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 trigger an immune response that leads to intestinal mucosal inflammation. For reasons still not known, genetically susceptible patients lack the ability to turn off this immune system activation resulting in perpetual intestinal mucosal inflammation and clinical symptoms of IBD [1]. Additionally, patients with Crohn disease (CD) who have diverting ileostomies demonstrate a downstream decrease in disease activity when the fecal stream is 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 an infectious stimulus or to the commensal microbiota that ultimately results in the development of IBD in the susceptible individual. Antibiotics therefore possess the ability to change the course of inflammatory bowel disease in a variety of ways including reducing luminal bacterial content, changing the composition of the gut microbiota, reducing bacterial invasion of intestinal tissue, and limiting bacterial translocation [3]. An immunomodulatory effect has also been proposed [4].

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 must 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 development of musculoskeletal disorders noted in studies of juvenile animals. To date, no long-term ciprofloxacin studies in children have been published, but short-term treatment of urinary tract infections and other infectious illnesses 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 [5, 6].

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Active Crohn Disease

Several studies have been carried out over the last 30 years evaluating the use of antibiotics in active Crohn disease. While the results of many of these studies are conflicting, a recent meta-analysis of 15 randomized controlled trials demonstrated a small but statistically significant benefit of antibiotics in the treatment of Crohn disease [7]. In the only published prospective efficacy study in children, Hildebrand 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 15/20 patients (12 improved, three moderately improved) who were followed up for 6 months. Additionally, they reported that of 12 patients who were improved, nine discontinued the medication after 6 months with return of symptoms in seven patients within 11 months [8].

While pediatric studies evaluating the use of antibiotics in active Crohn disease are limited, several adult trials, both randomized and non-randomized, 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 [9]. 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 (CDAI) [3]. Further double-blinded studies, including one performed by Sutherland et al., evaluated two doses of metronidazole (20 and 10 mg/kg) versus 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 versus 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 [10].

Few randomized trials have been published evaluating the use of ciprofloxacin as monotherapy in active Crohn disease. In a randomized study conducted by Colombel 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 % versus 55 % among patients who received ciprofloxacin versus those who received mesalamine as assessed by improvements in CDAI scores [11]. 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 the patients for 6 months. Significant decreases in CDAI were observed in the ciprofloxacin-treated group 187–112 versus 230–205 in the placebo-treated group [12].

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 [13–15]. Interestingly, in one of these studies, ciprofloxacin and metronidazole in combination were compared to methylprednisolone among 41 adult patients with active Crohn disease. Similar reductions in symptoms and improvements in laboratory values (acute phase reactants, albumin, and hemoglobin) were seen in both groups [14]. Only one antibiotic combination study has been published in pediatric Crohn disease by Levine et al., and this was a limited 32-patient retrospective analysis of the combined use of azithromycin and metronidazole [16]. After 8 weeks of treatment, 66 % demonstrated clinical remission as defined by a Pediatric Crohn's Disease Activity Index (PCDAI) < 10. More severe disease with higher PCDAI and CRP values at baseline, presence of associated arthritis, and extensive disease (prominent upper intestinal disease or ileocolonic disease) were 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 [17], 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 [9]. In the first open-label 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 ten of 18 patients maintained on the drug [18]. 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 [19].

Topical metronidazole 10 % ointment has been evaluated as a means of minimizing adverse effects of systemic metronidazole in the treatment of perianal Crohn disease [20]. 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 [21]. 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 versus placebo in conjunction with infliximab among 24 patients with perianal Crohn disease [22]. Although statistical significance was not achieved, the authors noted a trend toward improved response among patients who received ciprofloxacin and infliximab versus placebo and infliximab at week 18 (73 % versus 38 %). There is evidence to suggest that antibiotics reduce fistula drainage but less evidence to suggest that antibiotics lead to fistula healing [23]. Therefore, a recent global consensus on the treatment of perianal disease recommended that antibiotics should only be used as adjunctive therapy [23].

Postoperative Recurrence of Crohn Disease

A large proportion of patients with Crohn disease 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 [24, 25]. Previous studies have suggested that bacteria may play a role in the recurrence of disease as inflammation recurs when the mucosa is reexposed to luminal contents and bacteria [26]. Based on this causal relationship, 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 [5]. 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 versus 52 % metronidazole group), the incidence of severe endoscopic disease recurrence was significantly reduced among the metronidazole-treated patients (13 % versus 43 %). The authors also found a statistically reduced recurrence rate among the metronidazole-treated group versus placebo at 1 year although no differences were seen at 2 and 3 years. A more recent study conducted with the use of ornidazole, a nitroimidazole antibiotic with fewer side effects than metronidazole (not available in the USA), has also been performed [27]. Eighty patients were randomized to receive ornidazole or placebo for 1 year beginning 1 week after ileal resection. Ornidazole significantly reduced the clinical recurrence rate at 1 year (7.9 % ornidazole group versus 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 who received ornidazole compared with placebo.

Taken together, available studies seem to indicate a reduction in postoperative recurrence among patients who receive antibiotics [28]. Optimal dosing and the duration of therapy needed to prevent recurrence are still unclear and will require future studies. Additionally, antibiotic selection may be critical. In a small randomized, double-blind, placebo-controlled pilot study, ciprofloxacin was not more effective than placebo for the prevention of postoperative recurrence in patients with Crohn disease [29].

Antibiotics in Ulcerative Colitis

There are few evidence-based studies demonstrating the utility of antibiotics in the treatment of ulcerative colitis aside from those involving colitis exacerbation secondary to *Clostridium difficile* superinfection. These patients were 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 [30], Chapman et al. also showed no advantage of intravenous metronidazole in 1986 [31], and Mantzaris et al. in 1997 showed no significance of ciprofloxacin use in mild to moderately active UC [32]. 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 versus placebo and hydrocortisone [32]. Turunen et al. in a longer-term 6-month study of ciprofloxacin in active UC patients without improvement on steroids and mesalamine demonstrated a lower treatment failure rate, 21 % versus 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 [33].

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 [34]. The authors found that only six of 23 patients in the metronidazole group improved versus 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 [35]. The authors found significant clinical improvements in the tobramycin group versus the placebo group after 3–4 weeks (74 % versus 43 %). Lobo et al. however reported that these response rates were short-lived as they followed up 81 of those previously followed up 84 patients for 2 years and found no difference in relapse rates between groups. 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 versus placebo and corticosteroids alone [36, 37].

More recently, Ohkusa et al. reported some success in the treatment of active ulcerative colitis with the use amoxicillin, tetracycline, and metronidazole [38]. 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 in an experimental model [39]. The authors reported significant improvements in endoscopic/histologic scores as well as clinical symptoms at 3–5 months and 12–14 months. They also reported a significantly higher remission rate among the treatment group versus 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 achieving remission in refractory and steroid-dependent cases of Crohn disease. Patients showed statistically significant reductions in their clinical activity indexes and 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 [40]. In pediatrics, a recent study by Turner and colleagues retrospectively reported on their experiences using a 2–3-week course of combination oral antibiotics in children with moderate to severe, refractory UC or indeterminate colitis (IC) [41]. This regimen primarily consisted of metronidazole, amoxicillin, and doxycycline, with the addition of vancomycin in hospitalized patients. The antibiotic regimen was effective in 7/15 (47 %) of patients, inducing complete short-term remission and preventing the need for additional interventions.

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. However, there is some suggestion that hospitalized patients with ulcerative colitis who receive both IV corticosteroids and antibiotics may have a decreased requirement for in-hospital rescue therapies than hospitalized patients with ulcerative colitis who receive IV corticosteroids alone [42]. This is a finding that needs to be further explored.

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 range of small bowel bacteria covering most gram-positive and gram-negative bacteria, both aerobes and anaerobes. Side effects are minimal and may include headache, constipation, vomiting, and/or abdominal cramp/pain. Rifaximin 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 Crohn disease. Shafran and Johnson first studied rifaximin in an open-label study among 29 adult patients with mild to moderate Crohn disease [43]. Patients received rifaximin for 16 weeks. The authors reported that 59 % of patients had a reduction in CDAI score of greater than or equal to 70 points at the end of 4 weeks and that 78 % had a reduction in CDAI score by greater than or equal to 70 points at the end of the 16-week treatment period. The authors concluded that rifaximin might 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 patients with Crohn disease. They reported that remission (CDAI less than 150) was achieved in 67 % of patients treated with rifaximin monotherapy, compared to 58 % in patients who received treatment with steroid [44].

One of the largest studies of the treatment of Crohn disease with rifaximin evaluated an extended release formulation, Rifaximin-EIR [45]. Rifaximin-EIR is coated with a gastric acid-resistant polymer and is designed to bypass the stomach and maximize delivery to the intestinal tract. In this study, 402 patients with moderately active Crohn disease received Rifaximin-EIR at different dosages versus placebo for 12 weeks. Patients could have active disease on stable dosages of mesalamine, thiopurines, or methotrexate, and

recent steroid, anti-TNF, or antibiotic use was not allowed. Treatment with Rifaximin-EIR 800 mg twice daily was able to induce remission by CDAI (62 % compared to 43 % in the placebo group).

Rifaximin has also been evaluated in patients with ulcerative colitis. In 1999, Gionchetti et al. in their study of 28 moderate to severe ulcerative colitis patients showed no significant difference in clinical outcome in patients not responding to intravenous methylprednisolone after 7–10 days with the additional use of 400 mg bid of rifaximin [46]. The authors did, however, note a reduction in stool frequency, rectal bleeding, and sigmoidoscopy scores among the rifaximin group as compared to the placebo-treated group. Also, in an open-label pilot study of patients with left-sided ulcerative colitis who were experiencing a clinical relapse with maintenance therapy with mesalamine, the addition of rifaximin 400 mg twice daily induced clinical remission in 70 % [47]. An extension of this study adding an additional 20 patients (increasing total *n* to 30) demonstrated similar findings [48]. These data are encouraging, but larger, controlled studies are needed to confirm the results.

As opposed to the modest efficacy seen in Crohn disease and ulcerative colitis, antibiotics are very effective for the treatment of pouchitis following total proctocolectomy [49, 50]. Rifaximin has also been studied in this setting. In a study by Gionchetti and colleagues of patients with treatment-resistant pouchitis, the combination of rifaximin 2 g/day plus ciprofloxacin 1 g/day led to improvement in disease activity in ten out of 18 patients and remission in six out of 18 patients by Pouchitis Disease Activity Index (PDAI) [51]. A randomized, double-blind, placebo-controlled pilot study suggested that clinical remission was more likely in patients with active pouchitis treated with rifaximin as compared to placebo; however, the improvement did not reach statistical significance likely secondary to small sample size [52]. Rifaximin has also been evaluated as a maintenance of remission therapy in pouchitis once remission has been induced with other antibiotics [50]. The results were favorable and adverse events were rare.

Rifaximin may also 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 [53].

Nitazoxanide comes in both tablet and suspension forms making this ideal for pediatric use with FDA indications for parasitic infectious diarrhea (*Cryptosporidium parvum* and *Giardia lamblia* as well as helminths 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 at similar rates as placebo. Some researchers have been studying its use to treat *Clostridium difficile* as well as in Crohn disease. To date, the only published data in inflammatory bowel disease is in patients with Crohn disease who have a concomitant cryptosporidial infection [54].

Both drugs, rifaximin and nitazoxanide, have shown some promise as primary therapies in inflammatory bowel disease. 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 [55]. While this initial study was promising, further studies are 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 phase 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 luminal pH to be effective such that with stenotic disease and the potential of bacterial overgrowth with a more locally acidic luminal 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 very young children. There is also one pediatric study which evaluated the 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 [56]. The authors reported that 85 % (11 of 13) had peripheral neuropathies based on abnormal nerve

conduction velocities or neurological examinations although only six 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 inflammatory bowel disease 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. However, more recent reports of combination antibiotics in the treatment of severe ulcerative colitis are promising. Vancomycin may be useful in IBD patients with primary sclerosing cholangitis. Additional prospective studies are needed to evaluate the role of vancomycin and other antimicrobials including rifaximin and nitazoxanide.

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