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Cent. Eur. J. Med. • 4(2) • 2009 • 164-170
DOI: 10.2478/s11536-009-0019-4

Central European Journal of **Medicine**

Benefit of antibiotic therapy on pouchitis after ileal pouch anal anastomosis: A systematic review and meta-analysis of clinical trials

Research Article

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Received 17 August 2008; Accepted 5 January 2009

Abstract: The aim of the study was to evaluate and collect current evidence on the effect of antibiotics in pretreatment of pouchitis after restorative ileal pouch anal anastomosis (IPAA). Pubmed, Embase, Web of Science, Scopus, and Cochrane Library databases were searched between 1966 and July 2008; and relevant clinical trials extracted, reviewed, and validated according to the study protocol. The outcome of interest was clinical improvement after treatment. Nine randomized, placebo-controlled clinical trials were found relevant and studied but 3 of them with 70 patients were entered into meta-analysis. Pooling of the results from these trials yielded an odds ratio of 15.96 with a 95% CI of 4.20-60.70, indicating a significant OR ($p<0.0001$) in treatment group in comparison to the placebo group. In conclusion, the meta-analysis confirms benefit of antibiotics in management of pouchitis after IPAA operation.

Keywords: *Meta-analysis • Ileal pouch anal anastomosis • Antibiotic • Pouchitis*

1. Introduction

Ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for patients who have medically refractory ulcerative Colitis (UC) with dysplasia or cancer, and for patients with familial adenomatous polyposis [1-3].

Pouchitis simply is a nonspecific inflammation of the ileal reservoir, and is the most common long-term complication of restorative proctocolectomy with IPAA operation, with the increasing number of patients undergoing IPAA operation we are encountering more and more patients with this chronic relapse and remitting hard to treat complication. Pouchitis is currently being defined with a clinical, endoscopic and histologic scoring system (PDAI) as the disease activity index of more than 7. The incidence of pouchitis is reported as 7% to more than half of the patients whom undergo IPAA operation [2,4-7].

The exact etiology of the pouchitis is not very clear; Crohn's disease (CD), recurrent UC [8], toxins, bile acids, and fatty acids can induce inflammation of the pouch [9] that is shown to take part in pathogenesis. Antibiotics are shown to be effective in the management of chronic state of inflammatory bowel disease (IBD) [10,11] and may also be beneficial in pouchitis however, some controversy exists among authorities about the proper treatment choice and management.

There is also debate on the effect of the antibiotics in various stages of the disease; pouch inflammation

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can be categorized from a therapeutic point of view and its response to treatment as acute, chronic (symptoms for more than 4 weeks or need for drugs for more than 15 days in a month), and treatment resistant pouchitis (no response and no improvement in symptoms after 4 weeks of treatment).

Antibiotics and probiotics are currently the most widely accepted treatment options for prevention and treatment in pouchitis patients. Antibiotics use in pouchitis has been subject of some narrative reviews [12-17]. In this study, we used meta-analysis technique to assess the magnitude and the benefits from antibiotics in the management of pouchitis. We pooled data from all eligible clinical studies.

2. Material and Methods

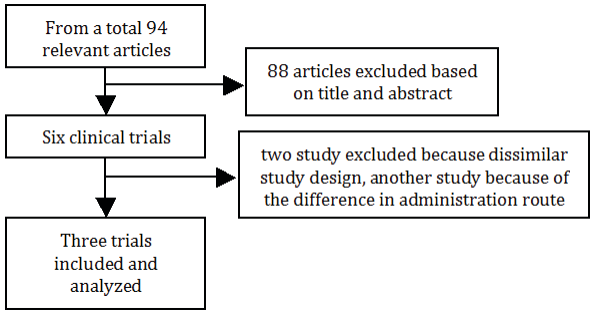
2.1. Data sources and study selection

A computer assisted search of the online bibliographic databases PubMed, Embase, Web of Sciences, Scopus, and Cochrane Central Register of Controlled Trials was carried out to collect relevant data from studies conducted between 1966 and July 2008. The search terms were, “antibiotics”, “pouchitis”, and “ileal pouch anal anastomosis” or “restorative proctocolectomy”. The search language was not limited. The reference list from retrieved articles was also reviewed for additional applicable studies.

Primary outcome of interests was proportion of patients with clinical improvement or remission of pouchitis. The exact definition of remission or improvement varied from study to study therefore the definition of these terms in each study was used for extraction of data from the individual studies for this analysis.

Both randomized controlled clinical trials comparing antibiotic therapy and placebo or other active therapies for the correction of any degree of pouchitis were considered and none randomized non-controlled studies included in our search. Each article was reviewed to eliminate duplicates, reviews, uncontrolled trials, and case studies. Trials were disqualified if their outcome was different from our outcome of interest and if their target groups were not patients with pouch inflammation. We considered completed, published studies. Full copies of all potentially or definitely relevant studies were obtained and assessed by two authors to determine whether they met standard quality criteria (Table 1).

Figure 1. Algorithm of the study selection and inclusion in meta-analysis.



2.2. Data extraction and statistical analysis

Data from selected studies were extracted in the form of 2×2 tables. All studies were pooled and weighted. The data were analyzed using Statsdirect (2.6.2). Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel method. The Breslow-Day test was used to test for heterogeneity, with significance regarded as $P<0.05$. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L’Abbe plot, as an aid to explore the heterogeneity of effect estimates.

3. Results

We reviewed abstracts of 94 articles. Our search resulted in a total of 9 articles. Six controlled and 3 open labeled none controlled studies; however, only three satisfied our inclusion criteria for meta-analysis and three studies excluded (Figure 1). One randomized study excluded because of its different outcome [22] and another one because of different route of administration[23]. Sambuelli et al study [19] was also excluded because two active drugs were examined in that double dummy, double blind, placebo controlled trial. They randomized patients to receive either budesonide enema (2 mg/100 ml at bedtime) plus two placebo tablets daily or oral metronidazole (500 mg tablets b.d.) and placebo enema for 6 weeks.

We pooled the data of seventy (37 patients in antibiotic arm) patients from three included studies for meta-analysis [18-21] (Table 2).

The summary odds ratio (OR) for clinical improvements outcomes among antibiotics intake in three trials was 15.96 with a 95% confidence interval (CI) of 4.20-60.70, indicating a significant OR ($P<0.0001$, Figure 2). The Breslow-Day test for heterogeneity ($P= 0.1804$) indicate that the studies were homogenous and could be combined, thus the fixed effects for individual and summary of OR for

Table 1. Summery of clinical studies investigating the effect of antibiotics in treatment of pouchitis.

Trial	Number of patients treated	Type of the study	Inclusion criteria	Drug(s)	Dosage	Duration	Concomitant treatment	Median changes in pouchitis disease activity index (PDAI) from baseline
Madden et al. 1994 [18]	13	RCT	Chronic unremitting pouchitis, stool frequency > 6/day	Metronidazole	400 mg thrice daily	7 days	None	Not scored
Shen et al. 2007 [20]	16	RCT	PDAI score of 7 or higher or chronic antibiotic refractory pouchitis	Ciprofloxacin + tinidazole	1g/day and 15 mg/kg/day	28 days	oral (4 g/day), enema (8 g/day), or suppository (1 g/day) mesalamine	-7.0
Isaacs et al. 2007 [21]	8	RCT	Active acute or chronic pouchitis	Rifaximin	400 mg 3 times daily	28 days	none	–1.6
Hurst et al. 1996[40]	52	Cohort	Acute Pouchitis	metronidazole or if failed ciprofloxacin	250 mg three times a day or 500mg twice a day	7days	none	Not scored, 94% improved after 1st episode
Gionchetti et al. [32]	18	OL	chronic active, treatment-resistant pouchitis	Rifaximin and ciprofloxacin	Rifaximin 1 g b.d. + ciprofloxacin 500 mg b.d.	15 days	none	-7
Mimura et al. 2002[30]	44	OL	Refractory acute pouchitis	combination of metronidazole and ciprofloxacin	400 or 500 mg b.d. (Metro) + 500 mg b.d. (Cip	28 days	none	-9
Shen et al. 2008[33]	51	OL	antibiotic-dependent pouchitis	Maintenance dose of Rifaximin	200 mg/day	3 months	none	-3
Shen et al. 2001[22]	18	RCT	acute pouchitis	Either Metronidazole or ciprofloxacin	20 mg/kg/d and 1g/d respectively	2 weeks	None	Ciprofloxacin -6.7 (n=7) Metronidazole -5.9 (n=9)
Madiba et al.[31]	47	Cohort	36 patients Acute pouchitis, 9 chronic, 2 treatment resistant	Metronidazole (ciprofloxacin single or combination therapy in chronic and resistant cases)	200mg three times a day	Minimum 1 month	none	Clinical Improvement in 77% acute cases

OL, Open labeled study; RCT, Randomized Clinical Trial;

meta-analysis of studies were applied (Figure 3).

L'Abbé plot shows the event rate in the experimental (intervention) group against the event rate in the control group, and envisage heterogeneity of effect estimates within a meta-analysis [24]. In this study, assessment of the clinical improvements among experimental group, trials in which the experimental treatment proves better than the control are in the upper left of the plot, between

Table 2. Summary of controlled clinical trials included in the meta-analysis.

Trial	Mean age (yr)	Gender (M/F)	Inclusion criteria	Drug(s)	Clinical improvements	
					Antibiotic	Placebo
Madden et al. 1994[18]	No data available	No data available	Chronic unremitting pouchitis,	Metronidazole	12/13	1/13
Shen et al. 2007[20]	48.6	18/26	chronic antibiotic refractory pouchitis	Ciprofloxacin + tinidazole	14/16	5/10
Isaacs et al. 2007[21]	No data available	No data available	Active acute or chronic pouchitis	Rifaximin	2/8	0/9

Figure 2. Individual and pooled odds ratios for the outcome of "clinical improvements" in the studies considering antibiotics therapy.

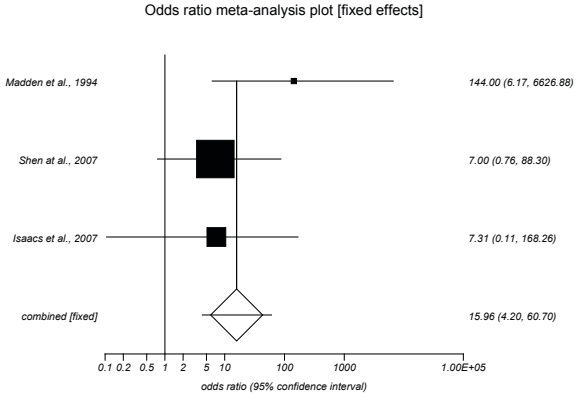
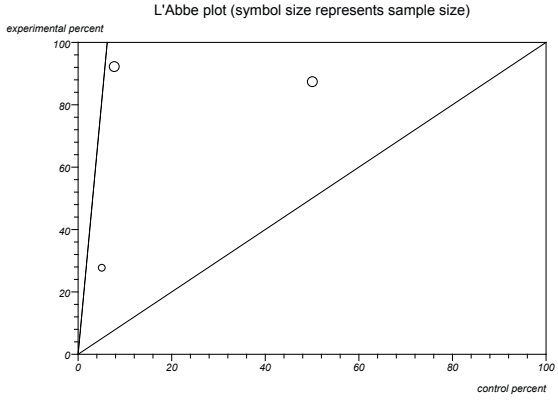


Figure 3. Heterogeneity indicators for the outcome of "clinical improvements" for studies including antibiotics therapy.



the y axis and the line of equality. If control is better than experimental then the point is in the lower right of the plot, between the x axis and the line of equality. As shown in Figures 3, the results reflect a single underlying effect, rather than a distribution of effects, and statistical homogeneity exists, thus the fixed effects have been applied in meta-analysis.

4. Discussion

Do antibiotics improve pouchitis symptoms? The answer to this question is yes. This meta-analysis showed significant OR in favor of antibiotic therapy and a pooled OR of 23.6 was obtained. Three clinical trials included with a total of 70 (37 in antibiotic arm) patients. However, the results should be interpreted with caution given small the number of trials and patients evaluated in each study. Authors would also like to draw readers attention to the fact that included studies are different both in their patients selection (2 chronic pouchitis and one acute case of pouchitis) and in their control group (2 had Placebo and one had mesalamine); however, we can see that antibiotics have promising results in spite of the chronicity or the design of the study.

Madden *et al.* [18] in 1994, examined patients with chronic pouchitis in a cross-over, double blind trial. They randomized 13 patients to receive either metronidazole 400 mg by mouth three times a day or placebo for two weeks. The outcome of interest was reduction in stool frequency and they showed that the median frequency of defecation decreased by 3 bowel actions/24 hr on metronidazole but increased by a median of 1/24 hr on placebo. The highest observed OR belonged to this study is mainly because of the interested outcome of measure considering the defecation frequency. Madden *et al.*have also reported no significant changes in endoscopic or pathology of their patients after treatment.

Shen and colleagues [20] in their study examined combination of ciprofloxacin 1 g/day and tinidazole 15 mg/kg/day for four weeks against 10 chronic refractory pouchitis patients treated with oral (4 g/day), enema (8 g/day), or suppository (1 g/day) mesalamine as controls. They found significant reduction in the total pouchitis disease activity index scores and subscores and a significant improvement in quality of life scores in treatment group.

A recent study by Isaacs *et al.* [21] evaluating nonabsorbable antibiotic rifaximin in patients with active acute or chronic pouchitis demonstrates 25% remission rate in treatment group while none of the control group were on remission by the end of week four.

Other none controlled studies [12,13,18,23,25-30] have also played a significant role for antibiotics; for instance Madiba and Bartolo in a long term study (median follow-up 60 months) described effect of oral metronidazole for 30 days on 139 patients who underwent proctocolectomy and ileal anal pouch creation, including 47 who experienced pouchitis from 2 to 102 months following surgery. Their study showed complete resolution of symptoms in 36 of 47 (77%) of these patients [31]. In a similar study by Gionchetti and coworkers, 18 patients were treated with a combination of ciprofloxacin and rifaximin. Their work revealed a reduction in symptoms as measured by the PDAI. Sixteen of 18 (89%) experienced a positive response, including 6 who experienced complete remission of symptoms and 10 who experienced partial relief [32].

Therefore, it is concluded that current evidence promotes antibiotic usage as standard of treatment for pouchitis following IPAA treatment.

Although there are scarce amount of evidence for antibiotic therapy in pouchitis we can conclude from the high OR (15.9 (95% CI: 4.2-60.7)) that antibiotics are indeed effective in management of the pouchitis and authors would like to emphasize this therapeutic role.

Does ciprofloxacin have any superiority to metronidazole? Only a few studies have looked for this question. From the only randomized clinical trial done by Shen and his colleague [22], both ciprofloxacin and metronidazole improves PDAI in acute pouchitis cases with slightly yet not significant better results for ciprofloxacin. It is also interesting to know that metronidazole as expected have more side effects in comparison to ciprofloxacin. Few other cohort studies have also shown significant PDAI improvement in metronidazole refractory or chronic case with the use of ciprofloxacin as a single or add on therapy [30-32].

What is the role of rifaximin? Rifaximin is a poorly absorbable antibiotic, which binds to beta-subunit of bacterial DNA dependent RNA polymerase. However, it has little effect in treatment of acute or chronic pouchitis. One randomized clinical trial shows no significant benefit from rifaximin in comparison to placebo [21]. Role of rifaximin in maintenance of remission in pouchitis is something which needs further investigation [33] and its role in combination and in comparison to probiotics is not clear.

What about other therapeutic options? Probiotics have shown potential benefits in remission maintenance and prophylaxis after IPAA. In one randomized placebo controlled clinical trial, the incidence of pouchitis was decreased from a high of 40% in placebo group to 10% in probiotic group [34]. Probiotics has also reduced stool frequency of patients without clinical pouchitis. Recent meta-analyses have confirmed positive effects of probiotics in the management of pouchitis [35], UC [41], CD [42], and irritable bowel syndrome (IBS) [43,44]. In fact, although use of antidepressants are the main managements but there are much similarities between IBS and IBD in terms of pathophysiology [45,46]. Also anti TNF-alpha compounds have been shown effective in both UC and CD [47,48]. In addition, benefit of potassium channel openers [49] and efficacy of antioxidants [50] have been hopefully established.

Unfortunately, other therapeutic options such as steroids did not have significant clinical benefits. These modalities include budesonide [36], bismuth carbomer enema [37], glutamine and butyrate suppository compounds [38], and allopurinol [39]. None of these therapies have shown significant beneficial effect in comparison to placebo [17].

Further trials to examine other treatment options and their additional benefits and effect of clinically relevant variables such as extension of the disease, characteristics of patients (e.g., age and gender), duration of therapy, and choice of antibiotic are also remain to be clarified. We highly emphasize usage of proper and standard definition for terms such as acute or chronic pouchitis and remission of the disease best described in PDAI.

Acknowledgment

There was no financial support for this study.

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