Seymour Katz, M.D., Series Editor

The Present Status of Antibiotic Therapy in Crohn's Disease

by Faten N. Aberra

Although the clear cause of Crohn's disease is not known, the etiology of Crohn's disease is believed to involve the interplay of the intestinal microbial environment, genetic predisposition, and dysregulation of the immune system. The basis of treating Crohn's disease with antibiotics stems from research revealing commensal intestinal bacteria playing a role in activation of the intestinal immune system. Antibiotics have a limited but vital role in the treatment of Crohn's disease. Broad spectrum antibiotics such as metronidazole, ciprofloxacin, and rifaximin have been evaluated in clinical trials for active Crohn's disease. There has also been suspicion of species as a possible cause for Crohn's disease, and anti-mycobacterial therapy has also been evaluated in clinical trials for treating active Crohn's disease. Specific indications for antibiotics in Crohn's disease, as well as dose and duration of antibiotic therapy in Crohn's disease are described in this review.

Crohn's disease (CD) is a disorder of the immune system leading to persistent inflammation and ulceration that may occur anywhere in the gastrointestinal tract, from mouth to anus. The etiology of CD is unknown but the disease is believed to manifest from a combination of factors which include genetic predisposition, immune dysregulation and environmental triggers. The interplay of these factors likely lead to a pathway of persistent gastrointestinal mucosal ulceration.

Several pieces of evidence reveal the microbial rich intestinal environment likely plays a critical role in the development of CD. For many years various animal models of colitis revealed that a sterile environment would lead to quiescent disease and introducing commensal bacteria to the gastrointestinal tract would lead to the development of active colitis. Several scientists have also reported that diverting the fecal stream away from the area of active disease helps heal CD. More recently it is believed that a pivotal factor may be the innate immune system's inability to clear microbial antigens, leading to an overactive adaptive immune response. The identification of the NOD2/CARD15 genetic mutation has strengthened the intricate interplay between the intestinal microbial environment and immune system. NOD2/CARD15 gene mutation is found more frequently in subjects with CD and involved in the expression of an intracellular receptor that senses muramyl dipeptide, a peptidoglycan component of gram-positive bacteria. Activation of NOD2 leads to activation of NF-$\varkappa$B which mediates transcription of numerous pro-inflammatory cytokines. A muta-

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Table 1.
Antibiotics Evaluated in Controlled Trials for Crohn's Disease

Antibiotic	*Crohn's Disease Indication*	*Duration of Antibiotic Therapy*
Metronidazole	• Active intestinal Crohn's disease	4–16 weeks
	• Perianal disease	10 weeks
	• Postoperative prevention of Crohn's recurrence	12 weeks
Ornidazole[1]	Postoperative prevention of Crohn's recurrence	12 weeks
Ciprofloxacin	Active intestinal Crohn's disease	6–24 weeks
	Perianal disease	10–12 weeks
Rifaximin	Active intestinal Crohn's disease	12 weeks

[1]Ornidazole is not available in the United States

tion in NOD2 in the leucine rich domain of the protein which interacts with bacterial lipopolysaccharide leads to failure in activation of NF-κB and the mutation is associated with developing CD. It is believed that the innate immune system's inability to clear microbial antigens may lead to an overactive adaptive immune response perpetuating inflammation. With intestinal bacteria possibly playing a role in the pathogenesis of CD antibiotics, particularly antibiotics with broad spectrum and anaerobic coverage have been evaluated for the treatment of CD.

Since the recognition of CD in the early 1900s, infection with *Mycobacterium* spp, specifically *avium* subspecies *paratuberculosis* and *kansasii*, were suspected as a cause for CD due to similarity of histopathologic findings. For many years it was difficult to isolate and identify *Mycobacterium* spp based on culture techniques. With the advent of polymerase chain reaction *Mycobacterium* spp can more easily be identified. Studies using PCR to assess the presence of *Mycobacterium* spp (*avium* subspecies *paratuberculosis* and *kansasii*) have been inconsistent in showing the presence of *Mycobacterium* spp in CD patients. The possibility of *Mycobacterium* spp playing a role in CD pathogenesis has lead to several anti-mycobacterial therapy trials for CD.

ANTIBIOTICS FOR ACTIVE CROHN'S DISEASE

Broad spectrum antibiotics may have the most benefit in inflammatory bowel disease by potentially eliminating bacterial overgrowth, eradicating bacterial antigenic trigger, and antibiotics such as metronidazole may have immunosuppressive properties. Of the handful of antibiotic controlled clinical trials published for the treatment of active CD, all were with metronidazole and/or ciprofloxacin (see Table 1). In an early study of antibiotic therapy for active CD, oral metronidazole 800 mg twice a day was compared to clotrimoxazole 480 mg twice a day, combination clotrimoxazole and metronidazole, and placebo after month of treatment (1). No significant difference in response was observed between groups, but no effect of antibiotic therapy on fecal flora was observed as well. Another two clinical trials of metronidazole (dosing: Blichfeldt 1 g/day for 8 weeks, Sutherland 10 mg/kg/day and 20 mg/kg/day for 16 weeks) for active CD compared to placebo also did not meet their primary endpoint (2,3). Although in the Blichfeldt study and Sutherland studies, subgroup analysis suggested a possible benefit in subjects with colonic disease. The combination ciprofloxacin, metronidazole and budesonide for 8 weeks has also been compared to budesonide alone for the treatment of active CD and no significant difference was seen in efficacy between the two groups (4). Yet, once again in subgroup analysis the subjects with colonic disease were more likely to be in remission with antibiotics compared to budesonide alone. A study investigating ciprofloxacin 500 mg twice a day for 6 months compared to placebo for moderately active CD revealed lower Crohn's disease activity index scores in subjects receiving antibiotics (5). Although one patient in the

ciprofloxacin group developed *Clostridium difficile* colitis and Achilles tendon pain which resolved after discontinuation of antibiotic.

The efficacy of antibiotics has also been compared to 5-aminosalicylates for the treatment of active CD. Ciprofloxacin 1 g/day was compared to mesalazine 4 g/day for 6 weeks for the treatment of mild-moderate Crohn's disease. Neither treatments were found to be superior; although equivalence could not be ascertained based on the design of the study (Colombel AJG 1999).

In a meta-analysis of placebo-controlled trials of antibiotics for Crohn's disease, patients receiving antibiotic therapy were 2.3 times more likely to have clinical improvement than controls (6). Based on the few controlled trials, there may be a possible benefit of antibiotic therapy for active CD, particularly in patients with colonic disease. Although, there is a need for more focused antibiotic clinical trials for Crohn's colitis to validate efficacy in this patient population before antibiotics are considered standard therapy, used alone or as adjunctive therapy.

Additionally, due to the safety concerns of long-term antibiotic therapy, the ideal duration of therapy needs to be better understood. Side effects of metronidazole include metallic taste, nausea, vomiting, disulfiram like reaction with alcohol intake, parathesias and neuropathy which is more likely to occur with high dose (>1.5 g/day) and long term (>3 month) use (see Table 2). Side effects of particular concern with ciprofloxacin include tendonitis with Achilles tendon rupture. Certainly, there is concern for antibiotic resistance and antibiotic associated diarrhea such as *Clostridium difficile* with frequent and chronic antibiotic usage

ANTIBIOTICS FOR POSTOPERATIVE PREVENTION OF CROHN'S DISEASE RECURRENCE

Based on population studies up to 70% of CD patients will eventually have at least one surgery. Surgery may remove all active disease in some patients but by one year after surgery 70% will have endoscopic recurrence. Antibiotics have a role in preventing the postoperative recurrence of CD. Rutgeerts and colleagues were the first to describe the use of antibiotics, specifically metronidazole, for the prevention of postoperative recurrence of CD (7). Twelve weeks of treatment with metronidazole 20 mg/kg/day was compared to placebo in patients that underwent "curative" ileal resection with primary anastomosis. The severity of endoscopic recurrence was significantly less in the metronidazole group after 12 weeks and after 1 year the clinical recurrence rate was lower in the metronidazole group with only 12 weeks of therapy. In 2002, the same investigators compared ornidazole, in the

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Table 2.
Antibiotics and Potential Side Effects

Antibiotic	*Potential Side Effects*
Metronidazole	Nausea, vomiting, metallic taste, parasthesias, alcohol intolerance, CNS toxicity, skin reaction, thrombophlebitis (IV), candidiasis
	With chronic therapy: Furry tongue, leukopenia, neuropathy with chronic therapy (>3 months and >= 1.5 g/day)
Ornidazole	Similar side effect profile to metronidazole but reportedly less frequent: nausea, vomiting, metallic taste, parasthesias, headache, alcohol intolerance, neuropathy, CNS toxicity, skin reactions, abnormal liver enzymes
Ciprofloxacin	Nausea, vomiting, abdominal pain, skin reactions, tendonitis, CNS symptoms, rare reported cases of tendon rupture, vaginitis, elevated LFTs, *Clostridium difficile* colitis
Rifaximin	Abdominal pain, increased flatulence , nausea, vomiting, urticaria

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same family as metronidazole (nitro-imidazole), 1 g/day for 52 weeks to placebo for the prevention of post-operative recurrence (8). Both endoscopic and clinical recurrence rates were significantly less in the ornidazole arm. Both antibiotic studies cited higher side effect rates in the antibiotic arm compared to placebo. One patient receiving metronidazole developed polyneuropathy after 10 weeks and took 6 months to resolve after discontinuation of the drug. Ornidazole may have fewer side effects than metronidazole and it is not available in the United States. D'Haens and colleagues have also evaluated the combination of an antibiotic with an immunesuppressant for the prevention of postoperative recurrence of Crohn's disease in high-risk patients (9). The combination of azathioprine for 1 year and metronidazole for 12 weeks in postsurgical patients was more effective in preventing endoscopic recurrence at 1 year, compared to 12 weeks of treatment with metronidazole alone.

ANTIBIOTICS FOR PERIANAL CROHN'S DISEASE

Approximately 30% of Crohn's disease patients develop perianal disease which includes complications of fistula, abscess, fissures and skin tags. Ciprofloxacin and metronidazole have been evaluated in a few small uncontrolled studies for treatment of perianal fistula. Fistula closure rates range from 62-83% based on these small studies with treatment as long as two months. Recently a small pilot controlled trial was completed comparing metronidazole, ciprofloxacin, and placebo (10).

After 10 weeks of therapy there was no statistically significant difference in remission or response, although there was trend for higher remission and response rates with ciprofloxacin (30% remission and 40% response), followed by metronidazole (0 remission and 14.3% response). The results and lack of statistical significance may be a result of a small study sample size. The authors noted a higher drop out rate in the metronidazole group, with only 2 out of 7 patients completing the study. Yet, the adverse reactions reported with metronidazole were not felt to be drug related. In a small clinical trial ciprofloxacin 500 mg PO BID along with induction dose infliximab was compared to infliximab alone for the treatment of perianal fistula. After 12 weeks of therapy and 18 weeks f/u, 73% that received combination ciprofloxacin and infliximab had a clinical response compared to 39% in the infliximab only group, although statistical significance was not reached (11). Despite the sparsity of controlled trials, antibiotics are the cornerstones of initial short-term therapy for perianal CD.

ANTI-MYCOBACTERIAL THERAPY FOR CROHN'S DISEASE

There have been several trials evaluating the benefit of treating *Mycobacterium avium* species *paratuberculosis* in subjects with CD. Clofazimine for 12 months and clarithromycin for 3 months have evaluated in controlled trials, as well as various medication combinations and durations; clofazimine, dapsone, ethambutol and rifampicin for 9 months, ethambutol and rifampicin for 2 years, and clarithromycin with ethambutol for 3 months. A meta-analysis of various antibiotic regimens at best suggests a possible benefit in Crohn's disease patients induced into a remission with corticosteroid therapy and maintained with antibiotics (12,13). At this point there are not enough supporting data to incorporate anti-mycobacterial therapy into standard of practice.

FUTURE INVESTIGATIONS

Rifaximin, a rifamycin derivative, is an antibiotic with broad spectrum coverage, gram positive and gram negative, as well as aerobic and anaerobic coverage. It is virtually non-absorbable with <1% of the oral dose excreted in the urine and generally well tolerated with few side effects. It is currently FDA approved for the treatment of traveler's diarrhea. With rifaximin's unique properties, rifaximin poses as a possible ideal antibiotic choice for CD therapy. Small open label studies suggest possible benefit for treating mild to moderate CD. Although prior antibiotic studies with metronidazole and ciprofloxacin suggest treatment benefit for primarily colonic CD, a case series of 3 patients with small bowel CD treated with rifaximin 800 mg once a day had small bowel ulceration healing by 4 to 7 weeks documented by capsule endoscopy (14). A gastro-resistant formulation of rifaximin was

also evaluated in a controlled trial for the treatment of mild to moderate CD (15). Although the study did not reach the primary endpoint, after 12 weeks the response and remission rates were higher in subjects receiving rifaximin 800 mg BID (67% response and 52% remission) compared to rifaximin 800 mg once a day (48% response and 12% remission) and placebo (41% response and 33% remission). In subgroup analysis of subjects with an elevated CRP, rifaximin 800 mg BID was superior to lower dose rifaximin and placebo.

CONCLUSION

At this juncture in time, the role of antibiotics for CD therapy is as a supporting short-term treatment for perianal disease and possibly also as short-term therapy for postoperative prevention of recurrence and colonic disease. ■

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