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Review Article

An Overview on Inflammatory Bowel Disease Treatment

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic relapsing, idiopathic disorder of the gastrointestinal tract of an unknown etiology. Ulcerative colitis (UC) and Crohn's disease (CD) have become important health problems. Current medical therapy of IBD has advanced dramatically with the introduction of new biologic therapies in addition to the optimization of conventional therapies that include drugs such as immunosuppressors and 5-aminosalicylic acid (5-ASA), and a better identification of factors involved in the pathogenesis of IBD.
The aim of this review is to provide a brief historical perspective of the available evidence for the use of various medications in IBD followed by a recent literature update. The intent is to enhance the clinician's perspective regarding IBD treatment.

Keywords: Crohn's disease; Inflammatory bowel disease; Ulcerative colitis; Immunomodulation therapy; Infliximab

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing disorder of the gastrointestinal tract which includes two main types, ulcerative colitis (UC) and Crohn's disease (CD). IBD affects approximately 3.6 million people in the USA and Europe Currently, there is an alarming rise in low incidence regions, such as Asia and southern Europe(1-3).However, the incidence rate and prevalence of IBD in Iran is not clear(4,5). Symptoms of IBD include diarrhea, abdominal pain, anemia, bleeding, and weight loss. Extra-intestinal manifestations of IBD include arthritis, ankylosing spondylitis, Sclerosing cholangitis, uveitis, iritis, pyoderma gangrenosum and erythema nodusom(6,7) Epidemiologic studies have shown a slight female predominance in CD, perhaps due to hormonal effects. In contrast, UC predominantly affects males(1).

Although the etiology of IBD is not well identified, genetic susceptibility, environmental factors, and a dysregulated immune response to bacterial antigens appear to play a role in its development(8-10). Treatment of IBD depends on disease location and severity. Currently, the primary goals of treatment are to induce and maintain clinical remission. Medical therapy for IBD comprises oral and topical

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5-aminosalicylate preparations, corticosteroids and immunomodulators, as well as biological therapies. Over the last decade, the clinical efficacy of probiotics in IBD is evident and numerous clinical trials have provided new insights into the role of probiotics for inducing and maintaining IBD remission.

In this paper, we present a thoroughly updated review of the best assessed medical agents for IBD treatment.

MEDICAL TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

I. Aminosalicylates and corticosteroids

Combined treatment with aminosalicylates and corticosteroids can be used to induce and maintain remission in IBD patients. The combination of topical steroids with topical salicylates is more efficacious than either, alone, in the treatment of distal UC(11). Foam preparations are more tolerable and may be easier to retain(12).

Mesalamine enemas should be used at bedtime in order to retain them for at least eight hours, but suppository preparations should be administered two to three times daily with the goal of retention for at least three hours. Topical treatments should continue for at least three to six weeks(13).

Topical budesonide is of comparable efficacy to prednisolone enemas(14)mesalamine enemas(15) and systemic corticosteroids(16)in the treatment of distal UC, however, rectal 5-aminosalicylic acid (5-ASA) is significantly better than conventional rectal glucocorticoids for inducing clinical, endoscopic, and histologic remission. Budesonide enemas should generally be reserved for patients who fail 5-ASA enemas(17).

In patients with mild-to-moderate active UC who do not respond to or tolerate topical therapy, oral sulfasalazine results in 60%-80% response rates. The dose is 4 g/day, usually divided into three to four doses. Newer 5-ASA formulations have similar efficacy in UC with fewer adverse reactions. Olsalazine can be prescribed at a dose of 800 mg/TDS, and balsalazide should be administered at a dose of 2250 mg/TDS(18).

Combination therapy with oral and topical 5-ASA appears to be appropriate in UC cases that have extensive colonic involvement beyond the left colonic flexure. The combination of oral mesalamine (2.4 g/day) and a mesalamine enema (4 g/day) is shown to be more effective in achieving clinical improvement, as well as an earlier response, than either agent alone(19).

The efficacy of salicylates in CD is less prominent, with a modest efficacy at best in controlled trials. However, some studies have demonstrated that both olsalazine and balsalazide (with higher doses than those prescribed in UC) are more effective than placebo in inducing remission in patients with CD colitis. There is no obvious benefit of 5-ASA therapy in maintenance treatment of CD. Mesalamine may be recommended for maintaining remission of quiescent CD, however the benefit is mainly observed in the postsurgical setting, in patients with ileitis, and those with prolonged disease duration(20).

Corticosteroids including hydrocortisone and prednisolone are the mainstay of treatment inactive IBD. The initial dose of prednisolone is between 40-60 mg/day; higher doses are not effective(21). Compared with sulfasalazine (8 mg/day), prednisolone (40 mg/day) has been shown to have a higher remission rate in patients with moderate-to-severe UC(22). The steroid dose should be tapered after two weeks; for prednisolone, a tapering range between 5 mg/week or 10 mg every ten days seems to be appropriate. Steroids are not effective in maintaining remission in UC and CD(23).

Hospitalized patients with severe disease can be treated with 300 mg/day of hydrocortisone administered intravenously in three divided doses. Intravenous therapy usually results in rapid improvement of symptoms and should be administered for six to eight days to achieve maximal benefits(21). Oral budesonide is ineffective in patients with distal UC (18), but a dose of 9 mg/day (instead of a systemic steroid) is useful for inducing remission in mild-to-moderate ileocecal CD. One study has demonstrated that controlled ileal release (CIR) budesonide is more effective than mesalamine for induction of remission in patients with ileocolonicCD(24).The efficacy of budesonide is comparable with prednisolone for inducing remission in active CD(25).

II. Immunomodulators

II-A. Azathioprine (AZA) and 6-mercaptopurine (6-MP)

In order to withdraw steroids in patients with steroid-dependent or steroid-refractory CD and UC, AZA and its metabolite 6-MP have been used since

the early 1970s. The onset of the full effects of AZA and 6-MP may not become apparent for up to three months(26,27).

Data supporting the use of AZA/6-MP for remission induction in patients with UC are limited. (28) However, their steroid sparing effects in patients with steroid-dependent UC is well established. Generally, thiopurines should not be used for induction of remission in active UC patients(29).

In a recent study, AZA was found to have similar long-term efficacy for both UC (42%) and CD (49%) patients(30). Generally, it appears that AZA is at least as effective in UC as in CD patients(28). The initial dosage of AZA is 1.5-2.5 mg/kg/day; for 6-MP, it is 1-1.5 mg/kg/day(31). It is reasonable to obtain a complete blood count with differential every two weeks during the initial phase of treatment in patients with active disease and every three months in patients on maintenance therapy(32). Drug-induced pancreatitis usually occurs during the first four weeks of therapy in up to 3% of patients(33). Pancreatitis is a contraindication of continuing these agents(34).

The risk of lymphoma is increased in IBD patients treated with AZA/6-MP(35) although benefits probably outweigh the risk of lymphoma(36).

II-B. Methotrexate (MTX)

Methotrexate was first used for cancer treatment in 1948. The efficacy of MTX injections has been effective in maintaining remission in adults with steroid-dependent CD(37). There are a few retrospective studies on MTX efficacy in UC patients. Wahed et al. have reported a clinical response rate of 60% in UC patients intolerant or non-responsive to AZA/MP who were treated with MTX(38).

However, the results of studies on MTX therapy in UC patients are heterogeneous. According to these evidences, MTX is not recommended for inducing and maintaining remission in UC(29). MTX is administered weekly by intramuscular injections of 15-25 mg.

The most common side effects of MTX include leucopenia, hypersensitivity interstitial pneumonitis, hepatic fibrosis, stomatitis and opportunistic infections(39). A baseline chest x-ray should be obtained. Occurrence of hepatic fibrosis in patients with concomitant alcohol abuse and/or obesity is more likely, thus MTX should not be administered in these patients.

II-C. Cyclosporine A (CsA)

Cyclosporine A is a calcineurin inhibitor which is used as a potent immunosuppressive agent in organ transplantation. Approximately 25% of fulminant UC patients are considered to be steroid-refractory as they are unresponsive to five-to-seven days of treatment with IV steroids(40). Several uncontrolled (41,42) and controlled trials (43) have shown the efficacy of CsA as a short course rescue-therapy in steroid-refractory patients with UC. In such patients, intravenous administration of CsA may preclude surgery. A recent trial has evaluated patients who failed a minimum five days of treatment with IV methylprednisolone at the daily dose of at least 0.8 mg/kg. Patients were randomly assigned to therapy with either CsA (2 mg/kg/day) for one week followed by switching to oral formulation during 98 days or three infusions of infliximab (5 mg/kg) administered at weeks 0, 2 and 6. The primary endpoint was treatment failure defined as either absence of clinical response at day 7, absence of remission at day 98, relapse between days 7 and 98, or severe adverse events that necessitated treatment discontinuation, colectomy, or death. This study enrolled 115 patients: 58 received cyclosporine and 57 received infliximab. There were similar rates of treatment failure observed between the CsA (60%) and infliximab (54%) groups (p=0.49). There were 10 severe adverse events reported in 9 patients who received CsA and 16 events in those who received infliximab, however there were no fatalities observed in either group(44).Despite the proven short-term efficacy of CsA at inducing remission in acute severe UC, the long-term efficacy remains undetermined(?) (45). Therefore, CsA is used as a bridge to AZA/6-MP(43).

Cyclosporine A has not been proven efficacious in luminal CD, but it is effective for treatment of fistulizing CD(46). After IV cyclosporine A, oral cyclosporine A should be continued for a few months, concomitant with a tapering dose of steroids, AZA/6-MP and prophylaxis against Pneumocystis carinii by oral trimethoprim-sulfamethoxazole or inhaled pentamidine(40).

Potential adverse effects of CsA include nephrotoxicity, hypertension, seizures, opportunistic infections, peripheral neuropathy, colonic perforation, anaphylaxis, hirsutism and headaches(47).Predisposing factors for seizures in patients treated with CsA are hypomagnesemia, hypercholesterolemia, hypertension

and a high plasma concentration of CsA(48).

II-D.Tacrolimus (FK506)

Tacrolimus is a macrolide antibiotic isolated from Streptomyces tsukubaensis with potent immunomodulating properties. Its immunosuppressive effects are greater than those of CsA. There are some open-label trials that have reported the efficacy of tacrolimus in UC patients(49,50). Although several studies have shown the short-term efficacy of tacrolimus in refractory UC, but data supporting its long-term effects are scarce(28). A recent study has reported that 62% of UC patients who achieved clinical remission with tacrolimus within 30 days did not require colectomy after 65 months(51).

An open-label study on 13 patients with CD has shown that tacrolimus improved symptoms in 11 patients after 6 months, but only one patient achieved clinical remission (52). In an uncontrolled study, combination therapy of tacrolimus with AZA improved remission rates of CD patients with perianal fistulas(53). Oral tacrolimus is effective for the treatment of fistulas but not for maintenance treatment of fistula remission(54).Topical tacrolimus is effective for the treatment of oral and perianal CD(55).

The initial dose of oral tacrolimus is 0.1-0.2 mg/kg/day; its plasma concentration should be maintained between 5-20 ng/mL(49, 50).

Potential side effects of tacrolimus include nephrotoxicity, tremors, opportunistic infections, diabetes mellitus and gastrointestinal discomfort(56).

II-E.Mycophenolatemofetil (MMF)

Mycophenolatemofetil is an antimetabolic agent most commonly used as adjunct therapy with calcineurin inhibitors and steroids in organ transplantation(57). Mycophenolatemofetil should be administered to IBD patients who are steroid-dependent or steroid-refractory, and intolerant to other conventional therapies(58). There is no placebo-controlled trial for MMF therapy in UC patients. One study has compared the efficacy of AZA/prednisolone versus MMF/prednisolone. Induction of remission and maintenance of remission for at least one year was achieved in 9 of 12 patients in the AZA/prednisolone group and 5 of 12 patients in the MMF/prednisolone group(59). In another study, 40% of UC patients showed increased disease activity despite MMF therapy(60). A recent study on 14 patients, 9 with CD and 5 with UC, assessed the short and long-term efficacy of MMF therapy in steroid-dependent or steroid-refractory and AZA/6-MP intolerant patients. After eight weeks of therapy there was a response rate of 71%. After 12 months of therapy, 57.1% of all patients remained in remission(61).

In one study, a higher proportion of patients with severe CD achieved clinical remission when treated with MMF (70%) than when treated with AZA (30%) during the first month of treatment(62). An open-label study demonstrated that MMF therapy improved fistulas in all four CD patients(63).

II-F.Tofacitinib (CP-690,550)

Tofacitinib is a selective oral inhibitor of the Janus kinase (JAK) family of kinases, which inhibit the activity of interleukins 2, 4, 7, 9, 15, and 21(64). In vitro, tofacitinib inhibits IL-2-dependent differentiation of helper T cells (types 2 and 17)(65).

In a recent study, 194 patients with moderate-to-severe UC were assigned to either tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo twice daily for eight weeks. The Mayo scoring system was used for assessment of UC activity. Clinical response at eight weeks was seen in 32% (0.5 mg; $p=0.39$), 48% (3 mg; $p=0.55$), 61% (10 mg; $p=0.10$) and 78% (15 mg; $p<0.001$) of patients who received tofacitinib compared with 42% of those who received placebo. Clinical remission (Mayo score ≤ 2) was achieved in 41% of patients who received 15 mg of tofacitinib ($p<0.001$) compared with 10% of those who received placebo. The side effects of tofacitinibincluded increases in LDL and HDL levels and neutropenia(66).

III. Biological agents

III-A. Infliximab

Infliximab was the first TNF-blocker approved for the treatment of moderate-to-severe CD and UC patients resistant to treatment with corticosteroids or immunomodulating agents.

The drug is administered at a dose of 5 mg/kg by two-hour intravenous infusion. Standard three infusions at 0, 2 and 6 weeks should be prescribed; for maintenance of remission, repeated infusions every 8 weeks should be administered(67). Concomitant treatment with steroids, AZA/6-MP or MTX to reduce the formation of antibodies against infliximab is recommended(68). ACT-1 and ACT-2 trials have demonstrated the efficacy of infliximab in inducing

remission among patients with UC(67,69).

Infliximab therapy can decrease the frequency of acute exacerbations in approximately two-thirds of patients with moderate-to-severe CD and allows the closure of enterocutaneous fistulas in CD patients(70). Its long-term role in CD is evolving but evidence exists to support its efficacy in maintaining remission(71) and preventing fistula recurrence(72).

In the case of refractory disease despite infliximab therapy, an increase in dose to 10 mg/kg/day can be considered(68). All patients that are candidates for infliximab therapy should be tested for latent tuberculosis (TB) by the PPD test; those testing positive should receive isoniazid as prophylactic treatment. Infliximab is also contraindicated in patients with severe congestive heart failure (NYHA classes III, IV)(73).

III-B.Adalimumab

Adalimumab is a fully humanized TNF-blocker administered subcutaneously. The drug is administered as induction therapy at a dose of 80 mg followed by 40 mg at week two. To maintain remission, 40 mg is administered every two weeks. If there is no response within 4 weeks, continuation of maintenance therapy up to week 12 may be efficacious. The drug should be discontinued in patients who do not respond within that time period(74).

Adalimumab is comparable to infliximab in inducing and maintaining remission in patients with CD. It is also effective in healing anal fistulas associated with CD(75).

In a randomized double blind placebo-controlled trial, adalimumab was more effective than placebo in maintaining remission for patients with moderate-to-severe CD after 56 weeks of treatment. Improved quality of life and decreased hospitalization were also identified in that study(75).

Side effects of adalimumab include skin reactions at the injection site, sinusitis, lymphoma and nervous system inflammation (rare), and lupus-like syndrome(46).

III-C.Certolizumabpegol (CDP 870)

Certolizumab is a humanized anti-TNF monoclonal antibody. Data about the efficacy of this agent in the treatment of UC are scarce(4).

In one study, certolizumab was associated with better response rates compared with placebo at weeks 6 and 26 of induction therapy. A monthly subcutaneous injection of this agent was effective in maintaining remission in CD patients(76).

Certolizumab is administered by subcutaneous injection of 400 mg at weeks 0, 2 and 4, followed by maintenance therapy every 4 weeks(69).

III-D.Natalizumab

Natalizumab is a humanized IgG4 monoclonal antibody against α4 integrin that is effective in the induction and maintenance of remission in CD patients. It has been approved in February 2008 for the treatment of patients with refractory CD or those intolerant to anti-TNF therapy. In the ENACT-2 study, 354 patients who responded tonatalizumab in ENACT-1 were enrolled into maintenance therapy with natalizumab or placebo every 4 weeks through week 56. Natalizumab patients were more responsive (61%) compared to placebo (28%) patients. Remission rates were higher in those who received natalizumab (44%) compared to placebo (26%)(77).

The ENCORE trial was a randomized placebo-controlled trial that evaluated the efficacy of natalizumab induction therapy in CD patients. This study enrolled 509 patients diagnosed with moderate-to-severe CD. Patients were randomly assigned to receive natalizumab (300 mg) or placebo intravenously at weeks 0, 4, and 8. The primary goal was to induce a ≥70-point reduction in the Crohn's Disease Activity Index at week 8, maintained through week 12. The response rate at week 8 sustained through week 12 was 48% in the natalizumab group and 32% in the placebo group ($p<0.001$). Sustained remission occurred in 26% of natalizumab-treated patients and 16% of the placebo group ($p=0.002$)(78).

One of the most concerning side effects of this agent is the reactivation of latent human JC polyomavirus that can lead to progressive multifocal leukoencephalopathy(79).

IV. Additional Treatments for inflammatory bowel disease (IBD)

IV-A. Probiotics

Due to clear evidence addressing intestinal epithelial-mucosal immune interactions and the critical role of enteric bacteria in the development of IBD, probiotic treatment of IBD has been extensively studied.

Probiotics are a mixture of putatively beneficial

lyophilized bacteria that are administered orally. The role of these agents for treatment of IBD requires further evaluation(80).

Two open-label studies by Bibiloni et al. and Tursi et al. have demonstrated a beneficial therapeutic effect of the VSL#3 probiotic-mixture in inducing remission for UC patients(81,82).

In a recent study, 144 patients with mild-to-moderate UC were assigned to either VSL#3 or placebo , concomitant with standard maintenance treatment. No significant difference in achieving clinical remission was observed, however there was a significant clinical response in the VSL#3 group(82).

Fujimori et al. assessed the effect of Bifidobacteriumlongum on the quality of life of 120 UC patients who were in remission or had mild active UC. These patients were randomly assigned to either probiotics (2×109 CFU of Bifidobacteriumlongum), prebiotics (8 g of psyllium) or their combination (symbiotics). After four weeks of treatment there was no improvement in quality of life as assessed by IBDQ (Inflammatory Bowel Disease Questionnaires) scores of patients in the pre- or probiotic groups, however there was a significant improvement in the symbiotic group(83).

There are no reported randomized controlled trials of probiotics for induction of remission in CD patients. A small randomized controlled trial on patients with CD in remission showed that the S. boulardii treatment group remained in remission with improvement in their abnormal intestinal barrier function(84).

In 2008, one study reported that administration of VSL#3 at various times after ileal pouch anal anastomosis compared with placebo was associated with slight, but significant reduction inPouchitis Disease Activity Score in patients without acute pouchitis(85).

IV-B. Thalidomide

Thalidomide can inhibit TNF-α production and stabilize lysosomal membranes. A recent study enrolled 12 male patients who had CD Activity Index (CDAI) scores of ≥250 or ≤500 despite administration of ≥20 mg/day prednisolone. Patients were assigned to receive 50 mg/day or 100 mg/day thalidomide. Disease activity improved in all patients during weeks 1-4 with a response rate of 58%. Clinical remission occurred in 17% of patients. Maintenance of remission was also achieved during weeks 5-12(86).

INDICATION FOR SURGERY IN INFLAMMATORY BOWEL DISEASE (IBD)

Indications for surgery in IBD are categorized into two groups: emergent and elective. Developments in medical management of IBD have reduced the need for emergency surgery due to disease complications(87). Indications for surgery in UC and CD are as follows:

Elective surgery:

1. Lack of response to high-dose corticosteroid therapy.
2. Recurrence of symptoms upon cessation of corticosteroid therapy.
3. Disease progression under maximal medical therapy.
4. Significant treatment-related complications such as severe steroid or infliximab side effects.
5. Dysplasia or cancer in patients with long-standing colitis observed during endoscopic surveillance.
6. Suspicion of a malignant stricture or fistula in patients with CD.

Emergency surgery:

1. Acute exacerbation of the disease in cases unresponsive to rescue therapy such as intravenous steroids, cyclosporine A, or infliximab.
2. Acute complications such as massive hemorrhage, perforation, fulminant colitis, toxic megacolon, and acute colonic obstruction.

MANAGEMENT OF TOXIC MEGACOLON

Toxic megacolon represents a catastrophic complication of IBD. The main characteristics of toxic megacolon are signs of systemic toxicity and severe colonic distension. Medical therapy is the first line of treatment for patients with IBD and toxic megacolon, however management of toxic megacolon requires close collaboration between gastroenterologists and surgeons from the onset(88).Medical therapy can prevent surgery in up to 50% of patients(89) and includes fluid resuscitation and correction of laboratory abnormalities, administration of broad spectrum antibiotics, intravenous corticosteroids, complete bowel rest, and bowel decompression with a nasogastric or long intestinal tube.

I. Corticosteroids

For the treatment of toxic megacolon due to IBD we can use Hydrocortisone (100 mg) or its equivalent every six-to-eight hours or by continuous infusion which should be given to all patients for the treatment of underlying UC or CD; this does not increase the risk of perforation (90). Dexamethasone has been shown in experimental studies to decrease the colonic diameter by diminishing the expression of inducible NO synthase(91). Some clinicians prefer to use methylprednisolone because of its lower sodium retaining and potassium wasting properties, while others prefer prednisolone since the parenteral dose is equal to the oral dose.

II. Cyclosporine

Some reports indicate that cyclosporine may be useful in the treatment toxic megacolon or of severe colitis refractory to steroid therapy. The experience in toxic megacolon is limited. Although further studies are needed, cyclosporine therapy may obviate the need for an urgent colectomy(92).

III. Additional therapies

Some experimental therapies may help patients with toxic megacolon to avoid surgery. A case report has shown the successful effect of infliximab (an anti-TNF- α monoclonal antibody) in the treatment of toxic megacolon in a patient whose condition failed to respond to usual treatment and refused surgery(93,94).

Leukocytapheresis (LCAP) has been reported to be effective against toxic megacolon. A series of six patients whose conditions failed to improve after treatment with antibiotics and high-dose steroids received LCAP sessions three times per week for two weeks, followed by four sessions over the next four weeks. After completion of therapy, four patients showed improvements in their toxic megacolons. In two patients, the toxic megacolon resolved approximately 40 hours after treatment. Improvement continued in four of the six patients(95).Hyperbaric oxygen has also been reported to be of use in the treatment of toxic megacolon(96)however further studies are needed to confirm these results.

Shetler et al. have demonstrated that colonoscopic decompression and intracolonicvancomycin administration in the management of severe, acute, pseudomembranous colitis associated with ileus and toxic megacolon was feasible, safe and effective in approximately 57%-71% of cases(97).Tacrolimus has been successfully used in one case study in a patient with steroid-refractory UC complicated by a toxic megacolon. Further studies are needed to validate its use(98).

PERSPECTIVES IN INFLAMMATORY BOWEL DISEASE (IBD)

In recent years, quality improvement (QI) and quality assurance (QA) have become debating subjects in gastroenterology clinical practice and medicine. Quality improvement in IBD patients should focus on prevention of osteoporosis and osteopenia, infection and dysplasia or colorectal cancer(99).

I. Osteoporosis and osteopenia

Patients with IBD are at increased risk for developing osteoporosis and osteopenia; about 15% of patients with IBD also have osteoporosis(100). According to current guidelines, American Gastroenterological Association (AGA) recommends screening BMD testing for high-risk patients. Risk factors for osteoporosis have been identified and include a course of steroid therapy longer than three months or recurrent use of steroids, age >50 years, postmenopausal status, history of low-impact fracture and hypogonadism(100). However, despite these recommendations and their validation in a prospective cohort, only 23% of patients with risk factors at a representative tertiary institution were tested(101).

II. Vaccinations

Using immunosuppressive agents in the management of IBD may increase the risk of infection, therefore vaccinations are important(102,103). Appropriate routine vaccinations are recommended by the Advisory Committee for Immunization Practices (Table 1)(99,104,105). Consideration of vaccination at the initial visit could allow for safe vaccination before initiation of an immunosuppressive therapy. Many common vaccines such as hepatitis A virus, hepatitis B virus (HBV), pneumococcal, injectable influenza, and human papilloma virus are recommended for individuals on or under consideration for immunosuppressive regimens.

CONCLUSION

Inflammatory bowel disease is a multifactorial disease. Genetic susceptibility, environmental

Table 1: **Recommended vaccine schedule.**

Vaccine	Cohort
Influenza	All patients >50 years old with inflammatory bowel disease (IBD). Chronic liver disease, celiac disease,or immunosuppressed.
Pneumococcus	All patients >65 years old, with IBD,Chronic liver disease, celiac disease, or immunosuppressed.
Herpes zoster	All patients >60 years old, contraindicated in immunosuppressed patients.
Varicella zoster virus	All patients with IBD if no prior infection. Contraindicated in immunosuppressed patients.
Hepatitis A	Patients with chronic liver disease or IBD.
Hepatitis B (HBV)	Patients with chronic liver disease, or IBD.
Human papilloma virus	Males and females up to age 26 years.

elements and dysregulated immune response may be contributed to its pathogenesis.

Treatment of IBD has several aims which include improvement of symptoms, induction of remission, maintenance of remission, healing of fistulaes and avoidance of emergency surgery.

Medical treatment of IBD is composed of anti-inflammatory drugs (5-ASA preparations and corticosteroids), immunomodulating agents (such as AZA, MTX, and cyclosporine), biologic agents (infliximab and adalimumab) and other agents for symptom relief. The role of 5-ASA preparations in maintenance therapy of CD is limited. Frequent relapses should be treated with immunomodulators. Infliximab is especially useful for treating fistulaes associated with CD.

Adjunct treatment with probiotics may be useful in induction and maintenance of remission in UC patients.

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