Antibiotic Therapy

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Introduction

Treatment of inflammatory bowel disease (IBD) with antibiotics has been used for several decades. Such utilization was initially intuitive and over the past couple of decades shown to be effective. There is a triad relationship believed to be involved in the pathogenesis of IBD, genetic susceptibility–environmental antigen–host immune response. Given the exposure to foreign bacteria as well as host bacteria colonization, studies have shown that certain aspects of bacteria will trigger an immune response that leads to intestinal mucosal inflammation and for reasons still not known, patients susceptible to developing IBD will lack the ability to turn off this immune system activation resulting in perpetual intestinal mucosal inflammation and clinical symptoms of IBD [1]. Additionally, Crohn patients with diverting ileostomies demonstrate a downstream decrease in disease activity with the fecal stream interrupted and recurrence when placed back into continuity [2]. A specific infectious agent has yet to be identified but more likely than not, it may not be any one organism but rather the process of the host's immune reaction to that infectious stimulus that ultimately results in the development of IBD in the susceptible individual. Antibiotics therefore possess the ability to change the course of IBD in a variety of ways including reducing luminal bacterial content, changing the microflora of the colon, reducing bacterial invasion of intestinal tissue, and limiting bacterial translocation [3].

Unfortunately, there are no randomized therapeutic antibiotic studies that have been performed in children with IBD to assess the efficacy and validity of their use. Most reported pediatric studies have at best mentioned that concurrent antibiotic use was permitted if already taking it during that specific study involving another medication intervention. Consequently, the pediatric gastroenterologist has to the extrapolate from and rely on adult evidence-based medicine clinical trials (class I or II studies) regarding the role of antibiotic therapy in the treatment of IBD.

The most frequently used maintenance antibiotics in management of adult IBD are metronidazole and ciprofloxacin. Ciprofloxacin has uniformly not been used in the treatment of children due to concerns regarding adverse bone growth effects noted in animal studies. To date, no long-term ciprofloxacin studies in children have been published but short-term treatment of urinary tract infections and other infectious illness without adverse events can be found. Metronidazole has Food and Drug Administration's approval for the use in children for the treatment of infections and has been utilized in the chronic treatment of IBD.

Antibiotic Use in Crohn Disease

Based on adult IBD trials, metronidazole and ciprofloxacin have shown significance in the management of mild to moderate Crohn disease involving the distal small bowel as well as perianal disease related to enterocutaneous fistula(e) and perhaps delay in recurrence after ileal resection [4, 5].

Active Crohn Disease

Several studies have been carried out over the last 30 years evaluating the use of antibiotics in active Crohn disease. In the only published efficacy study in children, Hildenbrand

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et al. evaluated the open label use of oral metronidazole 10–35 mg/kg in 20 children between the ages of 7 and 18 years with active Crohn disease. This group demonstrated improvement in clinical symptoms in 15 of 20 patients (12 improved, 3 moderately improved) who were followed for 6 months. Additionally, they reported that of 12 patients who were improved, 9 discontinued the medication after 6 months with return of symptoms in 7 patients within 11 months [6].

While pediatric studies evaluating the use of antibiotics in active Crohn disease are limited, several adult trials, both randomized and nonrandomized, have been published. Ursing and Kamme described the use of metronidazole in five patients with Crohn disease and reported a response in four of them [7]. In the first double-blinded comparative study involving antibiotics, metronidazole was compared to sulfasalazine in active Crohn disease in 78 patients. Patients were randomized to receive either metronidazole or sulfasalazine for 4 months and then crossed over to receive the alternate drug for an additional 4 months. The authors found that metronidazole was slightly more effective than sulfasalazine in treating active Crohn disease based on improvements in the Crohn Disease Activity Index [3]. Further double-blinded studies, including one performed by Sutherland et al. evaluated two doses of metronidazole (20 and 10 mg/kg) with placebo. One hundred and five patients were randomized, and 56 completed the 16-week study. The authors found significant reductions in disease activity index scores and serum orosomucoid levels among the groups receiving metronidazole vs. those who received placebo. The authors also found that patients with both large and small disease responded better to therapy than those with isolated small bowel disease [8].

Few randomized trials have been published evaluating the use of ciprofloxacin as monotherapy in active Crohn disease. In a randomized study conducted by Columbel et al., 40 patients with mild to moderate active Crohn disease received either ciprofloxacin or mesalamine for 6 weeks. The authors found similar response rates 56% vs. 55% among patients who received ciprofloxacin vs. those who received mesalamine as assessed by improvements in CDAI scores [9]. Ciprofloxacin was also compared to placebo in a study conducted by Arnold et al. The authors randomized 47 patients with active, resistant moderate Crohn disease to receive ciprofloxacin or placebo in combination with their previously prescribed conventional therapies and followed for 6 months. Significant decreases in CDAI were observed in the ciprofloxacin-treated group 187 to 112 vs. 230 to 205 in the placebo-treated group [10].

Several studies conducted in adults have evaluated the use of combination therapy with ciprofloxacin and metronidazole in active Crohn disease. Response rates varied among the studies but all demonstrated improvements ranging from 45 to 90% in patients who used combined therapies with the best responses among those patients with colonic involvement [11–13]. Interestingly, in one of these studies ciprofloxacin and metronidazole in combination were compared to methylprednisolone among 41 adult patients with active Crohn disease and similar reductions in symptoms and improvements in laboratory values (acute phase reactants, albumin, and hemoglobin) were seen in both groups [12]. Only one combination study has been published in pediatric Crohn disease by Levin et al. and this was a limited 32-patient retrospective analysis of the combined use of azithromycin and metronidazole [14]. After 8 weeks of treatment 66% demonstrated clinical remission as defined by a PCDAI < 10 with more severe disease, higher baseline PCDAI and CRP, associated arthritis and extensive disease, upper intestinal or ileocolonic involvement, found to be associated with a lack of response.

Perianal Disease

Perianal Crohn disease including fistulae and abscesses occur in almost 50% of patients with Crohn disease [15] and while a combination of surgical and medical treatment is preferred, antibiotics have shown some efficacy in several trials. Early reports by Ursing and Kamme noted improvements in perianal disease with the use of metronidazole [7]. In an uncontrolled trial, Allan and Cooke reported significant improvement in two patients with severe perianal disease after taking metronidazole [16]. In the first study evaluating the use of metronidazole for perianal disease only, Bernstein et al. placed 21 consecutive patients with perianal Crohn disease on metronidazole. The authors reported that all 21 had a dramatic reduction in drainage, erythema, and induration and complete healing in 10 of 18 patients maintained on the drug [17]. A follow-up study conducted by the same authors found continued efficacy of the drug in those patients maintained for longer periods of time including up to 1 year in 16 of 26 patients followed. The authors did however note that disease frequently returned when the drug dose was lowered, or the drug was discontinued [18].

Topical metronidazole 10% ointment has been evaluated as a means of minimizing adverse effects of systemic metronidazole in the treatment of perianal Crohn disease [19]. Maeda et al. performed a double-blind controlled trial comparing metronidazole ointment to placebo, and showed no statistical reduction in PCDAI scores. However, metronidazole application three times daily for 4 weeks showed a significant reduction in perianal pain and discharge.

Antibiotics have also been investigated in conjunction with other medications including azathioprine and infliximab in the treatment of perianal Crohn disease. Dejaco et al. evaluated 52 adult patients with perianal fistulas in an open-labeled trial using ciprofloxacin and/or metronidazole [20].

Patients who were on azathioprine were allowed to continue (17 patients), and an additional 14 patients received azathioprine after 8 weeks of antibiotic therapy. The authors found that 50% of patients had a clinical response to antibiotics at 8 weeks and 25% continued to respond at week 20. They also found that patients who received azathioprine and antibiotics were more likely to respond than those who received antibiotics alone. They concluded that antibiotics may, therefore offer a bridge to immunosuppression as there was a good short-term response. In a more recent randomized, controlled trial, West et al. evaluated ciprofloxacin vs. placebo in conjunction with infliximab among 24 patients with perianal Crohn disease [21]. Although statistical significance was not achieved, the authors noted a trend toward a better response among patients who received ciprofloxacin and infliximab vs. placebo and infliximab at week 18 (73% vs. 38%).

Postoperative Recurrence of Crohn Disease

A large proportion of patients with Crohn disease will require surgery at some point during the course of their disease, and a majority of these patients will eventually develop recurrence of disease requiring additional surgery [22, 23]. Previous studies have suggested that bacteria may play a role in the recurrence of disease as it occurs when the mucosa is re-exposed to luminal contents and bacteria [24] and thus antibiotics may have a beneficial role in the prevention of postoperative recurrence of Crohn disease.

In a double-blind, placebo-controlled trial, Rutgeerts et al. evaluated the efficacy of metronidazole in the prevention of postoperative recurrence of Crohn disease following ileal resection [25]. Sixty adult patients were randomized to receive metronidazole or placebo for 3 months. While both groups demonstrated some endoscopic recurrence of disease at 3 months (75% placebo group vs. 52% metronidazole group), the incidence of severe endoscopic disease recurrence was significantly reduced among the metronidazole-treated group (13% vs. 43%). The authors also found a statistically reduced recurrence rate among the treated group at 1 year vs. placebo although no differences were seen at 2 and 3 years. A more recent study conducted with the use of ornidazole, a nitromidazole antibiotic with fewer side effects than metronidazole (not available in the United States), has also been performed [26]. Eighty patients were randomized to receive ornidazole or placebo for 1 year beginning a week after ileal resection. Ornidazole significantly reduced the clinical recurrence rate at 1 year (7.9% ornidazole group vs. 37.5% placebo group), although no significant difference in clinical recurrence was seen at 24 and 36 months. The endoscopic recurrence rate at 12 months was also lower among those patients that received ornidazole compared with placebo.

Both studies seem to indicate a reduction in postoperative recurrence among patients who receive antibiotics. Optimal dosing and the duration of therapy needed to prevent recurrence are still unclear and may require future studies.

Antibiotics in Ulcerative Colitis

There are few evidence-based studies demonstrating the utility of antibiotics in the treatment of ulcerative colitis (UC) aside from those involving colitis exacerbation secondary to *Clostridium difficile* superinfection treated with antibiotics targeted for this organism or due to toxic megacolon in which case treatment with antibiotics is employed until surgical resection can be performed. Dickinson et al. showed no significance in the use of vancomycin in patients with ulcerative colitis (UC) in 1985; Chapman et al. also showed no advantage of intravenous metronidazole in 1986, and Mantzaris et al. in 1997 showed no significance of ciprofloxacin use in mild-to-moderate active UC [27–29]. A subsequent study by Mantzaris et al. also showed no difference in response rates between patients with severe, acute colitis who were randomized to receive intravenous ciprofloxacin and hydrocortisone vs. placebo and hydrocortisone [29]. Turunen et al. in a longer-term 6 months study of ciprofloxacin in active UC patients not doing well on steroids and mesalamine did demonstrate a lower treatment failure rate, 21% vs. 44%, ($p<0.002$) along with endoscopic and histologic improvement at 3 months, but not at 6 months. The authors also found that at 12 months, there was no longer a significant difference in response rates between the two groups [30].

Antibiotics were compared with sulfasalazine in a double-blinded, controlled trial of patients with active, non-severe ulcerative colitis. Forty-six patients were randomized to receive metronidazole or sulfasalazine for 28 days [31]. The authors found that only 6 of 23 patients in the metronidazole group improved vs. 13 of 19 patients in the sulfasalazine group and concluded that metronidazole was ineffective in the treatment of active ulcerative colitis.

Additional antibiotics including tobramycin, amoxicillin-clavulanic acid, amoxicillin, and tetracycline have also been studied in patients with active ulcerative colitis. Mixed results have been reported regarding the use of tobramycin. Burke et al. randomized 84 patients with acute relapse of their ulcerative colitis to receive tobramycin or placebo along with steroids for 7 days [32]. The authors found significant clinical improvements in the tobramycin group vs. the placebo group after 3–4 weeks (74% vs. 43%). Lobo et al. however reported that these response rates were short lived as they followed 81 of those previously followed 84 patients for 2 years and found no difference in relapse rates between groups, and a second study by Mantzaris et al. showed no

difference in response rates in patients with severe active ulcerative colitis who received intravenous tobramycin and metronidazole in conjunction with corticosteroids vs. placebo and corticosteroids alone [33, 34]. More recently, Ohkusa et al. reported some success in the treatment of active ulcerative colitis with the use of amoxicillin, tetracycline, and metronidazole [35]. In this randomized, controlled trial 20 patients with chronic, active ulcerative colitis were randomized to receive the above combination of antibiotics or placebo for 2 weeks. The antibiotics were selected based on their sensitivities toward *Fusobacterium varium* which has been proposed as a pathogenic factor in the development of UC. The authors reported significant improvements in endoscopic/histologic scores as well as clinical symptoms at 3–5 and 12–14 months. They also reported a significantly higher remission rate among the treatment group vs. those who received placebo. In a follow-up study, Uehara et al. showed that antibiotic combination therapy with amoxicillin, tetracycline, and metronidazole was also useful in obtaining remission in refractory and steroid-dependent cases of Crohn disease. Patients showed statistically significant reductions in their clinical activity indexes, histologic, and endoscopic scores following 2 weeks of therapy. Moreover, 70.6% of steroid refractory or steroid-dependent patients were able to discontinue steroid therapy at 12 months [36].

Finally, patients who present with fever and a colitis exacerbation admitted to the hospital may also be treated with triple antibiotics, ampicillin, gentamicin and metronidazole, until a bacterial superinfection triggering the disease exacerbation has been excluded at which point the antibiotics are stopped after negative stool cultures and negative blood cultures.

Emerging Therapies

More recently with the development of newer antimicrobials that have the majority of their action within the bowel lumen with minimal systemic absorption, researchers have started to study their effect in the management of IBD. Rifaximin (Xifaxan®) and Nitazoxanide (Alinia®) are the two most recent potential therapeutic candidates.

Rifaximin comes in a tablet form to treat *Escherichia coli*-related traveler's diarrhea and also has effect against a broad coverage of small bowel bacteria covering most gram-positive and gram-negative bacteria, both aerobes and anaerobes. Side effects are minimal: headache, constipation, vomiting, abdominal cramp/pain, and it has no bowel absorption but is not FDA-approved for use in IBD or in children.

There are limited adult randomized controlled studies or placebo-controlled studies involving rifaximin reported in the treatment of IBD. Campieri et al. in 2000 reported in abstract form only their results of a randomized postoperative recurrence prevention trial evaluating the efficacy of rifaximin 1.8 g/day for 12 weeks followed by probiotic VSL#3 of 6 g/day for another 9 months compared to mesalamine 4 g/day for 1 year after resection of disease bowel in 40 Crohn disease patients [37]. After 3 months there was a lower incidence of endoscopic recurrence in the rifaximin group 10% vs. 40% which was maintained after 1 year: 20% vs. 40%. Shafran and Johnson conducted an open-labeled study among 29 adult patients with mild to moderate Crohn disease [38]. Patients received rifaximin for 16 weeks. The authors reported 59% of patients had a significant reduction in disease activity scores at the end of 4 weeks and 78% had decreased their CDAI score by greater than 70 points at the end of 16 weeks. Fifty-nine percent of patients had achieved clinical remission by the end of the study, and the authors conclude that rifaximin may show some promise in the treatment of Crohn disease. In a follow-up study, Shafran and Burgunder showed that rifaximin monotherapy led to clinical improvement in Crohn disease patients. They reported that remission (CDAI < 150) was achieved in 67% of patients on rifaximin monotherapy, compared to 58% in patients who received steroids [39]. Kornbluth et al. also reported some success in the treatment of mild to moderate, refractory Crohn disease with rifaximin daily at 2 doses (200 mg three times daily and 400 mg twice daily) [40]. Thirty patients were studied in an open-labeled, retrospective study. The authors found that 43% of patients with ileitis, 67% of patients with ileocolitis and 63% of patients with colitis improved, and they concluded that rifaximin may be effective in treating mild to moderate refractory Crohn disease.

Rifaximin has also been evaluated in patients with ulcerative colitis. Gionchetti et al. in 1999 in their study of 28 moderate to severe ulcerative colitis patients showed no significant differences in outcome in patients not responding to intravenous methylprednisolone after 7–10 days with the additional use of 400 mg bid of rifaximin [41]. The authors did, however, note a reduction in stool frequency, rectal bleeding, and sigmoidoscopy scores among the rifaximin group. In abstract form in 2002 regarding an open-label study by Lukas et al. of mildly active ulcerative patients, the authors reported a 30% reduction in disease activity after 1 month in their patients who used rifaximin as additional therapy [42]. Also, in left-sided ulcerative colitis relapsing on mesalamine, Guslandi et al. in an open label study of 400 mg by mouth twice daily bid with 2.4 g/day mesalamine demonstrated that the addition of rifaximin resulted in 70% clinical remission [43]. An open label study for its use in ulcerative pouchitis demonstrated an 81% efficacy for a dose of 600–800 mg daily [44]. Another study involving chronic-resistant ulcerative pouchitis by Gionchetti using rifaximin at 2 g/day along with ciprofloxacin 1 g/day demonstrated an 89% remission [45].

Rifaximin has shown to be a promising treatment in pediatric IBD patients. Muniyappa et al. showed a significant improvement in symptoms following initiation of rifaximin during disease flares. Twenty-three patients (12 with CD and

11 with UC) with a median age of 15.1 years were given varying doses of rifaximin at onset of flare symptoms, which included diarrhea (87%), abdominal pain (74%), and bloody stools (65%). Addition of rifaximin as the only treatment change resulted in symptom relief for 61% of patients after 4 weeks of treatment. Of these patients, 80% had resolution of all of their flare symptoms [46].

Nitazoxanide comes in both tablet and suspension forms making this ideal for pediatric use with FDA indications for parasitic infectious diarrhea (*Cryptosporidium parvum* and G*iardia lamblia* as well as helminthes and tapeworms). The drug is metabolized by the cytochrome P450 mechanism in the liver with bile, feces and urinary excretion. Its side effect profile is minimal with abdominal pain, diarrhea, headache and nausea reported and is similar to placebo. Some researchers have been studying its use to treat *C. difficile* as well as in Crohn disease but published results are not available.

Both drugs, rifaximin and nitazoxanide, have shown some promise as primary therapies in IBD. More rigorous testing including randomized, controlled trials are necessary before the drugs are accepted as appropriate mainstream treatment, however.

Limited data exist on the use of antibiotics for extra-intestinal manifestations associated with IBD. Oral vancomycin has shown some promise in treating the subset of pediatric IBD patients with Primary Sclerosing Cholangitis (PSC). Davies et al. treated 14 IBD patients (11 ulcerative colitis) diagnosed with PSC with 50 mg/kg/day of oral vancomycin for 14 days. All showed significant improvement in their alanine aminotransferase, gamma-glutamyl transpeptidase, erythrocyte sedimentation rate, and clinical symptoms. Three patients who were rebiopsied demonstrated reversal of their fibrosis [47]. While this initial study was promising, more information is needed to verify whether oral vancomycin is an effective long-term treatment in preventing the progression of PSC to cirrhosis in IBD patients.

Additional Considerations

When utilizing antibiotics in the acute or maintenance arm of therapy, careful consideration for which form of mesalamine treatment being used concurrently is especially necessary since medications such as olsalazine or sulfasalazine require the presence of bacteria to cleave their disulfide bond in order to permit action of the medication. Asacol requires a basic/neutral lumenal pH to be effective such that with stenotic disease and the potential of bacterial overgrowth with a more locally acidic lumenal pH, concurrent antimicrobial therapy theoretically may be beneficial.

While generally well tolerated, antibiotics can lead to side effects that may require discontinuation and should be monitored closely. As previously mentioned, ciprofloxacin has been noted to cause arthropathies in immature animals, and long-term use is generally avoided among children. One pediatric study evaluated side effects associated with long-term metronidazole use. Duffy et al. reported on their experience among 13 pediatric Crohn disease patients who received metronidazole for 4–11 months [48]. They found that 85% (11 of 13) had peripheral neuropathies based on abnormal nerve conduction velocities or neurological examinations although only 6 of 11 were symptomatic. Complete resolution of the neuropathy occurred in five children, improvement occurred in three children and there was no change in one child.

Summary

In summary, limited prospective studies investigating antibiotic use in pediatric IBD are available. Based on available literature, some role for antibiotics including metronidazole and/or ciprofloxacin has been shown for acute exacerbations of Crohn disease and chronic penetrating Crohn disease. No available, objective evidence supports their use in acute ulcerative colitis. Vancomycin may be useful in IBD patients with PSC. Additional prospective studies are needed to evaluate the role of vancomycin and other antibiotics including rifamixin and nitazoxanide.

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