

MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

Pages with reference to book, From 162 To 167

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Since the definite etiology of inflammatory bowel disease, (Crohn's Disease and ulcerative colitis) is not yet known, the management of both these diseases is largely empirical and symptomatic. Both these diseases exhibit natural periods of remission and relapse, so many controlled trials have been essential to determine the true value of any therapeutic agent. Crohn's disease and ulcerative colitis are both different with regard to pathology, clinical course and response to medical and surgical therapy. An attempt is made to discuss the management of both these diseases separately but there may be considerable overlap in the treatment aspects.

Management of Crohn's disease

Medical treatment: The medical management of Crohn's disease involves:

1. General supportive measures including symptomatic therapy.
2. Treatment with anti-inflammatory drugs and immunosuppressive agents.
3. Management of nutritional status including enteral and parenteral feeding.
4. Treatment of complications and specialized problems and surgical treatment.

1. General supportive measures:

The patients have to be managed individually as they present with different manifestations. The disease activity can be assessed by the presence of inflammatory symptoms and signs, fever, night sweats, abdominal tenderness, supported by laboratory findings of increased WBC count, raised ESR, faecal leukocytosis, an increase in faecal alpha 1 antitrypsin, and radiographic and endoscopic evidence of mucosal oedema and ulceration.

Rest: This is of considerable value when the disease is active. But as the disease remits normal daily routine of life should be resumed.

Diarrhoea: Diarrhoea is effectively treated with codeine, lomotil or loperamide with concomitant decrease in abdominal cramps. If more potent analgesia is required then complication like obstruction, bowel perforation or abscess formations should be thought and surgical consultation should be sought early.

Anaemia: Anaemia may respond to oral iron. Sometimes due to mucosal problems involving the duodenum and upper small intestine, oral iron may not be absorbed and parenteral therapy may be necessary. Macrocytic and megaloblastic anaemia is due to vitamin B12 and folate malabsorption and require specific therapy. Patients who have had previous operations and with severe disease of the terminal ileum should not take high fibre foods because that might precipitate intestinal obstruction. The possibility of lactose intolerance should be thought since acquired lactase deficiency may occur in Crohn's disease¹ or it may already be present and is precipitated by the disease activity. Generally a good nutritious and appetizing diet should be advised.

2. Anti-inflammatory and immunosuppressive agents:

Sulphasalazine: Sulphasalazine has been widely used as a therapeutic agent in the management of Crohn's disease². Its use was widespread in the treatment of ulcerative colitis and because of its relative safety in long term use, considerable interest arose in early 70s regarding its use in the treatment of Crohn's disease, several studies approved its benefits in treating Crohn's disease³⁻⁸. Sulphasalazine is an azo bond conjugate of 5-aminosalicylic acid (5ASA) and sulphapyridine. The potent anti-inflammatory effect is provided by the 5ASA component whereas the sulphapyridine acts as a carrier^{2,9}. During upper intestinal transit the sulphasalazine is protected by the presence of the Azo-bond. Cleavage occurs in colon⁸ but in Crohn's ileitis, the cleavage may occur in distal ileum too.

Blood levels of 5ASA are low compared with suiphapyridine. Patients who are genetically slow acetylators develop higher blood levels and show greater adverse reactions to sulphasalazine⁹⁻¹¹. The patients who have undergone prior surgical treatment show very little or no response to sulphasalazine. Doses as high as 1 GIKg showed a definitive effect over placebo for patients with active disease of the colon or ileocolitis⁶, but those with isolated small bowel disease showed no effect. For patients with quiescent or surgically resected disease sulphasalazine appears to have no significant role¹²⁻¹⁴. It is recommended as the initial treatment in patients with mild to moderate disease and in acutely ill patients with steroids. To start with the dosage of sulphasalazine should be low (500mg BD) and then increased to full 2-3 gm daily over a week's time. It should be continued for a period of 3 months before considering the patient unresponsive to the drug. After remission, the drug should be continued for several months. The most common side effects are dyspeptic symptoms, nausea, vomiting and generalised headaches¹⁵ which are noted when 4-6G are used daily¹³. Male infertility due to decreased sperm count and immotility has been reported, which is reversed on discontinuation of the therapy¹³. Haemolytic anaemia and leukopenia are often idiosyncratic reactions which require cessation of therapy. Combination of sulphasalazine and prednisolone is less effective than prednisolone alone in the treatment of acute Crohn's disease^{14,15}. Unlike ulcerative colitis, sulphasalazine has been of no benefit in maintaining remission in Crohn's disease regardless of disease distribution,^{6,16,17} because a 25-40% flare up rate was reported at land 2 years irrespective of the use of drug or placebo⁶.

Corticosteroids:

For patients with active, acute disease, corticosteroids are the single most valuable therapeutic agent. For severely ill patients, especially those with features of intestinal obstruction, the intravenous route may be preferable. Nearly two decades ago it was reported that prolonged use of prednisolone in a dosage of 30-60mg showed a good response in 40-65% patients,¹⁸ further studies have clearly shown the benefits with both prednisolone and methylprednisolone in suppressing small bowel Crohn's disease.^{6,16,18} Low dose steroids showed no benefit in maintaining remission or postoperatively after excision of all diseased bowel for recurrence^{16,19}. In mild to moderate disease a trial of sulphasalazine should be given even in those with Crohn's ileitis for 7-10 days. Non-responders should be given 40-60mg of prednisolone/day for 7-15 days. Though response varies but the general condition of the patient starts to improve within 24 to 48 hours though it may take 2-4 weeks for a definitive remission. A common problem is flare up of disease on tapering doses of steroids; remission in these cases can be brought about by increasing the dose of steroids. If this becomes a common problem then addition of immunosuppressive agents or surgical intervention may be required. Minor side effects like moon faces, acne, and ecchymosis is noted in 50%, 35% and 15% cases respectively⁶ while major side effects like hypertension, peptic ulcer and acute psychosis requiring reduction of dose or cessation occurred in 32% cases.

Immunosuppressive Therapy:

Azathioprine and 6-mercaptopurine are often used in the treatment of Crohn's disease. Brooks and coworkers showed with much controversy in the use of these drugs²⁰. Three studies, failed to show any benefit of Azathioprine in patients with active acute Crohn's disease²¹⁻²³ while others suggested a prophylactic role of the drug remission^{2,24}. The efficacy of 6 Mercaptopurine in active disease was reported in 1980²⁵, and it was found more effective in closing fistulas and in permitting discontinuation or reduction of steroid dosage than that with placebo. The onset of response to 6 Mercaptopurine was often delayed with 32% cases requiring more than three months to respond and 19% requiring more than four months. Adverse side effects seen in 10% patients were uniformly reversible. Azathioprine has been generally accepted as a drug which has steroid sparing effect in patients who need large doses of corticosteroids over a prolonged period. The dose of 6 MP ranges between 1.5-3 mg/kg daily for a

minimum of six months with close attention to potential toxicities. NCCD trial showed serious side effects to Azathioprine in 16% cases requiring withdrawal of the drug⁶. The most serious side effect was bone marrow suppression and pancreatitis. There is a higher risk of lymphomas in patients taking immunosuppressive agents²³.

Metronidazole

It is potentially useful in patients with Crohn's colitis especially those with perianal Crohn's²⁶. In a comparative study of metronidazole 800mg/day and sulphasalazine 3g/day for active Crohn's disease, it was reported that in those patients who failed or showed inadequate response to sulphasalazine showed significant improvement on crossing over to metronidazole. The side effects of metronidazole are minor like anorexia, nausea, metallic taste; peripheral neuropathy is more troublesome and dose related.

Newer Agents

5 ASA compounds are being evaluated in the management of Crohn's disease though presently they are effective in treating ulcerative colitis²⁷.

Complicated problems and their management Perianal Crohn's disease:

For symptomatic benefit measures like sitz bath and the application of cleansing agents may be useful. Metronidazole²⁸ in a dose of 20 mg/kg/day was successful in healing chronic perianal Crohn's disease but in 10 of 18 patients discontinuation of treatment resulted in relapse²⁹. 6-MP in a dose of 1.5 mg/kg/day healed 15 of 41 fistulas completely but fistulae relapsed on discontinuation of the therapy. Surgical intervention may be helpful for local abscesses or resistant perianal fistulas.

Short bowel syndrome

Appropriate diet with the bulk of calories from complex CHO and restriction of fats is helpful. Electrolyte imbalance must be corrected and fat soluble vitamins if necessary may be given parenterally. If less than 100cm of bowel is resected or damaged choloretic diarrhoea results which is secretory due to unabsorbed bile salts being discharged into the colon. This type of diarrhoea responds to cholestyramin in a dosage of 4-16 g/day due to its binding action with bile salts. If more than 100 cm of the small bowel is resected or damaged then in addition to bile salt diarrhoea significant malabsorption of fats occurs resulting in decrease in micellar concentration of bile salts, therefore medium chain triglyceride therapy is helpful

Acute intestinal obstruction:

Decompression of the duodenum by a nasogastric tube and suction every 12 hours alongwith replacement of electrolytes and intravenous infusions should be started soon. Relief may be obtained after 12 hours NPO (Nil Per Oral) and this should be followed by clear liquids and then soft foods may be started which contain little fiber. Intravenous steroids should be given as a single dose of 40 to 60 mg prednisolone.

4. Nutritional review

It is not always easy to maintain adequate nutritional status in patients with Crohn's disease, particularly when there is extensive resection or damage to greater lengths of terminal ileum. Deficiencies of specific nutrients like calcium, iron, vitamin D, vitamin K, vitamin B12 and folic acid, should be replaced. Parenteral vitamin B12 should be administered to all patients with abnormal schilling tests following ileal resection. MCT (Medium Chain Triglycerides) are better absorbed especially in malabsorption due to poor bile salt absorption. Large quantities of fat if eaten at breakfast from the recommended allowance are better absorbed than at other times. In situations of bile salt diarrhoea cholestyramine or aluminumhydroxide would be useful agents to use. However steatorrhoea may get worse. The use of artificial nutritional programmes with reasons to "rest" the bowel, allowing fistulas to heal inducing positive nitrogen balance and even causing weight gain are proving very useful Total parenteral hyperalimentation is very beneficial for patients with extensive bowel resection and in patients with extensive acute disease. It helps in conditions such as growth retardation.

5. Surgical intervention

The indications for surgery include:

Medical failure like uncontrolled symptoms and excessive toxicity of drugs or complications like bowel obstruction, complex fistulae, abscess, perforation, toxic megacolon, uncontrolled perianal disease, massive haemorrhage and cancer. In a long term study of 615 patients those with isolated small bowel disease had an operative incidence of 65%, ileocolic disease 91% and colonic disease 58%³⁰.

Post-operative recurrence

Post-operative recurrence is common and often requires reoperation.³¹ Those who have ileocecal disease have a higher recurrence rate (53%) than those with colonic or small bowel disease (45%).

Management of ulcerative colitis:

The management of ulcerative colitis involves almost the same therapeutic approach as in Crohn's disease, and involves the control of bowel inflammation and alleviation of symptoms. As the proctosigmoiditis generally stays localised conservative localised medical treatment is usually quite appropriate. Surgical treatment in ulcerative colitis is definitive. The extent of the disease and the duration of illness, especially with pancolitis, and if the activity of the disease extends beyond the first decade, emphasizes the need for appropriate surveillance programmes. Specialised problems like delays in growth, toxic megacolon, extra intestinal manifestations like pyoderma gangrenosum need attention and sound therapeutic approach. Drugs that are used for Crohn's disease are also used for ulcerative colitis, except that for limited left sided disease, in addition to oral preparations, some medications are applied rectally and are administered either in suppository or enema form.

Specific drug therapy

Sulphasalazine:

The first report of a randomised controlled trial of sulphasalazine in ulcerative colitis was published in 1962³² showing good response of the drug. Later Truelove et al reported a comparative study of sulphasalazine and low dose prednisolone and hydrocortisone retention enemas used in combination³³. Response to steroids was more prompt. Sulphasalazine was effective in preventing relapse in 24 of 34 patients who were treated with 2 gm/day for a year with only 8 of 33 patients given placebo³⁴. Prophylaxis beyond one year with continuous use of sulphasalazine has been studied with conflicting reports, in one study there was no significant benefit beyond one year over placebo³⁵. Whereas 18 months of prophylaxis proved beneficial in 4 of 33 patients given sulphasalazine compared to 7 of 31 given placebo³⁶. The optimum maintenance dose was studied in 1980³⁷ and a daily dose of 2gm was found to be more efficacious than one gram and a daily dose of 4 gm was more efficacious than 2gm but at the risk of fairly frequent side effects. Haematological abnormalities were seen at all doses but they mostly occurred when doses of over 4 gm/day were used or who were slow acetylators. To avoid frequent side effects the initial dose should be low, gradually increased to therapeutic ranges of 3-6 gm/day. When used as a single agent it is acceptable for mild to moderately active ulcerative colitis. For acutely ill patients it should not be used alone. The maintenance dose of 2 gm/day needs to be established by tapering the dose once remission is obtained with maintenance therapy continued for a year or more. Sulphasalazine may be given in enema form for localised distal disease with satisfactory results.

Corticosteroids

In acute ulcerative colitis the use of corticosteroids is mandatory. The combination of oral prednisolone and rectally administered steroids was found to be superior to sulphasalazine alone.³⁸ Prednisolone is the most frequently used steroid, response is generally rapid and gradual tapering is advised. Optimal dosage is difficult to predict but in acutely ill patients an initial dose of 40-60mg prednisolone is suggested. Long term prophylactic prednisolone has not been shown to be effective in preventing relapse in patients who are in remission³⁹. Intravenous ACTH given in a dose of 20-40 units over a

period of 8 hours for an initial course of 5-10 days is equal in effect to 300mg of hydrocortisone given intravenously over eight hours. Prednisolone or hydrocortisone appears to be superior to ACTH in patients who have had previous treatment with oral steroids whereas Meyers et al suggested that ACTH is superior to corticosteroids in a group of patients who have not received recent corticosteroids⁴⁰. For left sided colitis alone topical corticosteroids are beneficial particularly for proctitis and/or proctosigmoiditis. Various preparations of hydrocortisone and prednisolone are available. The enema form of corticosteroid is best administered at bed time and retained for at least 2 hours preferably overnight. Systemic absorption is variable but as the duration of therapy is generally short, systemic side effects are often not readily seen with topical steroids. Suppository and enema preparations are better tolerated but reach only to the distal sigmoid. Complications that respond readily to steroids include arthritis, iritis, uveitis alongwith skin manifestations of ulcerative colitis. The treatment of fulminant acute ulcerative colitis includes parenteral fluids, electrolytes and nutrition, intravenous prednisolone 60mg daily, and broad spectrum antibiotic coverage after taking blood and stool cultures. Nasogastric suction may be helpful. Anticholinergic drugs are dangerous in patients with fulminant disease because of a fear of precipitating toxic megacolon.

Immunosuppressive agents

A trial of immunosuppressives is reasonable in those requiring steroids who refuse surgery or who are at poor surgical risks. Azathioprine in a dose of 2.0 to 2.5 mg/kg/day over 6 months provide a steroid sparing effect in chronic ulcerative colitis. But as the disease is precancerous in patients with pancolitis and with a disease duration of more than 10 years and since the use of immunosuppressives also increases the chance of malignancy, the routine use of these drugs in ulcerative colitis is not advised.

Sodium Cromoglycate:

In a double blind multicentre study the efficacy of sodium cromoglycate 600 mg/100ml enema was compared with prednisolone 20 mg/100 ml enema⁴¹. A significant decrease in symptoms was noted in both at 4 and 8 weeks with a significantly greater reduction in rectal bleeding after 4 weeks in the prednisolone group. Sigmoidoscopy and histology of the rectal biopsies showed no significant difference. Cámpieri et al demonstrated that 5ASA enemas were more effective than hydrocortisone enemas for the treatment of mild to moderate distal colitis⁴². Olsalazine was tried on patients intolerant to sulphasalazine in a double blind randomised trial⁴³. Overall 35% patients receiving olsalazine improved clinically compared to 16% of those receiving placebo. Olsalazine sodium consists of 2 salicylate radicals linked by an Azo bond. When ingested orally it undergoes minimal small bowel absorption. The Azo bond is split in the colon releasing 2 radicals of 5ASA that would then exert local therapeutic effect. This drug may represent a therapeutic advance especially for those patients who cannot take sulphasalazine.

Ulcerative proctitis and proctosigmoiditis

Oral sulphasalazine and local corticosteroids are the main therapeutic agents. Sulphasalazine should be prescribed in small doses of 500mg twice daily and increased to 2-4 gm/day for therapeutic response and then tapered to about 2 gm/day as a maintenance dose. Hydrocortisone enemas are given twice daily. The newer preparations of 5ASA can be used instead of sulphasalazine or in patients showing side effects to the parent compound. Oral prednisolone may be tried for short periods in patients whose disease cannot be controlled with oral sulphasalazine and local steroids.

Mild and moderate colitis

When patients present with diarrhoea, intermittent abdominal pain and tenesmus but without signs of toxicity oral sulphasalazine and hydrocortisone enema should be started in addition to oral prednisolone in a dose of 40-60 mg/day. After the response, steroids should be tapered. Sulphasalazine should be continued for one year or more to maintain the remission. Initial hospitalization can be of benefit in these patients.

Severe colitis

Fever, leucocytosis, abdominal pain, frequent bloody bowel movement and general acute toxicity suggest active acute severe disease. Hospitalization of these patients is indicated for intravenous hydration, parenteral nutrition and intravenous steroids. Before intravenous steroids, complications like perforation should be excluded. If the patient shows no signs of improvement after 5-7 days of intensive medical therapy, operative intervention should be considered. Proctocolectomy is curative in ulcerative colitis and if ileoanal anastomosis is performed it will be more acceptable to the patient and ileostomy is avoided.

Pregnancy and inflammatory bowel disease

Patients with ulcerative colitis who become pregnant have prospects of a normal child except if the patient is ill enough to require operation during pregnancy as this runs a considerably increased risk. But in Crohn's disease higher abortion rates (10-25%) have been reported. About half of the patients with known ulcerative colitis at conception may have a flare up of symptoms during pregnancy. Women with quiescent disease do somewhat better than the patients with active disease. Recurrence tends to be more frequent during the first trimester and the immediate postpartum period. Patients who first developed the disease during pregnancy or postpartum period run a greater risk. Overall about half of the patients may have a relapse during the postpartum period. The use of prednisolone in a dose 2W40 mg to control symptoms and sulphasalazine in a maintenance dose of 2 gm/day is generally considered safe. Sulphasalazine should, if possible, not be used in the last trimester of pregnancy because it can cause kernicterus in the fetus. Azathioprine and 6 mercaptopurine cause fetal abnormalities and should not be used. Again the patient needs to be informed about the potential hazards and risks of all drugs during pregnancy and if the use is a must and unavoidable then certainly they should be used.

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