Antimicrobial therapy of inflammatory bowel disease: Implications for pathogenesis and management

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RB SARTOR. Antimicrobial therapy of inflammatory bowel disease: Implications for pathogenesis and management. Can J Gastroenterol 1993;7(2):132-138. Universally accepted indications for the use of antibiotics in inflammatory bowel disease include treatment of septic complications such as abscesses, bacterial overgrowth and toxic megacolon. The role of antibiotics as primary or secondary therapeutic agents for active intestinal inflammation is more controversial. Tetracycline, trimethoprim-sulphamethoxazole and ampicillin are used empirically by some experienced clinicians as alternatives to corticosteroids in patients with Crohn's disease but have not been subjected to well designed clinical trials. Only anecdotal reports suggest a benefit of broad spectrum antibiotics and bowel decontamination in patients with active ulcerative colitis. However, metronidazole (10 mg/kg) is equal to sulphasalazine and superior to placebo in well designed studies of patients with active Crohn's disease, with a particular benefit to those patients with colonic involvement. High dose metronidazole (20 mg/kg) is widely used for perianal complications of Crohn's disease, although its utility has never been documented by controlled trials. Reduction of luminal bacterial concentrations by intestinal lavage and nonabsorbable antibiotics induces remissions of Crohn's disease in uncontrolled trials but have not been used clinically. Long term use of antibiotics is tempered by the risk of complications, notably *Clostridium difficile* toxin-induced colitis with broad spectrum antibiotics and peripheral neuropathy after high dose metronidazole. The author advocates use of metronidazole 250 mg tid or qid (10 mg/kg) in patients with Crohn's colitis or ileocolitis who do not respond to sulphasalazine or 5-ASA, and treatment of perianal complications of Crohn's disease with metronidazole 500 mg tid (20 mg/kg), with immediate cessation of the drug if peripheral neuropathy occurs. (*Pour résumé, voir page 133*)

Key Words: *Antibiotics, Crohn's disease, Metronidazole, Therapy, Ulcerative colitis*

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ANTIBIOTICS AND OTHER APPROACHES to decrease luminal bacterial concentrations are frequently used for therapy of inflammatory bowel disease (IBD). However, their use remains controversial because of the paucity of rigorously controlled trials, which forces the clinician to rely on personal experience and empiric observations rather than objective evidence of efficacy. This controversy was the subject of a recent debate in which the participants expressed conflicting opinions concerning use of antibiotics as primary therapy in IBD, but reached a consensus in several areas (1). Antibiotics are clearly indicated for the frequent septic complications of IBD (Table 1), bowel preparation before elective surgery, before colonoscopy in patients with cardiac valvular abnormalities and for inflamed ileal pouches following ileal pouch-anal anastomosis (pouchitis). Although never subjected to placebo controlled trials, most clinicians agree that long term metronidazole 20 mg/kg is beneficial for two thirds of patients with perianal complications of Crohn's disease although toxicity is substantial (2). The controversy concerns the use of antibiotics and other antimicrobial modalities to

Traitement antimicrobien de la maladie intestinale inflammatoire : impact au plan de la pathogenèse et du traitement

RÉSUMÉ: Les indications universellement acceptées pour le recours aux antibiotiques dans la maladie intestinale inflammatoire incluent le traitement de complications septiques comme les abcès, l'infection bactérienne avérée et le syndrome colectasique. Le rôle des antibiotiques comme agents thérapeutiques primaires ou secondaires pour l'inflammation intestinale active est plus controversé. La tétracycline, le triméthoprim-sulphaméthoxazole et l'ampicilline sont utilisés empiriquement par certains cliniciens d'expérience comme solutions de rechange aux corticostéroïdes chez les patients atteints de maladie de Crohn, mais n'ont pas été soumis à des essais cliniques bien conçus. Seulement quelques rapports anecdotiques suggèrent un avantage des antibiotiques à large spectre et la décontamination intestinale chez les patients porteurs de colite ulcéreuse active. Le métronidasole (10 mg/kg) est cependant égal à la sulphasalazine et supérieur au placebo dans le cadre d'études bien conçues chez des patients porteurs de maladie de Crohn active avec un avantage particulier pour les patients dont le côlon est atteint. Le métronidazole (20 mg/kg) à dose élevée est très utilisé pour les complications périanales de la maladie de Crohn, bien que son utilité n'ait jamais été documentée dans le cadre d'essais contrôlés. La réduction des concentrations bactériennes luminales par lavage intestinal et antibiotiques non absorbables induit des rémissions de la maladie de Crohn dans le cadre d'essais non contrôlés et n'a pas été utilisée en clinique. L'utilisation à long terme d'antibiotiques est restreinte par le risque de complications, notamment la colite induite par la toxine *Clostridium difficile* avec des antibiotiques à large spectre et la neuropathie périphérique après des doses élevées à métronidazole. L'auteur favorise le recours de métronidazole 250 mg tid ou qid (10 mg/kg) chez les patients atteints de colite de Crohn ou d'iléocolite qui ne répondent pas à la sulphasalazine ou au 5-AAS et le traitement des complications périanales de la maladie de Crohn avec le métronidazole 500 mg tid (20 mg/kg) et interruption immédiate du médicament s'il survient une neuropathie périphérique.

treat active Crohn's disease and ulcerative colitis. This article discusses the rationale and goals of antimicrobial therapy of intestinal inflammation, summarizes the clinical and experimental evidence for the use of antibiotics in ulcerative colitis and Crohn's disease, lists less conventional approaches to decreasing luminal bacterial concentrations, and makes recommendations for clinical treatment and future research. Pathogenic mechanisms are stressed during discussions of clinical and experimental results.

RATIONALE FOR ANTIMICROBIAL THERAPY

Conventional drug therapy of ulcerative colitis and Crohn's disease blocks production or activity of inflammatory mediators and cytokines involved in the inflammatory response. However, redundant pathways hamper this approach, as evidenced by suppression but not elimination of inflammation by conventional drugs. An alternative and theoretically superior approach is to prevent activation of the inflammatory cascade by eliminating factors that initiate and/or perpetuate intestinal inflammation. Bacteria and bacterial products normally found in high concentrations in the distal ileum and colon have well defined pro-inflammatory activities and have been linked by strong circumstantial evidence to the pathogenesis of IBD (3,4). Although Crohn's disease and ulcerative colitis are virtually indistinguishable from several infectious intestinal disorders, no compelling epidemiologic, clinical or experimental data suggest that a substantial number of idiopathic IBD patients are infected by a transmissible etiologic agent. However, alterations of the anaerobic fecal flora of Crohn's disease (5) and virulence factors of aerobic bacteria, especially *Escherichia coli* (6,7), in ulcerative colitis have important implications for the pathogenesis of these diseases.

TABLE 1
Complications of IBD requiring antibiotics

Intra-abdominal and perirectal abscesses
Perianal fistulae, fissures and abscesses
Intestinal fistulae
Small intestinal bacterial overgrowth
Postoperative infections
Toxic megacolon
Secondary infection with *Clostridium difficile, Aeromonas,* etc

Luminal bacteria secondarily invade mucosal ulcers and fistulae and in the process almost certainly potentiate intestinal inflammation. Endogenous bacteria are more frequently cultured from the serosal surface and mesenteric lymph nodes of resected Crohn's disease intestines than controls (8). We postulated that Crohn's disease arises from an inappropriately aggressive immune response to products of the normal microbial flora. This response is mediated by a genetically determined defective downregulation of inflammation (3,9). Luminal bacterial and dietary antigens easily cross the permeable mucosal barrier of patients with active IBD, especially Crohn's disease. Bacterial products such as formylated oligopeptides (FMLP), endotoxin (lipopolysaccharide [LPS]) and peptidoglycan-polysaccharide polymers (PG-PS) activate phagocytic cells to produce arachidonic acid metabolites and cytokines, activate the complement and kallikrein-kinin cascades and induce experimental intestinal and systemic inflammation (3,9). The important role of normal luminal bacteria in potentiating intestinal inflammation is best illustrated by the ability of antibiotics and the bacterial-free state to attenuate experimental enterocolitis (10,11). Thus, the well documented inflammatory potential of distal intestinal bacteria and their products and the ability of these luminal microbial agents to induce and perpetuate experimental intestinal injury provide a firm rationale for antimicrobial treatment in IBD.

TABLE 2
Strategies to decrease concentrations of luminal bacteria and bacterial products

Oral or parenteral antibiotics
Bowel rest: surgical diversion, elemental diet, TPN
Nonabsorbable antibiotics
Intestinal lavage
Bind or degrade LPS, FMLP and PG-PS

TPN Total parenteral nutrition; LPS Lipopolysaccharide; FMLP Formylated oligopeptides; PG-PS Peptidoglycan-polysaccharide polymers

GOALS AND STRATEGIES OF ANTIMICROBIAL THERAPY

The goals of antimicrobial therapy are listed below and the mechanisms to achieve these goals are provided in Table 2.

Decreasing luminal concentrations of bacteria and bacterial products: Most antibiotics induce only transient changes in concentrations of luminal bacteria because of rapid proliferation of resistant strains, although significant decreases in total anaerobes occur following clindamycin and erythromycin therapy (12). Prolonged use of metronidazole (up to six months) eliminated *Bacteroides* species from stools of most patients with Crohn's disease, but did not alter Bacteroides in normal volunteers since the drug is completely absorbed proximally and only secreted into the lumen when the colon is inflamed (13). LPS is inactivated when bound to polymyxin B and PG-PS is degraded by the muralytic enzyme mutanolysin, which can prevent and treat PG-PS-induced granulomatous enterocolitis (14). Nonabsorbable antibiotics can eliminate FMLP from the lumen of patients with active Crohn's disease (15).

Decreasing mucosal invasion by bacteria: Maintaining high tissue concentrations of antibiotics should inhibit bacterial proliferation following secondary invasion of mucosal ulcers or fistulae in active IBD.

Preventing extraintestinal dissemination of bacteria and bacterial products: Maintaining adequate tissue, plasma and lymphatic antibiotic concentrations diminish risks of regional and systemic infections whereas decreased absorption of bacterial polymers diminish chances of extraintestinal inflammation (9).

TABLE 3
Broad spectrum antibiotic trials in active Crohn's disease

	Therapy	Improvement
Moss (16)	Ampicillin, cephalothin, tetracycline, erythromycin	41/44 (93%)
Danzi (17)	Trimethoprim-sulphamethoxazole	10/12 (83%)
Ambrose (18)	Cotrimoxazole	7/16 (41%)

TABLE 4
Adjunctive antibiotic therapy of acute ulcerative colitis

	Drug	Duration	Acute benefit	Chronic benefit
Burke (19,20)	Tobramycin	7 days	31/42 (74%)*	34/40 (85%)*
	Placebo		18/42 (43%)	22/40 (55%)
Danzi (17)	Trimethoprim-sulphamethoxazole	18 months	9/10 (90%)	9/10 (90%)
Dickinson (21)	Vancomycin	7 days	16/18 (89%)	7/16 (44%)
	Placebo		8/15 (53%)	3/7 (43%)

**P<0.01 versus placebo*

RESULTS OF ANTIMICROBIAL THERAPY.

Broad spectrum antibiotics: A number of experienced clinicians use ampicillin, tetracycline, sulphamethoxazole or trimethoprim-sulphamethoxazole either singly or on a rotational basis in preference to steroids to treat patients with mild to moderate Crohn's disease (1). Two uncontrolled trials show dramatic benefits of chronic broad spectrum antibiotics in patients with Crohn's disease (Table 3). Moss et al (16) treated patients refractory to conventional therapy with either ampicillin, tetracycline, clindamycin, cephalothin or erythromycin for at least six months. Symptomatic improvement was noted in 93% of patients, radiographic improvement was obtained in 57%, and 41% were able to discontinue steroids. Danzi (17) has briefly reported that 83% of patients with fistulizing ileocolonic Crohn's disease who had trimethoprim sulphamethoxazole added to high dose steroid and sulphasalazine therapy achieved a clinical remission which permitted steroid withdrawal. Remission was maintained in all responders for 18 months with no reported side effects. Although results of these uncontrolled trials are clearly positive, widespread use of chronic broad spectrum antibiotics in Crohn's disease should await carefully controlled trials, particularly in view of the lack of benefit of four weeks treatment with cotrimoxazole compared to placebo (18).

Few clinicians use antibiotics in ambulatory patients with active ulcerative colitis although several poorly publicized studies suggest a beneficial role for the addition of these agents to conventional steroid and sulphasalazine therapy (Table 4). Burke et al (19) demonstrated a statistically significant improvement in histologic scores and an increase in the number of patients who achieved clinical remission following a seven-day course of oral tobramycin in ulcerative colitis. This therapy eradicated fecal *E coli* and had a symptomatic benefit for at least six months (20). In an uncontrolled trial Danzi (17) demonstrated a long term remission with steroid withdrawal in 90% of patients with severe pancolonic ulcerative colitis treated with trimethoprim-sulphamethoxazole. Although results were significant only at the P=0.057 level, Dickinson et al (21) reported that only two of 18 vancomycin treated (11%) but seven of 15 placebo controls (47%) required colectomy for moderate to severe ulcerative colitis. None of these patients had

TABLE 5
Metronidazole as primary therapy of Crohn's disease: controlled trials

Study	Drug	Duration	Number of patients	Clinical improvement	
				All patients	Colonic involvement
Blichfeldt (22)	Metronidazole 1000 mg	8 weeks	22	2.1 "Total score"	5.3*
	Placebo	8 weeks	22	0.9 "Total score"	0.8
Ambrose (18)	Metronidazole 800 mg	4 weeks	18	44%†	NS
	Placebo		17	41%	NS
Krook (23)	Metronidazole 800 mg	16 weeks	10	50%	71%
	Sulphasalazine	16 weeks	10	60%	50%
Ursing (24)	Metronidazole 800 mg	16 weeks	37	57%	62%
	Sulphasalazine	16 weeks	40	55%	58%
Schneider (25)	Metronidazole 1000 mg	12 weeks	13	NS	−117 CDAI**
	Medprednisone + sulphasalazine + metronidazole	12 weeks	14	NS	−169 CDAI
	Prednisone + sulphasalazine	12 weeks	17	NS	−168 CDAI
Sutherland (26)	Metronidazole 10 mg/kg	16 weeks	33	−67 CDAI*	−77 CDAI*‡
	Metronidazole 20 mg/kg	16 weeks	30	−97 CDAI*	
	Placebo	16 weeks	36	−1 CDAI	+47 CDAI

**P<0.01 compared to placebo; †Response rate of patients entering the trial; **Change in the Crohn's Disease Activity Index (CDAI) from pretrial values; ‡Metronidazole 10 and 20 mg/kg groups were combined and ileitis and colitis patient groups were combined. Change from baseline CDAI is given. NS Not studied*

detectable *Clostridium difficile* in their stools. These provocative studies need to be reproduced and extended to investigate the effect of antibiotic therapy on the fecal carriage ratio of *E coli* expressing abnormal epithelial adhesion properties previously reported in patients with ulcerative colitis (6).

Metronidazole: Metronidazole has been shown to be superior to placebo and equal to sulphasalazine in treatment of active Crohn's disease by controlled trials (Table 5). In all studies where location of disease was independently evaluated, metronidazole was more effective for colonic involvement (Crohn's colitis and ileocolitis) than for isolated small intestinal disease. In the one trial showing no benefit of metronidazole (18), patients with colonic involvement were not evaluated separately. In this study results after two weeks of metronidazole appeared promising, with 67% of patients improving versus 35% placebo response, but differences were not apparent after four weeks. The recently completed North American Cooperative Study showed a dose responsive effect of metronidazole which was significantly more effective than placebo as judged by clinical parameters (Crohn's disease activity index) and serum orosomucoid levels (26). This study can be criticized because only 53% of patients completed the trial, although adverse effects were not greater in the metronidazole groups.

A preliminary report suggests that metronidazole may be effective in decreasing recurrent Crohn's disease after ileal resection. Rutgeerts et al (27) reported that endoscopic evidence of 'severe' inflammation was present in 13% of patients treated with metronidazole 20 mg/kg/day for three months beginning within one week of ileal resection and ileocolonic anastomosis compared with 43% of placebo-treated patients. Symptomatic recurrence at seven months occurred in 8% of metronidazole-treated patients and 25% of controls. However, 23% of metronidazole-treated patients versus 7% of controls dropped out of the study because of adverse events. This provocative study suggests that anaerobic flora may contribute to recurrence after 'curative' resection in Crohn's disease.

Metronidazole is not effective as sole therapy of active ulcerative colitis (28), but recently was shown by Gilat and colleagues (29) to be slightly more effective than sulphasalazine 2 g/day in a 12-month trial of maintenance of remission of ulcerative colitis. Confirmatory studies must be performed before long term use of this potentially toxic drug is recommended.

Bowel decontamination and lavage: Several groups have demonstrated that transiently decreasing luminal bacteria and bacterial product concentrations can diminish acute inflammation in Crohn's disease. In a 10-day controlled trial, poorly absorbed antibiotics (framycetin, colistin and nystatin) plus an elemental diet were equal to prednisolone 0.5 mg/kg/day and an oral diet in inducing remission in active Crohn's disease (15). Fecal dialysates from patients completing the decontamination protocol contained unmeasurable chemotactic activity, used as a bioassay of FMLP, in contrast to high levels before therapy (30). Saline lavage and 5-ASA hastened clinical improvement and clearance of endotoxemia when added to total parenteral nutrition (TPN) and steroid therapy of 18 patients hospitalized for acute exacerbation of Crohn's disease (31). These studies clearly suggest that luminal bacteria and bacterial products play a role in maintaining activity in Crohn's disease, but the combination of two treat-

ment variables in each case prevent definitive conclusions. In a preliminary study oral colistin or lactulose diminished fecal bacterial concentrations and positive blood cultures in rats treated with trinitrobenzene sulphonic acid but had little effect on experimental colitis (32).

Provocative preliminary studies suggest that altering fecal bacterial composition can treat ulcerative colitis. Bennett et al (33) reduced bowel flora in a patient with longstanding refractory ulcerative colitis with a preoperative bowel preparation protocol, then introduced 'normal flora' with retention enemas of feces from a healthy donor. The patient remained symptom free for at least six months and rectal biopsy showed mild chronic but no active inflammation. A small uncontrolled series by McCann et al (34) replaced flora with nonpathogenic *E coli* and *Lactobacillus fermentis* after decontamination with multiple antibiotics. Five of seven patients (71%) with ulcerative colitis and Crohn's disease had significant improvements which were associated with persistence of donor *E coli* stains. These early attempts to address the issue of altering virulence factors of indigenous bacteria in IBD, especially ulcerative colitis, need to be followed by rigorously controlled studies with long term analysis of the functional activity (epithelial adherence and toxin production) of luminal bacterial strains (6,7).

Antimycobacterial agents: Based on recovery of mycobacteria from a small percentage of resected Crohn's disease tissues (3), several groups have used antimycobacterial drugs to treat patients with active Crohn's disease. These reports have been difficult to interpret because different agents have been used for variable durations, most communications have been in letter, abstract or case report form and some patients have had concurrent tuberculosis or had acid-fast organisms on intestinal biopsies. The only placebo controlled trials describe conflicting results. Shaffer et al (35) found no benefit of rifampicin and ethambutol in a two-year placebo-controlled crossover study of 27 patients with Crohn's disease. No subset of patients responded and steroid dose was not affected by these drugs. Kohn et al (36) recently reported that Crohn's disease patients treated for nine months with ethambutol, dapsone, clofazimine and rifampicine had a significantly lower relapse rate (16.7%) than patients treated with placebo (68.7%). While further trials using drugs with even greater activity against *Mycobacterium paratuberculosis* are awaited with interest, it should be noted that the currently investigated drugs have a broad spectrum of activity and also clearly affect normal colonic bacteria. Positive results of such trials do not necessarily incriminate mycobacteria as causal agents of Crohn's disease, given the lack of specificity of the antibiotics tested and the immunoregulatory properties of dapsone.

Bowel rest: An alternative approach to antibiotics in decreasing concentrations of luminal bacteria is elimination of bacterial constituents by surgical diversion, elemental diets or TPN. Ileal diversion (split ileostomy) diminishes activity of Crohn's colitis in 95% of patients, although most patients experience reactivation of symptoms when intestinal continuity is re-established (37). Several studies demonstrate the importance of luminal contents in maintaining activity of Crohn's disease. Harper et al (38) produced a clinical recurrence of symptoms in 60% of patients with Crohn's colitis in remission after split ileostomy by challenging the colon with ileostomy effluent. However, an ultrafiltrate of ileostomy contents did not induce symptoms, incriminating intact bacteria or particulate matter above 22 nm in diameter. Rutgeerts and colleagues (39) reported that 0% of Crohn's disease patients undergoing a diverting ileostomy at the time of ileal resection and ileocolonic anastomoses had colonoscopic evidence of recurrent inflammation in the neoterminal ileum, in contrast to 70% of patients with standard anastomosis. When the ileostomy was taken down, 100% of the patients developed ileal inflammation within six months. The importance of colonic flora in reactivation of ileal Crohn's disease is further illustrated by the increased recurrence rate of ileocolonic anastomosis compared with end ileostomy.

Both elemental diets and TPN decrease activity in 60 to 80% of patients with active Crohn's disease, but most patients develop recurrent symptoms after resuming a regular diet. The relative contributions of altered luminal bacterial loads, dietary antigens, luminal arachidonic acid precursors and mucosal nutrition in therapeutic effectiveness of elemental diets and TPN remain to be determined. Interestingly, fecal diversion, elemental diets and TPN do not predictably decrease activity of ulcerative colitis, reinforcing the concept of different mechanisms of tissue injury of this disorder and Crohn's disease.

ADVERSE REACTIONS TO ANTIMICROBIAL THERAPY

Widespread clinical experience with antibiotics and bowel rest permit accurate assessment of risks of these treatments in IBD (1). Nine per cent of patients with Crohn's disease treated with broad spectrum antibiotics developed hypersensitivity reactions and none developed pseudomembraneous colitis (16). No adverse effects were noted with trimethoprim-sulphamethoxazole therapy for 18 months (17). Overgrowth of resistant organisms is a predictable consequence of antibiotics which achieve high luminal concentrations (12,18) and must be considered when patients on antibiotics develop complications or reactivation of disease. Although *C difficile* toxin-induced colitis (pseudomembraneous colitis) has not been reported in the trials discussed above (16-21), the frequency of this condition is clearly increased by broad spectrum antibiotics and can mimic spontaneous relapse of IBD (40).

Metronidazole has predictable adverse effects which limit its long term use in high doses. Most patients learn to tolerate the metallic taste, dark urine and alcohol sensitivity associated with this drug, but some patients develop clinically significant nausea and anorexia. These symptoms were not increased compared to placebo (26) or sulphasalazine (24) in the two largest controlled trials of metronidazole in

Crohn's disease. Extensive experimental and clinical studies show no evidence of mutagenicity or carcinogenicity of metronidazole in humans (1), although its use during pregnancy cannot be advocated. Peripheral neuropathy is the most severe common complication of high dose metronidazole, but is rare in doses of 10 mg/kg/day or lower (1). This complication was not evident in the Swedish or North American Cooperative studies (24,26) and was not detected by neurophysiologic studies of 19 adult patients receiving 800 mg/day for at least one year (41). However, peripheral neuropathy occurs in 10 to 50% of Crohn's disease patients with perianal disease who receive high dose metronidazole (20 mg/kg/day) (1,2). Duffy et al (42) reported an 85% incidence of sensory peripheral neuropathy by neurologic exam or nerve conduction velocity in children taking metronidazole 20 mg/kg/day for seven months, although only 46% were symptomatic. Neuropathy totally resolved with discontinuation of metronidazole in 55%, improved in 33% and did not change in 11%. Patients taking metronidazole, particularly in high dose, should be warned to report the first evidence of sensory changes so that the drug can be stopped. This medication, like all used for Crohn's disease, has no documented prophylactic benefit and should be tapered gradually and stopped once a remission has been achieved.

CONCLUSIONS AND FUTURE DIRECTIONS

The role for antimicrobial approaches in the management of IBD patients remains controversial due to a paucity of well designed clinical trials. However, this is a promising area for future research which provides the definite possibility of developing relatively nontoxic modes of therapy designed to prevent initiation and perpetuation of inflammation rather than to inhibit the multiple pathways of the immune response that are operative in the advanced stages of clinically apparent IBD. The following recommendations for clinical management are provided. At the present time routine therapeutic use of broad spectrum antibiotics, bowel decontamination and antituberculous agents in IBD patients is not suggested. Clinical studies of these approaches are inconclusive due to lack of appropriate controls, small numbers of subjects, simultaneous investigation of multiple agents and lack of separate consideration of disease subsets, especially colonic versus small intestinal involvement. More consistent observations support the use of low dose metronidazole (10 mg/kg/day in divided doses) in active Crohn's colitis. The author uses metronidazole 250 mg tid or qid in patients with Crohn's colitis or ileocolitis who do not respond to sulphasalazine before resorting to steroids and as first line therapy for pouchitis. The addition of metronidazole to sulphasalazine and steroids has proved successful in treating the steroid resistant or dependent patient with Crohn's colitis or ileocolitis and this drug is used preferentially by the author in patients with associated infectious complications, such as fistulae and inflammatory masses. Drugs should be tapered in parallel with their toxicities once remission has been achieved: corticosteroids before metronidazole before sulphasalazine. The patient must be carefully observed for evidence of peripheral neuropathy, which should be anticipated in the patient with perianal disease who requires high dose (20 mg/kg/day) metronidazole for four to six months. This drug should be stopped immediately upon evidence of sensory deficits.

The studies and observations described above provide important insights into the pathogenesis of Crohn's disease and ulcerative colitis. They suggest that anaerobic bacteria are involved in maintaining inflammation in Crohn's colitis, recurrence after ileal resection with ileocolonic anastomosis and pouchitis following colectomy. Anaerobic bacteria are less important in the pathogenesis of ulcerative colitis, but virulence factors such as epithelial adhesion and toxin production by common intestinal aerobes may be extremely important. Finally, products of normal intestinal bacteria (FMLP, LPS, PG-PS) induce and perpetuate experimental intestinal and systemic inflammation and may have a similar role in IBD.

Certain avenues for future clinical research in this area appear particularly promising. Antibiotic protocols need to be optimized for active Crohn's colonic disease and explored further as adjunctive therapy for ulcerative colitis. Antibiotic prevention of postoperative recurrence of Crohn's ileitis needs to be confirmed and extended using nontoxic doses. Experimental methods to bind or degrade pro-inflammatory bacterial products need to be explored clinically. Decontamination and replacement of bowel flora in ulcerative colitis should be explored in a scientific fashion. These investigations, proceeding in concert with exciting advances in understanding mechanisms of immunoregulation, cellular adhesion and cytokine blockade, should yield significantly better therapeutic alternatives for control of IBD in the near future.

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