Quantitative assessment of histological changes in chronic gastritis after eradication of *Helicobacter pylori*

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Abstract

Aims: To evaluate the effect of 10 day triple treatment on *H pylori* eradication and associated gastritis.

Methods: Fifty patients with *H pylori* positive non-ulcer dyspepsia were treated for 10 days with amoxicillin, tinidazole, and bismuth salts. Histological examination of the antral mucosa was performed before (T0), six weeks (T1), and six months (T2) after treatment. The new Sydney classification of gastritis was used, using a score from 0 to 3 to grade degree of inflammation, atrophy, activity (intraepithelial or lamina propria damage) and *H pylori*.

Results: At T0 all patients had chronic active gastritis. Lymphoid follicles were present in 12 cases. At T1 33 patients were *H pylori* negative: the score showed a decrease of activity (from 2.5 to 0.54). The result was confirmed at T2 (mean score 0.22). Inflammation decreased from 1.8 to 1.4 at T2. Only one case of follicular gastritis was observed. In *H pylori* positive patients the scores did not show significant modifications.

Conclusions: Ten day triple treatment is effective in eradicating *H pylori* in 69% of cases, causing a decrease of the total score for gastritis. Activity, defined by polymorph infiltration, was promptly reduced when *H pylori* was eradicated. There was a trend to a reduction in inflammation, but atrophy was irreversible.

The pathogenic role of *Helicobacter pylori* in chronic active gastritis is now well recognised and supported by many studies.¹⁻³ Histological observations show that *H pylori* can adhere to the luminal surface of glandular cells beneath the mucous layer.⁴⁻⁵ Recent studies have shown that *H pylori* produces cytotoxins and enzymes which cause mucosal damage: loss of microvilli, cellular vacuolisation, destruction of intercellular junctions, erosion of the mucosal surface.⁶⁻⁷ These changes always coincide with lymphocytic and polymorphonuclear infiltration that is particularly concentrated in the pit-isthmus region.²⁻³

Treatment of *H pylori* infection with combinations of different antimicrobial drugs can eradicate the bacteria, and consequently modify the histological picture.⁸⁻⁹

Recognition of the importance of *H pylori* in producing gastric inflammatory lesions resulted in a review of the histological classification

of gastritis: a new scheme was proposed during the 1990 Sydney World Congress of Gastroenterology, called, for short, the Sydney system.¹⁰

Methods

Fifty consecutive patients, 28 of whom were male (mean age 48 years), with *H pylori* positive non-ulcer dyspepsia were treated for 10 days with colloidal bismuth subcitrate 120 mg four times a day, tinidazole 500 mg twice a day, and amoxicillin 1 g twice a day. Infection was confirmed by histological evaluation of four antral biopsy specimens taken during endoscopy, and by a positive urease test. The same evaluations were performed six weeks (T1) and six months (T2) after treatment.

Paraffin wax sections were stained with haematoxylin and eosin and Giemsa. All the slides were observed blind by a pathologist (DB) and graded for the presence of gastritis and *H pylori* according to the criteria outlined in the Sydney system.¹⁰ The variables considered were as follows:

Inflammation: indicated by the presence of chronic inflammatory cells in the lamina propria—lymphocytes, plasma cells, macrophages and histiocytes. The different types of gastritis, previously classified as superficial, diffuse, follicular and atrophic,¹¹ were no longer considered separately, but were included, instead, in the degree of inflammation. Furthermore, the presence of lymphoid follicles was considered to be an aspect of the immunological reaction to *H pylori*.¹²⁻¹³

Atrophy: indicated gastric gland loss; this was considered independently from inflammation and graded separately.

Activity of gastritis: the grade of "acute injury" suggested by polymorph infiltration in the lamina propria or in intraepithelial sites.

These variables were graded as 0 = absent, 1 = mild, 2 = moderate, 3 = severe. *H pylori* was graded according to density: 0 = absent, 1 = occasional micro-organisms, 2 = patchy, 3 = layer of bacteria. Intestinal metaplasia, when present, was given a score of 1. The sum of the scores, ranging from 0 to 12, or 13, if intestinal metaplasia was present, was made for each patient, thus giving a quantitative evaluation of gastritis.

Variations in the scores from T0 for gastritis and *H pylori* eradication were analysed by Student's *t* test for matched data, calculating the confidence interval (CI). Significance was assessed using the Freedman test for non-

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Accepted for publication
14 February 1992

Figure 1 Mean scores for gastritis in patients in whom *H pylori* infection had been eradicated.

Figure 2 Mean scores for gastritis in patients with continuing *H pylori* infection.

parametric data. The Spearman correlation coefficient was calculated to evaluate the possible relation between *H pylori* positivity and histological damage.

Results

Before treatment all the patients infected with *H pylori* had chronic active gastritis. Table 1 shows the prevalence of histological features in our series. The scores for single variables are illustrated in figs 1 and 2. As regards inflammation, at T0 lymphoid follicles were found in 12 cases. The sum of the score is given in table 2.

All the patients completed the treatment, but two who refused a second endoscopy were excluded from further study. During treatment only four patients reported slight side effects, mainly vertigo, but this did not require them to stop or change treatment. Almost all patients reported relief of dyspeptic symptoms.

SIX WEEK RESULTS (T1)

At the second endoscopy 33 patients out of 48 (69%) gave a negative result to the urea test and there was no histological evidence of *H pylori* infection. For these patients the total score for gastritis showed a significant decrease (mean from 7.76 at T0 to 3.22 at T1; $p < 0.01$, 95% CI 2.94 to 5.28), while in non-responders the score was only slightly reduced (6.31 at T2; $p > 0.1$, CI - 0.57 to 3.32). A reduction in gastritis activity in those who were *H pylori* positive was not significant (2.33 at T0, 1.46 at T1; CI 0.08 to 1.56; $p = 0.04$), but was highly significant in *H pylori* negative patients (2.13 at

Table 1 Percentage distribution of gastric lesions at T0, T1, and T2

	Score	T0 (n = 48)	T1 - (n = 33)	T1 + (n = 15)	T2 - (n = 18)	T2 + (n = 8)
Inflammation:	0		10% (3)		22% (4)	
	1	63% (11)	10% (8)	40% (6)	17% (3)	50% (4)
	2	53% (30)	67% (22)	47% (7)	61% (11)	38% (3)
	3	15% (7)		13% (2)		12% (1)
Atrophy:	0	50% (27)	44% (14)	53% (8)	33% (6)	38% (3)
	1	12% (4)	17% (8)	20% (3)	33% (6)	12% (1)
	2	27% (14)	28% (9)	13% (2)	17% (3)	25% (2)
	3	12% (3)	11% (2)	13% (2)	17% (3)	25% (2)
Activity:	0	6% (3)	61% (21)	27% (4)	83% (15)	
	1	13% (5)	28% (8)	13% (2)	11% (2)	12% (1)
	2	15% (13)	6% (2)	47% (7)	6% (1)	63% (5)
	3	66% (27)	6% (2)	13% (2)		25% (2)
<i>H pylori</i> infection:	0		100% (33)		100% (18)	
	1	8% (4)		20% (3)		38% (3)
	2	36% (17)		60% (9)		38% (3)
	3	56% (27)		20% (3)		25% (2)
Intestinal metaplasia:	0	82% (39)	85% (28)	73% (11)	67% (12)	88% (7)
	1	18% (9)	15% (5)	27% (4)	33% (6)	12% (1)

Table 2 Mean value of scores for variables studied and of total score for gastritis

	T0 (n = 48)	T1 - (n = 33)	T1 + (n = 15)	T2 - (n = 18)	T2 + (n = 8)
Inflammation:	1.9	1.57	1.73	1.4	1.62
Atrophy:	0.85	0.96	0.86	1.16	1.37
Activity:	2.33	0.54*	1.46**	0.22***	2.12
<i>H pylori</i> infection:	2.48	0	2	0	1.87
Intestinal metaplasia:	0.2	0.15	0.26	0.33	0.12
Total score	7.76	3.22	6.31	3.11	7.1

* Difference v T0 = 1; CI 95% 1 to 2; $p < 0.001$.

** Difference v T0 = 0.87; CI 95% 0.08 to 1; $p < 0.05$.

*** Difference v T0 = 2.11; CI 95% 1 to 2; $p < 0.001$.

T0, 0.5 at T1; CI 1.23 to 2.05; $p < 0.001$). Inflammation did not seem to reduce significantly even though lymphoid follicles were found in seven cases (three *H pylori* negative and four *H pylori* positive).

SIX MONTH RESULTS (T2)

Only 26 patients returned for six month follow up. The other 22 refused endoscopy, mostly because they were asymptomatic.

Eighteen patients were *H pylori* negative; in three cases reinfection had occurred. Two patients, who were *H pylori* positive at T1, were now negative without any further treatment. The score for gastritis was further reduced in *H pylori* negative patients (mean value 3.0 at T2; $p < 0.001$; CI 3.45 to 6.11), while in non-responders it relapsed to 7.1. Gastritis activity was significantly reduced by *H pylori* eradication (mean difference v T0 = 2; CI 1.49 to 2.51; $p < 0.001$). In fact, reduction in polymorph infiltration, evident soon after treatment, continued until virtual disappearance during follow up when eradication was stable (0.22 at T2). In *H pylori* positive patients there was a rapid reactivation of gastritis (from 1.5 to 2.1). In *H pylori* negative patients there was a trend towards a reduction in inflammation (1.9 at T0, 1.57 at T1 and 1.4 at T2) with only one case of follicular gastritis, even though this was not significant at six month follow up.

Discussion

The therapeutic approach to *H pylori* gastric infection is not yet standardised. Single treatment with antibiotics or bismuth salts for four to eight weeks gives poor results.^{14 15} Better outcomes were obtained with combined treatments using these drugs, obtaining more than 90% eradication in some cases.¹⁶ The main drawback of these treatments is the high rate of side effects, which impairs the compliance of patients.

In our study we have shown that triple treatment for 10 days can eradicate *H pylori* gastric mucosa in 69% of cases, with excellent compliance among patients.

Histological assessment showed a close association between antral lesions and *H pylori* infection, which agrees with the findings of other authors.^{11 17 18} In fact, normal gastric mucosa with *H pylori* positivity has rarely been reported.^{19 20} In our series all the patients showed altered histology before treatment.

The inflammatory process is characterised by lymphocyte and polymorph infiltration of the superficial lamina propria in the earliest stage of gastritis, while in severe cases the infiltrate extends towards the mucosal surface,^{2 5} sometimes forming lymphoid follicles.¹² It has been recently suggested that such lymphocytic reaction to *H pylori* could be a pathogenic factor for primary B cell gastric lymphoma.¹³

In our patients the grade of polymorph infiltration (activity) strongly correlated with the density of *H pylori* colonisation. The absence of polymorphs was always associated with eradication of the bacteria. Furthermore,

in the three cases of reinfection we observed a rapid reactivation of gastritis.

The Sydney system¹⁰ distinguishes activity, which is an expression of how the ongoing situation is directly influenced by the presence or absence of bacteria, from inflammation and atrophy. Our results suggest that inflammation can be reduced (approaching statistical significance) after a long follow up period, but that atrophy is irreversible. When the damage is advanced, inflammation evolves in atrophy even if *H pylori* has been eradicated.

In conclusion, short term triple treatment is effective in eradicating *H pylori* from gastric mucosa, immediately decreasing gastritis activity until it has virtually disappeared after six months. Inflammation shows a tendency to resolve, particularly in cases in which histological damage is not advanced. In cases of chronic inflammation atrophic damage is irreversible, and can become more evident with the disappearance of infiltrate.

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