

## Antibiotic treatment of small bowel bacterial overgrowth in patients with Crohn's disease

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### SUMMARY

**Background:** Small bowel bacterial overgrowth is common in Crohn's disease but its treatment is not clearly defined. Metronidazole and ciprofloxacin are effective antibiotics in active Crohn's disease.

**Aim:** To investigate the efficacy of metronidazole and ciprofloxacin in the treatment of bacterial overgrowth in patients with Crohn's disease.

**Patients and methods:** We performed the lactulose breath test in 145 consecutive patients affected by Crohn's disease. Patients positive to the lactulose breath test underwent a glucose breath test to confirm the overgrowth. These patients were randomized in two treatment groups: metronidazole 250 mg t.d.s. (Group A

and ciprofloxacin 500 mg b.d. (Group B), both orally for 10 days. The glucose breath test was repeated at the end of treatment. The clinical outcome after therapy was also recorded.

**Results:** Bacterial overgrowth was present in 29 patients (20%). Breath test normalization occurred in 13 out of 15 patients treated by metronidazole and in all 14 patients treated by ciprofloxacin ( $P = ns$ ). In both groups antibiotic treatment induced an improvement of intestinal symptoms: bloating (Group A 85% and Group B 83%), stool softness (44% and 50%), and abdominal pain (50% and 43%).

**Conclusions:** Small bowel bacterial overgrowth is a frequent condition in Crohn's disease which can be effectively treated by metronidazole or ciprofloxacin.

### INTRODUCTION

The hydrogen/methane breath test has been proposed as a sensitive and simple tool for the diagnosis of bacterial overgrowth,<sup>1</sup> being non-invasive and inexpensive compared to a culture of intestinal aspirates and <sup>14</sup>C-xylose breath test, respectively.<sup>2, 3</sup> The H<sub>2</sub> and CH<sub>4</sub> produced in the human body after lactulose or glucose ingestion derive entirely from intestinal bacterial fermentation. Therefore, the appearance of an early increase in breath H<sub>2</sub> or CH<sub>4</sub> concentration indicates

the presence of a small bowel bacterial overgrowth.<sup>1, 4</sup> The lactulose breath test allows for the simultaneous assessment of bacterial overgrowth and oro-coecal transit time, and has been previously evaluated in patients with Crohn's disease.<sup>4, 5</sup> The glucose breath test seems to be more specific although less sensitive than the lactulose breath test for bacterial overgrowth; however, it does not allow for transit time assessment.<sup>6, 7</sup>

Small bowel bacterial overgrowth is a frequent condition in patients affected by Crohn's disease, particularly in those with stenosis and entero-enteric fistula.<sup>1, 8</sup> In a previous study we showed by a lactulose breath test that 23% of unselected patients with Crohn's disease presented bacterial overgrowth, and that this proportion was even higher in patients with previous surgery.<sup>4</sup> We

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also found that one of the possible reasons for the high prevalence of bacterial overgrowth can be the prolonged oro-colonic transit time, particularly in operated subjects.<sup>4</sup>

The detection of bacterial overgrowth is important in the clinical management of these patients because it can contribute to the worsening of intestinal symptoms (diarrhoea, abdominal pain and bloating) and because it is a treatable condition in most instances.<sup>4, 9</sup>

Antibiotic therapy of bacterial overgrowth has been studied in patients with several conditions,<sup>9–11</sup> while there are no specific data on treatment of bacterial overgrowth complicating Crohn's disease. Metronidazole and ciprofloxacin are two drugs widely used in the treatment of active Crohn's disease,<sup>12–14</sup> but their effectiveness in patients with small bowel bacterial overgrowth is not proven.

The aim of this study was to investigate the efficacy of metronidazole and ciprofloxacin in the treatment of small bowel bacterial overgrowth in patients affected by Crohn's disease selected by the lactulose and glucose hydrogen/methane breath test.

#### PATIENTS AND METHODS

From June 2000 to September 2002 we performed a lactulose hydrogen/methane breath test in 145 eligible consecutive patients affected by Crohn's disease who attended the Inflammatory Bowel Disease Clinic in our Department. Twenty further patients were considered ineligible because of diarrhoea and were excluded from the study. Patients positive for bacterial overgrowth underwent a glucose breath test in order to confirm the result. The main characteristics of the all the subjects are reported in Table 1.

A lactulose breath test was performed after an overnight fast. According to Corazza *et al.*<sup>15</sup> exclusion criteria were starch ingestion in the 48 h before the test, antibiotic treatment during the last month before the test and diarrhoea (more than three bowel movements/day). After the ingestion of a 100-mL water solution containing 10 g of lactulose, breath samples were taken at 15-min intervals for 3 h. During the test, subjects were forbidden to eat, smoke or to exercise. Alveolar air samples were obtained after a normal inspiration by having the subjects exhale through a mouthpiece into the bags connected by a three-way valve. When the first 500 mL of expiratory air filled one plastic bag, the end alveolar air was then collected in a

Table 1. Characteristics of 145 patients with Crohn's disease

Sex (M/F)	79/66
Mean age (range)	38.6 21–70
CDAI	
< 150	86
> 150	59
Localization	
Ileal	71
Ileo-colonic	50
Colonic	24
Pattern	
Inflammatory	60
Strictureing	55
Penetrating	30
Previous surgery	45

Data are presented as number except when indicated.

second bag (a 1–1 rubber anaesthesia bag adapted with a one-way valve). The end alveolar air was then transferred immediately into 50 mL plastic syringes fitted with two-way stopcocks and was analysed within a 2-h period.

The H<sub>2</sub> and CH<sub>4</sub> concentrations in breath samples were determined simultaneously with a Micro Lyser DP gas chromatograph (Quintron Instrument Company, Milwaukee, WI, USA) using a molecular sieve column (12'Hysep Q, 60/80 mesh). Dry air was used as the carrier gas at a flow rate of 30 mL/min. The chromatograph was calibrated with H<sub>2</sub> and CH<sub>4</sub> reference mixture in compressed air (Quingas 2). Results were expressed as parts per million (ppm) (1 ppm = approximately 0.05 µmol/L for H<sub>2</sub> and CH<sub>4</sub>). For both gases, the smallest detectable concentration was 1 ppm, with a linear accuracy response range of 1–150 ppm.

The presence of a small bowel bacterial overgrowth was defined by the evidence of a peak > 20 ppm occurring 15 min before the colonic peak. Also, patients with an elevated fasting H<sub>2</sub> and/or CH<sub>4</sub> level (> 12–15 ppm) were considered positive for bacterial overgrowth in accordance with the literature.<sup>15–18</sup> If the lactulose breath test was positive, a glucose breath test was performed after 1 week to confirm the diagnosis.<sup>6, 7</sup> The glucose breath test was performed by the administration of 50 g glucose following the same aforesaid modalities and with the same device. The glucose breath test was considered positive in the presence of an increase in H<sub>2</sub> excretion > 12 ppm over the baseline value within 2 h. Also, an increase in H<sub>2</sub> excretion > 12–15 ppm in the fasting state was considered

diagnostic for bacterial overgrowth, according to the literature.<sup>15–18</sup>

Patients with bacterial overgrowth were randomized in two groups receiving metronidazole 250 mg t.d.s. orally for 10 days (Group A) or ciprofloxacin 500 mg b.d. orally for 10 days (Group B).

The randomization list to allocate the patients to receive metronidazole or ciprofloxacin was performed by the use of StatsDirect statistical software.

A glucose breath test was repeated 1 week after the end of treatment.

The severity of three symptoms (pain, bloating, soft stools) was recorded at baseline and 1 week after antibiotics on a four-point severity scale (severe, moderate, mild, absent), as previously described.<sup>4</sup> Assessment was done by the patients on a visual analogic scale with a score ranging from 0 to 3.

#### Statistical analysis

For categorical variables the Pearson chi-square test or Fisher's exact were applied as appropriate. Continuous variables were compared with the Mann–Whitney *U*-test and Wilcoxon's sum rank test. All analyses were two-tailed. For all analyses, probability values of 5% or less were taken to be statistically significant. The statistical analysis was performed using the SPSS software package for Windows (release 11.0.1, 15 November 2001; SPSS Inc., Chicago, Ill., USA).

## RESULTS

A lactulose hydrogen/methane breath test was performed in 145 eligible consecutive patients affected by Crohn's disease attending our clinic. The mean oro-caecal transit time was  $159 \pm 40$ , thus being longer than those reported for the normal population of our area (data not shown).<sup>4</sup> The lactulose breath test was positive for bacterial overgrowth in 30 cases. In all positive breath tests an increase of H<sub>2</sub> levels was seen, while no patient showed an isolated methane peak. In 29 out of 30 patients the positive results were confirmed at the glucose breath test. Thus, small bowel bacterial overgrowth was present in 29 out of 145 patients with Crohn's disease (20%). As expected, the prevalence of bacterial overgrowth was higher in patients with previous surgery vs. those patients not operated upon (33% vs. 14%;  $P = 0.007$ ) and in those with at least one stricture compared to those without (29% vs. 14%;

$P = 0.03$ ). Accordingly, a history of previous surgery was present in 17 out of 29 patients with overgrowth (58%), while at least one stricture was recognizable in 16 out of 29 of these patients (55%).

The main reported symptoms present in patients with small bowel bacterial overgrowth were abdominal bloating (90%), abdominal pain (48%) and soft stools (59%).

The 29 patients with bacterial overgrowth were randomized in two groups: Group A (15 patients) receiving metronidazole 250 mg t.d.s. orally for 10 days and Group B (14 patients) receiving ciprofloxacin 500 mg b.d. orally for 10 days. The characteristics of the 29 randomized patients are reported in Table 2. Sex, age, Crohn's disease activity index (CDAI), localization and pattern of disease were well distributed between the two groups.

Treatment was well tolerated in both study groups. One patient withdrew from metronidazole treatment after 2 days because of nausea. No other significant side-effects were recorded.

Glucose breath test normalization occurred in 13 out of 15 patients treated by metronidazole and in all patients treated by ciprofloxacin ( $P = \text{ns}$ ) (Figure 1). As shown in Table 3, both antibiotic treatments induced a significant improvement in intestinal symptom scores compared to basal values. No significant difference in

Table 2. Characteristics of patients with bacterial overgrowth in treatment with metronidazole 250 mg t.d.s. (Group A) or ciprofloxacin 500 mg b.d. (Group B)

Variable	Group A ( <i>n</i> = 15)	Group B ( <i>n</i> = 14)	<i>P</i>
Sex (M/F)	9/6	8/6	ns
Mean age (range)	39.5 (21–70)	38 (21–69)	ns
CDAI			
< 150	8	8	ns
> 150	7	6	
Localization			
Ileal	8	7	ns
Ileo-colonic	4	3	
Colonic	3	4	
Pattern			
Inflammatory	3	2	ns
Strictureing	8	8	
Penetrating	4	4	
Previous surgery	8	7	ns

Data are presented as number except when indicated. CDAI, Crohn's disease activity index.

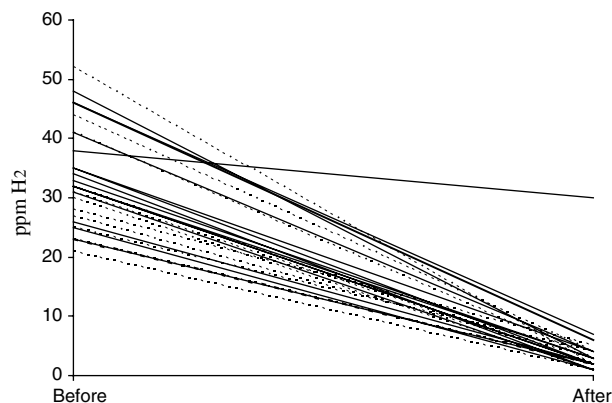


Figure 1. Expiratory H<sub>2</sub> level at glucose breath test before and after therapy with metronidazole (continuous line) and ciprofloxacin (dotted line).

the proportion of patients responding to therapy was recorded between the two treatment groups, in consideration of abdominal bloating (85% vs. 83%;  $P = ns$ ), decrease in faecal softness (44% vs. 50%;  $P = ns$ ), and abdominal pain (50% vs. 43%;  $P = ns$ ) (Table 4).

Both the patient resistant and one intolerant to metronidazole were successfully treated by ciprofloxacin.

All patients were followed up for a median time of 16 months. The breath test has been repeated after 1 year in 20 patients. At September 2003 nine patients have a follow up lower than 1 year. Six out of 16 patients with structuring disease had their stricture resected. Only one patient presented a recurrence of

bacterial overgrowth 12 months after the end of antibiotics, confirmed by the glucose breath test.

## DISCUSSION

Our study confirms that small bowel bacterial overgrowth frequently complicates the course of Crohn's disease, thereby worsening the intestinal symptomatology in many patients.

In the present study, the prevalence of small bowel bacterial overgrowth was about 20% of patients affected by Crohn's disease (up to 30% in patients with previous surgery; up to 25% in patients with strictures). These data confirm what we have previously described in a smaller series.<sup>4</sup> In all patients overgrowth was identified by H<sub>2</sub> peak or high H<sub>2</sub> fasting levels, while no CH<sub>4</sub> producer was identified. The absence of CH<sub>4</sub> producers confirms that, at least in our area, the proportion of methanogenic bacteria is small.<sup>4</sup>

Patients affected by this complication normally show a worsening of abdominal pain and bloating with an increase in faecal softness, and often it is not easy to determine if the clinical exacerbation is due to the primary intestinal inflammatory disease or to a secondary bacterial overgrowth. In this context a hydrogen/methane breath test can be a useful tool for the diagnosis of this potentially treatable condition. In addition, recent reports have highlighted the utility and accuracy of this simple and noninvasive test for

Symptom	Group A (n = 15)			Group B (n = 14)		
	Basal	After treatment	P	Basal	After treatment	P
Bloating	2.3 ± 0.7	0.7 ± 0.9	< 0.001	2.3 ± 0.4	1.3 ± 0.4	< 0.001
Stool softness	2.3 ± 0.4	1.3 ± 0.4	0.02	1.8 ± 0.6	1.6 ± 0.5	0.04
Abdominal pain	1.8 ± 0.6	1.5 ± 0.6	0.04	1.9 ± 0.7	1.6 ± 0.5	0.04

Data are presented as mean ± standard deviation.

Table 3. Modification in clinical scores induced by antibiotic therapy in 29 patients treated with metronidazole 250 mg t.d.s. (Group A) or ciprofloxacin 500 mg b.d. (Group B)

Symptom	Before therapy			Improvement after therapy		
	Group A n (%)	Group B n (%)	P	Group A n (%)	Group B n (%)	P
Bloating	14/15 (93)	12/14 (86)	ns	12/14 (85)	10/12 (83)	ns
Soft stools	9/15 (60)	8/14 (57)	ns	4/9 (44)	4/8 (50)	ns
Abdominal pain	8/15 (53)	7/14 (50)	ns	4/8 (50)	3/7 (43)	ns

Table 4. Clinical response to therapy in 29 patients treated with metronidazole 250 mg t.d.s. (Group A) or ciprofloxacin 500 mg b.d. (Group B)

detection of bowel strictures and secondary bacterial overgrowth in patients with Crohn's disease.<sup>8</sup>

Data on the treatment of small bowel bacterial overgrowth complicating Crohn's disease are scanty. Previous reports of patients not affected by Crohn's disease have revealed the efficacy of antibiotics such as norfloxacin,<sup>10</sup> amoxicillin-clavulanate<sup>10</sup> and rifaximin<sup>11</sup> in the treatment of bacterial overgrowth.

Metronidazole is an effective antibiotic against Gram-negative and Gram-positive anaerobic bacteria such as *Bacterioides*, *Fusobacterium* and *peptostreptococci*,<sup>19</sup> and as such is potentially useful in the treatment of small bowel bacterial overgrowth. On the contrary, ciprofloxacin is not effective against anaerobic bacteria;<sup>20</sup> however, it has been successfully prescribed for intestinal decontamination in several conditions where the Gram-negative microflora play a key role.<sup>21, 22</sup>

Our study is the first demonstration of the efficacy of metronidazole and ciprofloxacin in the treatment of small bowel bacterial overgrowth in patients affected by Crohn's disease, even if these drugs have been widely used in the active disease for many years.<sup>11-13</sup>

In our experience both antibiotics were effective and well tolerated in the treatment of this condition, although ciprofloxacin showed a small, but not statistically significant, gain in terms of efficacy and tolerability compared to metronidazole.

Most patients in both study groups presented a normalization of breath test parameters and a significant improvement of symptoms after antibiotic treatment. The most significant improvement regarded abdominal bloating (about 80%), perhaps due to the resolution of the small bowel bacterial over-fermentation. The other two recorded clinical symptoms (abdominal pain, soft stools) improved in only half the patients, probably because more symptoms related to the underlying intestinal disease (inflammation, strictures).

Our data suggest that a routine use of breath test may be useful during the follow-up of patients with Crohn's disease in order to identify patients with bacterial overgrowth that can be effectively treated with antibiotics. The main limitation of the test is the difficulties in interpreting the results in patients with rapid transit due to diarrhoea.<sup>15</sup> In fact, about 12% of consecutive patients in our series were not eligible for the test due to the presence of diarrhoea. Furthermore, since intestinal permeability is increased in patients with

Crohn's disease<sup>23</sup> it could be hypothesized that this may account for the high incidence of a positive breath test in this population. However, the normalization of the breath test after antibiotics and the clinical response to therapy seem to indicate that breath-test abnormalities are directly related to bacterial overgrowth.

In conclusion, our paper confirms that small bowel bacterial overgrowth is frequent in patients affected by Crohn's disease and that it is associated with symptoms that can worsen patient conditions. This complication is more frequent in patients with a history of previous surgery and in those with stricturing pattern of disease. Metronidazole and ciprofloxacin are both effective and safe drugs in the treatment of this condition.

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#### REFERENCES

- Rhodes JM, Middleton T, Jewell DP. The lactulose breath test as a diagnostic test for small bowel bacterial overgrowth. *Scand J Gastroenterol* 1979; 14: 333-6.
- Hamilton I, Worsley BW, Cobden I *et al.* Simultaneous culture of saliva and jejunal aspirate in the investigation of small bowel bacterial overgrowth. *Gut* 1982; 23: 847-53.
- Valdovinos MA, Camilleri M, Thomforde G *et al.* Reduced accuracy of 14C-D-xylose breath test for detecting of bacterial overgrowth in gastrointestinal motility disorders. *Scand J Gastroenterol* 1993; 28: 963-8.
- Castiglione F, Del Vecchio Blanco G, Rispo A *et al.* Orocecal transit time and bacterial overgrowth in patients with Crohn's disease. *J Clin Gastroenterol* 2000; 31: 63-6.
- Hirikawa M, Iida M, Kohorogi N *et al.* Hydrogen breath test assessment of orocecal transit time: comparison with barium meal study. *Am J Gastroenterol* 1988; 83: 1158-66.
- Kerlin P. Glucose-H<sub>2</sub> breath test for small intestinal bacterial overgrowth. *Gastroenterology* 1990; 98: 253-4.
- Corazza GR, Menozzi MG, Strocchi A *et al.* The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. *Gastroenterology* 1990; 98: 302-9.
- Mishkin D, Boston FM, Blank D *et al.* The glucose breath-test: a diagnostic test for small bowel strictures in Crohn's disease. *Dig Dis Sci* 2002; 47: 489-94.
- Funayama Y, Sasaki I, Naito H *et al.* Monitoring and anti-bacterial treatment for postoperative bacterial overgrowth in Crohn's disease. *Dis Col Rectum* 1999; 42: 1072-7.
- Attar A, Flourie B, Rambaud JC *et al.* Antibiotic efficacy in small bowel bacterial overgrowth-related chronic diarrhoea: a

- crossover, randomised trial. *Gastroenterology* 1999; 117: 794–7.
- 11 Di Stefano M, Malservisi S, Veneto G *et al.* Rifaximin versus chlortetracycline in the short term treatment of small bowel bacterial overgrowth. *Aliment Pharmacol Ther* 2000; 14: 551–6.
  - 12 Prantero C, Berto E, Scribano ML *et al.* Use of antibiotics in the treatment of active Crohn's disease: experience with metronidazole and ciprofloxacin. *Ital J Gastroenterol Hepatol* 1998; 30: 602–6.
  - 13 Greenboole SL, Steinhart AH, Greenberg GR. Combination ciprofloxacin and metronidazole for active Crohn's disease. *Can J Gastroenterol* 1998; 12: 53–6.
  - 14 Prantero 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* 1996; 91: 328–32.
  - 15 Corazza GR, Strocchi A, Sorge M *et al.* Prevalence and consistency of low breath H<sub>2</sub> excretion following lactulose ingestion. *Dig Dis Sci* 1993; 38: 300–4.
  - 16 Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. *Gastroenterology* 1988; 95: 982–8.
  - 17 Corazza GR, Strocchi A, Gasbarrini G. Fasting breath hydrogen in celiac disease. *Gastroenterology* 1987; 93: 53–6.
  - 18 Perman JA, Modier S, Barr RG *et al.* Fasting breath hydrogen concentration: normal values and clinical application. *Gastroenterology* 1984; 87: 1358–63.
  - 19 Freeman CD, Klutman NE, Lamp KC. Metronidazole. A therapeutic review and update. *Drugs* 1997; 54: 679–708.
  - 20 Appelbaum PC. Quinolone activity against anaerobes. *Drugs* 1999; 58: 60–4.
  - 21 Borzio M, Salerno F, Sbudelli M *et al.* Efficacy of oral ciprofloxacin as selective intestinal decontamination in cirrhosis. *Ital J Gastroenterol Hepatol* 1997; 29: 262–6.
  - 22 Tillonen J, Homann N, Rautio M *et al.* Ciprofloxacin decreases the rate of ethanol elimination in humans. *Gut* 1999; 44: 347–52.
  - 23 Meddings JB. Review article: Intestinal permeability in Crohn's disease. *Aliment Pharmacol Ther* 1997; 11: 47–53.