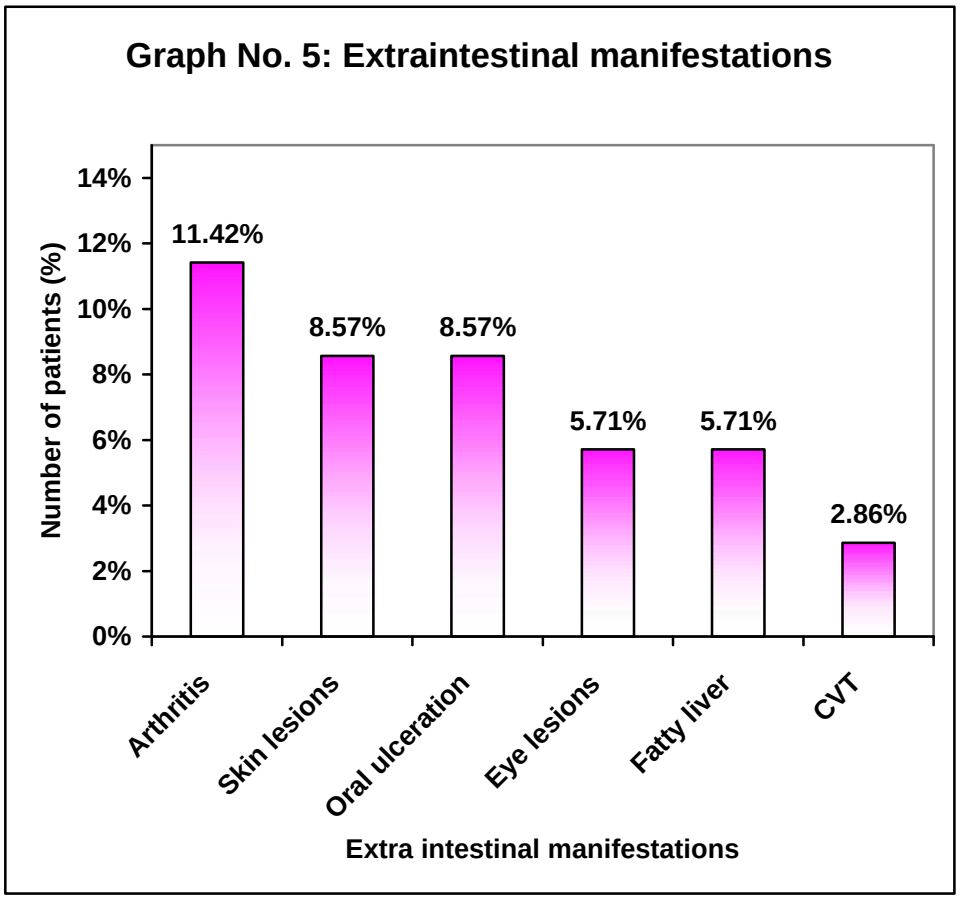
Physical findings	Patients	
	Number	**Percentage**
Pallor	16	45.71%
Clubbing	6	17.15%
Tenderness in lower abdomen	5	14.29%
Hepatomegaly	3	8.57%
Icterus	1	2.86%



Inference: Pallor (45.71%) was most common finding. Clubbing, tenderness in lower abdomen, hepatomegaly and icterus were present in decreasing order.

Table 12: Extraintestinal manifestations

Extraintestinal manifestations	Patients	
	Number	**Percentage**
Arthritis	4	11.42%
Skin lesions	3	8.57%
Oral Ulceration	3	8.57%
Eye lesion	2	5.71%
Fatty liver	2	5.71%
CVT	1	2.86%



Inference: 25.71% (9) of patients had extra intestine manifestations. Peripheral arthritis was found in 11.42% patients. Out of them three had pauciarticular peripheral arthritis and one had spondylitis with sacroileits. 8.57% of patients presented with skin manifestations. Out of them one had psoriasis, one had pyoderma gangrenosum and one had erythmatous rashes. Oral ulcers (8.57%) fatty liver (5.71%), eye lesion (5.71%), and CVT (2.86%) were also seen in our patients.

Table 13: Correlation between extraintestinal manifestations and clinical severity of the disease (Truelove Witts criteria)

Symptom	Mild	Moderate	Severe
Arthritis	0	3	1
Skin lesions	1	2	0
Oral Ulceration	0	2	1
Eye lesion	0	2	0
Fatty liver	0	2	0
CVT	1	0	0

x^2=11.5341; p=0.3174; NS

Inference: Majority of patients with extra intestine manifestations had moderate disease activity, but correlation with clinical severity was not statistically significant.

Table 14: Correlation of Smoking to Severity of disease (Truelove Witts criteria)

	Clinical Severity			Total	Percentage
	Mild	Moderate	Severe		
Smokers	5	1	0	6	17.14%
Non smokers	5	17	7	29	82.86%
Total	10	18	7	35	

x^2=10.75; p=0.0046; VS

Inference: Most of the patients in our study were non-smokers (82.86%). Out of 17.14% smokers, 83.33% (5) had mild disease and 16.77% (1) had moderate disease severity. Smoking correlated inversely with clinical severity. (p=0.0046)

Table 15: Correlation between alcohol intake to severity of the disease (Truelove Witts criteria)

Alcoholics	Clinical severity				Percentage
	Mild	Moderate	Severe	Total	
Alcoholics	2	4	2	8	22.86%
Non Alcoholics	8	14	5	27	77.14%
Total	10	18	07	35	

x^2= 0.180; p=0.9139; NS

Inference: Majority of the patients in our study were non alcoholics (77.14%). Only 22.86% of patients were alcoholics. Out of them mild disease was seen in 2, moderate in 4 and severe disease in 2 patients.

There was no statistical correlation between clinical severity and alcohol intake.

Table 16: Correlation between Hemoglobin & severity of disease (Truelove Witts criteria)

Clinical Severity	Hemoglobin gm%		
	>10	**8 – 10**	**<8**
Mild (n = 10)	10	00	00
Moderate (n = 18)	13	04	01
Severe (n = 07)	00	00	07
Total	23	4	8

x^2= 33.151; p<0.0001; VS

Inference: The mean Hb of patient was 10.19±2.68 gm%. All patients with severe disease and one patient with moderate disease had Hb <8 gm%. All patients with mild disease and 13 patients with moderate disease had Hb >10gm%. 4 patients had Hb between 8-10 gm%. Hb levels correlate significantly with clinical severity (p<0.0001)

Table 17: Correlation between Serum Albumin levels & disease severity (Truelove Witts criteria)

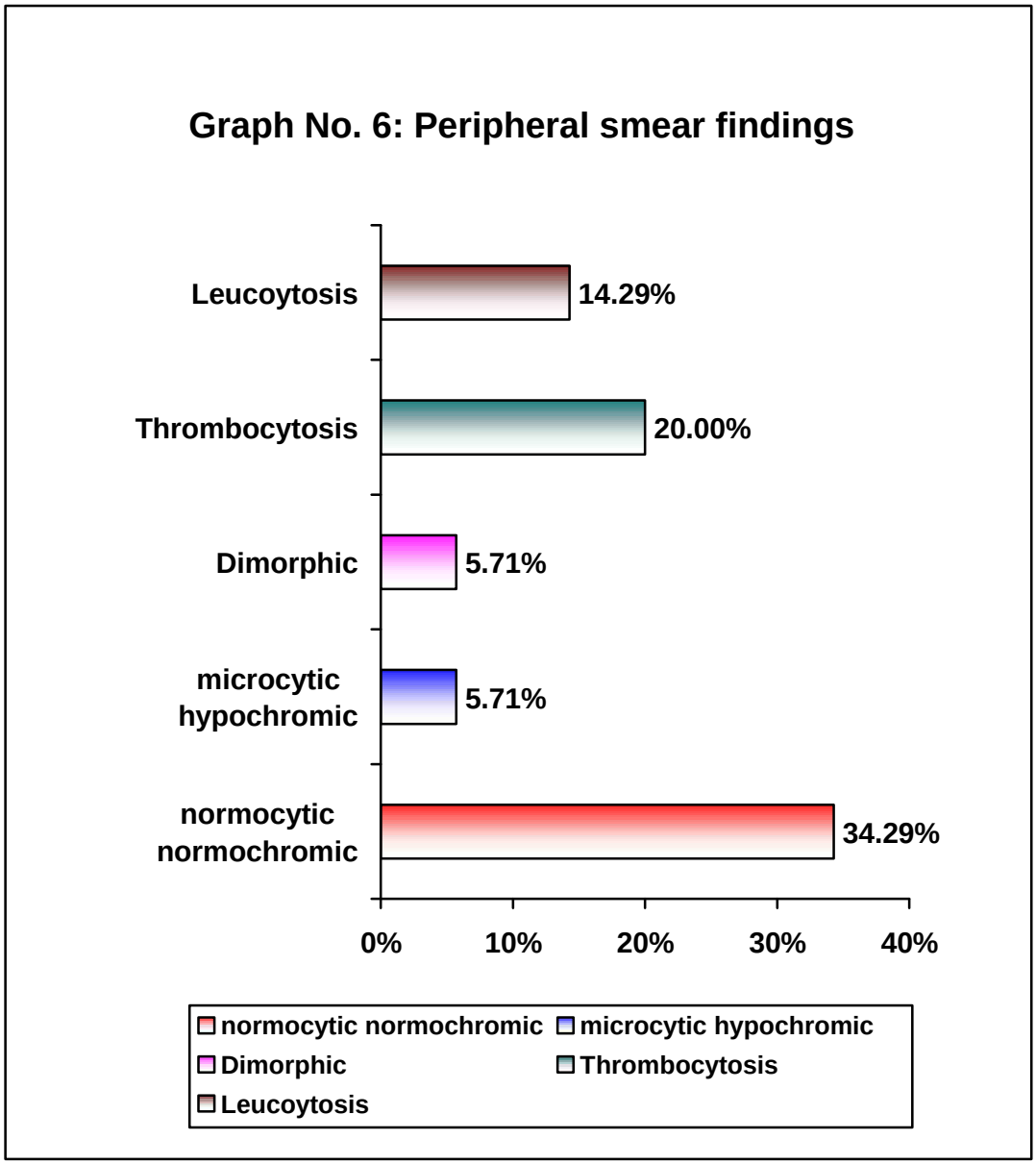
Clinical Severity	Serum albumin (gm/dl)		
	> 3.5	**3 – 3.5**	**<3**
Mild (n = 10)	7	2	1
Moderate (n = 18)	5	9	4
Severe (n = 07)	1	2	4
Total	13	13	9

x^2=9.782; p=0.0443; S

Inference: Most of the patients with severe disease had albumin <3gm%. Most of the patients with mild disease had Albumin >3.5 gm%. Albumin levels correlated significantly with clinical severity.

Table 18: Peripheral Smear findings

Peripehral smear	No. of patients	Percentage
Normocytic hypochronic	12	34.28%
Microcytic hypochronic	2	5.71%
Dimorphic Anemia	2	5.71%
Thrombocytosis	7	20.00%
Leucocytosis	5	14.29%



Inference: Normocytic hypochromic blood picture was seen in 34.28%, microcytic hypochromic in 5.71% and dimorphic anemia in 5.71% patients. Thromocytosis (20%) and Leucocytosis (14.29%) were also found in peripheral smear studies.

Table 19: Correlation of blood group with severity of disease (Truelove Witts criteria)

Blood group	Clinical severity of disease				Percentage
	Mild	Moderate	Severe	Total	
O+	4	5	4	13	37.13%
B+	4	3	2	9	25.71%
A+	0	5	1	6	17.15%
AB+	2	3	0	5	14.29%
A-	0	1	0	1	2.86%
O-	0	1	0	1	2.86%
Total	10	18	7	35	

x^2=8.714; p=0.5595; NS

Inference: 37.13% of patients had O positive, 25.72% had B positive and 17.15% had A positive blood group. There was no statistical correlation between blood group and disease severity.

Table 20: Stool examination

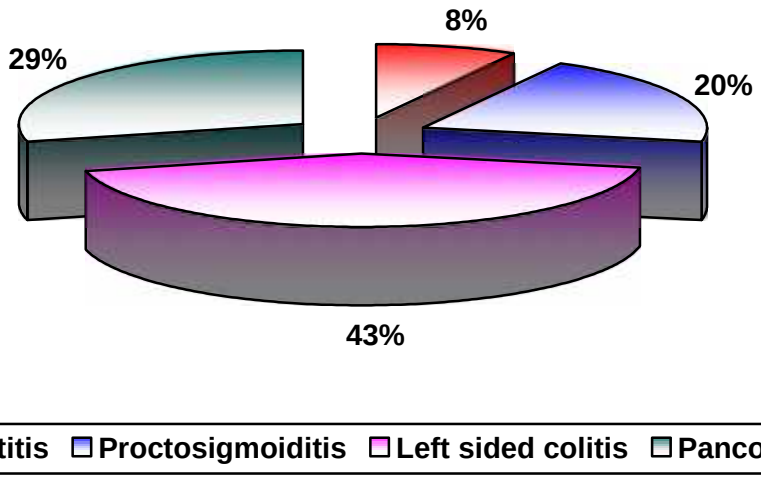
Microscopic examination	Patients	
	Number	**Percentage**
Stool for occult blood	34	97.14%
Stool for pus cell	31	88.57%
Stool for ova/cyst	0	0

Inference: Stool for occult blood was positive in 97.45% Pus cell were present 85.57%. No patient had ova/cyst.

Table 21: Distribution of extent of disease assessed by colonoscopy

Disease extent	Patients	
	Number	**Percentage**
Proctitis	03	8%
Proctosigmoiditis	07	20%
Left sided colitis	15	43%
Pancolitis	10	29%

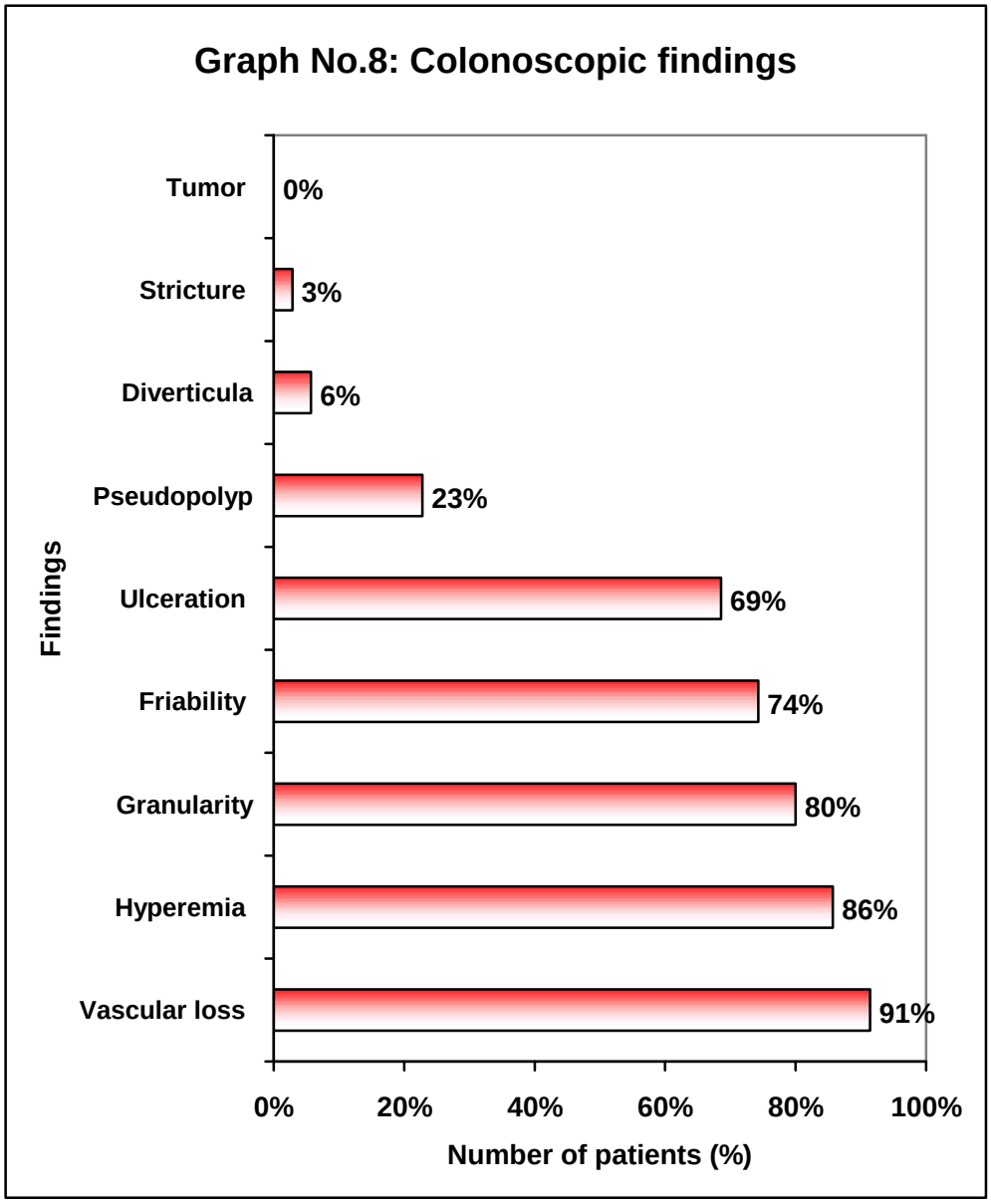
Graph No. 7: Distribution of extent of disease assessed by colonoscopy



Inference: Colonoscopic evaluation of patients in our study revealed 43% had left sided colitis, 29% pancolitis, 20% had proctosigmoiditis, and 8% had proctitis. No patient had evidence of ileitis. Rectum was involved in 94.29% case while rectal sparing with patchy involvement was seen in 5.71% (2) patients.

Table 22: Colonoscopic findings

Colonoscopic findings	Patients	
	Number	**Percentage**
Vascular loss	32	91.42%
Hyperemia (congestion)	30	85.71%
Granularity	28	80%
Friability	26	74.28%
Ulceration	24	68.57%
Pseudopolyp	08	22.8%
Diverticula	02	5.71%
Stricture	01	2.86%
Tumor	00	00



Inference: The major colonoscopic features of UC were vascular loss, hyperemia, granularity, friability and ulceration.

Table 23: Correlation between clinical severity (Truelove Witts criteria) and endoscopic grade (Baron's criteria) in ulcerative colitis

Severity	Endoscopic activity			
	Grade I	**Grade II**	**Grade III**	**Grade IV**
Mild (n = 10)	2	2	2	4
Moderate (n = 18)	0	5	7	6
Severe (n = 7)	0	0	1	6
Total	2	7	10	16

x^2=11.497; p=0.0742; NS

Inference: It was seen that clinical severity did not correlate significantly with endoscopic grading in our patients.

Table 24: Histopathological findings

Histopathological findings	Patients	
	Number	**Percentage**
Lymphoplasmocytic infiltration	35	100
Crypt distortion	24	68.57
Goblet cell destruction	22	62.85
Crypt abscess	28	80
Superficial erosion	13	37.14
Deep ulcerations	10	28.57
Granuloma/Dysplasia/Parasite	0	0

Inference: Histopathological evaluation of 35 patients of UC revealed that the basal lymphoplasmocytic proliferation in 100% of patients, crypt distortion in 68.57% patients. Globlet cell destruction in 62.85% were common features. None of the patients had epitherloid granuloma. 7 (20%) patients had Grade I severity, 19 (54.29%) patients had Grade II severity and 9 (25.71%) patients had Grade III severity.

Table 25: Correlation between H-P grading and Clinical Severity (Truelove Witts criteria)

Clinical severity	H-P findings		
	Grade I	**Grade II**	**Grade III**
Mild (n = 10)	05	4	01
Moderate (n = 18)	02	12	04
Severe (n = 7)	00	03	04
Total	07	19	9

x^2=11.398; p=0.0224; S

Inference: There was significant correlation between clinical and HP grading.

Table 26: Correlation between H-P grading and Endoscopic criteria (Baron's Criteria)

H-P Grade	Endoscopic grade				Total
	Grade I	**Grade II**	**Grade III**	**Grade IV**	
Grade I	02	02	03	0	07
Grade II	00	05	06	08	19
Grade III	00	00	01	08	09
Total	02	07	10	16	35

x^2= 18. 881; p=0.0044; VS

Inference: There was a very significant correlation between endoscopic grading and HP grading.

Table 27: Management

Treatment	No. of patients
5- ASA	18
5-ASA and Steroids	14
5-ASA, Steroids, Infliximab	1
5-ASA, Steroids, cyclosporine	1
Surgery	1

Inference: Majority of patients were managed with medical therapy. Most common drug was 5 ASA. Steroids were given in16 patients. Cyclosporine and Infliximab were started in one patient each. Surgery was done in one patient with fulminant colitis.

DISCUSSION

There were 35 proved cases of Ulcerative Colitis (UC) admitted in wards of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, from January 2008 to December 2008. Out of 35 cases, there were 23 males (65.17%) and 12 females (34.29%).

In our study, the peak incidence of disease was seen in 20 to 40 years age group which is correlating with western[107,108,109] and Indian studies.[110, 111, 112]

We observed unimodal presentation of disease in contrast to western study and South Indian study, which showed a second peak in 6^{th} to 7^{th} decade.[109,113] We have only one patient above 60 years of age. However various other Indian studies have shown a unimodal peak.[110, 111, 112]

There was a male predominance in our study, male: female ratio was 1.91:1, which was in concordance with other Indian and Western studies.[107,108,110,111,112,113,114]

In our study, we found that UC affected all socioeconomic classes equally. In western studies, upper socioeconomic classes were affected more often than lower,[115] while in Indian studies most of the patients came from the lower socioeconomic groups.[110]

The mean duration of symptoms in our study was 10.9 months which is comparable to most recent studies.[58]

In our study, majority of patients were non smokers (82.86%). Out of 17.14% smokers, 83.33% had mild disease and 16.77% had moderate disease. We also found significant inverse relation between UC and smoking. (p = 0.0046) which is comparable to Indian and western studies. [38,39,113] In our study there were no ex smokers. Other studies found increased severity of disease in ex smokers.[39]

In present study 77.14% were non alcoholics and there was no correlation between alcohol intake and disease severity index, whereas earlier study showed alcoholics had increased severity of disease.[116]

Diarrhea (100%), passage of blood in stools (97.14%) and pain in abdomen (68.57%) were major presenting complaints. Constitutional symptoms like fever and weight loss were found in 28.57% and 25.71% of patients. In our study; one patient had constipation and hematochezia; and one patient tenesmus and hematochezia. Both of them were found to have limited colonic involvement either in form of proctitis or proctosigmioiditis, which was comparable with other studies.[115]

On physical examination commonest finding was pallor in 45.71% (16). Other findings like clubbing (17.15%), tenderness in lower abdomen (14.29%), hepatomegaly (8.57%) and icterus (2.86%) were also present.

In our study, 25.71% (9) patients had extra intestinal manifestations, most common was peripheral arthritis in 4 patients (11.42%) which is comparable with western and Indian studies.[117, 118, 119] Out of four, three had pauciarticular peripheral arthritis and 1 patient had spondylitis and

sacroileitis. Three patients (8.57%) had skin lesions. One patient presented with Pyoderma gangrenosum, which developed nine months after bowel symptoms and had moderate clinical disease activity. Another patient had history of onset of psoriasis 10 years prior to developing bowel symptoms and third one had erythematous rashes in which there was severe disease. Oral ulceration was seen in 3 patients (8.57%), eye lesions in form of Scleritis was seen in 2 (5.71%) patients, fatty liver in 2 (5.71%) and CVT (left transverse and sigmoid cortical venous sinus thrombosis) was seen in 1 patient (2.86%). It was observed that majority of patients with extra intestinal manifestations had moderate disease activity but was statistically not significant.

Hb and albumin levels correlated with clinical severity in UC patients. Most patients had O positive blood group (37.13%), followed by B positive (25.71%) and A positive (17.15%) blood group. Blood group had no statistical correlation with clinical disease severity, which is comparable to a western study.[120] Macroscopic examination of stool showed semi solid or jelly like appearance with blood and mucous ,and microscopic examination of stool showed occult blood and pus cells in most of our patients. There was no evidence of ova or cyst.

Loss of haustrations and superficial ulcers were common features on barium studies. CT Abdomen was done in 5 patients. The hallmark of CT was diffuse continuous thickening of large bowel walls with loss of haustral pattern. The mean wall thickness was 8 mm.

Colonoscopic evaluation revealed 43% patients had left sided colitis, 29% had pancolitis, 20% had proctosigmoiditis and 8% had proctitis. No patient had illietis. Rectum was involved in 94.29% cases, showing continuous involvement. 5.71 % (2 patients) patients had rectal sparing and patchy involvement. Patchy distribution of inflammatory changes and rectal sparing in UC (both endoscope and histology) has been noted in various studies.[121,122,123,124,] The major colonoscopic features in our study were hyperemia, granularity, loss of normal vascularity, friability, ulcerations and pseudopolyps. 16 patients had endoscopic grade IV (46%), 10 patients had grade III (28%), 7 patients had grade II (20%) and 2 patients had grade I (6%) severity. Endoscopic severity (Baron's criteria) did not correlate significantly with clinical severity (Truelove Witts criteria).

Histopathological evaluation revealed basal lymphoplasmacytic infiltration (100%), crypt abscess (80%), crypt distortion (68.57%) and goblet cell destruction (62.85%) These findings were quite similar to western studies.[125,126]

In our study 48% (17) patients had histopathological grade I, 23% (8) patients had grade II severity and 29% (10) had grade III severity. Histopathologic grades correlated significantly with endoscopic grade (Baron's criteria) (p=0.0044). Histopathologic grading correlated significantly with clinical severity (Truelove Witts criteria) (p=0.0224).

Majority of patients were managed with medical therapy. 5-ASAs were the most commonly used drugs. Most commonly used agents in 5-

ASAs group were measalamine and balsalazide (in enema and/or oral forms depending on severity). Steroids were given in 16 patients (i.v., oral and/or enema depending on severity). In 2 steroid non responsive patients, cyclosporine was given to one and infliximab was given to another patient. They did not respond to the same and went against medical advice. One patient with fulminant colitis underwent total colectomy. One patient had stricture; which according to various studies is rare in UC. There was no evidence of colonic malignancy in our cases.

Mean duration of stay in hospital was 18 days and mean cost of hospital stay was Rs. 19,000, indicating increased morbidity and increased financial burden. The increase in the substantial health care cost (acute & long term treatment) and morbidity (loss of working days) disturbed the family budget, as males at their peak years of career, were more affected.

CONCLUSION

The present study gives an overview of the present disease scenario of Ulcerative colitis in this part of our country.

In our study of 35 patients with Ulcerative Colitis, we found that males are more affected than females. The peak incidence is seen in 20 to 40 years age group. The patients usually reach hospital after prolonged symptomatology. Diarrhea with blood in stools and pain in abdomen is most common presentation. Extraintestinal manifestations are seen in moderate to severe disease group in about 25.71% of patients, arthritis is most common extraintestinal manifestation. UC is more common in non smokers. Smoking has significant inverse relation with the disease severity. Nearly two third of the patients have left sided disease or pancolitis. There is no correlation of endoscopic grading (Baron's criteria) with clinical severity (Truelove Witts). There is a very significant correlation between endoscopic grading and histopathological grading. There is significant correlation between histopathological grading and clinical severity. The disease causes substantial morbidity and health care costs. Further studies and regular followup is needed for better understanding of this disease.

SUMMARY

1. The peak incidence of UC was seen in 20 – 40 years age group.
2. Males were more affected than females, male:female=1.91:1
3. Mean duration of symptoms was about 10.9 months before diagnosis.
4. UC was common in non-smokers. Smoking had statistically significant inverse relation with severity of disease
5. Diarrhea and blood in stools were the most common presenting complaint.
6. Pallor was most common finding on physical examination.
7. Extraintestinal manifestations were seen in 25.71% of patients.
8. Arthritis was most common extra intestinal manifestation.
9. Majority of patients with extraintestinal manifestations had moderate disease severity.
10. UC was more common in O positive blood group patients. Blood group did not correlate significantly with disease severity.
11. Loss of haustration and superficial ulcers were prominent features on Barium study.
12. CT scan of Abdomen showed diffuse thickening of large bowel with loss of haustral pattern with mean bowel thickness of 8mm.
13. Rectum was most common site involved.
14. Rectal sparing and patchy involvement cannot essentially rule out UC as was seen in 5.71% patients.

15. Endoscopic grading (Baron's criteria) did not correlate significantly with clinical disease severity (Truewitts criteria).
16. Histopathological grading correlated significantly with disease severity.
17. Histopathological grading correlated significantly with endoscopic grades.

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ANNEXURE I

CONSENT FORM

Objective and Purpose of the study

The objective is to study the clinical profile of ulcerative colitis. The principal investigator of the study is Dr. Rekha S. Patil M.D. and the co-investigator is Dr. Ashish R. Bhootra This research is intended to study the clinical profile of ulcerative colitis and my co-operation will be of great help to the patients of ulcerative colitis.

Procedure

If I agree to be a part of the study I will be asked the relevant history and will be subjected to relevant clinical examination. I will undergo colonoscopy and biopsy.

Risk and Benefit

The only risk and possible discomfort I might get is while undergoing biopsy. There may be bleed from biopsy site (rarely happens) and chances of infection may increase.

Alternatives

Taking part in this study is voluntary I may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. My decision will not change the present or future health care or other

services that I receive. The study doctor or sponsor may stop my participation in this study any time. If I choose not to take part in the study I will receive standard treatment for patients with my condition.

Privacy and Confidentiality

All information collected about me during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify me in this research record.

Institutional / Sponsors Policy

Does not apply to this research.

Financial Incentives for Participation

I will not be charged any amount for the investigations subjected to me. I will not receive compensation or reimbursement for taking part in this study.

Authorization to Publish Results

Information from this study may be published but my identity will be confidential in any publication.

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of any legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of Study Participant or legally authorised representative:

Signature / Thumb Print

In case of the queries during study or in future you may contact following person

Principal investigator	: Dr. Rekha Patil	Phone: 9448371125
Co-investigator	: Ashish Bhootra	Phone : 9845238945
Name of Witness	:	Signature :
Investigator Name	:	Signature :
Date	:	Place :

ANNEXURE II

PROFOMA

NAME:	
I.P. No.	OPD No.
AGE:	SEX:
DOB:	PLACE OF BIRTH:
MARITAL STATUS:	BLOOD GROUP:
RELIGION:	OCCUPATION:
ADDRESS:	

ULCERATIVE COLITIS:

HISTORY:

SYMPTOMS	PRESENT (duration)	ABSENT
Diarrhea: Blood Mucus Pain		
Anorexia		
Nausea		
Vomiting		
Weight loss		

Constipation		
Fever		
Others:		

PAST HISTORY:

	YES	NO
SIMILAR COMPLAINTS		
HYPERTENSION		
DIABETES		
JAUNDICE		
BLOOD TRANSFUSION		
DRUG ALLERGY/ABUSE		
RADIATION EXPOSURE		
ANY OTHER		

PERSONAL HISTORY :

DIET	VEGETERIAN	NON-VEG	MIXED
APPETITE	NORMAL	INCREASED	DECREASED
SLEEP	NORMAL	INCREASED	DECREASED
MICTURATION			
SMOKING	YES	NO	
IF YES	QUANTITY:		
ALCOHOL	YES	NO	
IF YES	QUANTITY:		
DRUG HISTORY:			

FAMILY HISTORY:

MARRIED	UNMARRIED	
No. OF CHILDREN		
HISTORY OF DISEASE IN ANY OTHER FAMILY MEMBER	YES	NO
IF YES DETAILS:		

GENERAL EXAMINATION:

BUILD AND NOURISHMENT	
HEIGHT	WEIGHT
PALLOR	CLUBBING
CYANOSIS	ICTERUS
ANY OTHER SIGNIFICANT FINDING:	

VITALS:

TEMP	PULSE	BP	RR
	/ minute	mm Hg	/ minute

SYSTEMIC EXAMINATION: UPPER GI:

TEETH & GUMS		
ANGULAR STOMATITS	PRESENT	ABSENT
TONGUE		
OROPHARYNX		

GI SYSTEM PROPER:

INSPECTION:

SHAPE OF ABDOMEN:

NORMAL	SCAPHOID	GEN. FULLNESS	LOCALY FUL

UMBILICUS:

NORMAL	EVERTED	OMPHALOLITH	SLIT

PERISTALSIS	ENGORGED VEIN	HERNIAL ORIFICE:	DIVARICATION OF RECTI

OVERLYING SKIN:

SCROTUM EXAMINATION:

OTHERS:

PALPATION:

SUPERFICIAL					
GUARDING		RIGIDITY		TENDERNESS	
DEEP: If palpable give tick mark and give details :					
ORGAN	SIZE	SURFACE	MARGIN	CONSIS	TENDER
LIVER					
SPLEEN					
LUMP					
KIDNEY					

PR EXAMINATION:

PERCUSSION:

TYMPANIC	
DULL : IF FREE FLUID THEN TICK WHICH IS PRESENT:	
PUDDLE SIGN	SHIFTING DULNESS
HORSE SHOE	FLUID THRILL
ORGAN PERCUSSION: IF PALPABLE/PRESENT LIVER SPLEEN LUMP	

AUSCULTATION:

PERISTALTIC SOUND	ARTERIAL BRUIT
VENOUS HUM	ORGAN RUBS
FHS AND UTERINE SOUFFLE	

OTHER SYSTEMS:

CVS	
RS	
CNS	

EXTRA INTESTINAL MANIFESTATIONS:
CLINICAL SEVERITY (TRUELOVE AND WITTS CLASSIFICATION):
COLONOSCOPY:
HISTOLOGY:
DIAGNOSIS

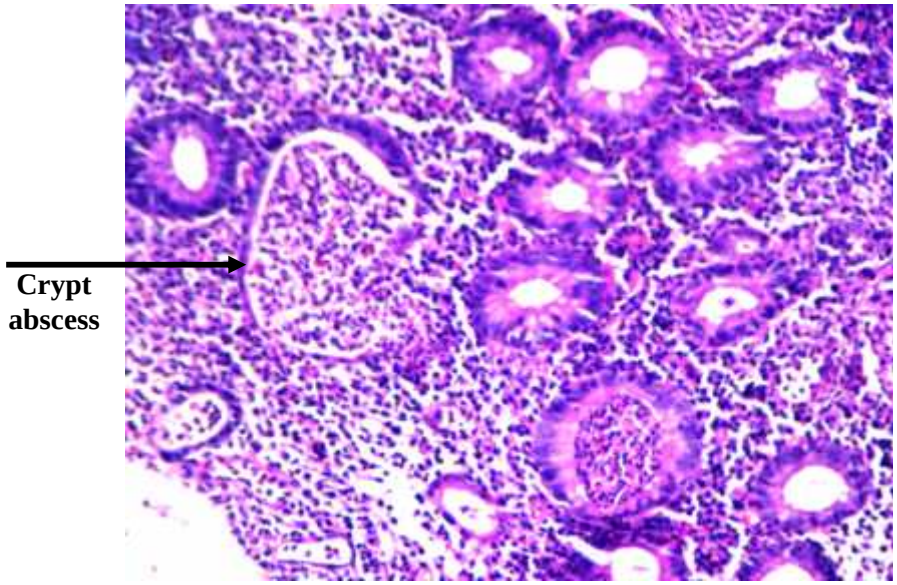
INVESTIGATIONS

Investigations	**Date**			
Blood Group				
Hb				
TC				
DC N L E M B				
ESR				
Platelets				
Peripheral smear				
Urea				
Creatinine				
Na K				
Total Bilirubin				
Direct Bilirubin				
Indirect Bilirubin				
ALT/AST				
Alkaline Phos				

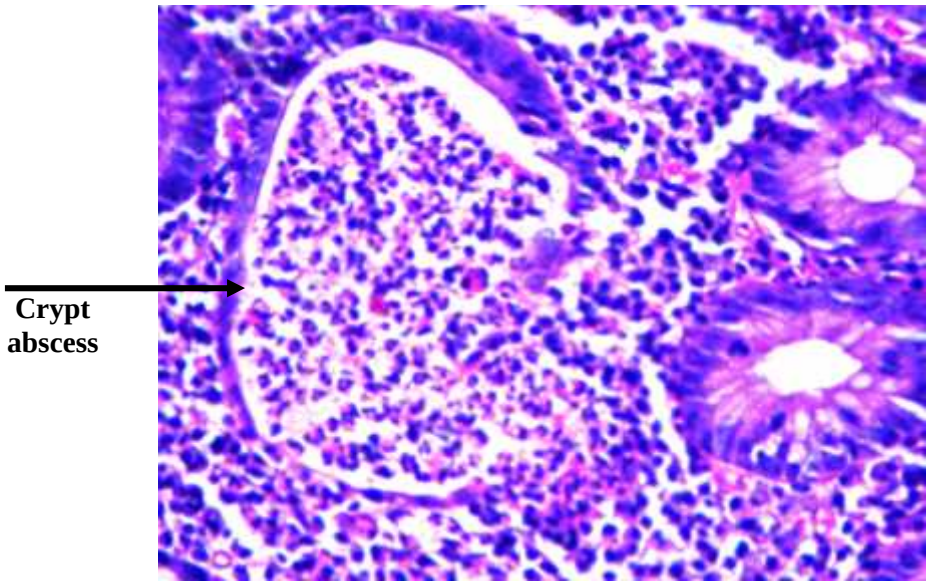
Total proteins				
Albumin				
aPTT				
PT INR				
Stool Ova/Cyst Occult blood				
Urine R/M				
HIV HBsAG HCV				
Others:				

ANNEXURE III

PHOTOGRAPHS



Photograph 1: Crypt abscess with distortion of the crypt, with thinning of mucosa and infiltration of neutrophils, lymphocytes and plasma cells.



Photograph 2: 200 x view of above picture showing crypt abscess

ANNEXURE IV - MASTER CHART

Sr. No.	IP No.	Age (Years)	Sex	Religion	Blood group	Diet	Smoking	Alcholol	Family history	Diarrhoea					Fever	Wt. Loss	Constipation	Abd. Distension	Pallor	Clubbin	Abd. Tenderness	Icterus	Hepatomegaly	EIM	Hematological				Sr. Albumin	urine R/M	
										Duration	Pain in abd	Blood	Mucus	Pus											Hb gm%	TC	P.S.	ESR			RBC
1	295014	28	M	Hindu	O+	Veg	-	+	-	8	+	+	+	+	-	-	-	-	-	-	-	-	-	Art	11.0	14,400	NH,Th,Le,	28	3.4	Normal	+
2	268472	54	M	Hindu	O+	Veg	+	-	-	4	-	+	+	+	-	-	-	-	-	-	-	-	-	-	13.2	7,600	Normal	24	2.4	Normal	+
3	246830	21	M	Hindu	O+	Mixed	-	-	-	1	+	+	+	+	-	-	-	-	+	-	-	-	-	-	8.6	6,500	NH	20	3.1	Normal	+
4	268396	51	M	Christian	B+	Mixed	-	+	-	12	-	+	+	+	-	-	-	-	-	-	-	-	-	-	14.0	8,800	Normal	20	3.2	Normal	+
5	260209	36	M	Muslim	B+	Mixed	-	-	-	3	+	+	+	+	+	+	-	-	+	-	+	-	-	-	6.6	13,500	MH,Le	90	2.4	Normal	+
6	313450	32	M	Hindu	B+	Mixed	-	+	-	6	-	+	+	+	-	-	-	-	-	-	-	-	-	-	12.0	7,500	Normal	20	3.8	Normal	+
7	254637	52	M	Hindu	B+	Veg	-	-	-	12	-	+	+	+	-		-	-	-	+	-	-	-	-	12.9	7,650	Normal	8	3.4	Normal	+
8	286389	58	M	Hindu	AB+	Mixed	+	+	-	5	+	+	+	+	-	-	-	-	-	-	-	-	-	-	12.0	6,000	Normal	38	3.2	Normal	+
9	304289	35	M	Hindu	B+	Mixed	-	+	-	17	-	+	+	+	-	-	-	-	-	-	-	-	-	+	11.9	7,800	Normal	30	3.6	Normal	+
10	307338	33	M	Hindu	O+	Mixed	-	-	-	3	+	+	+	+	-	-	-	-	+	-	-	-	-	-	10.5	6,400	NH,Th	22	2.4	Normal	+
11	326249	29	M	Hindu	A-	Mixed	+	-	-	6	+	+	+	+	-	-	-	-	+	-	-	-	-	-	7.4	5,900	NH	40	3.8	Normal	+
12	286427	37	M	Hindu	O+	Veg	-	-	-	7	+	+	+	-	-	-	-	-	-	-	-	-	-	-	12.0	6,600	Normal	28	3.6	Normal	+
13	245063	40	M	Hindu	A+	Veg	-	+	-	12	+	+	+	+	+	+	-	-	+	-	-	-	-	-	5.4	15,450	D,Th,Le	61	1.8	Normal	+
14	316032	35	M	Hindu	O+	Veg	+	-	-	2	-	+	+	+	-	-	+	-	-	-	-	-	-	-	Psoriasis	12.0	8,900	Normal	22	4	Normal	+
15	298646	39	M	Muslim	AB+	Mixed	+	-	-	24	-	+	+	+	-	+	-	-	+	-	-	-	-	-	-	10.8	9,460	NH	20	4	Normal	-
16	295728	29	M	Hindu	O+	Mixed	-	-	-	4	+	+	+	+	+	-	-	-	+	-	-	-	-	-	7.0	7,500	NH,Th	38	3.2	Normal	+
17	263334	59	M	Muslim	O+	Mixed	-	+	-	24	+	+	+	+	+	+	-	-	+	-	-	-	-	-	4.8	16,400	MH,Le	63	3.6	Normal	+
18	269122	23	M	Hindu	AB+	Mixed	-	-	-	24	+	+	+	+	-	-	-	-	+	+	-	-	-	-	9.0	7,800	NH	32	3.4	Normal	+
19	276359	27	M	Christian	A+	Mixed	-	+	-	48	+	+	+	+	-	-	-	-	+	+	-	-	-	-	10.6	10	NH	12	2.2	Normal	+
20	293618	50	M	Muslim	B+	Mixed	-	-	-	6	+	+	+	+	+	-	-	-	+	-	+	-	-	-	7.2	8,600	NH	44	2	Normal	+
21	264213	51	M	Hindu	O+	Veg	-	-	-	5	+	+	+	+	-	-	-	-	-	-	-	-	-	-	11.0	5,640	Normal	18	3.6	Normal	+

Sr. No.	Stool			True witts clinical index	Colonoscopy										Histo pathological								Complications	Management
	Occult Bl.	Pus cell	Mucus		Anatomical location	Grade	Psuedopolyp	Ulceration	Vascular loss	Hyperemia	granularity	Friability	Stricture	Tumor	Grade	Crypt distortion	Goblet cell destruction	Crypt abscess	Superficial erosion	Deep ulcerations	Granuloma/Dysplasia/Parasite	Lymphoplasmocytic infiltration		
1	+	+	+	Moderate	Left sided colitis	4	+	+	+	+	+	+	-	-	2	+	+	+	-	-	-	+	-	5-ASA
2	+	+	+	Mild	Left sided colitis	4	-	+	+	+	-	+	-	-	2	+	+	+	-	-	-	+	-	5-ASA
3	+	+	+	Moderate	Proctitis	2	-	-	+	+	+	-	-	-	2	+	+	+	-	-	-	+	-	5-ASA, Steroids
4	+	+	+	Mild	Pan	4	+	+	+	+	+	+	-	-	2	+	+	+	-	-	-	+	-	5-ASA
5	+	+	+	Severe	Pan	4	-	+	+	+	+	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA, Steroids
6	+	+	+	Mild	Proctosigmoditis	2	-	-	+	-	-	-	-	-	1	-	-	-	-	-	-	+	-	5-ASA
7	+	+	+	Mild	Pan	4	-	+	+	-	-	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA
8	+	+	+	Moderate	Left sided colitis	2	-	-	+	+	+	-	-	-	2	+	+	+	-	-	-	+	-	5-ASA, Steroids
9	+	+	+	Moderate	Left sided colitis	3	+	+	+	+	+	+	-	-	2	+	-	+	-	-	-	+	-	5-ASA
10	+	+	+	Moderate	Proctosigmoditis	3	-	-	+	+	+	+	-	-	2	+	+	+	+	-	-	+	-	5-ASA
11	+	+	+	Moderate	Left sided colitis	3	-	+	+	+	+	+	-	-	2	+	+	+	-	-	-	+	-	5-ASA, Steroids
12	-	+	+	Mild	Proctosigmoditis	3	-	+	+	+	-	+	-	-	1	-	-	-	-	-	-	+	-	5-ASA
13	+	+	+	Severe	Left sided colitis	4	-	+	+	+	+	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA, Steroids
14	+	-	+	Mild	Proctitis	1	-	-	-	-	+	-	-	-	1	-	+	-	-	-	-	+	-	5-ASA
15	+	-	+	Mild	Proctitis	1	-	-	-	+	-	-	-	-	1	-	-	-	-	-	-	+	-	5-ASA
16	+	+	+	Severe	Pan	4	-	+	+	+	-	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA, Steroids
17	+	+	+	Severe	Pan	3	+	+	+	+	+	+	-	-	2	+	+	+	+	-	-	+	-	5-ASA, Steroids
18	+	+	+	Moderate	Left sided colitis	2	+	-	+	+	+	-	-	-	2	-	-	+	-	-	-	+	-	5-ASA
19	+	+	+	Moderate	Left sided colitis	3	+	+	+	+	+	+	-	-	2	-	-	+	-	-	-	+	-	5-ASA
20	+	+	+	Severe	Left sided colitis	4	-	+	+	+	+	+	+	-	3	+	+	+	+	+	-	+	Stricture	5-ASA, Steroids
21	+	+	+	Mild	Proctosigmoditis	3	-	+	-	+	-	+	-	-	2	-	-	+	-	-	-	+	-	5-ASA, Steroids

Sr. No.	IP No.	Age (Years)	Sex	Religion	Blood group	Diet	Smoking	Alcholol	Family history	Diarrhoea					Fever	Wt. Loss	Constipation	Abd. Distension	Pallor	Clubbin	Abd. Tenderness	Icterus	Hepatomegaly	EIM	Hematological				Sr. Albumin	urine R/M	RBC
										Duration	Pain in abd	Blood	Mucus	Pus											Hb gm%	TC	P.S.	ESR			
22	326841	19	M	Hindu	AB+	Veg	+	-	-	4	+	+	+	+	-	-	-	-	-	-	-	-	-	CVT	14.0	8,400	Th	12	3.6	Normal	+
23	309466	43	M	Hindu	O+	Mixed	-	-	-	6	-	+	+	+	-	-	-	-	+	-	-	-	-	-	9.4	7,590	NH	34	1.9	Normal	+
24	276513	28	F	Hindu	B+	Mixed	-	-	-	4	-	+	+	+	+	+	-	-	-	-	-	-	+	Art,FL	12.0	7,700	Normal	36	3.6	Normal	+
25	320460	79	F	Hindu	B+	Veg	-	-	-	6	+	+	+	+	-	+	-	-	-	-	-	-	-	-	11.0	8,300	Normal	58	3.2	Normal	+
26	286020	30	F	Hindu	B+	Mixed	-	-	-	3	-	+	+	+	-	-	-	-	-	-	-	-	-	-	11.5	9,400	Normal	32	3.8	Normal	+
27	285369	37	F	Hindu	O+	Mixed	-	-	-	8	-	+	+	+	+	-	-	-	-	-	-	-	-	-	12.9	6,790	Normal	30	3.3	Normal	+
28	296564	38	F	Hindu	A+	Veg	-	-	-	48	+	+	+	+	+	-	-	-	-	+	-	-	-	-	12.4	7,800	Normal	28	3	Normal	+
29	270281	46	F	Hindu	A+	Veg	-	-	-	12	+	+	+	+	-	-	-	-	-	+	-	+	+	PG,Art,Sc,FL,OU	10.4	8,200	Th	29	3.1	Normal	+
30	296871	16	F	Hindu	O+	Veg	-	-	-	3	+	+	+	+	-	-	-	-	-	-	+	-	-	-	13.6	7,100	Normal	8	3.8	Normal	+
31	288454	45	F	Hindu	A+	Mixed	-	-	-	12	+	+	+	+	-	+	-	-	-	-	-	-	-	OU	10.2	6,150	Normal	38	4	Normal	+
32	268832	48	F	Hindu	O-	Mixed	-	-	-	17	+	+	+	+	-	-	-	-	+	-	-	-	-	-	9.6	9,750	NH	20	3.1	Normal	+
33	268516	45	F	Hindu	A+	Mixed	-	-	-	6	+	+	+	+	-	-	-	-	+	-	-	-	-	-	10.1	7,300	Normal	23	2.6	Normal	+
34	296734	28	F	Hindu	AB+	Mixed	-	-	-	6	+	+	+	+	+	+	-	-	+	-	+	-	-	OU	6.6	6,500	NH	54	2.6	Normal	+
35	274177	24	F	Hindu	O+	Mixed	-	-	-	12	+	+	+	+	+	+	-	-	+	-	+	-	-	Art	3.2	17,500	D,Th,Le	70	3.3	Normal	+

Sr. No.	Stool			True witts clinical index	Colonoscopy										Histo pathological								Complications	Management
	Occult Bl.	Pus cell	Mucus		Anatomical location	Grade	Psuedopolyp	Ulceration	Vascular loss	Hyperemia	granularity	Friability	Stricture	Tumor	Grade	Crypt distortion	Goblet cell destruction	Crypt abscess	Superficial erosion	Deep ulcerations	Granuloma/Dysplasia/Parasite	Lymphoplasmocytic infiltration		
22	+	+	+	Mild	Proctosigmoditis	2	-	-	+	-	+	-	-	-	1	-	-	-	-	-	-	+	-	5-ASA
23	+	+	+	Moderate	Left sided colitis	4	-	+	+	+	+	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA
24	+	+	+	Moderate	Pan	4	-	+	+	+	+	+	-	-	2	-	-	+	-	-	-	+	-	5- ASA , Steriods , Infliximab
25	+	+	+	Moderate	Left sided colitis	2	-	-	+	+	+	-	-	-	2	+	+	+	-	-	-	+	-	5-ASA
26	+	+	+	Moderate	Proctosigmoditis	2	-	-	+	+	+	-	-	-	2	+	-	+	-	-	-	+	-	5-ASA
27	+	+	+	Moderate	Left sided colitis	4	-	+	+	+	+	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA, Steroids
28	+	+	+	Moderate	Left sided colitis	4	+	+	+	+	+	+	-	-	2	+	-	+	-	-	-	+	-	5-ASA
29	+	+	+	Moderate	Left sided colitis	3	-	+	+	+	+	+	-	-	1	-	-	-	-	-	-	+	-	5- ASA , Steriods , cyclosporine
30	+	-	+	Mild	Pan	4	-	+	+	-	+	+	-	-	2	+	+	+	-	-	-	+	Fulminant colitis	Surgery
31	+	+	+	Moderate	Proctosigmoditis	3	-	+	+	+	+	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA
32	+	+	+	Moderate	Left sided colitis	3	-	-	+	+	+	+	-	-	1	-	-	-	-	-	-	+	-	5-ASA, Steroids
33	+	+	+	Moderate	Pan	4	-	+	+	+	+	+	-	-	3	+	+	+	+	+	-	+	-	5-ASA, Steroids
34	+	+	+	Severe	Pan	4	-	+	+	+	+	+	-	-	2	+	+	+	+	-	-	+	-	5-ASA, Steroids
35	+	+	+	Severe	Pan	4	+	+	+	+	+	+	-	-	2	+	+	+	+	+	-	+	-	5-ASA, Steroids

ANNEXURE IV

KEY TO MASTER CHART

-	-	Negative / absent
+	-	Positive / Present
Abd	-	Abdomen
Art	-	Arthritis
Bl	-	Blood
CVT	-	Cortical venous thrombosis
D	-	Dimorphic
EIM	-	Extra Intestinal Manifestations
ESR	-	Erythrocyte sedementaion rate
F	-	Female
FL	-	Fatty liver
Hb	-	Hemoglobin
Le	-	Leucoytosis
M	-	Male
MH	-	Microcytic Hypochromic
NH	-	Normocytic Hypochromic
OU	-	Oral ulceration
P.S.	-	Peripheral smear
Pan	-	Pancolitis
PG	-	Pyoderma Gangrenosum
Sc	-	Scleritis

Sr.	-	Serum
TC	-	Total Count
Th	-	Thrombocytosis
Veg	-	Vegetarian
Wt	-	Weight