Current view

The role of antibiotics in inflammatory bowel disease

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SUMMARY

Antibiotics are the mainstay of therapy for patients with Crohn's disease who present with localized peritonitis due to a microperforation and bacterial overgrowth secondary to chronic strictures. They are essential adjuncts to drainage therapy for Crohn's disease-associated abscesses and for perineal disease. Antibiotics have a role as primary therapy in active uncomplicated CD. The efficacy of their response must be considered in well-defined subsets of patients. Ciprofloxacin and metronidazole, the two most widely studied antibiotics, are effective therapy for patients with active ileocolonic and colonic disease and have been shown to reduce recurrence rates after ileocolonic resection. The benefits of these drugs are less clear for patients with uncomplicated ileal disease. Ciprofloxacin and metronidazole may also serve as an adjunct to immunomodulator therapy. In toxic patients with fulminant ulcerative colitis, with or without megacolon, antibiotics should be administered along with corticosteroids and other supporting measures. In less severely ill patients requiring hospitalization, antibiotics may be given to cover for the potential of a superimposed infection until the workup for infection, including Clostridium *difficile*, amoeba and salmonella is available. There may be a subset of patients with severe nontoxic colitis who respond to antibiotics, but to date controlled trials have not shown efficacy in this group. However, antibiotics should not be routinely used for mild to moderately ulcerative colitis, although a trial of ciprofloxacin is not unreasonable prior to colectomy for otherwise refractory patients. The use of rifaximin in UC seems promising but further evaluation is required. Altough further clinical trials evaluating the role of antibiotics in inflammatory bowel disease are required the available data are in favour of the widely adopted assumption that antibiotics are useful and valuable drugs in patients with either Crohn's disease or ulcerative colitis.

Key-words: Antibiotics, Crohn's disease, ulcerative colitis, inflammatory bowel disease

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1. INTRODUCTION

Every day clinical practice and experience suggest that some antibiotics, mainly metronidazole, ornidazole and ciprofloxacine could be of benefit in some patients with inflammatory bowel disease (IBD) via either their antimicrobial action or because they act as "non-specific protective drugs". This view has been adopted by so many experts that it seems reasonable to suggest that "*antibiotics could be used as a first-line treatment for patients with Crohn's disease*".[1] Indeed the indications for antibiotic therapy are widely ranging, from specific situations such as abscesses or fistulae, to patients with severe disease. This suggestion is based on the fact that the altered immunological reaction against certain enteric microbes in genetically predisposed subjects plays an important role in perpetuating the inflammatory process in the bowel wall. Another reason is related to bacterial overgrowth appearing in 20% of patients with Crohn's disease (CD) and incomplete bowel obstruction. In this subset of patients, administration of metronidazole and ciprofloxacin seems to be of benefit.[2]

On the other hand, it is well known that a quite large number of infections by parasites or pathogenic microbes like amoeba, C. difficile, Cambylobacter, and Salmonella in patients with IBD can be observed. The administration of antibiotics in these cases along with drugs for the under-

lying IBD is mandatory3. It has been well established that normal, nonpathogenic enteric bacteria induce and perpetuate chronic intestinal inflammation in genetically susceptible hosts with defective immunoregulation, bacterial clearance or mucosal barrier function. Altering the composition and decreasing mucosal adherence and invasion of commensal bacteria with antibiotics, can potentially prevent and treat CD, pouchitis, and possibly severe UC.

However, the role of antibiotics in IBD is more complex. In an epidemiological study it was found that consumption of antibiotics by patients with CD two to five years before the establishment of diagnosis was greater compared to the consumption of antibiotics by matched normal controls.[4]

So far, a relatively small number of clinical studies dealing with the use of antibiotics in IBD has been published. Some of the published studies include relatively small numbers of patients probably because of the appearance of side-effects.[5-16] The lack of interest of the large pharmaceutical companies is another contributing factor.

In the following sections we discuss the existing data giving special emphasis on the contribution of Greek researchers.

2. RATIONALE FOR THE USE OF ANTIBIOTICS IN IBD

The distal ileum and the colon which are the sites of inflammation in IBD are also the areas with the highest bacterial concentrations. It is of interest that, pouchitis appears to be associated with bacterial overgrowth and dysbiosis. Moreover, patients with CD consistently respond to diversion of faecal stream, with immediate recurrence of inflammation after restoration of intestinal continuity or infusion of luminal content into the bypassed ileum.[17] On the other hand, an increased number of aggressive bacteria such as *Bacteroides,* adherent/invasive *Escherichia coli* and enterococci, and decreased number of protective lactobacilli and bifidobacteria have been observed in IBD patients.[18]

Clinical and experimental studies suggest that the relative balance of aggressive and protective bacterial species is altered in CD, UC, and pouchitis. Antibiotics can selectively decrease tissue invasion and eliminate aggressive bacterial species or globally decrease luminal and mucosal bacterial concentrations. Experimental colitis does not occur in a sterile environment and is prevented by broad-spectrum antibiotics. CD and UC patients exhibit pathogenic immune responses to multiple normal enteric bacterial species and serologic responses to *Mycobacterium paratuberculosis.*

In patients with established diagnosis of UC the mechanism of action of antibiotics could be related to the modification of the normal enteric flora, suppression of pathogenic microbes and inhibition of formation of micro-abscesses. Some of the proposed mechanisms of action of antibiotics are shown in table 1.

3. ANIMAL MODEL STUDIES

So far, the most compelling evidence that intestinal bacteria play a role in IBD has been derived from animal models. It is well established that the presence of normal enteric flora is required for full expression of inflammation[19] and that immunological tolerance to commensal bacteria is lost in patients with IBD.[20] These findings have led to the proposal that manipulation of intestinal microbiota flora with antibiotics may be therapeutic in IBD.

In rodent models the use of antibiotics can both prevent and treat experimental colitis, whereas metronidazole and ciprofloxacin can only prevent experimental colitis but cannot reverse the established disease.[21] Broad-spectrum antibiotics are effective in almost all models of acute and chronic colitis.[22] Ciprofloxacin and metronidazole have selective efficacy in different colonic regions of interleukin-10 knockout mice, suggesting that different bacteria cause inflammation in different colonic segments.[23] These studies suggest that IBD may respond to a combination of broad-spectrum antibiotics.

4. ANTIBIOTICS USED IN PATIENTS WITH IBD

4.1 Metronidazole

Metronidazole represents the best-studied single antibiotic compound in patients with IBD. It was used in patients with CD for first time on 1975. Soon after, it was realized that the drug was effective in patients with active CD and especially in those with perianal disease and fistulas. Later it was noticed that the drug could be effective in reducing the rate of relapses and preventing endoscop-

Table 1. Proposed mechanisms of action of antibiotics in IBD

1. Eradication of bacterial antigenic triggers
2. Elimination of bacterial overgrowth
3. Reduction of proinflammatory bacterial toxins
4. Potential immunosuppressive properties of antibiotics
5. Reduction of the colonic oxidative damage

ic and clinical recurrences after local excision of the diseased bowel and end-to-end anastomosis.

Clinical studies: In 1978, Blichfeldt *et al*[24] found that there is no difference between metronidazole and placebo-treated patients in a placebo-controlled, double-blind, crossover trial. However, a positive trend in favour of metronidazole was observed when only the colon was involved. In the National Cooperative Swedish Study, metronidazole was compared with sulphasalazine as a primary treatment for CD. It was found that metronidazole was effective in patients who fail to respond to sulphasalazine.[25] In another study, metronidazole was used either as a single therapy or in combination with cotrimoxazole and compared to cotrimoxazole alone and a double placebo in patients with a symptomatic relapse of CD. The results showed that after four weeks there was no difference in response among the three treatment groups.[26] Sutherland et al[27] showed that treatment with metronidazole for 16 weeks significantly decreases the Crohn's disease activity index, but no difference was found in the rates of remission compared with placebo. Again it was shown that metronidazole was effective for colonic and ileocolonic CD, but not for ileitis. Rutgeerts et al[28] have assessed the efficacy of metronidazole at 20 mg/kg per day in a placebo-controlled double-blind study. Sixty patients received either metronidazole or placebo for 12 weeks and endoscopic relapse was evaluated at the end of the treatment. It was found that metronidazole significantly decreases the incidence of severe endoscopic relapse and the clinical recurrence rate. Table 2 shows the results of randomized clinical trials of antibiotics on patients with IBD.[24-31,40,41]

The dose of 20mg/Kg BW for 3 months of metronidazole seems to be the optimum one. In patients with perianal disease the recommended dose is 20 mg/Kg BW although doses of 15 or even 10 mg/Kg BW produce satisfactory results with fewer side-effects. If the dose of 20 mg/Kg BW produces no adverse effects, it must be continued for 6 months. After this period the dose could be reduced by 250mg per month. Treatment must not exceed a period of one year. At the beginning the dose should be half of the recommended in order for the possible side-effects to be as mild as possible. Clinical improvement can be seen after 2 to 4 weeks. Therefore it is of paramount importance not to interrupt the administration of the drug before 2 or 4 weeks. Many patients would show improvement after one or two months with complete response to therapy appearing after 3 to 4 months. Premature interruption of treatment leads to early recurrence. For patients with perianal CD, topical 10% metronidazole decreases the Perianal Crohn's Disease Activity Index and anorectal pain.[31]

Mode of action: The exact mode of action of metronidazole is not fully understood. It has been found that the drug has immunosuppressive action in experimental animals as well as leucocyte chemotactic activity in man. However, its action in man is probably related to its antimicrobial action because clinical improvement is parallel to the rate of reduction of the number of bacteroids in the feaces.

It is well known that reactive oxygen species, primarily

Table 2. Antibiotic trials in active Crohn's disease

Study	Patients	wk	Main outcome	Study design	Treatment schedules
Blichfeldt et al [24]	22	8	Improvement (clinical/lab score)	DB crossover study	MZ (+ SASP/CS) Placebo (+ SASP/CS)
Ursing et al [25]	22	16	Change in CDAI and orosomucoid	DB crossover study	MZ SASP
Ambrose et al [26]	72	4	Improvement (Clinical/lab.score)	DB RCT	MZ CO, MZ/CO, placebo
Sutherland et al [27]	99	16	Change in CDAI from baseline	DR RCT	MZ (10/20 mg/kg) Placebo
Prantera et al [28]	41	12	Clinical remission (CDAI < 150)	NB RCT	MZ + Cipro Steroids
Colombel et al [29]	40	6	Clinical remission (CDAI < 150)	NB RCT	CIPRO 5-ASA
Arnold et al [30]	47	24	Change in CDAI	NB RCT	CIPRO (+ conc drugs) Placebo (+ conc drugs)
Steinhart et al [31]	134	8	Clinical remission (CDAI < 150)	DB RCT	MZ+CIPRO (+bud 9mg)

generated in the mitochondria, contribute to tissue injury in IBD. The efficacy of metronidazole may result not only from its antibiotic effect, but also from an antioxidant effect. In a recently performed study it was found that metronidazole significantly reduced the colonic oxidative damage to proteins without any side effect in the liver.[32]

Side effects: Metronidazole has numerous side-effects including nausea, anorexia, dysgeusia, dyspepsia and peripheral neuropathy, which limit its use in approximately 20% of patients. Other side-effects include metallic taste, headache, allergic reactions, and leucopenia. Most of these side-effects are eliminated with reduction of the dose. However, the most serious adverse effect is related to damage of the peripheral neurus system. Paresthesias which usually are clinically menifested after few months of the beginning of treatment are dose dependent. Reduction of the dose results in improvement of paresthesias, although damage of peripheral neures could persist for a long period. Isolated cases of pancreatitis have also been described. Avoidance of alcohol during treatment with metronidazole is recommended.

Indications of use

Table 3 summarises the indications of use of metronidazole in patients with IBD. It must be stressed that the main indication of use of metronidazole in CD is perianal disease and fistulas.

Conclusion: Metronidazole in a dose of 20mg/kg/d is a very useful drug in the treatment of CD especially in the presence of perianal disease. It seems to achieve better results in Crohn's colitis and ileocolitis. It should not be used if the drug shows no clinical benefit after three months.

4.2 Ornidazole

Ornidazole is a drug chemically similar to metronidazole. The first description of the effectiveness of ornidazole in CD was described on 1978. Ammann et al described 9 patients with active CD who received ornidazole for 2.5 to 14 months. Six of them improved significantly and the improvement lasted for 9 months.[33] Without knowledge of this publication Triantafillidis et al[34] described in 1988 the results of the administration of ornidazole in a series of 11 patients with active CD and gained similar results to those described by Ammann et al. In a subsequent study the same authors described the results of the administration of ornidazole in a cohort of 25 patients with mild to moderate CD. The analysis of the results was based on changes in the severity of the Crohn's disease activity index measured at entry and at the end of the first, second, third and fourth week. The results showed that Crohn's disease activity index fell gradually from week 0 to week 4 ($p < 0.001$), while the number of patients going into remission increased gradually from week 0 to week 4 (18/25 patients, 75%). Side effects were minimal.[35] The same group of investigators on 1998 described the results of the long-term administration (6 to 12 months) of ornidazole in a dose of 0.5d/d only in those patients with good initial response.[36] A significant proportion of patients remained on remission with no significant side-effects. Finally, the results of a recent study showed that ornidazole can reduce the rate of recurrence in patients who had undergone surgical excision of the terminal ileum.[37]

Table 3. Indications of metronidazole administration in patients with Crohn's disease.

1. Persistent and severe perianal disease
2. Enteroabdominal fistulas
3. Active Crohn's disease of the large bowel.
4. Persistent ileocolonic disease
5. Poor response to other drugs
6. Postoperative prophylaxis

Safety: The drug seems to be quite safe. The case of a patient who received 0.5g/d voluntarily for ten consequtive years without appearance of significant side-effects is indicative.[38] However, it seems necessary to check regularly the renal and liver function as well as the possibility of appearance of peripheral neuritis.

Mode of action: The mode of action again is unknown, although it seems logical to hypothesize that it is similar to metronidazole. In a study of healthy volunteers it was found that the drug significantly reduces the levels of serum complement C_3.[39]

4.3 Ciprofloxacine

In a controlled study ciprofloxacin (1g/d) was compared to mesalazine (4g/d) in mild to moderate active CD for 6 wk. The results showed that ciprofloxacin was as efficacious as mesalazine (remission observed in 56% and 55% of patients treated with ciprofloxacin and mesalazine respectively), thus offering a potential alternative treatment for active CD.[40] Furthermore, ciprofloxacin has been shown to be effective when used in combination with standard treatment in patients with resistant disease.[11]

4.4 Antimycobacterial treatment

Many studies have tried to evaluate the efficacy of antimycobacterial drugs in patients with CD, pursuing the possibility that a strain of *Mycobacterium* might be an aetiological agent in CD. A meta-analysis of all randomised

controlled trials in which antimycobacterial therapy was compared with placebo showed that antimycobacterial therapy is only efficacious in the maintenance of remission after a combined treatment of corticosteroids and antimycobacterial agents.[41] However, because of the high incidence of side-effects and the small number of studies included in the meta-analysis, the data are inconclusive and should be interpreted with caution.

In a prospective, parallel, placebo-controlled, double-blind, randomized trial of 2 years of clarithromycin, rifabutin, and clofazimine in active CD, with a further year of follow-up, 213 patients were randomized to clarithromycin 750 mg/day, rifabutin 450 mg/day, clofazimine 50 mg/day or placebo, in addition to a 16-week tapering course of prednisolone42. Those in remission at week 16 continued their study medications in the maintenance phase of the trial. Primary end points were the proportion of patients experiencing at least 1 relapse at 12, 24, and 36 months. At week 16, there were significantly more subjects in remission in the antibiotic arm (66%) than the placebo arm (50%; P=.02). Of 122 subjects entering the maintenance phase, 39% taking antibiotics experienced at least 1 relapse between weeks 16 and 52, compared with 56% taking placebo (P=.054). At week 104, differences were not significant. During the following year, 59% of the antibiotic group and 50% of the placebo group relapsed. The findings of this study do not support a significant role for Mycobacterium avium subspecies paratuberculosis in the pathogenesis of CD in the majority of patients. Short-term improvement was seen when this combination was added to corticosteroids, most likely because of non-specific antibacterial effects.

4.5 Rifaximine

Rifaximin is a poorly absorbed, broad-spectrum antibiotic that, thanks to its efficacy and long-term safety, could represent the preferred tool of manipulating enteric flora in patients with IBD. Rifaximine has mainly been used in patients with exacerbations of large bowel diverticular disease. In a recently published study43, 83 patients with mild-to-moderate CD were randomized to three treatments: Group A (rifaximin 800 mg o.d. + placebo), Group B (rifaximin 800 mg b.d.) and Group C (placebo b.d.). After 12 weeks clinical remission was achieved by 52% of group B, 32% of group A and 33% of group C. Clinical response was seen in 67% (group B), 48% (group A) and 41% (group C), without reaching a statistically significant difference. Treatment failures were: 4% (group B), 12% (group A) and 33% (group C), (P=0.010). Remission and response rates of rifaximin 800 mg b.d. were significantly higher than those of placebo and rifaximin 800 mg o.d. in patients with elevated CRP levels.

In an open-label study on the efficacy and safety of rifaximin (600 mg/d) for 16 wk in the treatment of mild to moderate active CD44 it was found that 59% of patients were in remission (CDAI<150) at the end of the study, with a significant reduction of the mean CDAI score compared to baseline. Rifaximine should be further evaluated in patients with active CD especially in those with perianal disease and patients with fistulas.

4.6 Clarithromycin

Clarithromycin is a macrolide antibiotic with immunomodulatory activity. Leiper *et al*[45] reported that 64% patients had an impressive positive response to clarithromycin, many of whom were unresponsive to other treatments. In a study from Japan,[46] 14 patients with active CD were treated with oral clarithromycin 200 mg twice daily for 4 weeks. Patients who showed a clinical response within 4 weeks continued the therapy for up to 24 weeks. Four patients also received azathioprine. Clinical activity was assessed at entry and at 4, 12, and 24 weeks after starting clarithromycin. Within 4 weeks, eight (57.1%) of the 14 patients showed clinical improvement, and five (35.7%) of the eight patients achieved remission. All of those eight patients continued clarithromycin therapy after 4 weeks, and six (42.9%) were in clinical remission at 12 weeks. Of the 14 total patients, four (28.6%) continued clarithromycin for more than 24 weeks, and have remained in remission. Patients who received azathioprine concomitantly had a better response to clarithromycin therapy. No severe side-effects were observed during the study period. Clarithromycine needs further clinical exploration as the clinical practice and the available data, so far, produced encouraging results.

4.7 Combination of antibiotics

An antibiotic combination was used in a randomised controlled study[29] in which 250 mg metronidazole four times daily plus 500 mg ciprofloxacin twice daily were compared to a standard steroid treatment for 12 wk. No significant differences were reported in the rates of remission between treatments (46% with ciprofloxacin plus metronidazole and 63% with methylprednisolone), suggesting that this antibiotic combination is a potential alternative to steroid treatment in the acute phase of CD. In another study,[30] the combination of metronidazole and ciprofloxacin was supplemented with budesonide (9 mg/d) in patients with active CD. No difference was noticed compared to placebo, but the overall response in the two groups was lower than that in previous studies using budesonide, suggesting that antibiotic treatment is more effective in colonic disease than in isolated small bowel disease.

5. ANTIBIOTICS IN DIFFERENT CLINICAL TYPES OF CD

5.1 Inflammatory disease

Multiple studies and clinical experience suggest that metronidazole and/or ciprofloxacin can treat Crohn's colitis and ileocolitis (but not isolated ileal disease), perianal fistulae and pouchitis. Metronidazole and ornidazole are effective in the control of active CD in the postoperative setting.

Rifaximin 800 mg b.d. seems to be superior to placebo in inducing clinical remission of active CD, although differences did not reach statistical significance.

5.2 Fistulizing disease

Fistulas are common in CD, with a cumulative risk of 33% after 10 years and 50% after 20 years. Perianal fistulas were the most common (54%). Medical therapy is the main option for perianal fistula once abscesses, if present, have been drained.

The same antibiotics used to treat luminal CD are beneficial for the treatment of perianal CD, but no controlled trials are available.[47] Metronidazole (20mg/kg) can close 62%-83% fistulae.[48,49] The combination of metronidazole and ciprofloxacin results in an improvement in 64% of patients with closure of fistulae in 21%.[50] Unfortunately, fistulae tend to recur in most patients following cessation of treatment. Although the results of these uncontrolled studies are inconclusive, metronidazole and ciprofloxacin alone or in combination, are used by most clinicians as first-line treatments for patients with perianal disease in conjunction with surgical drainage of abscesses.

5.3 Postsurgical treatment

The majority of patients with CD require resectional surgery in the course of their disease. Most of them will suffer symptomatic recurrence in the years after their operation, leading to new complications and sometimes repeated surgery. After first resection in CD at 1 year 60-80% of patients had endoscopic recurrence, 10-20% had clinical relapse and 5% had surgical recurrence.

The use of antibiotics in the prevention of post-operative disease recurrence has also been investigated. Rutgeerts et al[28] found that metronidazole significantly decreases the incidence of severe endoscopic relapse and the clinical recurrence rate. More recently, the same group of authors described that ornidazole used continuously for 1 year, is significantly more effective than placebo in the prevention of clinical and endoscopic recurrence in the neoterminal ileum.[51] In more detail, 80 patients were randomized to ornidazole 1 g/day or placebo started within 1 week of resection and continued for 1 year. Ornidazole significantly reduced the clinical recurrence rate at 1 year from 15 of 40 (37.5%) patients in the placebo group to 3 of 38 (7.9%) patients in the ornidazole group. Ornidazole reduced endoscopic recurrence at 12 months from 26 of 33 (79%) in the placebo group to 15 of 28 (53.6%) in the ornidazole group. However, significantly more patients in the ornidazole group dropped out from the study because of side effects.

In conclusion, broad spectrum antibiotics are the mainstay of therapy for patients with CD who present with localized peritonitis due to microperforation bacterial overgrowth secondary to chronic strictures. They are essential adjuncts to drainage therapy for CD associated abscesses and for complicated perineal disease. A careful review of the experience with antibiotics, should lead to the conclusion that this kind of drugs have a role as primary therapy in active uncomplicated CD. This assumption is further supported by the findings of a recent meta-analysis of all trials contucted so far in patients with CD using antibiotics or combination of antibiotics. Pooling of the results from six randomized, placebo-controlled clinical trials the authors yielded an odds ratio of 2.257 (95% CI, 1.678-3.036; $P<0.001$) for antimicrobial therapy compared with placebo in patients with CD52.

6. ANTIBIOTICS IN ULCERATIVE COLITIS

It has been shown that colonic infusion of donor human intestinal flora can reverse UC in selected patients. These anecdotal results support the concept of abnormal bowel flora or even a specific, albeit unidentified, bacterial pathogen causing UC.

So far, only a few trials on the use of antibacterial agents have been carried out in UC and most clinicians have used antibiotics as an adjuvant therapy for severe UC.

6.1 Metronidazole

The addition of 1000-1500 mg/d IV of metronidazole in the therapeutic regimen for acute exacerbations of UC offers no additional clinical benefit.[53] In another study intravenous metronidazole used in conjunction with corticosteroids, was as effective as placebo in inducing remission in patients with severe UC.[54]

However, in our country it seems logical to start treatment with metronidazole in patients with acute exacerbations of UC for some days while waiting for the results of stool cultures.

6.2 Ciprofloxacine

Ciprofloxacine has also been used in patients with exacerbations of UC. Mantzaris *et al*[55] randomized 70 patients with mild to moderate active UC to receive either 250 mg ciprofloxacin twice a day or placebo for 14 d and found that 70.5% of patients in the ciprofloxacin group and 72% in the placebo group achieve remission. The same group of authors noticed that a short course of intravenous ciprofloxacin is not effective as an adjunctive treatment to corticosteroids in severe UC.[56] In contrast, some efficacy of ciprofloxan has been shown in a randomised placebo-controlled trial when ciprofloxacin was administered for 6 months to patients with active UC poorly responding to conventional therapy with steroids and mesalazine.[57] At the end of the study, the treatment-failure rate was 21% in the ciprofloxacin-treated group and 44% in the placebo group (P<0.002).

6.3 Vancomycine

Vancomycin has also been investigated in patients with active UC. Dickinson *et al*[58] in a double-blind controlled trial on the use of oral vancomycin as an adjunct to acute exacerbations of UC, found no difference between the two treatment groups. However, a trend towards a reduction in the need for surgery in patients treated with vancomycin was noticed.

6.4 Tobramycine

A limited experience of the use of tobramycine showed superiority over placebo probably due to some effectiveness of the drug against strains of E. *Coli*. Burke *et al*[59] randomized 84 patients with acute exacerbations of UC to receive corticosteroids plus oral tobramycin or placebo and found that after 1 wk of treatment, 74% of patients in the tobramycin group and 43% in the placebo group achieve symptomatic remission. However, the combination of tobramycin and metronidazole does not have any beneficial effect when compared with a standard steroid treatment in severely acute UC.[60]

6.5 Rifaximin

Rifaximin was investigated in patients with moderate to severe active UC refractory to steroid treatment. Twenty-eight patients were randomised to receive either rifaximin 400 mg twice daily or placebo for 10 days as an adjunct to standard steroid treatment. Although there was no significant difference in the clinical efficacy score between the two treatments, only rifaximin determines a significant improvement in stool frequency, rectal bleeding and sigmoidoscopic score.[61] It is of interest that resistant *Bifidobacterium* species have been found after 3 intermittent courses in patients with UC.[62]

The use of rifaximin in UC requires further evaluation in larger number of patients.

7. ANTIBIOTICS IN POUCHITIS

The awareness of the crucial importance that faecal stasis and bacterial overgrowth may play a role in the pathogenesis of acute pouchitis has led clinicians to treat these patients with antibiotics. Despite the fact that properly controlled trials have not been carried out, antimicrobials are the mainstay of the treatment of pouchitis.

7.1 Metronidazole

Metronidazole is the first-line treatment of patients with pouchitis. It has been noticed that most patients respond quickly to the administration of metronidazole at a dose of 1-1.5 g/d.[63,64]

Madden *et al*[65] assessed the efficacy of 400 mg of metronidazole three times daily *per os* for two weeks in 13 patients with chronic, unremitting pouchitis. They found that metronidazole is significantly more effective than placebo in reducing stool frequency (73% and 9%), even without improvement in endoscopic appearance and histological grade of activity. However, 55% of patients may experience side-effects while using metronidazole.

7.2 Ciprofloxacine

Shen et al[66] compared the efficacy of ciprofloxacin and metronidazole in patients with pouchitis. Seven patients received ciprofloxacin (1 g/d) and nine patients received metronidazole (20 mg/kg per day) for 2 wk. It was shown that both ciprofloxacin and metronidazole were efficacious. Both reduce the total pouchitis disease activity index scores and lead to a significant improvement in symptoms as well as endoscopic and histological scores. However, ciprofloxacin leads to a greater reduction in pouchitis disease activity index scores as well as improvement in symptoms and endoscopic scores.

7.3 Combination of antibiotics

In an attempt to improve the outcome of treatment in patients with chronic refractory pouchitis, combined antibiotic treatment has also been explored. In an open trial, 18 patients with active pouchitis not responding to standard therapy were treated orally with rifaximin (2 g/d) plus ciprofloxacin (1 g/d) for 15 days. Sixteen out of 18 patients improved or went into remission.[67]

In another trial, 44 patients with refractory pouchitis received metronidazole (800 mg to 1 g/d) and ciprofloxacin (1 g/d) for 28 days. The results revealed that 82% pa-

tients went into remission and the patients' quality of life was significantly improved.[68]

In conclusion and based on the above mentioned trials it seems reasonable to suggest that antibiotics certainly should not be routinely used for mild UC, although a trial of ciprofloxacin is not unreasonable prior to colectomy for otherwise refractory patients.

In patients with severe acute exacerbations of UC we must take into account the results of a recently published meta-analysis of 10 randomized placebo-controlled clinical trials. Pooling of these trials yielded odds ratio of 2.14 in favour of antimicrobial therapy.[69] Moreover, meta-analysis of short-term trials (5-14 days) showed a higher rate of clinical remission in patients treated with antibiotics (odds ratio 2.02; 95% CI, 1.36-3).

The results suggested that adjunctive antibacterial therapy is effective for induction of clinical remission in patients with UC. In toxic patients with fulminant UC, with or without megacolon, broad-spectrum antibiotics should be a part of the treatment program. Finally, pouchitis can be successfully treated with various antibiotics or combination of antibiotics.

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