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Ulcerative Colitis

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1. Introduction

Ulcerative colitis (UC) is chronic remitting relapsing disease of gastrointestinal tract which together with Crohn's disease (CD) is often grouped as inflammatory bowel disease (IBD). For a long time, all diarrhoeal diseases were believed to be caused by infectious agents such as bacteria. In 1875 Wilks and Moxon for the first time described UC as a separate entity different from infectious colitis [1]. Later in 1960, formal criteria to differentiate UC from CD were established. UC has an annual incidence of 10-20 per 100,000 compared to 5-10 per 100,000 for CD, however these data are generally considered to be an underestimate [2, 3]. It predominantly affects younger population with a peak incidence between ages 20-40 yrs, however they may affect any age group; and up to 15% of individuals are above 60 yrs of age at the time of diagnosis. Currently IBD is estimated to affect as many as 1.4 million people in the United States and 2.2 millions in Europe [3]. UC usually causes continuous mucosal inflammation and is confined to the large bowel, except in a minority of patients where involvement extends to the terminal ileum, called "backwash ileitis". Bloody diarrhoea, abdominal pain and passage of rectal mucous and blood are the predominant presenting symptoms of UC. In addition, extra-intestinal manifestations are also prevalent in UC although less common than CD; the most common being rheumatological (ankylosing spondylitis, axial arthritis), dermatological (erythema nodosum, pyoderma gangrenosum), and ophthalmological (scleritis, episcleritis) [4]. A small subgroup of patients (approximately 10%) have disease affecting colon with histological features of both CD and UC which is termed as indeterminate colitis [5].

2. Epidemiology

Epidemiological studies have revealed gender-related differences in UC with a slight predominance of males. It is traditionally considered to be most common in Western countries and least common in Asian pacific region, however its low incidence in the later is considered to be due to under-diagnosis and its overlap with infective diarrhoea [6]. The incidence of UC has increased markedly in the West since 1950s. The increase in the incidence of UC precedes that of CD by about 15-20 years [7]. Geographically, the prevalence of the disease has a gradient from North to South and, to a lesser degree, from West to East. The Western-Eastern discrepancy can be attributed to urbanization and a difference in Western lifestyles [8].

The incidence of the disease has been increasing worldwide of late, but the rate of increase has been slowing in highly affected countries [9]. Racial and ethnic observations in different populations reflect genetic, inherited, environmental and behavioural factors. The disease seems to have a characteristic racial-ethnic distribution: blacks are less affected by the UC than whites and the Jewish population is highly susceptible to both UC and CD everywhere, but its prevalence in a particular population nears that of the domestic society in which they live [10]. A study from northern England suggested that the prevalence of UC in 1995 was as high as 243 cases per 100,000 persons [2]. Recent data from Cardiff, UK showed that incidence of CD continue to rise slowly with female preponderance [11], and a similar trend has been seen in juvenile onset CD and UC in Scotland [12].

3. Aetiology

Despite progress in our understanding of its immunopathogenesis, the exact aetiology of UC remains elusive and appears to be polygenic and multifactorial. It is postulated that there is chronic activation of immune and inflammatory cascade in genetically susceptible individual. Environmental factors play a significant role in the disease manifestation, course and prognosis of UC. A rapid increase in its incidence in developed countries, the occurrence of UC in spouses and a lack of complete concordance in monozygotic twins are strong arguments for the role of environmental factors in UC. Observations on temporal trends and geographical distribution point to risk factors associated with a Western lifestyle. Many studies have specifically looked for involvement of factors such as diet, smoking, and several infectious agents but, so far, only smoking cessation can be considered established risk factors for the manifestation of the disease [13]. A strong negative association between appendectomy and UC has been found consistently across many studies; however, the implications of this finding are still obscure [14].

Interaction of these various factors (environmental, microbial and immunological) contributes to the development of chronic intestinal inflammation in a genetically susceptible host. Genetic susceptibility is influenced by the luminal microbiota, which provides antigens and adjuvant that stimulate either pathogenic or protective immune responses.

The gut microbiota has been known to be involved in the induction and perpetuation of immune-mediated bowel inflammation for a long time and the most revealing evidence for its potential involvement came from the study of genetically engineered mice in which colitis did not develop if mice were kept in a germ-free environment [15],[16]. More importantly, UC preferentially occurs in the colon which contains the highest intestinal bacterial concentrations. Moreover, the composition and function of microbiota in UC, and pouchitis are abnormal. Such evidence points towards a strong association between mucosal microbiota and the development of CD. However, few investigators have examined in depth the involvement of disturbed intestinal microbiota composition in the pathogenesis of IBD. This is due to the difficulty in culturing relevant bacteria by conventional means. Over half of the intestinal bacteria are almost impossible to culture; their characterisation requires complex, labour-intensive, and time-consuming methods [17]. Furthermore, identifying bacterial strains can be inaccurate and determining the strain abundance can be difficult.

More recently, the development of advanced molecular techniques has shown a breakdown in the balance between putative "protective" and "harmful" intestinal bacteria [18], [19]. The

decreased concentration of protective bacteria that produce short chain fatty acid (SCFA) such as butyrate can enhance mucosal permeability. Conversely, increased concentration of harmful bacteria might increases the production of toxic metabolites such as hydrogen sulfide that increase mucosal permeability and block butyrate metabolism. The increase in mucosal permeability may lead to activation of pathogenic T cell mediated and innate immune response through exposure of bacterial TLR ligands and antigen [20].

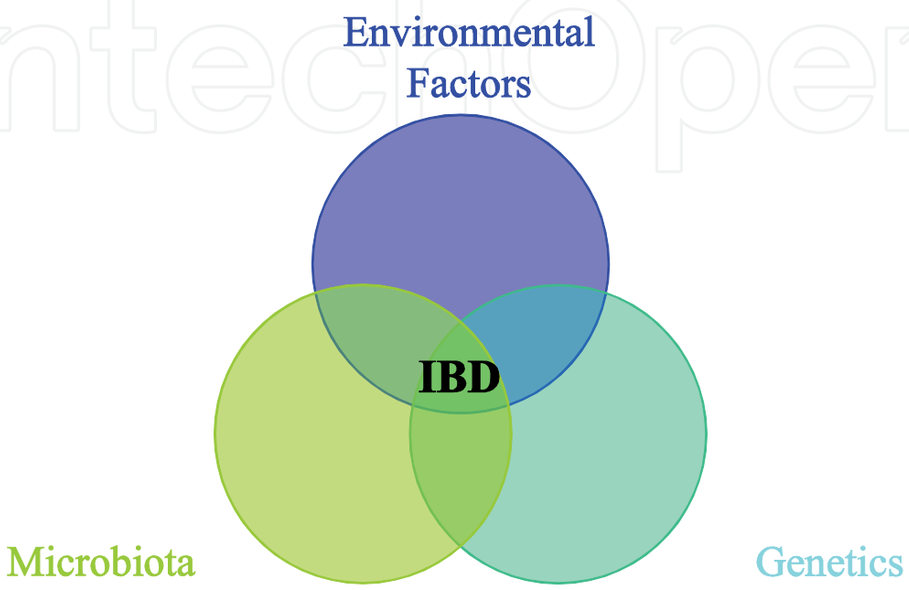

Fig. 1. Possible etiological mechanisms for the development of IBD

Altered composition of gut microbiota has been demonstrated by many studies both in CD and UC and also in pouchitis [21]. There is an increase in gut Enterobacteria mainly *E. Coli* [22], [23] and decrease in the Firmicutes in IBD, although no fundamental difference between CD and UC was found [22],[24] some studies demonstrated microbial difference in active and inactive disease [23], [25].

Other possible mechanisms by which gut microbiota can play a role in immune mediated intestinal injury are; functional alteration in commensal bacteria (such as increased epithelial adherence, mucosal invasion, and resistant to killing) [26], defective containment of commensal bacteria where by defective killing of phagocytosed bacterial and ineffective clearance of bacterial antigen provide a persistent source of mucosal immune stimulation [27] and exaggerated mucosal immune response to commensal bacteria due to discoordinated homeostatic mechanism in intestinal epithelial cells [28] .

4. Diagnosis

Diagnosis of UC is based on clinical assessment followed by a combination of biochemical, endoscopic, radiological, histological, or nuclear medicine based investigations. Endoscopy with histology is considered to be the so called "gold standard" diagnostic modality

History: Important aspects in history of patients with UC are duration and severity of symptoms, recent travel, medication, smoking, family history, stool frequency and consistency, urgency, rectal bleeding, abdominal pain, malaise, fever, weight loss, and

symptoms of extra-intestinal manifestations. Majority of patients presents with diarrhoea with or without blood, urgency abdominal pain, rectal bleed and systemic illness. The pattern of symptoms is usually depends on the extent of bowel involvement. For example, patients with pan-colitis are usually systemically ill and present with abdominal pain and bloody diarrhoea compared to those with limited colitis who remains systemically well despite similar symptoms of bloody diarrhoea.

Examination: Examination findings may suggest the severity of disease and extent of involvement. For example, patient with limited colitis and mild disease may have no specific clinical findings on examination and will be systemically well as compared to those with severe disease who may be systemically unwell, hypotensive, tachycardic and may have generalised abdominal tenderness on examination.

Investigation: Initial laboratory workup includes full blood count (FBC), U&Es, liver function tests, and erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), and microbiological testing for infectious diarrhoea including *Clostridium difficile* toxin. Abdominal radiography is also important in patients with suspected severe UC.

Endoscopic investigation: A flexible sigmoidoscopy should be performed to confirm the diagnosis. It enables taking biopsies for histology and also helps excluding other causes for diarrhoea such as infective, ischemic or CMV colitis. Endoscopic changes characteristically extend in continuous fashion from anal verge to proximal colon. Full colonoscopy in acute severe colitis is not recommended as high risks of complications.

Radiological investigations: A plan radiograph should be performed on admission to estimate the extent of disease and also to exclude colonic dilatation. Certain features on abdominal radiograph such as presence of mucosal islands or more than two gas-filled loops of small bowel may suggest severity of the disease and may predict poor response to medical treatment [29].

Generally large bowel radiology is inferior to endoscopy in the diagnosic evaluation of UC but double contrast barium enemas; CT or MRI (with or without contrast) may have a place where endoscopy is contraindicated or unsuitable. Ultrasound scanning is very sensitive for thickened bowel wall in slimmer patients. Capsule endoscopy and white cell scanning lack sensitivity and specificity.

Depending upon the extent of bowel involvement, the disease can be categorized as follows:

- **Proctitis:** Where disease is limited to the rectum only
- **Left sided**: disease involvement limited to the proportion of the colon distal to the splenic flexure
- **Extensive Colitis**: Where bowel involvement extend proximal to the splenic flexure including Pancolitis

Majority of patients have long standing diarrhoea before the diagnosis of UC is eventually made.

The main differential is infective colitis, ischemic colitis, CMV colitis and drug induced colitis.

5. Management

Management is usually depends upon the severity, complexity and extent of disease. No treatment is an option in case of very mild and limited disease. In this section, we discuss in more detail the therapeutic options in sever UC and briefly about mild and moderate disease.

5.1 Management of severe colitis

Acute severe colitis is a serious and life threatening emergency and in about 10% of all newly diagnosed cases, the first presentation is with acute severe colitis. Early recognition and prompt start of treatment is vital to the successful management and prevention of complications. Prior to the discovery of steroids in 1955 the mortality of acute severe UC was described to be as high as 33% in some studies and 75% in other study [30]. Early use of intravenous steroids has reduced the mortality to 7 % and even <1% in specialized centre [31].

Several criteria are in use to define severe colitis. One of the simple and most commonly used criteria is proposed by Truelove and Witts as shown in the table 1.

	Mild UC	Moderate	Severe
Bloody stool / day	< 4	4-6	> 6
Pulse	< 90	90 - 100	> 100
Temp	< 37.5°C	≤ 37.8 °C	>37.8 °C
Hb	>11.5g/dl	> 10.5g/dl	< 10.5 g/dl
ESR	< 20mm /h	< 30 mm/h	> 30 mm/h
CRP	Normal	< 30mg/L	> 30 mg/L
Albumin	Normal	30 - 35	< 30

Table 1. Truelove & Witts criteria for severity of UC [32]

A thorough clinical assessment is important to identify patients at risks and immediate admission to hospital is warranted for all those fulfilling the Truelove and Witts' criteria for severe colitis [32] . Differential diagnosis for these patients will include infective, ischaemic, drug-induced and other inflammatory causes of colitis. Routine lab investigation such as full blood count, electrolyte and liver function tests and inflammatory markers along with plain abdominal radiograph should be carried out and a faecal specimen should be sent to exclude infective causes including C-Difficile. If the mucosa on a plain abdominal radiograph is unremarkable, a sensible approach is to treat decisively with corticosteroids, review the patient within a few days and admit for intensive treatment if there is no improvement. Early sigmoidoscopy and biopsy should be performed as part of the initial assessment of the patient. Biopsies confirm the severity of the inflammation and allow other diagnoses such as cytomegalovirus (CMV), indicated by viral inclusion bodies, to be excluded. CMV colitis can mimic UC and is thought to be responsible for treatment failure in up to 10% of patients labelled as steroid-refractory. Treatment of CMV may obviate

colectomy. Care should be taken to monitor and correct electrolytes on a daily basis as almost every patient with severe colitis becomes hypokalaemic during intensive treatment as a result of loss through bowel in the form of diarrhoea and also intensive therapy with steroids contribute to the development of hypokalaemia. Since acute UC is associated with higher risk of venous thromboembolism, unfractionated heparin should be administered for prophylaxis purposes.

5.2 Corticosteroids

Steroids remain the treatment of choice in severe UC and usually given as intravenous Hydrocortisone 100mg four times a day. Early use of IV steroids has shown a significant reduction in mortality and therefore, should not be delayed whilst awaiting microbiological results for possible infective causes. IV treatment is best given for about 5 days while monitoring parameters for response objectively and on satisfactory response to IV steroids; oral Prednisolone can be instituted at 40 mg daily dose and tapered down gradually. It is important to attain a full remission before beginning tapering of steroids or rapid recurrence of symptoms may ensue [33].

Approximately 60% of patients will only show partial response to corticosteroids which can be predicted through objective measures such as lack of clinical improvement and persistent raised inflammatory markers [34]. At presentation, low albumin, high CRP, short duration of illness and prior steroid use all portend an increased risk of medical failure. In an analysis of 189 patients with acute severe UC, a stool frequency >9 in the first 24 h, an albumin <30 g/l or a pulse rate >90 beats per minute after 24 hours of IV steroid was predictive of a 62% failure rate to steroids. Similarly in another prospective study, a stool frequency > 8/day or CRP > 45 mg/l on day 3 of intensive therapy were predictive of the need for colectomy in 85% during that admission [35]. In case of failure of treatment with IV steroids, early use of Ciclosporin or Infliximab is now considered a rescue therapy in order to prevent colectomy.

5.3 Ciclosporin

Ciclosporin is a calcineurin inhibitor and prevents a cascade of downstream events that are necessary for T-cell activation and proliferation.

It is used in an attempt to prevent surgery when intravenous corticosteroids have failed to induce a response [36] or in those with contraindication or intolerance of steroids due to psychoses, severe osteoporosis, uncontrolled diabetes or patient preference . It is usually started after steroid failure preferable on day 3 when little or no response is seen with IV steroids, and is converted to oral cyclosporine 5 mg/kg once a response has occurred. Oral ciclosporin is then generally continued for about 3 months, and azathioprine or mercaptopurine (6-MP) introduced to maintain remission once the steroid dose tapers below 20 mg/day.

5.4 Infliximab

Infliximab is a monoclonal antibody to tumour necrosis factor-α (TNFα) and is established treatment in active CD. In cases of UC, there are only few small trials which have shown its use in case of steroid failure. The recently published Active Ulcerative Colitis Trials (ACTs) 1 and 2 support the use of Infliximab in moderately active UC refractory to aminosalicylates,

steroids or thiopurines [37]. Infliximab has emerged a promising therapeutic option in circumstances where intravenous steroids show signs of failing.
5-aminosalcylic acid (5-ASA) drugs are of little use during severe attacks of colitis and their role is usually reserved for maintenance of remission. Use of opioids and anticholinergic medication should be avoided during the acute attack in order to prevent development of megacolon, and NSAIDs should also be ceased.

5.5 Surgery

Surgical therapy requires a mutual decision by patient, surgeon and physician with consideration of optimum timing and remains a definitive procedure for the treatment of UC. Early involvement of an experienced colorectal surgical team with the gastroenterologist is crucial in decision-making. Close liaison with a stoma therapist is also necessary for continued education, support and postoperative follow-up.
The most commonly performed procedure is a subtotal colectomy and ileostomy initially which later on followed by an elective completion proctectomy and the formation of an ileal-pouch anal anastomosis (IPAA). With timely surgery, a marked improvement in clinical condition is noted within a short span after colectomy. It improves quality of life, provide confidence and control in >90%, allow patients to stop immunomodulators and prevent the long-term risk of cancer. Most follow-up studies of patients undergoing IPAA report an average of six bowel motions per day, but up to 50% experience episodes of faecal leakage at some stage
Surgery is associated with certain complications such as small bowel obstruction, anastomotic stricture, pouch leak and pelvic abscesses, and some late complications such as pouchitis. However, this has to be balanced against the poor outcome of medical therapy in patients who have had an episode of severe colitis.

5.6 Management of Left sided UC

The ECCO guidelines suggest that left sided UC with mild to moderate severity should be initially treated with combined oral and topical mesalazine therapy. Higher doses of mesalazine, usually a daily dose of 4.8gm is more effective than lower doses of 2.4 gm daily. The treatment does of topical mesalazine is usually 1gm daily and various studies have shown no additional benefits with higher topical doses. Treatment with systemic steroids is reserved for cases not responding to combined mesalazine therapy. A usually starting dose of Prednisolone is 40mg daily for 2 weeks which is then tapered down by 5 mg every week. Topical steroids are reserved for patients who are intolerant to topical mesalazine.

5.7 Management of limited UC

The preferred treatment for active proctitis is with topical therapy either with 5ASA based suppository or enema or steroid based enema. The usual daily dose of mesalazine suppositories is 1gm per day and is considered to be better in proctitis than enema. Various studies have shown topical mesalazine to be twice as effective as topical steroids in inducing remission. Therefore, mesalazine suppositories are recommended as first line treatment for active Proctitis while topical steroids are reserved for those who are less responsive or intolerant to topical mesalazine.

A significant proportion of patients with left sided UC or proctitis either remain refractory to treatment with 5ASA medication and steroids or are steroid dependant. Patients refractory to initial treatment would require more intensive treatment such as Infliximab, cyclosporine or Tacrolimus. Those who are steroid dependant would be a candidate for immunosuppressant and Azathioprin has shown better efficacy than mesalazine in inducing and maintaining remission in this groups of patient.

A careful evaluation of patients who remain symptomatic despite initial treatment with mesalazine and or steroids is important and other causes such IBS and CMV colitis with a review of the diagnosis should be considered. Poor compliance with medication is another aspect which should be considered while dealing with treatment refractory patients.

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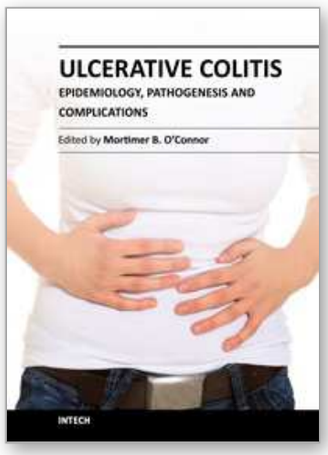

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This book is intended to act as an up-to-date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular, Ulcerative Colitis. All authors of the chapters are experts in their fields of publication, and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating, and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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