Non ulcer dyspepsia and Helicobacter pylori

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Introduction

Dyspepsia is a symptom with multiple etiologic factors and successive explanations : acidity in the seventies with the advent of antisecretory agents, motility in the eighties with the advent of prokinetic drugs, then *Helicobacter pylori* and eventually visceral sensitivity with the promise of opioid receptor agonists.

By definition, non ulcer dyspepsia requires an endoscopy to demonstrate the absence of an active ulcer. In dyspepsia, endoscopy is cost-effective when costs are calculated over a year, compared to systematic and continuous consumption of antisecretory drugs (1). Ultrasonography is also required before labeling chronic or recurent epigastric symptoms as non ulcer dyspepsia (NUD).

What is the role of *Helicobacter pylori* in this syndrome ? The present paper is an attempt to summarize the enormous literature (> 700 papers) on this topic. We will successively consider : the prevalence of *H. pylori* in NUD, the suggestive symptoms, the results of eradication and the costs.

Prevalence of *H. pylori* in NUD

Considering the planet, the prevalence of *H. pylori* and the prevalence of NUD are similar over the continents (Table I). In epidemiology, three methods are used : the first is a comparison between positive cases and controls, that is patients with dyspepsia and controls without dyspepsia. The second is the study of a population, comparing within this group individuals with and without symptoms, a transversal study. The third considers patients over time, a cohort analysis, a longitudinal study.

Table I. — **Prévalence of *H. pylori* and NUD in the world**

	H. pylori	NUD
USA	25%	25%
Europe	30%	25%
Asia	60%	45%
Africa	85%	65%

The fourteen case-control studies of more than 30 patient, undergoing endoscopy, in each study show a prevalence of *H. pylori* between 34 and 81% in dyspeptics, and between 13 and 81% in controls. In eleven studies, the prevalence is higher in dyspeptics, with a difference ranging between 8 and 49%. The difficulty of those studies resides in the choice of controls who should have the same age and socio-economic status as dyspeptics. Indeed, the prevalence of *H. pylori* increases with age and decreases in higher socio-economic status.

Transversal studies, in workers, health-care workers or populations reveal no difference in a given group, comparing serologic results in the diagnosis of *H. pylori* for dyspeptics and asymptomatic groups (Table II). Besides the lack of information for age, the absence of endoscopy limits those studies. In the only study with endoscopy of the whole population of a Norwegian city (2), the prevalence of *H. pylori* was higher ($p < 0,05$) in dyspeptics than in controls : 48% vs 36%.

Table II. — **Prévalence of *H. pylori* in NUD**
Transversal studies

	n	DNU	Controls	Country
Workers	500	25%	29%	Netherlands
Workers	231	80%	68%	Japan
Epidemiologists	371	29%	27%	USA
Dentists	239	25%	24%	USA
Population	1260	33%	48%	Sweden
Population	619	48%*	36%	Norway

* $p < 0,005$

Two longitudinal studies have been published. In the first one, epidemiologists evaluated by serology over a period of 8 years have a significantly higher prevalence of epigastric pain in seroconverters, acquiring *H. pylori* (3). In a second study of 3000 inhabitants of Copenhague over a five year period, in seropositive asymptomatic individuals at the beginning of the study, the relative risk of pain and ulcers is 2 over the five year period (4). Those two studies tend to prove that infection precedes symptoms, an important link in establishing causality.

Symptoms

Dyspeptic symptoms usually include three classes suggesting : an ulcer, dysmotility or reflux, each based

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on a different pathophysiologic mechanism. This logic, pragmatic classification has two drawbacks. Patients often have more than one class of symptoms, often including symptoms of irritable bowel. Moreover, the relationship between one symptom and it's presumed mechanism is not very well established : patients with bloating, suggesting dysmotility, do not always have an abnormal gastric manometry or an abnormal scintigraphic gastric emptying and abnormal tests are found in asymptomatic individuals.

Another difficulty concerns the evaluation of symptoms (5). The goal is to discriminate, to evaluate and to predict — for instance that ulcer-like symptoms suggest *H. pylori* gastritis. The results should be based on scales that should be validated, reproductible and sensitive to therapeutic response. For instance, when a LIKERT scale is used, at least five points are necessary in the evaluation. Those scales should include some characteristics of symptoms : severity, frequency and duration. Very few studies fulfill those requirements.

The synthesis of studies with various size, methodology and validity, evaluating the relationship between gastric physiology and infection with *H. pylori* reveals that eight of the thirteen studies assessing gastric acidity showed a normal gastric secretion (basal, maximal, over 24h, after various stimuli), one hypoacidity and four hyperacidity. In fact, hypergastrinemia is usually found and it's effect on acid secretion is related to the severity of corpus gastritis. Gastric motility, assessed by manometry of scintigraphic emptying, is decreased in three of ten studies, normal in six, increased in one. The relationship between gastroesophageal reflux and *H. pylori* has not been assessed.

Numerous studies explored the relationship between symptoms and *H. pylori*. Most do not fulfill the criteria detailed above. Table III is an extension of a synthesis by Dekorwin (6). A quarter of the studies mention a higher prevalence of ulcer-like symptoms in dyspeptics with *H. pylori* gastritis. This trend is supported by the better response of this symptom, that is pain, to eradication (7) and by the association between the severity of pain and the density of colonization (8).

Table III. — **Symptoms & *H. pylori* *HP* pos vs *HP* neg**

Symptoms	> *	=	<
Ulcer-like	6**	19	0
Reflux-like	3	18	0
Dysmotility	0	23	2

** number of studies
* > increased prevalence of *H. pylori*

In summary, a link between *H. pylori* and symptoms has not been formally established. It is howewer logic to propose hypersecretion of gastric acid and ulcer-like symptoms as candidates. This could constitute a subgroup of dyspectic patients with symptoms due to *H. pylori*.

Results of eradication

The causal link between *H. pylori* and duodenal ulcer has been established by eradication studies. What about dyspepsia ? Therapeutic studies should be randomized, double blind and placebo-controlled. In addition, they should include symptomatic scales that are valid, reproductible and sensitive to treatment. Finally, they should last for at least. six months. Indeed, a clear placebo effect is observed over short periods but is not maintained over time.

Three studies of at least six months include each between 41 and 100 patients (9-11). All three include bismuth and metronidazole, with tetracyclin in one (11) and amoxicillin in another (9). The control group did not receive placebo but bismuth in two studies (10-11), cimetidine in the third (9), that is drugs active in dyspepsia. The comparison of the results on symptoms did not compare the two initial groups but patients with and without eradication. A significantly lower symptom score is found in eradicated patients, that is even lower after six months and mantained after one year. In the Irish study, the symptom most influenced by eradication is pain (11).

Table IV. — **Eradication of *H. pylori* Randomized studies — Symptomatic scores**

Time	Treatment			Control		
	A	B	C	A	B	C
**M0	100	100	100	100	100	100
M2	81*	48	37*	90	46*	75*
M6	53*	39*	9*	76	64*	42*
M12	65*	—	13*	79	—	56*

**M0 : beginning of the study - symptoms = 100% ; M2 : after 2 months ; M6 : after 6 months ; M12 : after 1 year.
* $p < 0,05$.

Other benefits of eradication

Eradication probably prevents a subsequent ulcer disease, dyspepsia being an early symptom in some patients. Eradication should decrease the mortality in older subjects, as suggested by T. Axon in a recent editorial (12). Ulcer complications and gastric cancer are estimated to cause death in one of thirty five older men and in one of sixty older women (12). Eradication in cirrhosis is presumed to decrease ammonium blood bevels and is recommanded by R. Williams. Eradication in patients on non steroidal antiinflammatory drugs could prevent ulcers.

Pharmacoeconomics

The economic benefit of eradication is clearly established in duodenal ulcer. In dyspepsia, an economic benefit might be difficult to prove in the absence of a clearly proven medical benefit. The economic analysis

of the relation *H. pylori*-dyspepsia assesses the cost related to three factors : the efficacy, using then natural units such as the number of days without symptoms, utility with Qaly (quality adjusted years) as units or benefit usually in US dollars.

The cost-efficacy study of Fendrick (13) suggests that in patients with ulcer-li.e symptoms, an endoscopy before treatment is clinically and economically indicated if the cost of endoscopy is less than 500 US dollars, such as in Belgium. A cost-utility analysis (14) estimates the cost of one QALY year to be 1214 US dollars if a positive serology is followed by eradication in dyspeptics. A very nice cost-benefit study of Sonnenberg (15) reveals that a 5 to 10% complete response of symptoms to treatment makes screening and treatment beneficial without taking in account the other potential benefits (ulcer prevention etc ...). This number is also suggested by an epidemiologic study of Rosenstock (4) that calculates that 7% of epigastric pain in dyspeptic women and 10% in men are attributable to *H. pylori* (4).

Conclusion

H. pylori is not *the* cause of NUD, no more than acid secretion, dysmotility or visceral hypersensitivity. NUD has not a single cause. But *H. pylori* seems to us to be one cause of NUD. If *H. pylori* is the cause of 10% of NUD, eradication is economically beneficial but the scientific benefit is very difficult to establish. Therapeutic trials, very difficult, should include only patients with pain. My personal feeling is that eradication is useful in patients with ulcer-like symptoms, some of which may have undiagnosed past ulcers (fig. 1). The economic benefit, once established, will suppress all scientific doubts. Ethic considerations should also be included. In a dyspeptic, how to justify gastric biopsies if eradication is not a consideration ? What if this uneradicated patient develops an ulcer in 2000 or a cancer in 2010 ?

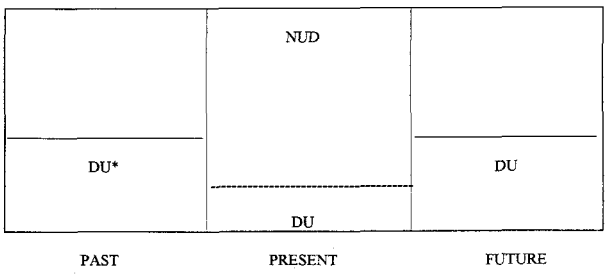

Fig. 1. — Dyspepsia : hidden ulcer ?
* Duodenal ulcer

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