Inflammatory Bowel Disease

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ABSTRACT

Inflammatory bowel disease (IBD) is the term used for a group of diseases with yet unknown etiology, prevalence of which is increasing almost everywhere in the world. The disease was almost non-existent four decades ago in the east, including the middle-east, while now a days it is seen more and more. In addition to the increasing prevalence, our knowledge about its pathogenesis, clinical course, diagnosis, and treatment has changed dramatically over the past couple of decades. This has changed our concept of this group of diseases, their diagnosis, treatment, and treatment goals. Considering the vast literature on the subject, it is timely to review major topics in IBD with a look on the regional progress and knowledge as well. This essay is aimed to cover this task.

KEYWORDS
Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Iran.

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INTRODUCTION

Inflammatory bowel disease (IBD) is the covering name for at least two distinct entities, namely ulcerative colitis (UC) and Crohn's disease (CD) each having its own spectrum of presentations and clinical course. These diseases, almost non-existent in Iran 50 years ago[1,2] are now relatively common and increasing.[3-7] The same has happened in other countries in the middle east region as well as other parts of the world, reaching a plateau in the United States.[8-13] Although the cause of IBD is still unknown, but the literature is extensive and our knowledge regarding its mechanisms, course and treatment have changed substantially over the past couple of decades. Considering this vast literature, it seems timely to review IBD, our current pathogenetic picture, and its diagnostic and therapeutic modalities.

What is IBD?

As mentioned, IBD currently consists of UC and CD.[8] The two diseases are basically different in that CD is usually a transmural inflammation, involving the whole thickness of the bowel wall, while UC is usually confined to the mucosa.[14] In addition, CD can involve anywhere from the mouth to the anal canal, while UC affects the colon almost exclusively. There are also genetic predispositions which differ between the two conditions.[14] Therefore, although UC and CD

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are categorized under the same more general term of IBD, their clinical behavior, response to therapy and prognoses are quite different.[15] We will try to summarize key features of each disease in the following essay.

Epidemiology and Risk Factors

IBD can happen at any age, but it starts more commonly between 15-30 years of age. UC is equally common between both sexes,[8] although it has been reported to be more common among Iranian females.[12,16] Some reports point to a higher incidence of CD among females, some have found no difference and yet some have reported higher incidence among men, the latter mostly from the east. CD has been reported to be almost equally common among males and females in Iran.[16] IBD is more common in the industrialized world and the west, but it is increasing in other parts of the world as well. Estimated incidence for CD is 6-8/100,000 population per year in the United States (US), while its prevalence is estimated to be 200-300/100,000 population.[8] Corresponding figures for UC are 9-12/100,000 and 205-240/100,000 population/year. Reported incidence for CD varies between European countries with the lowest incidence being reported from Poland (0.1/100,000 population/year) and the highest from Denmark (10.1/100,000 population/year). Incidence figures for UC are somewhat higher with the highest incidence again reported from Denmark (16.8/100,000 population/year) and the lowest figure (1/100,000 population/year) from Romania.[8] Very low incidence figures have been reported from East Asia.[17-19] Tozun et al evaluating IBD cases from 12 referral centers in Turkey, have estimated an incidence of 4.4 and 2.2/100,000 population in this country.[20] Another report from Kuwait has estimated the incidence of UC to be 2.8/100,000 population, equally distributed between the two sexes.[13] An interesting point is that there is a North-South gradient for the incidence of IBD, at least in the US and Europe, with the southern parts harboring less patients.[8] This is especially pronounced for CD. Therefore, an environmental agent which is more prevalent in areas farther from equator has been suggested to play a role in the pathogenesis of IBD. In addition, the risk of IBD is higher among the high socio-economic class as well as in urban areas as compared to that of the rural parts. Smoking, female sex hormones (oral contraceptives) and appendectomy have been found to be risk factors for CD in meta-analyses.[8] The highest risk for developing CD is in the first year after appendectomy and thereafter the association loosens substantially. Therefore, there is the possibility that the link found might be due to CD presenting with symptoms of acute appendicitis. The debate is ongoing. Passive smoking seems to be a risk factor in those under 12 years of age. On the other hand, case-control studies and a homogeneous meta-analysis of these studies have shown a strong protective effect of appendectomy for UC (OR: 0.31; 95% CI: 0.25– 0.38). Other risk factors for CD include increased intake of refined sugars and animal proteins.[8]

Different genes have been linked to increased risk for IBD, the most well-known being NOD2 for CD.[21,22] All these genes are somehow associated with the immune response, either innate or acquired.[21,23] This has led to proposals for classifying CD patients according to their genetic composition. The genetic make-up of CD may differ in different populations. For instance, the three common NOD2 mutations were not found among Iranians,[24] while 8 new mutations have been described in this population.[25] The latter group have found association between one of the common CARD15/NOD2 mutations (namely the R702W mutation) with CD in Iran, but no association for the other common mutations.[22] A recently published study from northern Iran indicated that the p53 polymorphism is associated with CD. In this study the Pro/Pro make up at codon 72 of p53 gene inferred an OR of 35.2 (95%CI: 12.6-98.7, $p<0.0001$) for UC.[26] The same polymorphism has been reported to be associated with more severe disease (as indicated by the need for colectomy and corticosteroid use) and familial aggregation in Turkish patients with UC.[27] The transforming growth factor gene polymorphism has been associated with UC. Again this is not a consistent finding and varies in different populations. For

instance, Farnood et al have reported a higher incidence of C/C homozygote and C/T heterozygote polymorphism for this gene among UC patients residing in Tehran, while Tamizfar et al have not found such an association in UC patients in southern Iran.[28,29]

Generally speaking, CD is associated with an abnormal Th-1 immune response, while abnormal Th-2 immune response is seen in UC.[8,21,23] But as the incidence of CD is increasing, there should be an environmental agent stimulating the abnormal immune response. The exact nature of this environmental agent is still to be determined, but animal and human studies all suggest a dysbiosis of bacteria within the gut.[8,21] Human studies have also found that the gut flora of patients with IBD is significantly less diverse than that of normal counterparts.[8,21] Again it cannot be determined whether this is a consequence of IBD, i.e. the micro-environment of the gut of IBD patients is hostile for existence of bacteria and that only strains with specific capabilities can survive, or a cause of IBD. This remains to be determined.[8] The link between dietary factors and IBD may also be explained by changes in the gut microbiome induced by different dietary habits.[21] Another point to emphasize is that, as mentioned before, the more hygienic the living conditions become, the higher goes the incidence of IBD. For instance early exposure to refrigeration has been associated with increased chance of developing CD.[30] Whether this is due to lack of training of the immune system by lack of exposure to different bacterial antigens early in life, or a lack of gaining the appropriate microbes within the gut is not known.[8,30]

So currently we do not know what exactly causes IBD, but we understand that the disease is seen in patients who are genetically predisposed to immune dysregulation, and are exposed to certain environmental factor(s) which are associated with industrialization and hygienic ways of living. We also know that the gut microbiome plays a key role in pathogenesis of IBD. Unraveling the exact nature of interaction between genetic factors, immune dysregulation, gut dysbiosis, dietary factors, and probably other yet unknown environmental factors will definitely affect our way of looking at and treating IBD in the future.

Diagnosis

In most instances the patient's symptoms bring him/her to medical attention. UC usually presents with prolonged diarrhea with or without blood in stool. Abdominal cramps and stool urgency may accompany the symptoms especially if the rectum is affected profoundly. Fever, although not common, may be in the constellation.[31] Occasionally patients with UC may present with fever of undetermined origin (FUO). The patient may be fatigued because of the severe ongoing inflammatory process, electrolyte imbalance, iron deficiency or the resulting anemia.[31] Extra-colonic symptoms include arthralgia, central or peripheral arthritis, ophthalmologic problems (e.g. red eye, scleritis, episcleritis), and skin manifestations (e.g. maculopapular rash, erythema nodosum, pyoderma gangrenosum).[32] On occasion, a patient may be diagnosed while being worked out for abnormal liver function tests which have turned out to be due to primary sclerosing cholangitis (PSC). Considering the close association of PSC and IBD, all patients with PSC need to be investigated with total colonoscopy for the presence of silent or minimally symptomatic IBD, especially UC.[33] When clinical suspicion is raised, the patient needs a battery of investigations, mainstay of which is a total colonoscopy with adequate biopsies.[34] During colonoscopy, the extent and severity of the endoscopic appearance are reported. The terminal ileum should be evaluated whenever possible. In addition to taking biopsies from the grossly involved areas, it is recommended to take biopsies from the uninvolved parts as well, as microscopic involvement may be present which affects prognosis. Stool should be examined for parasites, blood, bacterial infections, and *Clostridium Difficile* toxin (*C. diff*). In severe cases or those not responding to appropriate medical treatment, it is indicated to look for cytomegalovirus (CMV) both in colonic biopsies and through blood tests (i.e. CMV Ag, CMV Ab-IgM, and CMV DNA) as well

as human immunodeficiency virus (HIV).[35] Complete blood counts (CBC), erythrocyte sedimentation rate (ESR), quantitative C-reactive protein (CRP), liver enzymes and alkaline phosphatase, serum creatinine and electrolytes may also help in the management of the patient. Although clinical symptoms and endoscopic appearance are characteristic, compatible histopathologic findings are mandatory for confirmation of diagnosis. Presence of crypt abscess, glandular distortion and chronic crypt destructive colitis are characteristic histopathologic findings. To summarize, UC is diagnosed when a combination of characteristic colonoscopic and histopathologic findings are present in a patient clinically suspicious of having IBD. Extra-colonic symptoms may precede, appear concomitantly, or follow the gut manifestations of UC.

Crohn's disease, especially when inflammatory and affecting the colon with or without the small bowel, can have similar manifestations to UC.[36] When CD involves the small bowel, it may have other clinical manifestations including episodes of colicky abdominal pain not necessarily associated with changes in bowel movement. Other manifestations include partial or complete intestinal obstruction, chronic non-bloody diarrhea, weight loss, and FUO. CD may involve anywhere along the gut from the mouth to the anus, therefore, it may manifest with recurrent oral aphtous lesions, esophageal strictures, and epigastric pain as well.[36] Except for the oral aphtous lesions, the other presentations referable to the upper gastro-intestinal tract are rare. CD may cause fistulas in various parts of the gut, therefore, the initial presentation of the disease can be perianal fistulas (usually located laterally instead of anteriorly or posteriorly), complicated perianal abscesses, recto-vaginal or recto-vesical fistulas, and entero-cutaneous fistulas. Transmural inflammation, interloop fistulas and adhesions may give rise to conglomerates of boggy bowel loops presenting as an abdominal mass which may or may not be painful. Iron deficiency anemia due to chronic occult blood loss is another presenting picture. Mainstays of diagnosis are clinical suspicion followed by appropriate endoscopic, histopathologic and imaging verification as well as ruling out important diseases which can mimic CD's symptoms including small bowel lymphoma, Tuberculosis, malabsorption syndromes, and ileo-cecal area malignant tumors. At colonoscopy and terminal ileal intubation, one may see a range of findings of grossly normal mucosa to fine erosions to fissuring ulcers with or without intervening normal looking mucosa (skip areas). Characteristic findings on histopathologic examination of biopsy samples of the colonoscopic lesions include transmural inflammation, chronic crypt destructive colitis, crypt abscesses, non-caseating granulomas and distortion of the glandular pattern. These histological findings may even be detectable on samples taken from apparently normal mucosa, therefore, highlighting the importance of histological evaluation of grossly uninvolved segments.

Small bowel imaging is pivotal in assessment of patients with CD as in almost two-thirds of patients the small bowel is involved, either alone or alongside with the colon. Small bowel involvement may be inflammatory (therefore amenable to treatment with various anti-inflammatory agents), stricturing or fistulizing. In addition, involvement of the small bowel is highly suggestive of CD as UC does not involve the small intestine except as backwash ileitis in the distal few cm of the terminal ileum. Conventionally, small bowel imaging is done with contrast radiography, either small bowel follow-through or enteroclysis. High quality contrast-enhanced images including the terminal ileum and the ileo-cecal valve area are essential in evaluation of patients with CD. Recently, abdomino-pelvic CT-scan and magnetic resonance imaging (MRI) have been introduced as more useful modalities, not only being capable of evaluating mucosa but the whole thickness of the bowel wall as well as fistulas and small intra-abdominal abscesses.[37] In addition, these modalities can assess ongoing vs. silent disease in the mucosa. As it does not expose the patient to ionizing radiation, MRI may be preferable for repated evaluation of CD patients in this regard. In problematic cases where the colon and terminal ileum are spared and confirmatory hitological evidence

cannot be obtained through colonoscopy but the small bowel is affected, single or double balloon enteroscopy can be attempted to provide adequate tissue for diagnosis.

Various biomarkers in serum and stool have been used in IBD (especially CD) patients to assess different aspects of disease. Biomarkers such as calprotectin and lactoferrin have been used to determine the need for colonoscopy in a patient who is suspicious between harboring irritable bowel syndrome (IBS) or IBD. As both calprotectin and lactoferrin are components of the leukocyte cytosol, their finding in the stool would suggest IBD and therefore the need for careful colonoscopic assessment. The positive and negative predictive values of these tests are still such that they are not recommended for routine clinical use. A number of serologic tests such as anti-Streptomyces cerevisiae (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) have also been used to predict disease activity, severity, course, and the probability of developing complications. None of these, alone or in combination, have been universally helpful for the purpose they were intended for.[38] In a study assessing the performance characteristics of p-ANCA among Iranian IBD patients, similar results were achieved with an overall sensitivity and specificity of 40% and 80% for UC and 58% and 70% for CD respectively.[39] Therefore, currently their usefulness is limited to selected patients and their widespread use does not add much to careful clinical, endoscopic and imaging evaluation.[38]

Treatment

Goals of treatment in IBD are induction of remission, maintenance of remission, prevention of relapse, appropriate handling of complications, and minimization of drug/intervention-induced adverse reactions. As mentioned, UC and CD have different clinical behaviors, and even within a given category (i.e. either UC or CD) the disease behavior may differ substantially. Therefore, treatment should be tailored according to disease (i.e. CD or UC), disease severity (clinical, endoscopic), disease extent (i.e. small bowel involvement in CD, pancolitis vs. left sided colitis vs. proctosigmoiditis vs. proctitis in UC, exclusive colon involvement with CD), type of disease in CD (i.e. inflammatory, stricturing, fistulizing), and presence of comorbid illnesses (e.g. diabetes mellitus, hypertension,…). Therefore, all attempts should be made to distinguish between UC and CD and categorize the disease correctly at the earliest possible time. This needs careful use of diagnostic tests, endoscopy, adequate biopsies, expert interpretation of the histological findings, and appropriate, high quality imaging. Correct diagnosis and categorization, as well as careful follow-up and maintenance alongside with timely decision-making for resistant or recurrent cases and those with complications are the mainstays of sound, high quality management of IBD patients. Several classes of drugs are used for management of IBD. Below we will review them, their efficacy and current appropriate use.

5-aminosalicylates (5-ASA), mainly mesalamine or mesalazine, are the best treatment for induction of remission in mild to moderate UC. Their efficacy has been shown in multiple clinical trials as well as systematic reviews. The number needed to treat (NNT) for induction of remission in this category is 6 (95% CI: 5-8).[8] Overall 40% of patients treated as such achieve remission as compared to 20% of those treated with placebo. Increasing the dose beyond 2.4g of mesalamine (3g of mesalazine) will not add any clinical benefit. So the standard dose mesalamine of 2-2.4g (2.5-3g of mesalazine) is recommended for induction of remission in mild to moderate UC.[8] When clinical and endoscopic remission is achieved, 5-ASA compounds are very effective in prevention of relapse (NNT=4, 95% CI: 3-7). About 40% of patients on mesalamine relapse within a year after remission is achieved as compared to 63% of those on placebo. Sulphasalazine has a similar effect. The maintenance dose of mesalamine is the same as that used for induction of remission. Studies comparing lower doses with the standard dose of mesalamine or its equivalent have consistently shown higher chances of relapse with lowering the dose of 5-ASA. Different 5-ASA formulations are not different in this regard. There-

fore, it is strongly recommended to start 5-ASA at the standard dose (i.e. 2-2.4g of Mesalamine or its equivalent) and maintain the same dose for long term if remission is achieved.[8]

Unlike UC, 5-ASA compounds show a borderline effect, at most, for induction of remission in ileal or ileo-colonic CD.[8] In a systematic review of RCTs in CD, 32% of the 5-ASA-treated and 26% of the placebo-treated patients achieved remission (NNT=11, 95% CI: 6-100). Therefore, currently this group of medication is not recommended for induction of remission in CD. The same systematic review has looked at the effect of 5-ASA compounds on prevention of relapse in CD patients already in remission. Fifty-six percent of treated patients and 57% of the control group did not relapse within 4 years (p=NS). Therefore, currently there is no evidence of usefulness of 5-ASA family in prevention of relapse in CD and they are not recommended for this purpose as well.

The next category of drugs used for induction of remission in UC is the corticosteroids which are potent, nonspecific immunosuppressives. They have been shown to be effective in induction of remission in UC patients (NNT=3, 95% CI: 2-9) in a systematic review.[8] Within 8 weeks, 46% of those taking corticosteroids achieve remission as compared to 21% on placebo. The orally administered, poorly absorbed corticosteroid fluticasone is not effective for this purpose, but almost all others are equally effective. The same systematic review has shown that if corticosteroids which are locally active in the gut are excluded, then the NNT rises to 2 with a narrower 95% CI.[1,4-6] The problem with this systematic review was that the number of qualifying studies and patients they had included were small (6 studies with 445 patients) and the studies were heterogeneous, therefore the quality of evidence was low. Despite this, corticosteroids are strongly recommended for induction of remission in UC, especially the severe forms or those unresponsive to 5-ASAs. Considering their wide and serious adverse effects, corticosteroids are not recommended for prevention of relapse in UC.

Corticosteroids have been shown to be useful in inflammatory CD, but not in fistulizing or stricture-forming types. Randomized trials of systemic corticosteroids in active CD are few. A recent systematic review found 2 qualifying studies with 267 patients. Overall, 60% of those treated with systemic corticosteroids achieved remission in comparison to 31% of those on placebo. The pooled NNT for these two trials was 3 (95% CI: 2-11). Budesonide, a locally active corticosteroid in the gut lumen with less systemic adverse effects, has been shown to induce remission in 45% of CD patients with ileal and right-sided CD colitis as compared to 24% of the placebo group. The pooled NNT for the 2 trials included in a recent systematic review was 5 (95% CI: 3-9).[8] That systematic review has looked at head to head studies comparing corticosteroids to budesonide for induction of remission in ileal or right-sided CD colitis as well and found that 62% of those receiving systemic corticosteroids and 53% of those receiving budesonide achieved remission within 10 weeks (NNT: 11, 95% CI: 6-50, in favor of systemic corticosteroids). Drug-related adverse events were reported in 62% of the systemic corticosteroid users as compared to 37% of those receiving budesonide (number needed to harm, NNH=4, 95% CI: 3-6). This evidence suggests that adverse events are less frequent with budesonide, but it is also less effective than systemic corticosteroids. Therefore, the choice between the two in ileal and right-sided CD colitis should be individualized. Again systemic corticosteroids are not recommended for prevention of relapse in CD because of their frequent and serious adverse events. The same systematic review has shown that 63% of patients relapse on budesonide within one year after achieving remission vs. 70% on placebo (RR = 0.93; 95% CI: 0.83– 1.04). Overall frequency of adverse events was equal between the 2 groups, but corticosteroid-related adverse events were more common with budesonide (NNH=6, (95 % CI: 4 – 25). Therefore, according to current evidence, budesonide is not recommended for prevention of relapse in CD patients who have already achieved remission. The only exception may be those who are corticosteroid dependent. Limited evidence suggests that under

these circumstances budesonide may help.[8]

Thiopurines [Azathioprine (AZA) and 6-Mercaptopurine (6-MP)], calcineurin inhibitors [Cyclosporine-A (CsA) and Tacrolimus (FK-506)], and methotrexate (MTX), are collectively referred to as immunosuppressives and have been used in IBD both for induction of remission and prevention of relapse. Thiopurines and MTX are not effective in inducing remission in IBD (UC or CD) therefore they are not recommended for this purpose.[40] Intravenous CsA (2-4mg/Kg/day) followed by oral CsA is recommended for induction of remission in severe UC (20), but not for CD.[40,41] AZA has been shown to be effective in preventing relapse in patients with UC whose disease has been controlled with corticosteroids in placebo controlled studies (NNT: 4, 95% CI: 2-10), while weekly oral MTX is not useful for this purpose.[40] MTX at a dose of 25mg intramuscularly may be helpful for induction of remission in CD patients, but the data are not strong.[42] Long term maintenance on AZA seems to be effective in preventing relapse in CD patients, even in patients who have undergone surgery.[40]

The knowledge that the uncontrolled inflammation of the bowel in IBD is mediated by various cytokines has been the basis of introduction of anti-tumor necrosis factor-α (anti-TNF-α) into the armamentarium against CD and UC.[43] Infliximab (anti-TNF- α) has been shown to be effective in inducing remission in moderate to severe UC with about 60% of patients achieving remission (NNT: 4, 95%CI: 3-10).[44] Although it has been recommended to be used in hospitalized UC patients with very severe UC, but the evidence is rather poor and under these circumstances it should be used with caution.[8] Whether infliximab can be used for maintenance of patients with UC remains to be determined.[8] All three available anti-TNF- α agents (infliximab, adalimumab, and certolizumab pegol) have been shown to be effective for induction of remission in active CD in a systematic review of currently available evidence.[44] This systematic review showed that overall 28% of CD patients achieve remission on anti-TNF- α as compared to 19% on placebo (NNT: 8, 95%CI: 6-17). Biological agents are probably best to be used in patients who have failed first and second line therapies or are corticosteroid dependent. The other biological agent which has been used in CD is Natalizumab (anti-α-4 integrin). Overall 39% of those treated with Natalizumab and 23% of those on placebo achieved remission.[8] Therefore, the efficacy of Natalizumab is close to that of anti TNF-α antibodies. But the important issue is the serious adverse effect of progressive mulit-focal leuko-encephalopathy (PML) which has been reported in 1 of 1000 patients treated with Natalizumab. This has hampered the use of Natalizumab in CD and it is usually saved for patients unresponsive to anti TNF-α antibodies.[8]

Anti TNF-α antibodies have been used in fistulizing CD with an NNT of 3 (95%CI: 2-6).[45] In a meta-analysis of published studies on the subject, anti TNF-α antibodies were effective in healing CD fistulas in 33% vs. 22.5% on placebo (P=NS). Except for the mentioned study[45] which was designed specifically to address fistula healing, the other 5 studies included in the meta-analysis assessed fistula healing in their subgroup analyses. The effect has been shown for infliximab, but not for adalimumab or certolizumab-pegol. Infliximab has been tried for maintenance of healed fistulas in CD as well.[46] At 54 weeks, 66% of patients on infliximab and 81% of those on placebo had a recurrence of their fistulas (NNT: 7, 95%CI: 4-33).

All three of these antibodies have been used successfully for prevention of relapse in quiescent CD. Pooled data of the available trials show that 56% of those maintained on anti-TNF-α antibodies relapse within 26-56 weeks vs. 78% of those on placebo (NNT: 4, 95%CI: 3-5). Combining azathioprine with infliximab seems to be superior to infliximab monotherapy for maintaining remission in these patients.[47] Natalizumab (anti-α4 integrin antibody) is also effective for this purpose (61% recurrence rate at 60 months with Natalizumab as compared to 85% on placebo, NNT: 5, 95%CI: 4-5).[48] But as mentioned earlier, the risk of PML is serious, therefore, it is recommended to keep Natalizumab for patients unresponsive to anti TNF-α antibodies.

Dysbiosis is a phenomenon which has been

attributed to the pathogenesis of IBD. This has led to the idea antibiotics may be useful in treatment of IBD by altering the gut microflora. This has been the subject of several studies. A recent meta-analysis of the available studies has shown that antibiotics may help improve active CD and UC.[49] The problem is that no specific class of antibiotics has been used by different investigators and the quality of original data has been judged as poor by the authors. Therefore, despite the favorable results of the mentioned meta-analysis, antibiotics are not recommended for this purpose on a routine basis, but only in individual patients.[8] Antibiotics may be useful in healing of fistula in CD. Short course of antibiotics are not efficacious in preventing relapse in UC, but they have a statistically significant effect in prevention of relapse in quiescent CD.[49] Again, as the specific type of antibiotic cannot be deduced from the available evidence, these drugs are not recommended routinely for this purpose.[8]

How to use medications and make appropriate decisions in practice?

Traditionally a "step-up therapy" was suggested for treatment of IBD. This has mostly been replaced by "accelerated step-up therapy", i.e. going for more potent drugs within a given, arbitrary time-frame, achieving remission, and maintaining the patient on less toxic medication. Common mistakes in managing IBD include inappropriate use of corticosteroids (e.g. for maintenance or for perianal and fistulizing Crohn's disease), underuse or late introduction of thiopurines, overuse of 5-ASA compounds in inappropriate settings (e.g. for Crohn's disease, or unremitting ulcerative colitis), underdosing of 5-ASA drugs for maintenance, delaying surgery inappropriately when it is necessary, and inappropriate use of anti-TNF agents (both over- and underuse).

Knowing the extent of disease is crucial in planning for an effective treatment. The other important point is the timing of expectations from a given drug (i.e. having an appropriate time-frame for changing dose or type of the treatment used). For UC the disease is anatomically divided into "ulcerative proctitis", "ulcerative proctosigmoiditis", "ulcerative left sided colitis" (when the colon is involved above the sigmoid but not beyond the splenic flexure), and "pancolitis" (when the disease extends beyond the splenic flexure). Pancolitis does not necessarily involve the whole transverse and ascending colon down to the cecum. When the disease extends beyond the splenic flexure but does not involve the right colon or cecum, sometimes it is called "extensive colitis" and the term "universal colitis" is used for UC involving all the way to the cecum. UC is also categorized into "mild" (≤4 bloody stools/day), "moderate" (4-10 bloody stools/day without systemic toxicity), and severe (>10 bloody stools/day with signs of systemic toxicity, i.e. tachycardia>90/minutes, oral temperature>37.8°C, Hb<10.5 g/dl, and ESR>30mm/h). CD is usually categorized according to its behavior and extent of involvement. By behavior one means "inflammatory", "fistulizing, and "stricturing", and by extent one means involvement of the small bowel only, involvement of the colon only and involvement of both the small bowel and the colon. These characterizations are best made before starting treatment. If the patient is in a critical condition at presentation, appropriate investigations to characterize him/her should be done at the earliest possible time when the patient is stable.

As mentioned, 5-ASA compounds [prodrugs such as balsalazide, olsalazine, and Sulphasalazine, or pH-dependent ones like Asacol (mesalamine) and Salofalk, or slow-release ones such as Pentasa] are effective in treatment of mild to moderate UC. The point is that as we approach the rectum, the concentration of drug decreases (left to right gradient), so that less than 10% of a given dose reaches the distal colon. Therefore, adding a locally acting form (i.e. enema or suppository) may be necessary in cases with active distal disease. Therefore, in cases with mild to moderate extensive or pancolitis who have been started on adequate dose 5-ASA and in whom optimal clinical response is not achieved, it is important to look again and see whether it is the distal rectum which is active, or the whole colon is not in remission. Adding a local 5-ASA would probably solve the problem in the former case, while the lat-

ter may need getting switched to a more potent systemic drug. In patients with proctitis only, the best treatment is mesalamine suppositories (even better than enemas and foams).

In cases with mild to moderate left-sided colitis treatment options in decreasing order of efficacy are combined oral and rectal mesalamine, rectal mesalamine, and oral mesalamine (stop rectal bleeding in 89%, 69% and 46% of cases respectively). These patients then need to be maintained on local 5-ASA compounds (i.e. enemas) at least three times a week with or without oral 5-ASA. In patients with mild to moderate extensive colitis, a combination of oral and rectal mesalamine induces remission in almost two-thirds of patients, while oral mesalamine alone achieves this goal in less than half (43%) of the patients.

As mentioned, appropriate timing to escalation of treatment in patients started on 5-ASA compounds is very important. Although there is no consensus in this regard, but considering the median times of remission with 2.4g mesalamine (3 g of mesalazine) of about 16 days, it seems reasonable to increase the dosage to 4.8 g after 2 weeks if diarrhea/bleeding are still present and checking the patient for remission after about 4 weeks. If symptoms do not resolve in this time frame and hematochezia continues, then switching to corticosteroids is reasonable. An equivalent dose of 40mg prednisone (or prednisolone) is a good option to begin with. Higher doses usually do not have any added benefit, but definitely higher chances of adverse effects. Prednisone is then tapered at 5mg/week (sometimes slightly more slowly, e.g. at 10-14 day intervals). When the prednisolone dose is decreased to 30 mg/d, 5-ASA should be added and continued for maintenance (at the same dose as used for induction of remission). Going directly to an anti-TNF compound instead of corticosteroids if patients are unresponsive to 5-ASA is possible, but usually the anti-TNFs are kept for those unresponsive to corticosteroids.

In acute severe UC, one needs to rule out CMV infection by appropriate biopsies and blood tests (CMV Ag, CMV Ab IgM), C. diff colitis by stool toxin assay, and parasitic infestations and other bacterial infections by appropriate tests and cultures. Looking for *C. diff* judiciously is rather important as it has been shown that the presence of *C. diff* is associated with prolonged hospital admission and an almost 4 times higher mortality. The physician also needs to make sure that the colon is not dilated (toxic megacolon). Meanwhile 60mg of methyl-prednisolone or its equivalent (e.g. 300 mg of hydrocortisone) should be administered intravenously while the above results are pending. Higher doses have been shown not to be effective. Intravenous corticosteroids for 5-7 days results in clinical response in about two-thirds of the patients and the rest may need colectomy. Extending treatment beyond one week is not associated with a better response rate. Assessing the response on the third day is appropriate. If stool frequency is not decreased to less than 4/day and CRP is more than 45 mg/dl, then rescue therapy with either low dose (2mg/kg/day) cyclosporine or Infliximab (single 5 mg/kg) may be justified. Both alternatives are almost equally effective (67% response rate with Infliximab and 85% with low dose cyclosporine). As Infliximab has a higher half life, its safety under this condition (i.e. if emergency colectomy is needed) is questionable. None of these treatments should be continued beyond seven days. During this period the patient should be counseled about potential colectomy and the surgical team should be involved for preparation of the patient for a possible surgery. Inappropriate delaying of the surgery is associated with poorer outcomes and is discouraged.

In UC patients who receive corticosteroids, if the prednisolone cannot be discontinued within three months or symptoms recur within three months of discontinuing prednisolone, thiopurines need to be added.[8] Some authorities believe that almost all patients who need to be treated with corticosteroids are better off if maintained on Azathioprine. Azathioprine (at a dose of 2-2.5mg/kg/d or 6-mercaptopurine 1-1.5mg/kg/d) can decrease steroid dependency from almost 40% to less than 10%. Azathioprine is added at low dose and gradually increased until the optimal dose is achieved or white blood cells come

around 4000/mm^3. Checking for azathioprine toxicity with CBCs, liver enzymes and clinical follow-up frequently is essential. Some authorities suggest checking "thiopurine methyl transferase, TPMT" activity before starting azathioprine in order to predict serious bone marrow suppression.

The principles of treating CD patients are the same as for those with UC, but there are some major differences. These include a lack of response to 5-ASA compounds and cyclosporine as well as more need for surgery. As mentioned, stricturing disease and weight loss at presentation harbor a poorer prognosis, therefore, biological therapies and immunomodulators may be better introduced earlier in their course even if the disease activity is considered mild to moderate. For mild to moderate "inflammatory" ileo-colonic CD, budesonide at a daily dose of 9mg/day has been shown to be effective. For more distal inflammatory CD, extensive colonic disease, or severe disease (i.e. Crohn's Disease Activity Index, CDAI>300), prednisolone is recommended. Corticosteroids are not effective in patients presenting with strictures or fistulas only therefore their use for this purpose is strongly discouraged. Biologic agents including Adalimumab, Infliximab, and Certolizumab pegol are indicated in patients not responding to corticosteroids or those who are intolerant to it. In addition, the biologic agents are effective in about 40% of cases of fistulizing CD. All patients planned to be started on biologic agents should undergo evaluation for occult Tuberculosis by PPD skin test and chest X-ray. In addition, abdomino-pelvic abscesses should have been managed adequately before starting these drugs.

Outcomes of Interest, Handling of Relapse, and Follow-up

The goals of treatment in UC are achieving clinical remission (regular, non-diarrheal, non-bloody bowel movements with no systemic signs) and complete mucosal healing. In CD, in addition to the above, healing of fistulas and resolving of the strictures are also desired. These goals are not achievable in a sizeable portion of patients, but should be headed for in almost all instances. It has been shown that complete mucosal healing is the only factor predicting further relapse and the need for surgery in IBD. Therefore, re-assessing UC patients endoscopically at 8-12 weeks after clinical remission is achieved and CD patients at about 24 weeks is recommended to tailor therapy. As mentioned, an accelerated step-up therapy is the preferred method of treatment with set goals and assessing response within a given time-frame to make appropriate decisions for changing the dose or type of the administered therapy. Therefore, the patients need to be followed regularly and at each follow-up be checked for response as well as drug adverse effects (including bone marrow toxicity of AZA or 6-MP).

IBD status in other middle-eastern countries

Ozin et al.[50] have reported the clinical characteristics of 702 IBD patients followed at a single center over 14 years in Turkey. Most of them had UC (507 patients), mean age at diagnosis was in the fifth decade and CD patients were diagnosed at a younger age than UC patients (40 years vs.46 years). Male/female ratio was 1.6 for CD patients. Mean duration of disease was almost 10 years in their series with a mean follow-up of 6.5 year and more than half of their CD patients needed some form of surgical intervention. In another study from Saudi Arabia, Al-Ghamdi et al reported on 77 CD patients treated over 20 years in a single center.[9] Most of these patients were seen in the second decade of the report, indicating increased awareness of the disease, and probably increased incidence. Most of their patients presented in their 3rd decade of life and over 75% of their patients had small bowel and colonic involvement and there was a slight female dominance (M/F ratio: 0.75). Half of these patients achieved remission with corticosteroids and about 13% needed surgery. In a recently published paper from Turkey, Kekilli et al followed 275 UC patients (from a cohort of 844) with surveillance colonoscopies for 10-30 years.[51] They reported a low incidence of 1.1% for colorectal cancer among these patients.[51] Cutaneous manifestations have been reported in less than 9.3% of Turkish patients with three-fourths of

it being erythema nodosum,[52] while Moravveji et al have deteceted cutaneous manifestations in about 6% of 404 Iranian patients with IBD.[53] Osmanuglu et al found that slightly less than half of patients with PSC in Turkey have IBD.[10]

Summary

UC and CD are increasing in the east. Their exact etiology is unknown, but an unremitting immune response to an as yet unknown environmental factor in a genetically predisposed person is the currently understood mechanism for these diseases. Gut dysbiosis has a central role which needs to be elucidated further. Endoscopic and histologic evaluation in the appropriate clinical setting are mainstays of diagnosis. Imagings are especially useful for evaluation of the small bowel with MRI emerging as a useful tool for assessment of the full thickness of the bowel and mucosal inflammation. Various drugs including 5-ASAs, corticosteroids, immunomodulators, anti TNF-α agents, anti α-4 integrins, and antibiotics are effective under different circumstances. Careful clinical, endoscopic, and imaging studies are essential for correct classification of these diseases and direct appropriate use of medications. Setting time-frames for assessment of response to therapy, timely use of various drugs as well as avoiding continuing toxic drugs in patients not responding appropriately in the given time-frame are essential in effective management of patients with IBD.

CONFLICT OF INTEREST

The author declares no conflict of interest related to this work.

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