Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Rationale for the use of rifaximin in inflammatory bowel diseases based on clinical trial results

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The cause of inflammatory bowel disease is not completely understood. However, there is now a strong evidence that resident intestinal bacteria, which are normally considered to be commensal, can initiate the pathological inflammation in a susceptible host. Although this may be a good rationale for antibiotic use in the treatment of these diseases, previous trials with different antibiotics have given controversial results while their long-term use is accompanied by an elevated number of adverse events. Rifaximin is an oral, minimally absorbed (<1% of the ingested dose), antimicrobial agent that exerts its bactericidal activity in the intestinal lumen, and is apparently free of systemic side effects. The efficacy of a new gastroresistant formulation of rifaximin (rifaximin-extended intestinal release) in moderately active Crohn's disease has been recently shown in a multicenter, randomized, double-blind trial. In open-label studies promising results have also been obtained in ulcerative colitis and pouchitis. These findings need to be confirmed in larger randomized-controlled studies.

Keywords: Crohn's disease • inflammatory bowel diseases • pouchitis • rifaximin • rifaximin-extended intestinal release • ulcerative colitis

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The aetiology of inflammatory bowel diseases (IBDs) is not completely understood. Genetic, immunological and environmental factors could play a role in the development and maintenance of the intestinal inflammation in both Crohn's disease (CD) and ulcerative colitis (UC) [1,2]. Recently, the role of a dysregulated immune response towards intestinal microbiota has been proposed as one of the possible explanations of IBD pathogenesis [3,4]. Such a hypothesis implies a host susceptibility induced by genetic mutations in microflora-sensing genes, such as *NOD2/CARD* 15, that results in upregulation of mucosal proinflammatory cytokine production [5,6]. A concentration of intestinal bacteria higher than controls was observed in IBD patients as a result of impaired bacterial clearance [7]. Moreover, studies of luminal bacterial composition in patients with IBD have shown a decrease of 'beneficial' bacteria, such as *Bifidobacterium* and *Lactobacillus spp*, and an increase of pathogenic bacteria, such as *Bacteroides* and *Escherichia coli* [8,9]. The imbalance between protective versus harmful bacteria induces a dysbiosis that can promote inflammation [10]. Furthermore, the role of luminal bacteria in the pathogenesis of CD is also supported by the increase of inflammatory changes consequent to the flow of intestinal contents into excluded ileal segments and reinforced by the healing of lesions after diversion of fecal stream [11,12].

This large amount of data could be a strong rationale for the use of antibiotics in the treatment of IBD. However, several open-label and randomized-controlled trials have shown controversial results about the efficacy of ciprofloxacin [13–15], metronidazole [16–18] or a combination of them [19,20] in the treatment of CD. No

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consistent evidence about the efficacy of either metronidazole [21,22] or ciprofloxacin [23,24] in the treatment of UC was observed. On the other hand, these agents have been shown to be effective for the treatment of pouchitis [25]. In addition, long-term use of these systemic antibiotics is associated to a significant number of severe adverse events (AE) [20,26–28] that induce treatment withdrawal in over 20% of cases and a poor compliance in more than 30% of patients [29].

In recent years, the role of rifaximin – a rifamycin derivative, oral, nonsystemic, antimicrobial agent has been investigated for the treatment of IBD. This gastrointestinal selective antibiotic is currently approved in USA for the treatment of traveller's diarrhea [30]. In addition, its usefulness for the treatment of irritable bowel syndrome (IBS) [31], and hepatic encephalopathy [32] has been demonstrated in controlled trials.

Rifaximin mechanisms of action in IBD

Rifaximin is minimally absorbed and exerts its bactericidal activity in the intestinal lumen. The virtual absence of rifaximin absorption has been documented in animal and isotope studies, the maximum amount of detectable antibiotic in the blood being 0.2 µg/ml [33]. The human absorption of rifaximin has been studied in healthy volunteers and in IBD patients. After oral administration of 400-mg of rifaximin to patients with mild-to-moderate UC, blood drug concentration was found to be lower than 2 ng/ml (detection limit of the analytical method) in most of the plasma samples [34]. Very low plasma concentrations of the drug were detected in a small number of patients. The total amount of rifaximin excretion in the urine after 24 h was only 0.0009% of the dose. Notably, in another study, even after administration of high doses (2 g daily) of rifaximin, plasma levels of the antibiotic were undetectable in all the patients [35]. Consequently, since the systemic bioavailability of the drug is very low, its tolerability and safety profile is undoubtedly better compared with other systemically absorbed antibiotics, such as metronidazole or ciprofloxacin [20,26–28].

The rifaximin mechanism of action depends on inhibition of RNA synthesis by binding the β-subunit of the bacterial DNA-dependent RNA polymerase [33,36]. Therefore, it exhibits a broad-spectrum *in vitro* and *in vivo* activity against gram-positive and -negative bacteria, including aerobes and anaerobes [33,36,37]. It has been documented to be in detail active against bacteroides and *Escherichia coli*, that are frequently found in the intestinal mucosa of CD patients [7], although it seems not to be active against *E. coli* when it is adherent to the mucosa. Moreover, rifaximin seems to modulate the colonic microbiota of CD patients by increasing the concentration of *Bifidobacteria, Atopobium* and *Faecalibacterium prausnitzii*, that are proved to exert a beneficial effect on epithelial cell function and in gut homeostasis [38]. Rifaximin has been also reported to decrease *in vitro* the attachment of pathogenic bacteria, such as Bacillus anthracis or *Shigella sonnei*, to the epithelial cells of intestinal mucosa [39,40].

Other possible mechanisms of action of rifaximin, in addition to direct bactericidal activity, have been demonstrated in recent experimental studies. In a murine model of colitis, rifaximin can reduce the severity of trinitobenzene sulfonic acid-induced colitis and accelerates healing by preventing bacterial translocation [41]. Moreover, this antibiotic, that is a gut-specific human pregnane-X-receptor agonist [42], could exert a preventive and therapeutic role in IBD through down-regulation of inflammatory effects of tumor necrosis factor-κB on intestinal epithelial cells [43,44].

Rifaximin in Crohn's disease

On the basis of such experimental background the therapeutic role of rifaximin in the treatment of IBD, particularly CD, has been investigated (Table 1).

In an open-label study the efficacy of rifaximin 200 mg three times daily for 16 weeks was evaluated in 29 CD patients with Crohn's Disease Activity Index (CDAI) score >220 and <400. At the end of month 4, mean ± CDAI score was reduced by 43%, and 59% of patients were in clinical remission defined as CDAI score <150 [45].

In a multicentre, double-blind, randomized, placebo-controlled trial [46] two doses of rifaximin gastroresistant granules (extended intestinal release [EIR]), 800 mg once a day, and 800 mg twice a day, given for 12 weeks, were compared with placebo in 83 patients with mild-to-moderate CD. Immunosuppressors and or 5-aminosalicylic acid derivatives were maintained during the study period. Clinical remission (CDAI < 150) was achieved in 52% of patients treated with 800 mg twice a day compared with 32 and 33%, respectively, in once-daily administration and placebo groups. Clinical response (reduction of CDAI by ≥70 points from baseline) was seen in 67 and 48% with two dosages of rifaximin, and 41% with placebo. No statistically significant differences of efficacy were demonstrated probably because of the small number of patients enrolled. The number of the failures in the placebo group, however, was significantly higher than those who received rifaximin 800 mg twice a day. Remission and response rates of rifaximin 800 mg twice a day were significantly higher than those of placebo and rifaximin 800 mg once a day only in those patients with elevated C-reactive protein values ($p < 0.05$). Such an observation suggests that

response to rifaximin would depend on a reduction of inflammation rather than merely to control symptoms included in the CDAI.

Recently, data from the charts of 68 patients with mild CD who received adjunctive therapy with rifaximin at mean dose of 600 mg/day for 16 weeks were retrospectively analyzed [47]. The use of concomitant medications (e.g., steroids, anti-inflammatory agents) was allowed. Surprisingly, remission was achieved in 67% of patients who received rifaximin monotherapy, and in 58% of those who received rifaximin as adjunctive therapy to steroid. These data probably reflect a potential greater severity in the latter group. Notably, rifaximin seemed to be helpful for short-term maintenance remission in a small subset of patients.

The last study of rifaximin in CD recently published was an international, multicenter, randomized, double-blind trial, performed in 402 moderately active CD patients from 55 European centers and Israel [48]. The efficacy and safety of 400-, 800-, and 1200-mg rifaximin-EIR, given twice daily for 12 weeks, was evaluated. Concomitant therapy with mesalamine, thiopurines, methotrexate, and probiotics could be maintained at the same dosages throughout the full duration of the trial. At the end of the treatment period a statistically significant different remission rate (as defined as CDAI <150) was observed in the 800 mg twice a day group: 62% of patients were in remission compared with 43% of those in placebo group ($p = 0.005$). A difference was maintained throughout a subsequent 12-weeks follow-up period without treatment. No significant differences with placebo were observed with 400-mg and 1200-mg doses of rifaximin-EIR, most likely due to significantly higher rates of withdrawal observed among the latter group. Moreover, a posthoc explorative subgroup analysis revealed that patients with an early disease (as defined as first diagnosis ≤ 3 years before enrollment in the study), colonic involvement or a baseline CRP level >5 mg/l were significantly more likely to achieve remission with rifaximin-EIR 800 mg twice a day compared with placebo.

The therapeutic role of rifaximin in a pediatric setting was retrospectively evaluated collecting clinical data of 23 children, approximately half having CD and half UC [49]. Overall, 61% of these children had experienced relief of symptoms including diarrhea, abdominal pain and rectal bleeding.

Rifaximin in UC

Traditionally, the use of antibiotics in UC was limited to the treatment of the septic complications of the severe attacks of the disease. This may explain why rifaximin in the treatment of UC has not been extensively investigated (Table 1). The only double-blind, placebo-controlled trial was not randomized [50]. In this study 28 patients with moderate-to-severe UC, and were nonresponders to steroid treatment, received either rifaximin 400 mg b.i.d. or placebo for 10 days. Although there was no statistically significant difference with placebo in clinical outcome between the two groups, in 64.3% of rifaximin-treated patients a significant reduction in stool frequency ($p < 0.02$), rectal bleeding ($p < 0.05$) and sigmoidoscopic score ($p < 0.05$) was observed.

Other uncontrolled experiences with rifaximin in UC were reported in Italy. In an open-label study, 30 patients with mild-to-moderate UC flare-up in the course of mesalazine maintenance treatment received rifaximin 400 mg b.i.d. for 4 weeks as adjunctive therapy [51]. Clinical remission was obtained in about 77% of patients.

In a recent small pilot experience, six mesalazine-intolerant UC patients, in remission after a course of oral steroids, were treated with a combination of rifaximin 400 mg plus the probiotic agent *Saccharomyces boulardii* for three months [52]. At the end of the study period, all patients were still in clinical remission.

On the basis of available evidences, definitive indications for the use of rifaximin in UC cannot be drawn and other, randomized, placebo-controlled studies are warranted.

Rifaximin in pouchitis

Pouchitis is a nonspecific inflammation of the ileal reservoir that occurs in up to 50% of patients after restorative proctocolectomy with ileal-pouch anastomosis [53].

To date, only one randomized, double-blind, placebo-controlled trial of rifaximin for pouchitis has been published (Table 1) [54]. In this small pilot study, 18 patients with active pouchitis were randomized to receive oral rifaximin 400 mg or placebo three-times daily for 4 weeks. At the end of the study period, two patients (25%) in the rifaximin group were in remission (defined as a Pouchitis Disease Activity Index [PDAI] score <7 points and a decrease in the baseline PDAI score = 3 points) compared with none out of nine patients treated with placebo ($p = 0.2$). This difference was not statistically significant.

In an open-label study [35] the efficacy of a combination of rifaximin 1000 mg b.i.d. and ciprofloxacin 500 mg b.i.d. for 2 weeks had been previously reported in 18 patients with chronic active, treatment-resistant pouchitis. Either improvement (defined as a decrease of at least three points in PDAI score) in 55.5% or remission (defined as PDAI score of 0) in 33.3% were obtained, without any side effects.

Table 1. Clinical trials with rifaximin in inflammatory bowel disease.

Study	Phase	Patients (n)	Duration (weeks)	Primary end point	Rifaximin dose (mg)	Outcome	Ref.
Open-label study: efficacy of rifaximin in CD patients with CDAI 220–400	II	29	16	Remission (CDAI <150)	200 t.i.d.	Remission 59%	[45]
Multicenter, double blind, placebo-controlled RCT: efficacy of rifaximin-EIR in patients with mild-to-moderate CD	II	83	12	Remission (CDAI <150)	800 b.i.d.	Remission 52% vs placebo 33% (NS)	[46]
Retrospective study: efficacy of rifaximin as an adjunct to steroids in patients with mild CD	II	68	16	Remission (CDAI <150)	200 mg t.i.d.	Remission 67%	[47]
Multicenter, double-blind, placebo-controlled RCT: efficacy of rifaximin-EIR in patients with moderate CD	II	402	12	Remission (CDAI <150)	400–1200 b.i.d.	Remission 62% vs placebo 43% ($p = 0.005$)	[48]
Double-blind, placebo-controlled, nonrandomized trial: efficacy of rifaximin as an adjunct to steroids in patients with active UC	II	28	2	Improvement of clinical and endoscopic scores	400 mg t.i.d.	Improvement > placebo (NS)	[50]
Open-label study: efficacy of rifaximin in patients with mild-to-moderate active UC	II	30	4	Clinical remission	400 b.i.d.	Remission 77%	[51]
Double-blind placebo-controlled RCT: efficacy of rifaximin in patients with active pouchitis	II	18	4	Remission (PDAI = 0)	400 t.i.d.	Remission 25% vs placebo 0% ($p = 0.2$)	[54]
Open-label study: efficacy of rifaximin plus ciprofloxacin 500 mg b.i.d. in patients with resistant chronic pouchitis	II	18	2	Remission (PDAI = 0)	1000 b.i.d.	Remission 33%	[35]

b.i.d.: Twice daily; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; EIR: Extended intestinal release; NS: Not significant; PDAI: Pouchitis Disease Activity Index; RCT: Randomized controlled trial; t.i.d.: Three-times a day; UC: Ulcerative colitis.

Recently, data of a historical cohort of patients with pouchitis followed-up at Cleveland Clinic have been published [55]. Fifty-one patients with antibiotic-dependent pouchitis, after the induction of remission, received maintenance treatment with rifaximin at doses ranging from 200 to 1800 mg/day (median 200 mg/day) for up to 24 months. At month 3, 65% of patients were in remission and that was maintained in 79, 58%, and 6%, respectively, at months 6, 12 and 24.

Clinical safety data

Rifaximin has been proved to be safe and well tolerated in healthy subjects and in IBD patients. In a large randomized, double-blind, placebo-controlled, trial conducted in moderately-active CD no significant differences in the number of AEs were observed between rifaximin-EIR and placebo groups [48]. In detail, headache (6%), nausea (4%), flatulence (2%), nasopharyngitis (2%) and fever (2%) were the most common reported drug-related AEs. However, a significantly higher proportion of patients in the rifaximin-EIR 1200-mg twice daily group discontinued the treatment due to AEs ($p = 0.01$).

Safety of rifaximin was also analyzed in clinical trials for IBS, and hepatic encephalopathy (HE). In a recent meta-analysis [56] including five randomized, placebo-controlled, trials with rifaximin for IBS the percentage of patients reporting AEs resulted similar between the rifaximin and placebo groups. The most frequent AEs (all ≤6%) included headache, upper respiratory infection, nausea, nasopharygitis, diarrhea and abdominal pain. Serious AEs, such as confusional state, disorientation, dehydration, hypoxia, respiratory acidosis, hypotension, have been reported in less than 1% of patients. A meta-analysis including 12 randomized-controlled trials in the treatment and prevention of HE [57] showed that the patients who received rifaximin (n = 980) had less risk of suffering from diarrhea compared with those (n = 988) who received nonabsorbable disaccharides or another oral antibiotics, such as neomycin and paramomycin (Overall response = 0.20, 95% CI: 0.04–0.92; $p = 0.04$), although the rate of a combination of abdominal pain, nausea, anorexia and weight loss was similar between the two groups ($p = 0.40$; $p = 0.06$, respectively). However, the markedly

increased systemic absorption of rifaximin observed in liver cirrhosis patients compared with controls has caused some concern about long-term administration for HE prevention [58]. Although plasma concentrations as high as 10 ng/ml have been detected in cirrhotics [59], these levels, however, are still lower compared with those observed for systemically absorbed antibiotics.

Another issue for concern may be the potential onset of *Clostridium difficile* infection during long-term rifaximin therapy. Indeed, a drug-related *C. difficile* colitis was reported in one (1%) CD patient who received rifaximin-EIR 800 mg twice daily for 12 weeks [48]. In addition, *C. difficile* infection occurred in two (1.4%) cirrhotics during their 6-month treatment with rifaximin for HE [32]. Indeed, these events are unexpected, since rifaximin has been successfully used in the treatment of *C. difficile* refractory infections [60], and could be due to the infrequent development of rifaximin-resistant strains.

The development of resistance to rifaximin is mainly due to a chromosomal single-step alteration in the DNA-dependent RNA polymerase which is the drug target. This chromosomal-mediated resistance is less frequent than that commonly acquired by bacteria to aminoglycoside antibiotics, such as neomycin or bacitracin, which is due to a plasmid-mediated mechanism [33]. The selection of resistant mutant strains to rifaximin is very rare for anaerobic bacteria, such as *C. difficile*, particularly after exposing the microorganisms to the high level of antibiotic within the intestinal lumen. Furthermore, the occurrence of *C. difficile* infection in cirrhotic patients could be facilitated by concomitant proton-pump inhibitors use or be due to previous multiple courses of systemic antibiotics.

Future perspective

The potential role of intestinal bacteria in triggering inflammation in IBD patients unlocks new therapeutic strategies. However, data of clinical trials are controversial, and long-term antibiotic therapy may cause side effects. The role of rifaximin, – an oral, minimally absorbed, antimicrobial agent, – has been recently investigated in IBD treatment. Results of both open-label and randomized trials suggest an acceptable efficacy, mainly for symptom control. In detail, rifaximin therapy seems to be more effective in mild-to-moderately active CD, in those patients with colon involvement, and in early disease. On the contrary, the role of rifaximin therapy in patients with either UC or pouchitis is not supported by consistent data, although few open-label studies reported an overall improvement. However, to date, only a few studies have been published, the majority of them being open-label designed with small sample sizes. Consequently, the available evidence is limited and no definitive conclusions can be drawn.

Some obvious issues need to be addressed in future studies. First, the role of rifaximin in the maintenance of remission in IBD remains to be investigated, and safety data on long-term administration of the antibiotic are still lacking. Indeed, the longest study period available is limited to 16 weeks [47]. Second, it could be interesting to evaluate the efficacy of rifaximin as monotherapy because it has always been used as an adjunctive therapy to concomitant therapy, such as mesalamine, thiopurins, immunosuppressants or steroids, Third, although the results of randomized trials with rifaximin-EIR in CD seem to suggest a more favorable effect when the colon is involved [48], the efficacy of the antibiotic according to disease localization has to be evaluated more deeply in future studies. Moreover, evaluation of rifaximin efficacy in IBD was based only on clinical indicators, some of which – that is, abdominal pain, well-being – are subjective. Therefore, the overall improvement with rifaximin cannot be necessarily related to a regression of active mucosal inflammation. Consequently, the assessment of the mucosal healing that allows a more objective evaluation should be considered as primary outcome in future trials. In detail, endoscopic evaluation before and after rifaximin therapy could be useful to assess the actual impact of active inflammation on symptoms. Another issue which needs to be clarified is whether the long-lasting effects of rifaximin depend on either a direct effect on the intestinal inflammation or changes in the intestinal microbiota. Therefore, modifications of gut microbiota following rifaximin therapy in IBD patients need to be evaluated in future studies. In addition, whether rifaximin exerts a specific antibiotic effect against yet to be identified harmful bacteria in IBD patients should be proved in comparative studies including other nonabsorbable antibiotics. Finally, the incidence of *C. difficile* infection following long-term rifaximin therapy needs to be further estimated in large studies.

In conclusion, rifaximin appears to be an effective and safe nonabsorbable antibiotic for treating a subset of IBD patients. Further randomized-controlled studies are warranted to confirm these preliminary results.

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Executive summary

- Rifaximin is a rifamycin derivative, oral, nonsystemic, antimicrobial agent that is minimally absorbed and exerts its bactericidal activity in the intestinal lumen.
- Efficacy of rifaximin in inducing remission in moderately active Crohn's disease has been demonstrated in a multicenter, double-blind, randomized trial.
- Small, open-label, studies seem to suggest efficacy of rifaximin in ulcerative colitis and pouchitis.
- Rifaximin has been proved to be safe and well tolerated in inflammatory bowel disease patients.
- One case (1%) of drug-related *Clostridium difficile* colitis was reported in a patient with Crohn's disease who received rifaximin 800 mg b.i.d. for 12 weeks.
- Optimal dose and duration of treatment have to be established in larger, placebo-controlled, randomized trials.
- Assessment of mucosal healing should be considered as a primary end point in future trials evaluating efficacy of rifaximin in inflammatory bowel disease.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat. Clin. Pract. Gastroenterol. Hepatol.* 3(7), 390–407 (2006).

2 Scaldaferri F, Fiocchi C. Inflammatory bowel disease: progress and current concepts of etiopathogenesis. *J. Dig. Dis.* 8(4), 171–178 (2007).

3 Xavier RJ, Podolsky DK. Unraveling the pathogenesis of inflammatory bowel disease. *Nature* 448(7152), 427–434 (2007).

▪▪ **Shows the multifactorial pathogenesis of inflammatory bowel disease.**

4 Sartor RB. Microbial influences in inflammatory bowel diseases. *Gastroenterology* 134(2), 577–594 (2008).

5 Cario E. Bacterial interactions with cells of the intestinal mucosa: toll-like receptors and NOD2. *Gut* 54(8), 1182–1193 (2005).

6 Rogler G. The effects of NOD2/CARD15 mutations on the function of the intestinal barrier. *J. Crohns Colitis.* 1(2), 53–60 (2007).

7 Swidsinski A, Ladhoff A, Pernthaler A *et al.* Mucosal flora in inflammatory bowel disease. *Gastroenterology* 122(1), 44–54 (2002).

▪▪ **Describes specific changes in the mucosal flora in inflammatory bowel disease patients.**

8 Neut C, Bulois P, Desreumaux P *et al.* Changes in the bacterial flora of the neoterminal ileum after ileocolonic resection for Crohn's disease. *Am. J. Gastroenterol.* 97(4), 939–946 (2002).

9 Darfeuille-Michaud A, Neut C, Barnich N *et al.* Presence of adherent *Escherichia coli* strains in ileal mucosa of patients with Crohn's disease. *Gastroenterology* 115(6), 1405–1413 (1998).

10 Tamboli CP, Neut C, Desreumaux P, Colombel JF. Dysbiosis in inflammatory bowel disease. *Gut* 53(1), 1–4 (2004).

11 Rutgeerts P, Goboes K, Peeters M *et al.* Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet* 338(8770), 771–774 (1991).

12 D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology* 114(2), 262–267 (1998).

13 Ambrose NS, Allan RN, Keighley MR *et al.* Antibiotic therapy for treatment in relapse of intestinal Crohn's disease. A prospective randomized study. *Dis. Colon Rectum.* 28(2), 81–85 (1985).

14 Arnold GL, Beaves MR, Pryjdun VO, Mook WJ. Preliminary study of ciprofloxacin in active Crohn's disease. *Inflamm. Bowel Dis.* 8(1), 10–15 (2002).

15 Colombel JF, Lemann M, Cassagnou M *et al.* A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Am. J Gastroenterol.* 94(3), 674–678 (1999).

16 Blichfeldt P, Blomhoff JP, Myhre E, Gjone E. Metronidazole in Crohn's disease. A double blind cross-over clinical trial. *Scand. J. Gastroenterol.* 13(1), 123–127 (1978).

17 Sutherland L, Singleton J, Sessions J *et al.* Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 32(9), 1071–1075 (1991).

18 Ursing B, Alm T, Barany F *et al.* A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. II. Result. *Gastroenterology* 83(3), 550–562 (1982).

19 Prantera C, Zannoni F, Scribano ML *et al.* An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am. J. Gastroenterol.* 91(2), 328–332 (1996).

20 Steinhart AH, Feagan BG, Wong CJ *et al.* Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology* 123(1), 33–40 (2002).

21 Chapman RW, Selby WS, Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. *Gut* 27(10), 1210–1212 (1986).

22 Gilat T, Suissa A, Leichtman G *et al.* A comparative study of metronidazole and sulfasalazine in active, not severe, ulcerative colitis. An Israeli multicenter trial. *J. Clin. Gastroenterol.* 9(4), 415–417 (1987).

23 Mantzaris GJ, Archavlis E, Christoforidis P *et al.* A prospective randomized controlled trial of oral ciprofloxacin in acute ulcerative colitis. *Am. J. Gastroenterol.* 92(3), 454–456 (1997).

24 Mantzaris GJ, Petraki K, Archavlis E *et al.* A prospective randomized controlled trial of intravenous ciprofloxacin as an adjunct to corticosteroids in acute, severe ulcerative colitis. *Scand. J. Gastroenterol.* 36(9), 971–974 (2001).

25 Holubar SD, Cima RR, Sandborn WJ, Pardi DS. Treatment and prevention of pouchitis after ileal pouch–anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst. Rev.* 16(6), 1–34 (2010).

▪▪ **Excellent review paper on management of pouchitis.**

26 Duffy LF, Daum F, Fisher SE *et al.* Peripheral neuropathy in Crohn's disease patients treated with metronidazole. *Gastroenterology* 88(3), 681–684 (1985).

27 Dignass A, van Assche G, Lindsay JO *et al.* The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J. Crohns Colitis.* 4,(1) 28–62 (2010).

■■ **Updated management guidelines on Crohn's disease.**

28 Kahn KJ, Ulmann TA, Ford AC *et al.* Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 106(5), 661–673 (2011).

■■ **Describes the efficacy and safety of antibiotics in inflammatory bowel disease.**

29 Prantera C, Berto E, Scribano ML, Falasco G. Use of antibiotics in the treatment of active Crohn's disease: experience with metronidazole and ciprofloxacin. *Ital. J. Gastroenterol. Hepatol.* 30(6), 602–606 (1998).

30 Laustsen G, Wimmett L. 2004 drug approval highlights: FDA update. *Nurse Pract.* 30(2), 14–29 (2005).

31 Pimentel M, Lembo A, Chey WD *et al.* Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N. Engl. J. Med.* 364(1), 22–32 (2011)

32 Bass NM, Mullen KD, Sanyal A *et al.* Rifaximin treatment in hepatic encephalopathy. *N. Engl. J. Med.* 362(12), 1071–1081 (2010).

33 Scarpignato C, Pelosini I. Experimental and clinical pharmacology of rifaximin, a gastrointestinal selective antibiotic. *Digestion.* 73(Suppl. 1), 13–27 (2006).

■ **Illustrates the pharmacological properties and clinical indications of rifaximin.**

34 Rizzello F, Gionchetti P, Venturi A *et al.* Rifaximin systemic absorption in patients with ulcerative colitis. *Eur. J. Clin. Pharmacol.* 54(1), 91–93 (1998).

35 Gionchetti P, Rizzello F, Venturi A *et al.* Antibiotic combination therapy in patients with chronic, treatment-resistant pouchitis. *Aliment. Pharmacol. Ther.* 13(6), 713–718 (1999).

36 Jiang ZD, DuPont HL. Rifaximin: *in vitro* and *in vivo* antibacterial activity – a review. *Chemotherapy.* 51(Suppl. 1), 67–72 (2005).

37 Ojetti V, Lauritano EC, Barbaro F *et al.* Rifaximin pharmacology and clinical implications. *Expert Opin. Drug Metab. Toxicol.* 5(6), 675–682 (2009).

38 Maccaferri S, Vitali B, Klinder A *et al.* Rifaximin modulates the colonic microbiota of patients with Crohn's disease: an *in vitro* approach using a continuous culture colonic model system. *J. Antimicrob. Chemother.* 65(12), 2556–2565 (2010).

39 Jiang ZD, Ke S, Dupont HL. Rifaximin-induced alteration of virulence of diarrhoea-producing *Escherichia coli* and *Shigella sonnei*. *Int. J. Antimicrob. Agents.* 35(3), 278–281 (2010).

40 Brown EL, Xue Q, Jiang ZD, Xu Y, Dupont HL. Pretreatment of epithelial cell with rifaximin alters bacterial attachment and internalization profiles. *Antimicrob. Agents Chemother.* 54(1), 388–396 (2010).

41 Fiorucci S, Distrutti E, Mencarelli A, Barbanti M, Palazzini E, Morelli A. Inhibition of intestinal bacterial translocation with rifaximin modulates lamina propria monocytic cells reactivity and protects against inflammation in a rodent model of colitis. *Digestion* 66(4), 246–256 (2002).

42 Ma X, Shah YM, Guo GL *et al.* Rifaximin is a gut-specific human pregnane X receptor activator. *J. Pharmacol. Exp. Ther.* 322(1), 391–398 (2007).

43 Mencarelli A, Migliorati M, Barbanti M *et al.* Pregnane-X-receptor mediates the anti-inflammatory activities of rifaximin on detoxification pathways in intestinal epithelial cells. *Biochem. Pharmacol.* 80(11), 1700–1707 (2010).

44 Cheng J, Shah YM, Ma X *et al.* Therapeutic role of rifaximin in inflammatory bowel disease: clinical implication of human pregnane X receptor activation. *J. Pharmacol. Exp. Ther.* 335(1), 32–41 (2010).

45 Shafran I, Johnson LK. An open-label evaluation of rifaximin in the treatment of active Crohn's disease. *Curr. Med. Res. Opin.* 21(8), 1165–1169 (2005).

46 Prantera C, Lochs H, Campieri M *et al.* Antibiotic treatment of Crohn's disease: results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin. *Aliment. Pharmacol. Ther.* 23(8), 1117–1125 (2006).

47 Shafran I, Burgunder P. Adjunctive antibiotic therapy with rifaximin may help reduce Crohn's disease activity. *Dig. Dis. Sci.* 55(4), 1079–1084 (2010).

48 Prantera C, Lochs H, Grimaldi M, Danese S, Scribano ML, Gionchetti P. Rifaximin-extended release induces remission in patients with moderately active Crohn's disease. *Gastroenterology* 142(3), 473–481 (2012).

■■ **Largest randomized-controlled trial demonstrating efficacy of rifaximin in Crohn's disease.**

49 Muniyappa P, Gulati R, Mohr F, Hupertz V. Use and safety of rifaximin in children with inflammatory bowel disease. *J. Pediatr. Gastroenterol. Nutr.* 49(4), 400–404 (2009).

50 Gionchetti P, Rizzello F, Ferrieri A *et al.* Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. *Dig. Dis. Sci.* 44(6), 1220–1221 (1999).

51 Guslandi M, Petrone MC, Testoni PA. Rifaximin for active ulcerative colitis. *Inflamm. Bowel Dis.* 12(4), 335 (2006).

52 Guslandi M. *Saccharomyces boulardii* plus rifaximin in mesalamine-intolerant ulcerative colitis. *J. Clin. Gastroenterol.* 44(5), 385 (2010).

53 Shen B, Fazio VW, Remzi FH, Lashner BA. Clinical approach to diseases of ileal pouch–anal anastomosis. *Am. J. Gastroenterol.* 100(12), 2796–2807 (2005).

54 Isaacs KL, Sandler RS, Abreu M *et al.* Rifaximin for the treatment of active pouchitis: a randomized, double-blind, placebo-controlled pilot study. *Inflamm. Bowel Dis.* 13(10), 1250–1255 (2007).

55 Shen B, Remzi FH, Lopez AR, Queener E. Rifaximin for maintenance therapy in antibiotic-dependent pouchitis. *BMC Gastroenterol.* 8, 26 (2008).

56 Menees SB, Maneerattannaporn M, Kim HM, Chey WD. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 107(1), 28–35 (2012).

■ **Meta-analysis on treatment of irritable bowel syndrome with rifaximin.**

57 Eltawil KM, Laryea M, Peltekian K, Molinari M. Rifaximin versus conventional oral therapy for hepatic encephalopathy: a meta-analysis. *World J. Gastroenterol.* 18(8), 767–777 (2012).

■ **Meta-analysis on treatment of hepatic encephalopathy with rifaximin.**

58 Zullo A, Hassan C, Ridola L, Lorenzetti R, Campo SM, Riggio O. Rifaximin therapy and hepatic encephalopathy: pros and cons. *World J. Gastrointest. Pharmacol. Ther.* 3(4), 62–67 (2012).

59 Bajaj JS, Riggio O. Drug therapy: rifaximin. *Hepatology* 52(4), 1484–1488 (2010).

60 Basu P, Dinani A, Rayapudi K *et al.* Rifaximin therapy for metronidazole-unresponsive *Clostridium difficile* infection: a prospective pilot trial. *Therap. Adv. Gastroenterol.* 3(4), 221–225 (2010).