Antibiotic therapy for Crohn's disease: A review

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Increasing evidence suggests that gut bacteria play a pathogenic role in Crohn's disease (CD), providing a rationale for the use of antibiotics in the primary treatment of the disease. While there are data to suggest that antibiotics may be effective in treating active luminal, particularly colonic, and/or perianal CD, evidence for their use in these settings is hampered by the lack of well-designed, adequately powered, placebo-controlled trials. Furthermore, although nitroimidazole antibiotics have been shown to reduce postoperative recurrence following ileocolonic resection, their use is limited by side effects. There is a current need for rigorous multicentre studies looking into the role of antibiotics in treating perianal and luminal CD, as well as a need for the large-scale assessment of novel antibiotics, with low systemic absorption, which may improve patient tolerance.

Key Words: *Antibiotics; Crohn's disease; Inflammatory bowel disease; Perianal Crohn's disease; Postoperative Crohn's disease*

Le traitement de la maladie de Crohn par les antibiotiques : examen de la documentation

De plus en plus de preuves tendent à montrer que la flore intestinale joue un rôle pathogène dans l'apparition de la maladie de Crohn (MC), ce qui justifierait le recours aux antibiotiques pour le traitement principal de la maladie. Même si des données semblent montrer l'efficacité des antibiotiques dans le traitement de la MC évolutive, luminale, touchant le côlon ou la région péri-anale, le manque d'essais comparatifs avec placebo, bien conçus et suffisamment puissants limitent leur utilisation dans ce contexte. De plus, même si les antibiotiques nitro-imidazolés réduisent les risques de réapparition de la maladie après une résection iléo-colique, leurs effets indésirables limitent également leur utilisation. Aussi faut-il, d'une part, mener des études multicentriques, rigoureuses, sur le rôle des antibiotiques dans le traitement de la MC luminale ou péri-anale et, d'autre part, entreprendre une évaluation à grande échelle de nouveaux antibiotiques ayant une faible absorption générale, ce qui en améliorerait la tolérabilité.

While antibiotics have a definite role in treating specific, episodic or persisting bacterial infections that may complicate Crohn's disease (CD), such as intra-abdominal abscesses or small intestinal bacterial overgrowth, their therapeutic ability in controlling the primary disease is not fully established and has proven to be controversial (1-3).

Bacteria have long been implicated as potential contributing factors in the pathogenesis of CD and two schools of thought currently exist: CD results from infection with a specific organism and atypical mycobacteria have received the most attention in this regard (4), or the disease arises as a consequence of an abnormal immune response to commensal enteric flora (5). A number of studies have explored the use of traditional antimycobacterial agents to treat CD with limited success to date (6,7), and the pathogenic role of mycobacterium remains unresolved (4). However, there is increasing evidence that CD results from an imbalance between protective and harmful enteric organisms (called 'dysbiosis' [5]), leading to the initiation and then persistence of intestinal inflammation in genetically susceptible individuals with altered immune responses. Such evidence may provide a rationale for the use of antibiotics as primary therapy in CD.

ROLE OF GASTROINTESTINAL BACTERIA IN THE PATHOGENESIS OF CD

The role of commensal bacteria in the etiology of CD has gathered momentum over recent years, with evidence derived from both animal models and human studies. Genetically engineered germ-free rodents, for example, fail to develop experimental enterocolitis unless colonized with normal gut flora (8-11) and significantly, such models of intestinal inflammation display therapeutic responses to antibiotics (12-15). The observation that disease activity is attenuated by diversion but exacerbated by restoration of the fecal stream in patients with CD lends further support to the concept that luminal contents, possibly enteric flora, play a pathogenic role (16,17). Additionally, patients with inflammatory bowel disease (IBD) display increased concentrations of mucosal bacteria, both anaerobic (*Bacteroides*) and aerobic (*Enterobacteriaceae*) species, compared with control subjects, with increasing bacterial concentrations associated with more severe disease (18). While the latter commensal organisms may be harmful, the finding that there is a reduction in protective organisms, such as *Bifidobacterium* and *Lactobacillus*, in patients with IBD (19,20), adds support to the aforementioned concept of dysbiosis in CD (5).

For commensal organisms to be a causal factor in CD, host susceptibility is required to generate an abnormal inflammatory response to the normal intestinal flora. Therefore, it is relevant that patients with IBD display loss of immunological tolerance to commensal bacteria, with enhanced cell-mediated (21) and humoral (22) responses. Recent evidence strongly implicates host genetic susceptibility as a key factor in predisposing not only to such abnormal immune responses, but also to impaired mucosal bacterial clearance. It has been suggested, for example, that polymorphisms in the nucleotide-binding

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TABLE 1
Principal antibiotic trials in luminal Crohn's disease

References	Year	n	Antibiotic	Duration	Summary of results
Blichfeldt et al (30)	1978	22	Metronidazole 250 mg qid	2 months	Symptomatic improvement in six patients with colonic disease
Ursing et al (32)	1982	78	Metronidazole 400 mg bid	4 months	Slightly more effective than sulfasalazine
Ambrose et al (33)	1985	72	Metronidazole 400 mg bid and/or cotrimoxazole 960 mg bid	1 month	No benefit versus placebo
Sutherland et al (34)	1991	105	Metronidazole 10 mg/kg/day or 20 mg/kg/day	16 weeks	Reduction in Crohn's disease Activity Index versus placebo particularly with colonic disease, but no difference in remission rates
Colombel et al (38)	1999	40	Ciprofloxacin 1 g/day	6 weeks	Equally effective as mesalamine in inducing remission
Arnold et al (39)	2002	47	Ciprofloxacin 500 mg bid	6 months	Reduction in Crohn's disease Activity Index versus placebo
Prantera et al (40)	1996	41	Metronidazole 250 mg qid and ciprofloxacin 500 mg bid	12 weeks	Remission rate of 46% with antibiotic regimen versus 63% with methylprednisone
Greenbloom et al (42)	1998	72	Metronidazole 250 mg tid and ciprofloxacin 500 mg bid	10 weeks	Uncontrolled study: 68% remission rate, more likely if colonic disease
Steinhart et al (43)	2002	130	Metronidazole 500 mg bid and ciprofloxacin 500 mg bid	8 weeks	No benefit over budesonide alone, although remission rates higher if colonic disease
Leiper et al (44)	2000	25	Clarithromycin 250 mg bid	4 weeks	Uncontrolled study: 48% remission rate

bid Twice a day; tid Three times a day; qid Four times a day

oligomerization domain 2/caspase recruitment domain 15 gene, which has been found in a subset of patients with CD (23,24), may contribute to disease pathogenesis secondary to impaired clearance of invasive bacteria (25).

ANTIBIOTIC TREATMENT OF CD

The putative role that bacteria play in the etiology of CD clearly provides a sound rationale for the use of antibiotics in the primary treatment of the disease. There are existing data suggesting that antibiotics may be efficacious in the treatment of active luminal and/or perianal disease, as well as aid in preventing postoperative disease recurrence. The mechanism of action of antibiotics in these clinical settings remains to be fully elucidated; while it is likely that they act in a conventional antimicrobial manner to reduce the proportion of harmful bacterial species or to limit bacterial invasion and/or bacterial secretory products (26), some of the antibiotics used in CD may also exert direct immunomodulatory effects (27-29).

Antibiotic therapy in active luminal CD

A number of antibiotic regimens have been evaluated in the treatment of active luminal CD (Table 1), and have either been directed against a specific pathogen such as an atypical mycobacterium or have been used in an attempt to modulate normal gut flora.

For many years, most of the interest in antibiotics was centred on metronidazole, a nitroimidazole antibiotic with an antimicrobial spectrum of activity against anaerobes. Blichfeldt et al (30) compared the effect of metronidazole against placebo in an early double-blind crossover study in 22 patients; although no overall clinical benefit was observed, six patients with only colonic involvement displayed both symptomatic and biochemical improvement. In the Swedish cooperative CD study, metronidazole (400 mg taken twice a day) was compared to sulphasalazine (1.5 g taken twice a day) for the treatment of active CD using a double-blind crossover design (31,32). A total of 78 patients were randomly assigned and followed for up to eight months (two four-month periods). During the first four-month treatment period, reductions in the scores of the CD Activity Index (CDAI) were similar in both groups, although patients taking metronidazole had significantly greater reductions in plasma orosomucoid levels and greater increases in hemoglobin levels. However, only 10 of 40 (25%) patients in the metronidazole group achieved quiescent disease at the end of the first treatment period, compared with 15 of 38 (39.5%) patients in the sulfasalazine group. Patients who had not experienced a reduction in their CDAI scores in the first part of the study experienced a reduction in CDAI during the second portion of the study if they were crossed over to metronidazole, but not to sulfasalazine. It was concluded that metronidazole was slightly more effective than sulfasalazine in the treatment of active CD

Ambrose et al (33) subsequently compared the efficacy of metronidazole, cotrimoxazole or a combination of the two antibiotics, against placebo in 72 patients with active disease; unfortunately, no benefit was identified at one month following any of the treatment regimens. In 1991, Sutherland et al (34) randomly assigned 105 patients with active CD to receive placebo, metronidazole at 10 mg/kg per day or metronidazole at 20 mg/kg per day. Although metronidazole led to a reduction in patient CDAI scores, particularly in subjects with large rather than small bowel disease, the proportion of patients in clinical remission at the end of the 16-week study was relatively low and similar in the three groups. These disappointing results may have been due to the relatively high dropout rate caused by the side effects experienced by the patients in the high-dose metronidazole group. Indeed, most clinicians now advocate the use of doses that are significantly less than 20 mg/kg per day to minimize adverse events (35), and most also warn about the risk of peripheral neuropathy to those patients embarking on a prolonged course of the antibiotic (36).

Following the modest results obtained with metronidazole, investigators turned their attention to better tolerated antibiotics with a broader antibacterial spectrum. In 1993, Peppercorn (37) published the results of a small, uncontrolled study demonstrating a clinical response to ciprofloxacin in patients with Crohn's ileitis. After these preliminary findings, Colombel et al (38) carried out a larger, randomized study

involving 40 patients with mild to moderate disease activity, and found that a six-week course of ciprofloxacin (1 g/day) was equally as effective as mesalamine (4 g/day) in inducing disease remission (56% versus 55%, respectively). Subsequently, Arnold et al (39) demonstrated that ciprofloxacin (1 g/day for six months), when added to the treatment of a patients with moderately active CD, led to a clinically significant reduction in CDAI scores when compared with placebo.

A number of researchers have assessed the effect of a combination of ciprofloxacin and metronidazole in patients with active CD, but results have been mixed. Prantera et al (40) found that patients with moderately active disease who received a 12-week course of this antibiotic combination achieved clinical remission (46% remission rate) less often than patients treated with methylprednisolone (63% remission rate). The same investigators also performed a retrospective evaluation of the use of metronidazole and/or ciprofloxacin and found that complete or partial remission of the disease, as defined by the CDAI score, was approximately 70% in patients treated with either single or combined therapy (41). In an uncontrolled study, Greenbloom et al (42) demonstrated a similar clinical remission rate (68%) in patients with active CD of the ileum and/or colon who received a 10-week combination of ciprofloxacin and metronidazole; notably, a clinical response occurred in a greater proportion of patients with colonic disease compared with ileal disease alone. More recently, a prospective double-blind study evaluated the use of the same antibiotic combination in patients receiving oral budesonide for ileal CD with or without right-sided colonic involvement (43). Although the overall results showed no improvement in response or remission with the addition of antibiotics, among patients with some involvement of the colon, the proportion achieving remission was higher in patients taking antibiotics (53%) compared with those taking placebo (25%).

Other antibiotics have also been evaluated in active CD because of the frequent side effects requiring discontinuation of therapy observed in up to 20% of patients receiving ciprofloxacin and/or metronidazole (41). Indeed, individual agents used in antimycobacterial regimens have been assessed. For example, Leiper et al (44) performed an open-label study demonstrating a 48% remission rate following a four-week course of clarithromycin, with only two of the 25 patients withdrawing due to nonserious side effects. More recently, rifaximin, a rifamycin-derived antibiotic with a broad antibacterial spectrum and an excellent safety profile due to very low systemic absorption (45) has proven promising in preliminary studies of patients with mild to moderate (46) and moderate to severe (47) CD, although further large-scale controlled evaluation is required.

Antibiotic therapy in postoperative CD

Disease recurrence following intestinal resection for active CD is common: one year after ileocolonic anastamosis with clinical recurrence occuring in 20% to 37% of patients, and endoscopic recurrence occurring even more quickly, with observed rates between 73% and 93% (48,49). The ability of a variety of prophylactic medications (such as aminosalicylates, corticosteroids and purine analogues) to reduce postoperative recurrence has been assessed, with no clear regimen identified (for review see [50]). The observations that disease recurrence is prevented following an ileocolonic anastamosis if the fecal stream is diverted through a proximal loop ileostomy (51), while infusion of intestinal contents into the excluded distal ileal loop leading to the anastamosis rapidly induces inflammatory changes (16), provide indirect evidence that bacteria may play a role in postoperative disease recurrence and also provides a rationale for using prophylactic antibiotics in this setting. Moreover, the association of early disease recurrence with increased concentrations of *Escherichia coli* and *Bacteroides* species in the neoterminal ileum of patients following ileocolectomy adds further support to this rationale (19).

Rutgeerts et al (52,53) performed two double-blind, placebo-controlled studies to determine the efficacy of imidazole antibiotics in the prevention of postoperative recurrence of CD. In the first study (52), a three-month course of metronidazole, given immediately following 'curative' ileal resection, reduced symptomatic and endoscopic recurrence rates at one year, with an important trend toward reduced clinical recurrence for as long as 36 months after surgery. In the second study, a one-year course of ornidazole also reduced clinical and endoscopic recurrence rates at one year (53). Notably, more patients in the ornidazole group dropped out because of side effects and further work is required to gauge the optimal dose and duration of treatment required to maximize the efficacy and limit the toxicity of postoperative antibiotics in CD.

Antibiotic therapy in perianal CD

Antibiotics are established in treatment guidelines for simple and complex fistulizing perianal CD (54,55), although they have not been evaluated for this indication in placebo-controlled trials. However, uncontrolled studies (56-60) and clinical experience support their standing in such guidelines. For example, Bernstein et al (57) reported complete healing of perianal disease in 10 of 18 patients treated with 20 mg/kg of metronidazole, with subsequent exacerbation of disease on dose reduction in all patients (58). Ciprofloxacin is also widely used together with metronidazole to treat perianal CD (55), although evidence for its efficacy also derives only from small uncontrolled studies. Solomon et al (60), for example, found that this antibiotic combination led to clinical improvement in nine of 14 patients with fistula closure in three of 14 patients (60).

There is some evidence that concomitant use of antibiotics and immunomodulators, such as azathioprine (61) or infliximab (62) may be of mutual benefit in treating perianal CD. Dejaco et al (61) performed a prospective, open-label study to assess the effect of an eight-week course of ciprofloxacin and/or metronidazole as a bridge to azathioprine therapy in 52 patients with perianal fistulas. At week 20, patients who were maintained on azathioprine displayed a higher response rate (48%) than those who were not maintained on azathioprine (15%). West et al (62) recently investigated whether concomitant use of ciprofloxacin enhanced the efficacy of infliximab in patients with perianal fistulas. Twenty-four patients were randomly assigned to receive ciprofloxacin twice daily or placebo for 12 weeks, and all patients additionally received infliximab at weeks 6, 8 and 12. The combination of ciprofloxacin and infliximab (73% clinical response rate) tended to be more effective than infliximab alone (39% clinical response rate) at week 18 follow-up.

SUMMARY AND FUTURE DIRECTIONS

While it is now widely accepted that bacteria play a pathogenic role in the etiology of CD, current evidence supporting the use of antibiotics in active disease is hampered by the lack of well-designed, adequately powered, placebo-controlled trials. This

has led to understandable reticence by some clinicians to recommend antibiotics as primary therapy in luminal disease (1). This contrasts with wide acceptance of the use of antibiotics in treating perianal CD (54,55), despite a comparable lack of evidence for their efficacy in this setting. Why such a contradiction exists is unclear. However, based on the literature to date, there does appear to be reasonable, albeit circumstantial evidence that altering the intestinal bacterial milieu, through the use of broad-spectrum antibiotics, is effective in the treatment of active luminal CD. While individual studies have not proven that antibiotic therapy is efficacious, there seems to be a consistent biological effect, particularly in the subgroup of patients with colonic disease (30,34,42,43). Unfortunately, none of the studies have specifically examined this group of patients and none has had sufficient number of patients with colonic disease to definitively test the hypothesis that antibiotics are effective in the treatment of colonic disease. This emphasizes the importance of patient selection or, more correctly, phenotype selection when designing large therapeutic trials in CD. The reason for the differential response of colonic compared with ileal CD to antibiotic therapy is another question requiring evaluation, but likely relates to differences in enteric flora between the two sites (3).

Classification of patients into different clinical phenotypes for trials of antibiotic therapy may be further enhanced by preemptive assessment of an individual's seroreactivity to microbial components. Mow et al (63) recently provided preliminary data suggesting that CD patients with predominant serum antibody reactivity toward the bacterial antigens OmpC/I2 had the highest remission rate following treatment with budesonide combined with metronidazole and ciprofloxacin, whereas patients with no immunoreactivity had the lowest rate of response to this combination; by contrast, patients with the OmpC/I2-predominant profile displayed a poor remission rate following budesonide treatment alone. It is too early to say whether genotypic classification of patients will be of similar value in predicting antibiotic response. However, subgrouping patients according to clinical, serological and genetic markers in all therapeutic trials in CD remains a distinct possibility for the future, with the hope that improved stratification will predict which patients are likely to respond to specific interventions.

For the time being, more fundamental questions still exist regarding the optimal antibiotic regimen and duration of therapy and the place of antimicrobial therapy in the context of concomitant immunomodulating treatments. Information gleaned from animal models of IBD suggest that not all bacterial species have equal activities in inducing gastrointestinal inflammation (8); therefore, it is reasonable to infer that not all antibiotic regimens will be equally effective in treating all groups of patients with CD. While the existing data may point to a role for ciprofloxacin and/or metronidazole in certain clinical settings, these antibiotics have significant side effects at the doses studied and this calls for further assessment of novel, better-tolerated nonabsorbable agents. Clinical experience (3), coupled with limited information from therapeutic trials (58,61), suggest that long-term antibiotic use is required to avoid the disease relapses that typically occur following treatment cessation. Tolerability of long-term treatments again becomes an issue and further work is needed to confirm whether antibiotics can be used to induce remission as a bridge, not only to immunomodulators, but also to probiotics, which may be better tolerated for maintenance of remission.

There are clearly a number of unanswered questions as to the place of antibiotics in the therapeutic armamentarium in CD. While rationale exists for their use, as does preliminary evidence of their efficacy, there is an immediate need for further rigorous multicentre studies into the role of antibiotics in treating active luminal and perianal CD, and their role as prophylactic therapy following surgery.

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