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Risk factors for failure of Helicobacter pylori *therapy — results of an individual data analysis of 2751 patients*

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SUMMARY

Aim: To study risk factors for failure of *Helicobacter pylori* eradication treatment.

Methods: Individual data from 2751 patients included in 11 multicentre clinical trials carried out in France and using a triple therapy, were gathered in a unique database. The 27 treatment regimens were regrouped into four categories.

Results: The global failure rate was 25.8% [95% CI: 24–27]. There was a difference in failure rate between duodenal ulcer patients and non-ulcer dyspeptic patients, 21.9% and 33.7%, respectively ($P < 10^{-6}$). In a random-effect model, the risk factors identified for eradication failure in duodenal ulcer patients ($n = 1400$) were: to be a smoker, and to have received the group 4 treatment, while to receive a 10 day treatment vs. 7 days protected from failure. In non-ulcer dyspeptic patients ($n = 913$), the group 2 treatment was associated with failure. In both groups, age over 60 was associated with successful *H. pylori* eradication. There were less strains resistant to clarithromycin in duodenal ulcer patients than in non-ulcer dyspeptic patients. Clarithromycin resistance predicted failure almost perfectly.

Conclusion: Duodenal ulcer and non-ulcer dyspeptic patients should be managed differently in medical practice and considered independently in eradication trials.

INTRODUCTION

The discovery of *Helicobacter pylori* has led to the consideration that some severe diseases of the stomach, such as peptic ulcer, are infectious and therefore with a proper antibiotic regimen the bacterium could be easily eradicated and the disease cured. Twenty years after the discovery of *H. pylori*, although no simple eradication regimen has been proposed, several regimens are considered to be satisfactory.[1–4]

Treatment failures are, however, not uncommon and not homogeneous between countries, and the study of their possible causes has not been performed on a large scale. Antibiotic resistance is the first factor to be considered, and indeed seems to be a real cause of failure, especially for clarithromycin-based therapies.[5] Other factors such as the patient's characteristics, underlying disease and environmental factors have rarely been explored in a large group of patients. However, it is important to obtain this knowledge, given the economic aspects involved as well as the possible ecological consequences if the 'test and treat' strategy is applied widely, in developed countries, as recommended in the Maastricht Consensus Report.[1]

France is reputed to have higher failure rates for *H. pylori* eradication than neighbouring countries,[3, 6, 7] and therefore such a patient population is well suited for studies attempting to identify risk factors for treatment

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failure. This study was conducted to identify risk factors for failure of *H. pylori* eradication treatment using the individual data of all parallel multicentre randomized clinical trials, including triple therapies, performed in France.

PATIENTS AND METHODS

This is a retrospective analysis performed on individual data gathered from patients included in tri-therapy eradication trials performed in France. All multicentre, parallel, randomized, double-blind, comparative clinical trials carried out in France on *H. pylori* eradication using triple therapies, completed before January 1999 and having centralized diagnostic tests, were included.

Trial characteristics

The design of all these trials was identical for inclusion, intermediate and final visits when the outcome was measured. Patients were included after an endoscopy, according to the results of a rapid urease test (CLO test), confirmed later by another biopsy based test, such as culture or histology. A follow-up visit was performed at the end of the treatment to evaluate tolerance and compliance. Another follow-up visit was done 4–6 weeks later, during which a urea breath test (UBT) was carried out to evaluate the outcome: *H. pylori* eradication. In cases where a urea breath test was not performed, the results of biopsy based tests: histology and culture or PCR, were considered. Furthermore, all of the trials included in this study were homogeneous in relation to study population, inclusion and exclusion criteria of patients, no previous *H. pylori* eradication treatment, and the delay between the end of the treatment and determination of the outcome.

The data files received from the different sponsors of these trials (six pharmaceutical companies) were put into a similar format for analysis. First, variables based on the available data and the results of a former study[8] were selected; they also had to be common to all of the trials. Second, these common variables were re-coded in order to be homogeneous so that they could be combined into a final database.

Study population

The study population of the present analysis consisted of the randomized patients of each of the selected clinical trials with positive *H. pylori* status at inclusion, for whom the outcome was known, and who had taken at least one dose of the prescribed treatment.

Selected variables

Pooling of data was possible because all these studies had a similar design, and end-points were measured centrally, avoiding heterogeneity in the methods or interpretation.

The variables selected were related: (i) to the patient: socio-demographic and behavioural data, endoscopic and histological diagnosis, (ii) to the treatment received, and (iii) to the bacterial strain in terms of resistance to clarithromycin.

The first group of variables included: gender, age, geographical origin of the patients coded as born in France or of other origin (Northern or Black Africa, Asia or French overseas departments), region of inclusion coded as north, centre or south of France, body mass index (BMI) coded as normal or different from normal values (normal for men: 21.7–28.2 kg/m^2; and for women: 20.2–26.6 kg/m^2), tobacco consumption was coded as smoker or nonsmoker, and alcohol consumption coded as yes or no at inclusion.

Two major endoscopic diagnoses were considered, duodenal ulcer and non-ulcer dyspepsia. Endoscopic lesions such as gastritis, duodenitis and oesophagitis were coded as present or absent.

Histological diagnosis was only based on antral biopsies, because the majority of studies performed required only antral biopsies in their protocol. Histological diagnosis was centralized and performed by two expert pathologists and coded into two classes according to the Sydney System classification[9, 10] as follows: (i) non-atrophic chronic gastritis, when inflammation or activity of any grade, or antral atrophy grade 1 were present with no intestinal metaplasia lesions; and (ii) atrophic chronic gastritis, when lesions of atrophic mucosa of grade 2 or 3 were observed with or without intestinal metaplasia.

The different treatment arms were classified into four categories: (1) reference group: those including a double dose of proton pump inhibitor, amoxicillin (1 g b.d.) and clarithromycin (500 mg b.d.) for 7 days, which is the recommended and most widely used regimen amongst those prescribed in clinical practice in France;[11] (2) group 2: the same regimen but with

a single dose of proton pump inhibitor or double dose of anti-H_2; (3) group 3: regimens including 5-nitroimidazoles, regardless of the other antibiotic or antisecretory drug; and (4) group 4: the regimens which did not fit into one of the three previous groups, especially treatments including macrolides other than clarithromycin (roxithromycin, azithromycin), and other dosages of the antibiotics previously cited. Concerning treatment, the variable 'duration of treatment' was classified into three categories: 7, 10 or 14 days.

Finally, the diagnostic tests used to measure outcome were divided into two classes: (1) urea breath test, and (2) histology and culture or PCR on biopsies.

Data analysis

The present analysis of the database compiled from the clinical trials was performed in order to identify variables which were predictive or linked to the success or failure of *H. pylori* eradication therapy. STATA 7.0 software (Stata Corporation, College Station, TX) was used for univariate and multivariate analyses. The analysis was performed using information obtained at patient inclusion in the clinical trial and used *H. pylori* status evaluated at the end of the trial as the outcome measure. The Mantel–Haenszel χ^2 test to compare qualitative variables and the Student's *t*-test or an analysis of variance (ANOVA) to compare quantitative variables were used when appropriate. All variables with a *P*-value of 0.25 or less in the univariate analysis were included in a random-effect model. The significance of the coefficient of each variable was tested using the likelihood ratio test. Only significant co-variables ($P \leq 0.05$) were retained in the final model. Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated from the coefficient estimated by the random-effect model.[12]

This model was used to take into account the variance of the different studies included in the analysis. It estimates ρ, the proportion of the total variance contributed by the panel-level variance component. When ρ is not different from zero, the panel-level variance is not important and the panel estimation is not different from the pool estimation. A likelihood ratio formally tests the homogeneity of the trials by comparing the pooled estimator with the panel estimator. Confounding factors and interaction terms were taken into consideration as recommended.[13]

RESULTS

Sample description

Fifteen trials were identified but three were not completed in 1999 and for one, the tests were not performed centrally, so only 11 trials with 27 treatment arms were included, representing 3270 randomized patients.

Descriptive analysis

The analysis was performed on 2751 patients responding to the defined inclusion criteria. There were no statistically significant differences between the original population comprised of randomized patients and the analysed population. The mean age of these patients was 47.5 years (range 18–87 years, s.d. 14.1), 1726 (69.4%) were male, 1803 (84.2%) were born in France, and 854 (36.9%) were smokers. Among the 2751 patients, 1838 (66.8%) were duodenal ulcer patients and 913 (33.2%) were non-ulcer dyspeptic patients. The global rate of failure of *H. pylori* eradication was 25.8% (95% CI: 24–27). The description of the sample and the comparison of failure rates according to the patient's characteristics are presented in Table 1.

Age, taken as a continuous variable, was strongly associated with treatment outcome. However, this association was not linear: before 60 years of age, the failure rate varied between 26 and 29%, while after 60, the failure rate varied between 15.2 and 22.2% (Figure 1). It was then decided to use age as a binary variable, with patients aged 60 years or less, and patients older than 60.

There was also a statistically significant difference in failure rates between duodenal ulcer (21.9%) and non-ulcer dyspeptic patients (33.7%) ($P < 10^{-6}$) as well as between treatment groups: in group 1, the failure rate was 18.9%, increasing to 26.8% in group 2, to 30.9% in group 3, and reaching 35.2% in group 4. According to the treatment duration, the failure rate was 29.4% in patients undertaking a 7-day therapy and 16.1% in patients with a 10 day therapy ($P < 10^{-3}$). None of the other variables studied, in particular compliance, were associated with failure (Table 1).

Because there was a strong association between the type of disease, as diagnosed by endoscopy, and the outcome of eradication, the two populations, duodenal ulcer and non-ulcer dyspeptic, were compared and shown to be very different (Table 2). The duodenal ulcer patients were younger than the non-ulcer

Table 1. Risk factors for failure of *Helicobacter pylori* eradication in 2751 patients in France (1990–1998)

		Total (*n*)	Treatment failure		
			n	%	*P*
Age (years)	≤ 60	2129	595	27.9	$<10^{-3}$
	> 60	622	116	18.6	
Gender	Female	761	193	25.4	0.62
	Male	1726	422	24.4	
Smoking	Non-smoker	1459	372	25.5	0.13
	Smoker	854	242	28.3	
Alcohol consumption	Not currently	1364	364	26.7	0.37
	Currently	782	195	24.9	
Geographical origin	France	1803	458	25.4	0.3
	Others*	338	99	29.3	
Region of inclusion	North	1012	261	25.8	0.17
	Centre	836	199	23.8	
	South	891	247	27.7	
Endoscopic diagnosis†	DU	1838	403	21.9	$<10^{-6}$
	NUD	913	308	33.7	
Macroscopic lesions					
gastritis	Absent	655	171	26.1	0.39
	Present	953	267	28	
duodenitis	Absent	1062	292	27.5	0.74
	Present	546	146	26.7	
oesophagitis	Absent	424	146	34.4	0.84
	Present	25	9	36	
Treatment group	Group 1 (ref.)‡	1029	194	18.9	$<10^{-6}$
	Group 2	856	229	26.8	
	Group 3	391	121	30.9	
	Group 4	475	167	35.2	
Treatment duration	7 days	1849	543	29.4	$<10^{-3}$
	10 days	733	118	16.1	
	14 days	169	50	29.6	
Compliance	Poor	116	39	33.6	0.22
	Good	1811	513	28.3	
Side effects	Absent	1433	333	23.2	0.54
	Present	625	153	24.5	

* Others: Northern Africa, Black Africa, Asia, French overseas dept.
† DU, duodenal ulcer; NUD, non-ulcer dyspepsia.
‡ Reference group = PPI b.d. + amoxicillin + clarithromycin; group 2 = PPI o.d. + amoxicillin + clarithromycin, group 3 = imidazole + any other antibiotic + antisecretory drug; group 4 = any treatment not classified in the first three groups.

dyspeptic patients ($P < 10^{-6}$); there were almost twice as many smokers among duodenal ulcer as non-ulcer dyspeptic patients ($P < 10^{-6}$); while the proportion of alcohol consumers was also higher in duodenal ulcer patients, with a smaller difference between proportions. Among patients born in France, the proportion of duodenal ulcers was lower than that of non-ulcer dyspeptic patients ($P < 10^{-6}$), while the opposite was observed for those born outside of France. Although the same proportion of duodenal ulcer or non-ulcer dyspeptic patients came from the north of France, duodenal ulcer patients were more often included than non-ulcer dyspeptic patients in the centre of France and less often in the south ($P < 10^{-6}$); duodenal ulcer and non-ulcer dyspeptic patients received the reference treatment in the same proportion ($P = 0.2$), but this was not true for the other groups of treatment. Only duodenal ulcer patients had different treatment durations, non-ulcer dyspeptic patients were prescribed only a 7-day therapy. Compliance was better in non-ulcer dyspeptic patients than in duodenal ulcer patients ($P < 10^{-6}$).

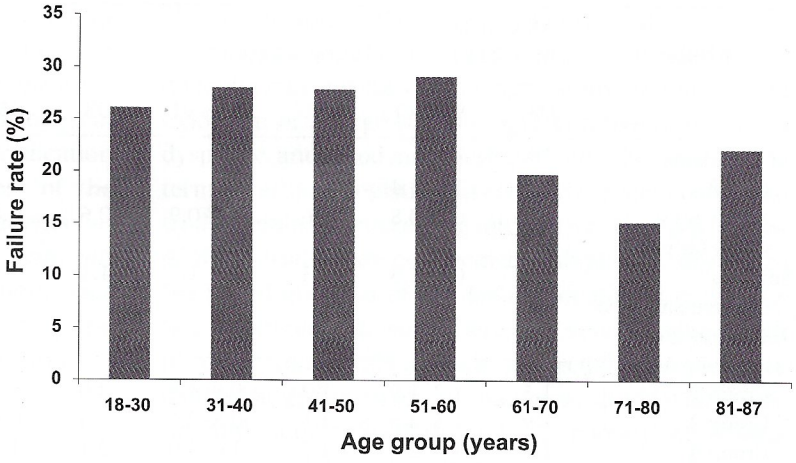

Figure 1. Failure rate of *Helicobacter pylori* eradication according to age group in a cohort of 2751 patients in France.

Table 2. Comparison of risk factors for failure of *Helicobacter pylori* eradication between duodenal ulcer (DU) and non-ulcer dyspepsia (NUD) patients

	DU (n = 1838)		NUD (n = 913)		
	n	%	n	%	P
Age (mean)	1838	mean = 47.1	913	mean = 50.0	$<10^{-6}$
Age ≤ 60 y	1465	79.7	664	72.7	$<10^{-6}$
Men	1347	73.3	379	58.4	$<10^{-6}$
Smokers	623	44.5	231	25.3	$<10^{-6}$
Alcohol consumers	483	39.2	299	32.7	0.002
Geographical origin					
France	1003	81.4	800	88.8	$<10^{-3}$
Others*	229	18.6	109	12.0	$<10^{-3}$
Region of inclusion					
North	669	36.6	343	37.6	0.62
Centre	634	34.7	202	22.1	$<10^{-6}$
South	524	28.7	367	40.2	$<10^{-6}$
Treatment group†					
Group 1 (ref.)	703	38.2	326	35.7	0.2
Group 2	231	12.6	160	17.5	$<10^{-3}$
Group 3	277	15.1	198	21.7	$<10^{-4}$
Group 4	627	34.1	226	25.1	$<10^{-6}$
Treatment duration					
7 days	936	50.9	913	100.0	$<10^{-3}$
10 days	733	39.9	0	0	$<10^{-3}$
14 days	169	9.2	0	0	$<10^{-3}$
Good compliance (>85%)	969	91.4	842	97.1	$<10^{-3}$

* Others: Northern Africa, Black Africa, Asia, French overseas dept.
† Reference group = PPI b.d. + amoxicillin + clarithromycin; group 2 = PPI o.d. + amoxicillin + clarithromycin; group 3 = imidazole + other antibiotic + antisecretory drug; group 4 = any treatment not classified in the first three groups.

Multivariable analysis

Due to these major differences, a random-effect model was constructed for the sample as a whole, as well as for the duodenal ulcer and non-ulcer dyspeptic patient groups separately (Table 3). In the whole sample, once adjusted to all the other variables, non-ulcer dyspepsia was a risk factor for eradication failure when compared to duodenal ulcer (OR = 1.2, 95% CI: 1.0–1.4), as well as taking any other treatment than the treatment from group 1. Conversely, to be older than 60 years (OR = 0.6, 95% CI: 0.5–0.8) and to have a 10-day therapy prescribed (OR = 0.5, 95% CI: 0.4–0.7) were protective factors for therapy failure. The effect of the

Table 3. Risk factors for failure of *Helicobacter pylori* eradication therapy in 2313 patients in France (1990–1998): result of a random-effect model, adjusted on study effect

	All samples ($n = 2313$)		DU* ($n = 1400$)		NUD† ($n = 913$)	
	OR	95% CI	OR	95% CI	OR	95% CI
NUD patients (vs. DU)	1.2	1.0–1.4	—	—	—	—
Age > 60 y (vs. ≤ 60 y)	0.6	0.5–0.8	0.6	0.4–0.9	0.6	0.4–0.8
Smokers (vs. non-smokers)	1.2	0.9–1.5	1.3	1.0–1.7	1.1	0.8–1.5
Treatment group‡ (vs. group 1)						
Group 2	1.5	1.2–1.9	1.2	0.9–1.8	2.0	1.4–3.1
Group 3	1.9	1.5–2.6	1.5	0.8–2.7	1.5	0.9–2.4
Group 4	1.9	1.4–2.6	1.7	1.0–3.0	2.1	1.4–3.2
Treatment duration (vs. 7 days)						
10 days	0.5	0.4–0.7	0.5	0.3–0.6	—	—
14 days	0.8	0.5–1.2	0.5	0.3–1.0	—	—
Outcome measure: UBT vs. histology & culture or PCR	0.8	0.6–0.9	0.6	0.3–1.1	0.6	0.4–1.1

* DU, duodenal ulcer; †NUD, non-ulcer dyspepsia.
‡ Reference group = PPI b.d. + amoxicillin + clarithromycin; group 2 = PPI o.d. + amoxicillin + clarithromycin; group 3 = imidazole + another antibiotic and antisecretory drug; group 4 = any treatment not classified in the first three groups.

treatment group was different in duodenal ulcer and non-ulcer dyspeptic patients. Indeed, in duodenal ulcer patients, the OR for failure was not different between groups 2 or 3 and group 1 (OR = 1.2, 95% CI: 0.9–1.8 and OR = 1.5, 95% CI: 0.8–2.7, respectively), while in non-ulcer dyspeptic patients the risk of failure was higher in group 2 than group 1 (OR = 2.0, 95% CI: 1.4–3.1). In duodenal ulcer patients, the protective effect of a 10-day therapy remained (OR = 0.5, 95% CI: 0.3–0.6). The model was adjusted on the diagnostic tests used to measure outcome. No interaction was found. The test of homogeneity showed that the studies included in the global analysis and those included in the sample comprised of duodenal ulcer patients were homogeneous, with a ρ not different from zero ($\rho = 8 \times 10^{-7}$ in both cases and $P = 1$). Conversely, the studies constituting the sample of non-ulcer dyspeptic patients were heterogeneous ($\rho = 0.05$ and $P = 0.029$).

Analysis taking into account resistance to clarithromycin

The susceptibility of the strains to clarithromycin was tested on a subsample of 179 duodenal ulcer patients and 257 non-ulcer dyspeptic patients. The prevalence of *H. pylori* resistance to clarithromycin was statistically different between the duodenal ulcer and non-ulcer dyspeptic patients, 10 (5.6%) and 43 (16.7%), respectively, $P = 0.0005$. The same analysis as previously performed on duodenal ulcer and non-ulcer dyspeptic patients was carried out on this population subsample. It indicated that the failure rate was different between duodenal ulcer and non-ulcer dyspeptic patients harbouring resistant strains. In non-ulcer dyspeptic patients, resistance to clarithromycin predicted failure perfectly: 43/43 patients, i.e. 100% (95% CI: 93.3–100), while in duodenal ulcer patients with resistant strains, the failure was 8/10, 80% (95% CI: 48.1–96.5).

Analysis taking into account histological diagnosis

Histological diagnosis was available for 1046 patients, 434 (41.5%) duodenal ulcer patients and 612 (58.5%) non-ulcer dyspeptic patients. Among them, 829 (79.2%) had non-atrophic chronic gastritis and 217 (20.7%) had atrophic chronic gastritis. There was no difference in the distribution of histological lesions between duodenal ulcer and non-ulcer dyspeptic patients. There was no difference in *H. pylori* eradication

failure according to histological lesions: 260 (31.4%) in patients with non-atrophic chronic gastritis and 62 (28.6%) in patients with atrophic chronic gastritis. When stratified by treatment group, the histological status of the gastric mucosa had no effect on eradication failure in duodenal ulcer patients, regardless of the treatment group; in non-ulcer dyspeptic patients an effect was observed in group 1 (Table 4) with an eradication failure rate of 27.9% in patients with non-atrophic chronic gastritis ($n = 208$) and of 10% in the patients with atrophic chronic gastritis ($P = 0.008$).

DISCUSSION

The main result of this study is that the failure rate of *H. pylori* eradication is significantly lower in duodenal ulcer patients than in non-ulcer dyspeptic patients and that the risk factors for failure are different in both groups. Because of the large number of patients included, these results are reliable.

The main criticism of this type of study is that the data comes from a selected population, i.e. it originates from clinical trials and thus, is not representative of the patient population as a whole. However, the explicit aim of this analysis—to identify factors implicated in eradication failure—does not render a representative population mandatory, but implies the selection of *H. pylori* positive patients with a known outcome from a randomized population. Furthermore, considering the difficulties in setting up the right study design, i.e. the follow-up of a large sample representative of non-ulcer dyspeptic and duodenal ulcer patients after therapy, in terms of ethical, logistic and economical aspects, clinical trials remain an interesting alternative. If at first the use of these trials does not seem be adapted to answering the initial question of risk factors for failure of eradication treatment, in fact, there are several advantages: (i) data from clinical trials are reliable in terms of methodology, accuracy of diagnosis, quality of follow-up and data collection; and (ii) pooling of a large amount of data issued from clinical trials allows the coverage of many different situations.

However, the missing data constitutes a problem which jeopardizes the value of the results. For example, in this study, data on potentially important risk factors, e.g. antibiotic resistance or histological diagnosis, were not available in all of the trials and the results were therefore not as reliable as for variables with complete data, e.g. endoscopic results. Nonetheless, databases were compared in order to evaluate possible bias due to the amount of missing data. The samples used in the univariate and multivariate analyses ($n = 2751$ and 2313, respectively) were strictly comparable to the sample which was comprised of the randomized patients

Table 4. Failure of *Helicobacter pylori* eradication treatment according to treatment group and histological diagnosis

	DU* patients Failure rate		NUD† patients Failure rate	
	n	%	*n*	%
Treatment group 1 ($n = 371$)				
NACG‡	18/94	19.1	58/208	27.8
ACG +/- IM§	5/19	26.3	5/50	10.0
P		0.45		0.009
Treatment group 2 ($n = 293$)				
NACG	25/102	24.5	57/131	43.5
ACG +/- IM	7/24	29.2	10/36	27.8
P		0.63		0.08
Treatment group 3 ($n = 173$)				
NACG	10/33	30.3	34/103	33.0
ACG +/- IM	0/8	0	14/29	48.3
P		0.7		0.13
Treatment group 4 ($n = 209$)				
NACG	32/115	27.8	26/43	60.5
ACG +/- IM	15/39	38.5	6/12	50.0
P		0.21		0.52

* DU, duodenal ulcer; †NUD, non-ulcer dyspepsia; ‡ NACG, non-atrophic chronic gastritis; § ACG +/- IM, atrophic chronic gastritis with or without intestinal metaplasia.
Note: treatment duration was 7 days for groups 1, 2 and 3 and 14 days for group 4.

($n = 3270$). The same results were observed between the different populations of duodenal ulcer and non-ulcer dyspeptic patients included in the univariate and multivariate analyses, when compared to the randomized population of duodenal ulcer and non-ulcer dyspeptic patients. In contrast, the smaller samples comprising the duodenal ulcer and non-ulcer dyspeptic patients, for which information on resistance to clarithromycin or histological diagnosis was available, were not strictly representative of the randomized sample. However, they remained comparable in terms of age, gender and compliance. The main differences concerned: (i) the treatment received; (ii) the geographical origin; and (iii) the failure rate, which was higher both in duodenal ulcer and non-ulcer dyspeptic patients in these subsamples.

Before stratification on endoscopic diagnosis and regardless of the diagnosis, the best conditions for treatment success were to be more than 60 years of age, and to have taken a group 1 treatment for 10 days. The result obtained in the case of a 14-day therapy is not relevant, because it concerned only one study whose treatment was classified in group 4.

However, there was a major difference (12%) in the failure rate between duodenal ulcer and non-ulcer dyspeptic patients. Similar results were found in a meta-analysis conducted by Huang & Hunt.[14] In other individual studies performed, a similar trend was noted but clear-cut conclusions could not be reached because of small sample sizes.[15–17] This difference in failure rate between duodenal ulcer and non-ulcer dyspeptic patients remained, even when considering only patients harbouring strains susceptible to clarithromycin. Furthermore, it is interesting to note that in non-ulcer dyspeptic patients a double dose of proton pump inhibitor plus amoxicillin and clarithromycin (treatment group 1) was more effective than a single dose (treatment group 2), while in duodenal ulcer patients no difference was observed. These results, in addition to the contradictory results obtained with regard to the benefits of eradication treatment in non-ulcer dyspeptic patients,[18–20] point out the importance of considering duodenal ulcer and non-ulcer dyspeptic patients independently in clinical trials, as well as in patient care.

The reasons for this difference are not yet clearly understood. It could be due to patient differences, especially concerning the status of the gastric mucosa, or to differences in the infecting *H. pylori* strain, i.e. antibiotic resistance or *cag* status. In this study, the status of the gastric mucosa did not influence the eradication rate in duodenal ulcer patients. In non-ulcer dyspeptic patients, interestingly, regardless of the treatment group, the failure rate was always higher in patients with non-atrophic chronic gastritis than in patients with atrophic chronic gastritis. However, this difference only reached significance in patients who received the group 1 treatment. This may be due to the fact that this group was homogeneous in terms of treatment received or because it was the largest sample.

In relation to resistance, a higher resistance rate to clarithromycin in non-ulcer dyspeptic patients in comparison to duodenal ulcer patients has already been described.[21] Among the 2751 patients, data on resistance was available for 436 (16%), and may therefore not be representative. However, the 12.3% resistance rate observed in this study is similar to the 14.3% observed during an active epidemiological survey carried out in France.[21] The number of missing values is due to the fact that *H. pylori* culture was not always mandatory for inclusion of a patient in a trial. Resistance to clarithromycin was the major predictor of failure in duodenal ulcer as well as in non-ulcer dyspeptic patients. Therefore, it was of no value to include it as a co-variable in the model. Predictive models drop any variable which predicts the outcome perfectly, because of co-linearity. Unfortunately, resistance to metronidazole could not be tested in this study, but because of the high prevalence of resistance in France, it is used only as a second line treatment.[22] However, since the overall rate of resistance to clarithromycin is still low, most of the previously published studies[3, 23] and meta-analyses[5] only included a limited number of such strains, and indeed its impact on eradication outcome is still limited. Despite incomplete information in many cases, this study presents the largest database of the impact of clarithromycin resistance in randomized clinical trials (53 cases).

Finally, we were unable to consider the *cagA* status of *H. pylori* strains in this study. However, it was previously shown by us and others that patients harbouring *cagA* positive strains have a lower failure rate than those harbouring *cagA* negative strains;[8] *cagA* positive strains are more likely to be present among duodenal ulcer patients[17, 24, 25] than among non-ulcer dyspeptic patients, as well as among patients with atrophic chronic gastritis and intestinal metaplasia.[26–28] Thus, *cagA* positive status could account for the lower failure rate in duodenal ulcer patients, as well

as in non-ulcer dyspeptic patients with atrophic chronic gastritis.

Because a large number of patients received the same regimen recommended by different consensus conferences and currently used in France,[11, 29] it was considered as group 1 and as the reference treatment in this study. A regimen with a single dose of antisecretory drug as the only difference was also received by a large number of patients and constituted group 2. There were not enough patients to separate those having received single and double doses of antisecretory drug in association with clarithromycin and metronidazole; therefore all treatments including 5-nitroimidazoles were grouped together (group 3), and then formed a heterogeneous group. Globally, the failure rate of group 3 was significantly different from group 1, but it may well be that if a group like group 1 could have been formed with metronidazole instead of amoxicillin as the only difference, it would have led to similar results, as in previously published individual studies.[2, 3, 6] Group 4 had an even higher heterogeneity and a lower success rate regardless of endoscopic diagnosis. However, the goal of this classification was not to delineate which regimen was the best, but to regroup the 27 treatment arms in order to control for the effect of the regimen when analysing factors associated with failure. Interestingly, the results obtained confirm that the currently used combination is the best thus far.

Conversely to what is commonly thought in clinical practice,[30] compliance was not associated with treatment failure in the global sample, in neither duodenal ulcer nor non-ulcer dyspeptic patients and, was therefore not included in the random-effect model. However, most of the patients for whom this data was available (70.0%) had a good compliance (94.0%). Furthermore, although compliance was better in non-ulcer dyspeptic (97.1%) than in duodenal ulcer patients (91.4%), the number of missing values was much lower in the former (5.0%) than in the latter (42.3%). This allows us to think that, if the compliance was better in duodenal ulcer patients, the difference in eradication rate between non-ulcer dyspeptic and duodenal ulcer would increase.

The intriguing association between age and failure rate was also explored. Three hypotheses were drawn to attempt to explain why older patients experienced a lower failure rate than younger patients. First, this could be due to underlying histological lesions, especially the presence of intestinal metaplasia. Intestinal metaplasia in patients with atrophic chronic gastritis was more common among older than among younger patients. Indeed, there were twice as many patients with intestinal metaplasia among patients older than 60 years than in those less than 60 (31.4% vs. 17.0%, $P < 10^{-3}$) and the proportion of cases with intestinal metaplasia was the same in duodenal ulcer patients as in non-ulcer dyspeptic patients. Indeed, only nine out of 216 with atrophic chronic gastritis did not have intestinal metaplasia. Furthermore, it was shown that non-ulcer dyspeptic patients with atrophic chronic gastritis with or without intestinal metaplasia also had a lower failure rate than patients with non-atrophic chronic gastritis in treatment group 1. Intestinal metaplasia provides an inhospitable environment for *H. pylori* and therefore leads to a decreased bacterial load which may be easier to eradicate. In addition, the transformation of a gastric-type epithelium with tight junctions into an intestinal-type epithelium may favour the diffusion of antibiotics towards the mucus where the bacteria are located.[31] Second, corpus atrophy is frequent in older patients, leading to hypochlorhydria and a more profound acid suppression with antisecretory drugs,[32] which would favour the activity of antibiotics. This hypothesis could not be verified because corpus biopsies were not obtained in these patients. Third, the hypothesis that diagnostic tests had a different sensitivity in older and younger patients, because of the presence of atrophy,[33] was tested. However, the adjustment on diagnostic tests in the multivariate model did not change any of the results, either in duodenal ulcer patients or in non-ulcer dyspeptic patients.

There was a large proportion of males (69.4%), which is common in clinical trials concerning this type of disease. This can be explained by the normally high proportion of male duodenal ulcer patients and by the more frequent exclusion of females of child-bearing age. There were 36.9% smokers, i.e. slightly more than the rate of people who smoke in the general population in France (30%). The failure rate of smokers was not significantly different from non-smokers in the global sample (28.3% vs. 25.5%, respectively). The same applied for alcohol consumption. However, the effect of smoking was different according to the patient's disease, and was associated with failure in duodenal ulcer patients. Smoking has been established as a risk factor for peptic ulcer disease, when it is associated with *H. pylori* infection.[34] The geographical origin of the

patients included in the trials can also account for the different failure rates observed. Approximately 10% of the French population are recent immigrants and, in this study, 12.3% of the patients were born outside metropolitan France. The failure rate was higher in immigrants (29.3% vs. 25.4% for the others) but was not statistically different. France is midway between Northern Europe and Mediterranean countries which have different success rates for *H. pylori* eradication therapy.[35] For this reason, we looked at the failure rate in the northern, central, and southern parts of France, but did not find a statistically significant difference.

In conclusion, this study indicates, firstly, that duodenal ulcer and non-ulcer dyspeptic patients should be considered separately when *H. pylori* eradication is intended: (i) in clinical trials in which, at the very least, variables should be adjusted for this characteristic; (ii) in patient care, duodenal ulcer and non-ulcer dyspeptic patients should be treated with specifically adapted regimens and treatment duration. Second, the effect of age, as well as that of *cagA* status of the bacteria on eradication outcome, should be explored further, taking into account the histological diagnosis of the gastric mucosa.

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