Is it justified to give antisecretory drugs before an endoscopy in case of symptoms suggestive of gastro-oesophageal reflux disease ?

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Introduction

In recent decades, upper gastrointestinal endoscopy has emerged as a major investigation in clinical medicine, and open-access endoscopy clinics now exist in most Western countries. In gastro-oesophageal reflux disease (GORD), endoscopy allows an excellent description and classification of oesophagitis (1). Moreover, the severity of lesions observed at initial endoscopy can to a certain extent predict therapeutic response and the long-term outcome of the disease (2). Finally, though healing of lesions was considered to be the main criterion of efficacy in most therapeutic trials on reflux oesophagitis until the early 1990s, symptom relief and prevention of recurrences are now also recognised as major therapeutic goals (3,4). However, even though endoscopy provides very useful information on "structural organic diseases" in general (e.g. ulcers or cancer), its clinical usefulness in GORD and dyspepsia has recently been reconsidered for several reasons (5). The most important ones are its lack of sensitivity (6) as far as primary care patients are concerned and its cost. Conversely, considerable progress has been made in drug therapy for GORD through the recent development of proton pump inhibitors (PPI) which can relieve reflux symptoms quickly and heal oesophagitis in nearly all GORD patients (7). Finally, there is some question about the most cost-effective strategy to apply in GORD. In other words, do we need to perform endoscopy in all patients before starting antireflux therapy or is it better to treat empirically with an antisecretory drug (i.e. an H_2-receptor antagonist or a PPI) or a prokinetic agent ? With respect to the very effective relief of reflux symptoms achieved with PPI, some authors have also proposed therapeutic response (e.g. the so-called "omeprazole test") for reliable diagnosis of GORD (8-10). Before considering the potential advantages and inconveniences of the different strategies now available for the clinical management of GORD, it would seem of critical importance to distinguish clearly between "*an empirical approach*", which consists in prescribing drug therapy for a patient whose symptoms are too typical to require a diagnostic investigation (especially an endoscopy), and a *therapeutic trial* (or *therapeutic test*) based on interpretation of the symptom relief obtained after a short course of PPI therapy (if the response is regarded as evidence for the *diagnosis* of GORD or, at least, of an acid-related disorder).

According to the format and recommendations of the organisers of this Conference, the task assigned to us was to provide the jury with arguments favouring an empirical approach to the treatment of GORD. Therefore, we will successively discuss the reasons (the "why") for an empirical approach, patient selection (the "when"), and the practical modalities (the "how") of such a strategy. Admittedly, we have selected and sometimes over-emphasised "pro" arguments since another article in this issue of the Journal (see Deltenre *et al.*) is intended to provide an opposite (or "con") view of the merits of immediate endoscopy. However, when appropriate, we have tried to introduce a critical and possibly more balanced view concerning data in the literature.

Technique for review of the literature

We conducted a Medline search covering the following fields and key words for the last 5-years : endoscopy and GORD ; reflux-like dyspepsia ; empirical treatment and GORD ; endoscopy and dyspepsia ; GORD strategies ; pain relief and antireflux therapy ; symptoms of GORD (time window extended to 10 years for the last item). Several general reviews on the treatment of GORD (3,4,11,12) or recently developed guidelines on the management of dyspepsia (13) have also been included in our reference list. We have also made a personal cross-selection more directly keyed to the following topics : a) the epidemiology and natural history of GORD, b) evaluation of symptoms, c) sensitivity of endoscopy in the primary-care setting, d) symptom relief in trials on the effects of antisecretory and prokinetic agents, e) treatment of endoscopy-negative patients and f) cost/utility analysis. Abstracts and book chapters were excluded, as recommended by the organisers of the conference.

An empirical approach : Why ?

There are several reasons (Table I) in support of an empirical approach for the management of GORD.

Table I. — **Reasons for advocating an empirical approach for the management of GORD in clinical practice**

- Heartburn and regurgitation are so frequent in the primary-care setting that it is not practical or even feasible to investigate all patients.
- In contrast with the high frequency of GORD symptoms in the general population, the prevalence of oesophagitis is very low.
- At least half of the patients referred to an open-access endoscopy unit are "endoscopy-negative" or show irrelevant findings.
- Most patients with oesophagitis have mild lesions at endoscopy, and severe complications (stenosis, ulcer) are very rare.
- There is no evidence that mild-to-moderate oesophagitis worsens with time.
- Typical symptoms are very specific for the diagnosis of GORD when they are dominant.
- Symptoms are what matter to the patient ! They can adversely impact the quality of life, whether oesophagitis is present or not at endoscopy. Symptom relief is the major therapeutic goal.
- Modern drugs are safe and very effective in achieving the goals of GORD therapy.
- Finally, for most patients with GORD symptoms, endoscopic findings do not influence the choice between the several drugs potentially available.
- Empirical therapy is better accepted than an invasive test like endoscopy.
- Empirical therapy is more cost-effective than an endoscopy-guided strategy.

Many are not based on scientific evidence or are still controversial. In our opinion, the most relevant literature, even though scarce, deals with epidemiology and recently published therapeutic studies in endoscopy-negative patients (14-17).

Epidemiology : high prevalence of heartburn and endoscopy-negative GORD in the primary-care setting

The prevalence of heartburn, the most typical symptom together with regurgitation, is extremely high in the community, probably affecting approximately 10 to 20% of adults at least weekly (18-23). For instance, Agréus *et al.* (23) found a prevalence of 7.4% for reflux symptoms and a 3-month incidence of 0.5 per 1 000 inhabitants in a previously asymptomatic Swedish population. Similarly, Ruth *et al.* (19) reported a 26% prevalence of heartburn and/or regurgitation in a general population, but moderate to severe symptoms in only 1 to 4%. These figures are consistent with our previous observations in the general French population (22). Interestingly, epidemiological studies have shown that heartburn and regurgitation are significantly associated with such different symptoms or clinical presentations as dysphagia, globus sensation, chest pain of non-cardiac origin, respiratory disorders and dyspepsia (with which there is frequently an important overlap in the primary care setting) (19, 23-25).

From a clinical standpoint, it seems relevant to distinguish those subjects (the bottom of the iceberg) in whom heartburn or regurgitation occurs intermittently but who do not seek medical help and/or use self-medication (mainly with antacids) from those patients who need medical management. For instance, in a study in Finland (18), 10.3% of the responders to a questionnaire mailed to a random sample of 2 500 people aged $\geq$ 20 years in the general population reported daily heartburn and/or regurgitation. However, only 5.5% of the responders had sought medical advice for symptoms during the previous year. In fact, the reasons for seeing a clinician were not very clearly known. However, as reported for dyspepsia, they may be more related in a substantial number of patients to fears or concerns about health or to social class and age, rather than to the severity of the symptoms themselves (25). However other studies have reported an association between physician visits and symptom frequency (20). The impact of normal endoscopic findings in reassuring patients has not been properly evaluated in GORD but has been suggested by some studies concerning dyspepsia (26).

The prevalence of oesophagitis in the community is far lower than heartburn, probably affecting about 2% of the general population and no more than half of those referred to an endoscopy unit because of symptoms suggestive of GORD (6). In all recent therapeutic studies with a primary-care enrolment (14,27) it has been consistently determined that most patients with macroscopic changes at endoscopy ("mucosal breaks") have mild-to-moderate lesions (non-circumferential lesions). On the contrary, severe oesophagitis or complications such as strictures or deep ulcers are very rare (20,28). Thus, these epidemiological data show that endoscopy has, at best, a relatively low diagnostic yield in everyday practice.

The rising incidence of adenocarcinoma of the cardia in most Western countries may be related to the increased incidence of GORD with subsequent development of intestinal metaplasia at the gastro-oesophageal junction. However, affected subjects may remain completely asymptomatic throughout their life (29) and there is no practical way to select these patients with intestinal metaplasia. Moreover, the prevalence of histological intestinal metaplasia detected on biopsies taken systematically at the cardia seems relatively high and the clinical relevance of that finding is not yet clear (30).

Natural history : lack of evidence of worsening of mild-to-moderate oesophagitis with time

The natural history of GORD varies widely and is still incompletely known (31-36). In most patients seen by gastroenterologists or surgeons, GORD appears as a chronic disease which relapses shortly after discontinuation of treatment, therefore needing maintenance drug therapy (or surgery) to prevent relapses. However, in the primary-care setting, the disease usually develops in a less severe manner, consisting in intermittent attacks (20,35).

One important reason for performing an endoscopy relatively early in the course of the disease is to identify a group of patients at risk of progressing to more severe

lesions or complications. As far as reflux oesophagitis is concerned, the severity of lesions seen at initial endoscopy is definitely predictive of the therapeutic response and the risk of recurrence after cessation of treatment (2). However, as already emphasised, most patients are endoscopy-negative or have mild oesophagitis. In this group of patients, there is little (if any) evidence that oesophagitis worsens with time. In most of these patients, lesions never develop or, if already present at first assessment, wax and wane without further worsening (32). For instance, in the recently published study of McDougall *et al.* (33), only 2 patients out of 101 with oesophagitis followed up for more than 10 years developed an oesophageal stricture and one a Barrett's oesophagus. Similarly, during a 6.5-year follow-up of 582 patients discharged from American Veterans Hospitals with a diagnosis of oesophagitis, only 2.6% developed a stenosis, and an additional 2.2% an ulcer of the oesophagus (36). The marked age-dependency of strictures and oesophageal ulcer suggested that these complications may take a long time to develop. This would be consistent with an epidemiological study showing that most patients with complications are $\geq$ 60 years of age (21).

In summary, there is no clear evidence that oesophagitis develops or progresses with time in most patients with reflux symptoms, and complications are extremely rare in young patients. Taken together, these data indicate that early endoscopic assessment is not advisable for all patients with reflux symptoms.

Symptom-based diagnosis of GORD is reliable

The term "GORD" encompasses a wide spectrum of pathological entities caused by the retrograde flow of gastric contents through an incompetent gastro-oesophageal junction. The basic underlying pathogenesis is the same whether oesophagitis is present or not (37). In fact, the clinical definition of GORD is much more difficult since there is no true "gold standard" to which symptoms and diagnostic tests can be compared. Even though mucosal breaks of the distal oesophagus are very specific for diagnosis of GORD, endoscopy lacks sensitivity (6). In clinical practice, the diagnosis can be made reliably when typical symptoms (i.e. of heartburn or regurgitation) are present and dominant (38). The same is not true for patients with atypical symptoms who may require more sophisticated investigation, especially 24-hour pH-monitoring with careful symptom analysis. However, we believe that the term "reflux-like dyspepsia", sometimes used to describe this kind of patient, is a misnomer which should be avoided. It seems better to consider endoscopy-negative patients with typical symptoms of GORD and those with a significant relationship between symptoms and acid reflux episodes at pH-monitoring as belonging to the GORD spectrum (39). Another frequent situation is the association in the same patient of symptoms suggestive of GORD and functional dyspepsia (early satiety, bloating, nausea, vomiting, etc.). Again the distinction between dysmotility-like dyspepsia or ulcer-like dyspepsia does not contribute to clarifying the pathophysiology or helping in adapting the management strategy (40).

GORD symptoms impact quality of life

Symptoms of GORD can severely impact quality of life and limit social activities, whether oesophagitis lesions are present or not at endoscopy (14,41). In GORD, the correlation between symptoms and oesophageal mucosal damage is poor. Severe lesions such as strictures are not always preceded by a long history, whereas endoscopy-negative patients may have severe symptoms. However, for the vast majority of patients, relief of symptoms is what matters, and several studies using appropriate questionnaires have clearly established that quality of life returns to normal values within a few weeks (Fig. 1) when an effective drug is administered (14,27,41). Therefore, symptom relief is now largely accepted as a primary goal of treatment and a major criterion of judgement for the efficacy of both medical and surgical therapy. On the contrary, the persistence after treatment of small patchy erosions at endoscopy in an asymptomatic patient should no longer be considered as indication of therapeutic failure.

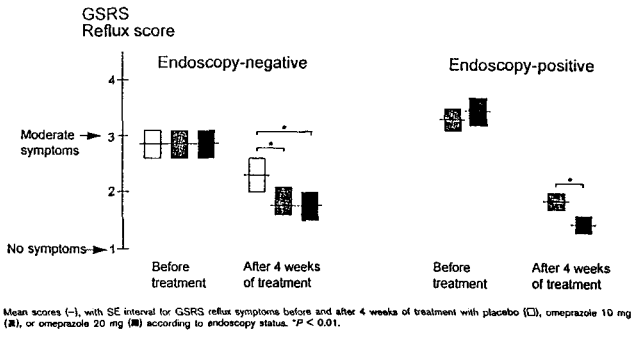

Fig. 1. — Quality of life (GSRS reflux score) in patients with heartburn, and the effect of treatment with omeprazole for 4 weeks (reproduced from Carlsson *et al.* (14) with permission of the Editor-in-Chief of the Eur. J. Gastroenterol. Hepatol.).

Modern drug therapy for GORD effectively reliefs symptoms and is safe (for review see 4)

Traditional drug therapy includes alginate/antacids, moderate acid suppression with H_2-blockers and prokinetics. *Lifestyle and dietary recommendations*, together with *antacids*, have been the mainstay of treatment for decades. In fact, their therapeutic efficacy has not really been established by wellcontrolled trials and is probably very limited. However, epidemiological studies have shown that antacids and alginate/antacids are often used successfully as selfmedication by non-consulting refluxers. The combination of *antacids with alginate* (Gaviscon®) seems more effective than antacids

alone. Overall, these compounds may be useful as a first approach to symptom control in patients with mild disease, but they are inadequate for treating those with moderate/severe oesophagitis. Despite their limited efficacy in GORD, but thanks to their excellent safety profile, *H_2-blockers* (42-44) are still useful drugs in patients with mild disease where they can be administered on-demand. Their role as OTC medications (45) has been evaluated in some countries, and they may eventually replace antacids as a firstline therapy of symptoms. Special formulations may be more appropriate for this specific use. Among prokinetics, *cisapride* has proved nearly as effective as H_2-blockers for symptom relief. Cisapride is also an effective prophylaxis for relapses in patients with mild oesophagitis.

The development of *proton pump inhibitors* (PPI) has revolutionised the therapeutic approach in GORD. Omeprazole was the first PPI extensively evaluated for treatment of reflux oesophagitis, whereas lansoprazole and pantoprazole have been developed more recently. A recent meta-analysis of 43 therapeutic trials conducted in moderate/severe oesophagitis confirmed the great advantage of PPI over H_2-blockers (7). The proportion of patients successfully treated was nearly doubled, and the rapidity of healing and symptom relief was about twice that of H_2-blockers. Their superiority is obvious, not only in severe cases or in patients refractory to H_2-blockers, but also in mild oesophagitis and endoscopy-negative patients. The superiority of omeprazole (20 mg or 10 mg daily) has also been shown against cisapride (27). The remarkable efficacy of PPI is maintained with time, and a meta-analysis of long-term trials (46) has shown that during maintenance therapy with omeprazole, the relief of heartburn is highly predictive of healing. Therefore, *no further endoscopic control is required in a patient asymptomatic under PPI* (unless initial endoscopy shows severe oesophagitis or complications).

Although PPI are well-tolerated, there has been some concern about the risk of malignancy after very prolonged potent acid suppression. Proliferation of endocrine cells has been reported in relation to hypergastrinemia as a result of hypochlorhydria. In fact, the risk of endocrine neoplasia seems extremely low and of no clinical relevance for the vast majority of patients. The risk of developing atrophic gastritis appears related to *Helicobacter pylori* infection. However the pathogenetic importance of *Helicobacter pylori* infection in GORD is not clear, and some controversy has recently developed as to whether *Helicobacter pylori* is an aggravating agent or a protective factor (47). Although the different issues about long-term safety of PPI are clearly out of the scope of this review, as far as the perspective of an empirical treatment is concerned, it is important to keep in mind that PPI are extremely well tolerated agents with little (if any) interference with other drugs, a point which may be a significant advantage in older patients.

Several factors influence the cost of management strategies in GORD

The long-term expense for different strategies (i.e. whether to treat or investigate) depends on the cost of endoscopy (with or without sedation), the cost of physician visits and the symptom recurrence rate. If GORD is associated with a high rate of recurrences, savings may be relatively modest with an empirical strategy. On the contrary, randomised clinical trials in the primary-care setting are needed to provide adequate evidence for a choice between empirical treatment or prompt endoscopy. Reducing the cost of endoscopy and developing open-access endoscopy units without long waiting-lists may be more cost-effective than promoting empirical treatment. The problem is further complicated by the possible interference of new strategies such as eradication of *Helicobacter pylori* in patients with dyspepsia, since this category frequently includes patients with reflux symptoms.

Other concerns about empirical therapy in GORD and dyspepsia include a) inappropriate prolonged use of drug therapy (especially if PPI are used more liberally), b) weakening of subsequent investigation, c) side effects and d) a great likelihood of symptom recurrence, possibly resulting in postponement of endoscopy and increased direct and indirect costs (sick-leave days). In this respect, Longstreth *et al.* (48) have demonstrated a statistically significant advantage for endoscopy and gastroenterological consultations with respect to subsequent visits and total costs.

An empirical approach : When ?

There is a quite good consensus that an empirical approach for the management of GORD (and dyspepsia in general) is acceptable provided the symptoms are typical, the patient is young ($\leq$ 45 years old) and that there are no alarming symptoms (13).

The presence of *typical symptoms* (i.e. heartburn and/or regurgitation) is a pre-requisite for an accurate symptom-based diagnosis (38). Moreover these typical symptoms must also be *dominant* in the patient's complaints.

Empirical therapy and even additional OTC should not result in masking organic diseases and delaying investigations of conditions in which late diagnosis and treatment could impact. These disorders include malignancies of the upper GI tract since the symptoms can be alleviated by antisecretory therapy. The risk of masking malignancy is age- context- and geographically-dependent (45,49). Recent studies have shown a decreased incidence of gastric cancer (which may be associated with a reduction of *H. pylori* infection in Western countries), whereas there is an increased incidence of adenocarcinoma of the cardia (which may be a result of Barrett's metaplasia occurring subsequent to GORD). Age is probably an extremely important

consideration since most cases of gastric cancer occur in individuals over 45. As far as gastric cancer is concerned, it has been estimated that OTC availability of H2-RA in the United States would not change the interval between symptom onset and diagnosis. Therefore, OTC is likely to have little (if any) effect on overall mortality, even though 10% of gastric cancer patients self-medicate. However, it is impossible to extrapolate this type of estimation to other classes of drugs, especially PPI which may result in more complete relief of dyspepsia and reflux symptoms, thereby falsely reassuring both the patient and the clinician.

In addition to *age*, it is recommended that *alarm symptoms* be taken into account in determining whether a patient should be explored by endoscopy. Williams *et al.* (50), have shown in a series of 707 patients with upper GI malignancy (identified at the Leiceister General Hospital) that only 13 cases (1.8%) occurred in patients under 45. All 13 had alarming symptoms such as weight loss, vomiting, dysphagia, gastro intestinal bleeding or anaemia. Other symptoms associated with abnormal findings at endoscopy included anorexia or nocturnal pain (50), duration of heartburn, left upper abdominal pain and previous peptic ulcer (51). However, it is more debatable whether these abnormal endoscopic findings are clinically relevant or not. For instance, it is unlikely that detection of mild patchy erosions of the distal oesophagus or gastritis will actually affect the long-term outcome, which is roughly the same as in endoscopy-negative patients (14). Finally, in dyspepsia, the empirical treatment strategy apparently misses 40% of presumed peptic ulcer cases, predominantly in patients with DU (26), but postpones the diagnosis of malignant disease by only a few weeks.

An empirical approach : How ?

The first step in clinical management of a patient with symptoms of GORD is *to make a reliable diagnosis*. As indicated above, a symptom-based strategy is reasonable because symptoms such as heartburn or regurgitation are highly specific, provided that they are correctly interpreted by the patient. In this respect, simple questionnaires (43) such as that presented in Table II may serve as extremely useful diagnostic tools. In dyspepsia, computer-based scoring systems have also been proposed to help select patients for endoscopy, but the transferability of such systems has been disappointingly limited (51).

Table II. — **Example of a questionnaire used to select patients with a high probability of GORD (43)**

1. Do you frequently experience a rising, spreading, uncomfortable feeling behind your breastbone ?
2. Is this feeling often combined with a burning sensation in your chest ?
3. Do antacids relieve your symptoms ?
4. Have you had your symptoms during four or more days in the last week ?

If a patient answers "yes" to all four questions there is an 85% probability of either erosive oesophagitis on endoscopy, a pathological 24-hour pH-monitoring, or both.

In young patients with no alarm symptoms and no special risk factors (including use of NSAIDs or systemic illness), a 4- to 8-week empirical treatment intended to relieve heartburn and regurgitation can be performed with excellent efficacy and safety (13). A diagnostic therapeutic trial (8-10) is attractive in patients with atypical symptoms because it may replace more expensive and/or invasive investigations (e.g. 24-hour pH monitoring). However, when a therapeutic trial is used for diagnostic purposes, it should fulfil all the criteria and characteristics normally expected of any other diagnostic test, i.e. sensitivity, specificity, predictive value, reproducibility, cost-effectiveness, etc. It also seems important to have a quick, clear answer regarding the end-point (i.e. symptom relief in the present case). As symptom relief is more complete and more rapid with PPI than with any H_2-blocker or prokinetic (7), this class of drugs should be considered as the best choice for such a short therapeutic trial.

Recent randomised controlled studies (Table III) have tested the sensitivity and specificity of one- and 2-week administration of *omeprazole for the diagnosis*

Table III. — **The "omeprazole-test" for the diagnosis of GORD. Results of 3 randomised controlled studies (8-10)**

Ref.	Inclusion criteria	Nb	"Gold standard"	Omepraz. regimen	Sensitivity (%)	Specificity (%)
(8)	Symptoms End (–) ve pH-metry	33	pH-metry	40 mg/d 40 mg bid (one week)	27 83	ND ND
(9)	Symptoms End (–) ve or grade 1	85	pH-metry	40 mg/d (2 weeks)	68	33
(10)	Dyspepsia Heartburn	159	pH-metry or mucosal breaks	40 mg bid (one week)	71-81	36-58

ND : not determined in study (8).
Studies (9) and (10) are placebo-controlled trials.
End : Endoscopy.

of GORD. In these studies, the gold standard for the diagnosis of GORD has not always been the same (abnormal acid exposure and/or mucosal breaks at endoscopy). The omeprazole-test seems reasonably sensitive but poorly specific (10). Indeed, symptom relief during omeprazole treatment may occur in several acid-related disorders, including the so-called hypersensitive oesophagus (52) and the different forms of dyspepsia which frequently overlap the GORD spectrum. Increasing the dosage of omeprazole (40 mg bid) seems to improve sensitivity (8). Experiences with other PPI that relieve symptoms more quickly and perhaps more completely than omeprazole (e.g. lansoprazole) are awaited. We also believe that, when pH-metry is used as the reference diagnostic test, it is mandatory to include symptom analysis as well as measurement of acid exposure in the interpretation of data. Finally, it should be kept in mind that the optimal dosage and duration for an accurate PPI diagnostic test still need to be determined.

Once the diagnosis of GORD has been made on the basis of symptom analysis and/or after a therapeutic test, one of the major issues concerning empirical treatment is *the choice of drug therapy.* The classical "*stepwise*" strategy calls for the use of less effective drugs in responders (e.g. H_2-blockers or cisapride) and PPI only in non-responders. The other alternative is to go directly to PPI either at full- or half-dosage (i.e. the *top-down* strategy). Both strategies have theoretical advantages and inconveniences (53). In fact, controversial studies have been published concerning the choice of the most cost-effective drug therapy (53,54), but none of these strategies has been prospectively evaluated in the real conditions of everyday medicine.

The last practical question is *whether endoscopy should be repeated when symptoms relapse* in patients with a known diagnosis of reflux oesophagitis. It has been clearly established, at least in patients with mild moderate oesophagitis, that symptom relief is quite predictive of healing, especially when the condition is treated with PPI (46). Therefore, endoscopic monitoring is not useful in patients who are symptomatic under PPI therapy.

In conclusion, a symptom-based strategy is practical and feasible in the majority of GORD patients seen by GPs in the primary-care setting. Indeed, most of these patients are endoscopy-negative or have mild lesions with little (if any) evidence of progression to severe or complicated oesophagitis. In these patients, H_2-blockers, prokinetics (mainly cisapride) and PPI can be safely prescribed in empirical conditions. Symptom relief is the major goal of treatment and can also be used as an indication of healing of oesophagitis in patients with mild or moderate cases. The role of the PPI-test for diagnosis of GORD should be further explored and validated before being strongly recommended.

Although most subjects in a primary-care setting can be managed solely on the basis of symptom analysis and physical examination, it is noteworthy that endoscopy still has many indications in patients with persistent or recurrent symptoms of GORD or dyspepsia. In the setting of an open-access endoscopy unit, the value of a case history for prediction of clinically relevant endoscopic disease (peptic ulcers or cancers) may be even more limited than in the primary care population (51). At the moment, it is apparent that many physicians often use endoscopic results to tailor medical therapy in patients with GORD (55). However, the cost/utility of this practice is not yet established, and the role of empirical management in GORD has to be further evaluated by well-designed studies which are unfortunately often difficult to conduct. Finally, as recently concluded by Talley *et al.* (13) concerning dyspepsia : "The decision to choose empirical therapy ... or initial endoscopy should be based not only on cost, but also on other considerations such as patient and physician attitudes toward uncertainty, the ethics of not identifying a curable disease ... patient satisfaction, institutional or societal forces to restrain the use of diagnostic procedures, and the background prevalence of the disease".

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Management of Gastro Oesophageal Reflux Disease (GORD) : magnitude of the problem

1. *Prevalence and Incidence of GORD*

Heartburn, the key symptom of gastro-oesophageal reflux disease (GORD) is very frequent in industrialised

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countries and its prevalence would reach 20-40% of adult population (1). The prevalence of reflux oesophagitis is much lower : around 2% with a yearly incidence around 4.5 up to 120/100 000 (2). One half to two-third of symptomatic peoples has no erosive lesions of the oesophagus and should be classified in "Endoscopy negative gastro-oesophageal reflux disease" or ENGORD (2,3). In Belgium, a recent randomtelephone survey of 3 000 individuals above 35 year-old revealed that, overall, 28.1% of the population experienced heartburn, at least once a week in 11.3% and daily in 4.1% (4). 13% of patients with reflux oesophagitis develop Barrett metaplasia, 0.5% oesophageal carcinoma and around 1% benign stricture (5). Therefore, despite a low mortality rate (1/100 000-1), GORD is obviously a huge public health issue.

2. *The predictive value of symptoms*

Besides the high proportion of ENGORD and cases of atypical extra-digestive symptomatic manifestations, (chest pain, ENT complaints, cough and asthma), the key problem in GORD is the absence of correlation between symptoms and oesophageal lesions (6). Before treatment, the accuracy of history-taking for the diagnosis of oesophagitis is lower than for the diagnosis of PUD : sensitivity is around 60-80% and specificity 60-70 (7,8). According to Johnsson *et al.* (9), the sensitivity of clinical history would be 85% when the patient answers "yes" to the four following questions : 1) Do you experience uncomfortable feeling behind breastbone ? 2) Is it burning in the chest ? 3) Is it relieved by antacids ? 4) Did it happen 4 days or more during the last week ? Moreover, symptoms poorly contribute to detect complications of reflux oesophagitis. Up to 40% of patients with oesophageal stricture have no previous history of reflux symptoms (10) and in a study by Spechler *et al.* (11), no complaint (heartburn, regurgitation's, odinophagia, dysphagia) was able to discriminate patients with Barrett's oesophagus, "Specialised Columnar Epithelium" (without macroscopic appearance of Barrett) or normal oesophageal histology.

During the follow-up of treated GORD, the recurrence of symptoms has a low predictive value for lesions relapse : only 27% of patients with recurrent heartburn had endoscopic relapse according to the review by Carlsson *et al.* (2). This is probably due to the fact that, in most cases, symptom precedes the lesion and, in therapeutic trials, endoscopy is immediately performed when symptoms recur. Conversely, the same study showed that 91% of asymptomatic patients were lesion-free : the absence of symptoms has a fairly good predictive value for endoscopic remission.

3. *A wide spectrum of treatments*

Between the first-line treatment (Alginate, dietary and postural precautions (12)) and surgical fundoplicature, most patients with GORD will benefit from the prescription of either acid suppressive drugs (proton pump inhibitors, H_2 receptors antagonists), procinetic drugs (metoclopramide, cisapride) or both. PPI has obviously the best score both for symptomatic and lesions remission : the extensive review by Armstrong (13) reported the following symptomatic resolution rates at 4 weeks : Omeprazole : 54.1% (95% Cl : 48.7-59.4), H2RA : 11.9 (6.03-17.7), Metoclopramide : 48.0 (34.2-61.8), Cisapride : 48.7 (43.0-53.7). The comparative discussion of the different compounds in the treatment of GORD and reflux oesophagitis is beyond the goal of the present paper but it must be stressed that even the best drugs (PPI) are only a remission treatment since 80% of patients will relapse within 6-8 months after cessation of the treatment. This implies huge and still-growing expenses for maintenance treatment of GORD.

What could be the role(s) of endoscopy in GORD ?

1. *Endoscopy is the only way to diagnose reflux oesophagitis and its complications*

If 24-hour pHmetry is theoretically the most accurate procedure to prove GORD, endoscopy is the most accurate tool for the diagnosis of lesions of reflux oesophagitis and complications of GORD even if up to 18% of Barrett's metaplasia are not macroscopically detected by endoscopy (11).

2. *Endoscopy has a prognosis value*

Besides factors like age above 65, smoking and absence of regurgitation, the presence of low-grade oesophagitis at initial endoscopy is correlated to a better remission rate under maintenance therapy by PPI (2). Moreover, it has been shown that in case of relapse under maintenance treatment, the grade of oesophagitis was usually identical or lower (2). It has been shown that most of mild oesophagitis remain stable on a long-term follow-up (14). On the opposite, circumferential lesions are at risk for developing stricture and long-segment Barrett metaplasia (15). Finally, patients with ENGORD has a symptomatic remission rate that is roughly 10% inferior when compared to patients with oesophagitis, whatever the treatment (PPI full or half doses, cisapride (16)).

3. *Endoscopy might or might not influence the initial treatment and further management of the patient with GORD. Should we treat a lesion, a symptom or a disease ? A personal study*

The extensive review of literature through Embase (Excerpta Medica) from 1983 till 1997 brings no answer to this very important question. No randomised, controlled studies has ever compare the symptomatic approach of treatment (with the risk of missing GORD complications or other life-threatening lesion of the

upper GI tract) and the systematic approach by endoscopy before treating. Artificial selection of patients for acid suppressive treatment by evidencing erosive endoscopy has been used for years in Belgium because of national health insurance regulations without any rationale. Therapeutic tests with PPI have been used in asthma, ENGORD and "non-ulcer dyspepsia" (17), some versus placebo. They have been deceiving because of an important placebo response (up to 40%) and the necessity to use very high doses of PPI (more than 40 mg Omeprazole daily) to get a reliable answer within one week.

a) Method

In order to try to answer that key-question, 1 200 consecutive out patients with *heartburn* (chronic or recurrent for at least 2 months), referred for the first time for upper GI endoscopy were retrieved from our database. Patients with extra digestive complaints suggesting GORD but without heartburn, have been ruled out. Every patient had been questioned in details about his current and past complaints, alarm symptoms and drug intake. For every patient, it has been hypothesised that a decision for a non-aggressive approach (prescription of usual doses of PPI and C13 breath test for diagnosis of Helicobacter pylori infection, without endoscopy) had been taken. The clinical data and the empirical management decisions were filed. Then the results of endoscopy and biopsies along with the possible change in treatment, further management and follow-up of every patient, based on endoscopy's results, were encoded and compared to the empirical attitude. Theoretically, four situations are possible : they are summarised in table I with examples.

b) Results I : population, diagnosis, consequences for management

From 1 200 patients, 533 were males (M/F ratio : 0.79), mean age was 53.2 year (extremes 10-91) and median age 54.0 year. Heartburn (associated with regurgitation's or not) was the only complaint in 282 patients (23.5%), the main symptom in 389 (32.4%) and an accessory symptom in 529 (44.1%). Alarm symptom(s), (such as dysphagia, significant weight loss, anaemia ...) was observed in 155 cases out of 1 200 (12.9%).

Endoscopic diagnosis are summarised in table II.

Table II. — **Lesions diagnosed at the first endoscopy in patients with heartburn**

Lesions	N	%
Normal Upper GI tract	263	21.9%
Hiatus Hernia	479 (uncomplicated : 74)	39.9% (6.2%)
Oesophagitis	635	52.9%
GDU	187 (99 DU)	15.6% (8.3%)
Gastric erosions	105	8.8%
Oesophageal Cancer	3	0.25%
Gastric Cancer	8	0.97%
Chronic atrophying gastritis	56	4.7%
Miscellaneous	101	8.4%

When present (in 635 patients), oesophagitis severity was grade 1 in 293 (46.1%), grade 2 in 254 (40.0%), grade 3 in 29 (4.6%) and grade 4 in 59 (9.3%). Among the 59 individuals classified in grade 4, 47 had uncomplicated Barrett oesophagus, 6 oesophageal stncture and 9, focal deep oesophageal ulcer. Heartburn was the main symptom in 457/635 oesophagitis (71.9%) but also in around one half of patients with GDU (81/187), gastric erosions (56/105) and severe chronic gastritis (26/56).

As a whole, endoscopy did not modify either the planned treatment or the follow-up in 675/1 200 patients (56.3%). In 24.6% (295 cases), treatment was modified because of endoscopic diagnosis and in 12.3% (147 cases), the follow-up planning changed. In 83 patients (6.9%), both initial treatment and follow-up were modified. So, endoscopy was poorly contributive in terms of management in more than 56% of the cases. Moreover, among the patients in whom initial treatment was modified after endoscopy, a large majority had normal upper GI tract or uncomplicated hiatus hernia : 248 out of 378 (66%). The crucial question is : are there discriminative pre-endoscopy data allowing to avoid useless endoscopy without missing life-threatening lesions ?

c) Results II : Malignant and pre-malignant lesions

Alarm symptoms remain a good predictor for significant lesions : among 155 patients with alarming complaints, only 20 had a normal upper GI endoscopy. 11 patients were found to have oesophageal or gastric malignancy. Reassuringly, none of them was younger than 57 year old and none had isolated heartburn as

Table I.

Endoscopy modified planned treatment	Endoscopy modified follow-up	Examples
No	No	Uncomplicated oesophagitis, DU [1]
No	Yes	Barrett Oesophagus [3], GU [1]
Yes	No	Normal Upper GI Tract [2]
Yes	Yes	Malignancy, Benign tumours, Chronic atrophying gastritis [3]

[1] HP infection is diagnosed by breath test and treated when indicated ; [2] Alginate and diet counselling in patients without oesophagitis ; [3] Endoscopic follow-up scheduled.

presenting symptom. Nevertheless, alarm symptom(s) were observed in only 6. Moreover, 55 patients had chronic atrophying gastritis and 47 uncomplicated Barrett oesophagus. Age was not discriminative : severe gastritis was found in patients from 23 up to 87 year old and Barrett oesophagus in refluxers from 15 up to 85 year old. More than 10% of the 282 patients with heartburn as the sole complaint had premalignant lesions : 16 had Barrett and 13 severe gastritis. Finally, alarm symptoms are not helpful : 81 patients out of 102 with pre-malignant condition had no alarm complaints. So, empirical treatment would have missed 5 cancers and 81 pre-malignant conditions (roughly 7% of the population studied).

d) Results III : Are they discriminative clinical factors to predict non-contributive endoscopy ?

The possible discriminative value of age has been studied (table III and IV).

Despite a trend for more frequent modification of follow-up planning in older classes of age and more frequent change in initial treatment in young people, age is not predictive of the impact of endoscopy in that matter : whatever the age, treatment and follow-up remain unchanged in more than a half of patients.

Symptoms are not more predictive either : therapeutic attitude and long-term management are less often modified in patients with pure reflux symptoms but one third of patients with isolated heartburn will be differently treated and followed-up after endoscopy (table V).

4. *Endoscopy might be cost-effective in the management of GORD*

According to our recent survey (4), around 210 000 individuals above 35 years old experience heartburn daily in our country, and 580 000 have heartburn at least once a week. If a symptomatic treatment policy is decided, the yearly cost to treat daily refluxers with half dose of PPI would be around 3 billions BF and for weekly refluxers, up to 8.3 billions BF with a symptomatic remission at 12 months below 50% (18). If we postulate that 60% of refluxers have oesophagitis and we decide to treat the lesion, we have to consider that around 75% of patients will remain lesion-free under Lansoprazole 10 mg daily for one-year and grossly, 25% of patients will need a full doses PPI daily. The yearly cost for treating symptomatic patients with lesions and obtain one-year lesions remission should be 2.25 billions BF for daily refluxers and 6.2 billions for weekly refluxers. Endoscopy could be an (unfair ?) way to select patients for efficient treatment of the lesions but not of the symptoms ...

Table III. — **Impact of endoscopy in the management according to age threshold**

Decision after endoscopy ⇓	< 35 year old n = 176	< 45 year old n = 378	< 55 year old n = 613	Whole population n = 1 200
Neither treatment, nor follow-up were modified	54.5%	55.02%	56.4%	56.3%
Only treatment was modified	34.1%	32.8%	29.7%	24.6%
Only follow-up was Modified	7.3%	8.2%	9.6%	12.3%
Both treatment and follow-up were modified	3.9%	4.0%	4.2%	6.9%

Table IV. — **Impact of endoscopy in the management according to age categories**

Decision after endoscopy ⇓	< 30 y old n = 103	30-45 y old n = 299	46-60 y old n = 350	61-75 y old n = 353	> 75 y old n = 95
Neither treatment, nor follow-up were modified	55.0%	55.0%	58.3%	55.5%	57.0%
Only treatment was Modified	35.0%	32.0%	21.0%	22.6%	9.5%
Only follow-up was Modified	5.0%	9.7%	11.8%	13.9%	24%
Both treatment and follow-up were modified	5.0%	3.3%	8.8%	7.9%	9.5%

Table V. — **Changes in management after endoscopy according to heartburn profile**

Decision after endoscopy ⇓	Heartburn as sole symptom n = 282	Heartburn as main symptom n = 389	Heartburn as accessory symptom n = 529	Total population n = 1 200
Neither treatment, nor follow-up were modified	65.2%	60.9%	48.1%	56.3%
Only treatment was Modified	18.4%	23.4%	28.7%	24.6%
Only follow-up was Modified	12.1%	10.8%	13.4%	12.3%
Both treatment and follow-up were modified	4.3%	4.9%	9.8%	6.9%

Proposed Conclusions

1. Heartburn is a very frequent complaint that is poorly predictive of oesophagitis lesion(s) and complications of GORD.

2. In follow-up, heartburn has a low predictive value for lesion's relapse but the absence of symptom is significantly indicative of lesion's remission.

3. PPI are so far, the most effective medical treatment for GORD.

4. Endoscopy is the most accurate procedure for the diagnosis of oesophagitis and oesophagitis' complications.

5. Endoscopy has a good prognosis value for the lesions' evolution under treatment and symptomatic remission in ENGORD.

6. The financial burden of symptomatic treatment with PPI for all patients with heartburn is unbearable and the 12-months symptomatic remission rate with a daily half-dose of PPI would be around a low 50%.

7. In patients with heartburn, endoscopy evidences oesophagitis in 53%, GDU in 16% cancer in 1% and preneoplastic condition (Barrett or chronic atrophying gastritis) in 8.5%. No malignancy was diagnosed in patients below 57 y old but around 80% of patients with malignant (5/11) or pre malignant (81/102) condition had no alarm symptom.

8. Despite endoscopy does not modify either initial treatment or follow-up in more than 50% of patients with heartburn (provided Helicobacter pylori status would be determined by another method), there is no discriminative clinical factors allowing to select patients in whom endoscopy should modify treatment, follow-up, or both.

9. Systematic endoscopy in patients with heartburn remains a good attitude. Saving money by treating only patients with oesophagitis might be controversial but finally, endoscopy modifies therapy and/or management in almost half of the patients whatever the age, detects malignancy in 1% and pre-malignant lesions in 8.5%.

10. Besides endoscopy, the solutions for expenses limitations in GORD should be a dramatic decrease of the cost of drugs, the extension of surgical indication (after careful study of the cost of morbidity and roughly 15% failures) or a prevention policy based on a better knowledge of the true causes of GORD that deserve extensive basic, epidemiological and clinical research.

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Endoscopy is not a sensitive diagnostic tool for gastro-oesophageal reflux disease (GORD) but is the only way to diagnose reflux oesophagitis and its complications (1). Moreover, endoscopy is the best method for diagnosing associated malignant or premalignant lesions of the upper gastro-intestinal tract that may be associated with typical reflux symptoms. It has a prognosis value (2) for the lesions evolution under

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treatment and the further development of possible complications (3). If a single endoscopy should be performed in a patient with GORD, it would preferably be the case at the time of initial presentation before any treatment, with PPI which have become the most effective and most cost-effective treatment of GORD.

Given the high and rising prevalence of reflux like symptoms in primary care, an empirical approach for the management of GORD may be acceptable provided the symptoms are typical, the patient is young and there are no alarming symptoms (4,5). Also these alarming symptoms are often not found in aged patients presenting with premalignant or malignant lesions (1).

Recent studies have tested the sensitivity of omeprazole administration for the diagnosis of GORD. This "omeprazole test" seems reasonably sensitive but poorly specific (6). Indeed, symptoms relief during this treatment may occur in several acid related disorders. It must be kept in mind that the optimal dosage and duration for an accurate PPI diagnostic test still needs to be determined.

The jury of this consensus has unanimously agreed on the following recommendations :

1. An endoscopy must be performed before any empirical treatment in every patient who ask a medical advice for the first time for symptoms suggestive of GORD (heartburn, retrosternal pain, regurgitations) :

a. In all the cases for patients aged more than 45 years.
b. Also in younger patients ($\leq$ 45 years old) when they have alarm symptoms (dysphagia, anemia, weight loss) or if they take non steroid anti-inflammatory drugs (NSAID).
c. If there are associated factors that may predispose to chronicity or increase the risk of malignancy (alcoholism, tabagism).
d. If the patients have already had an empirical therapy with a clinical improvement and present a relapse of symptoms.
e. If the patients have already had an empirical therapy without clinical improvement.

2. An endoscopy may be not formally indicated before starting an empirical treatment (for a period of maximum 1 month) in young patients aged $\leq$ 45 years old, who present typical reflux symptoms and are not included in the above mentioned exclusion categories.

3. The purpose of endoscopy in GORD is

a. to exclude another upper GI disease.
b. to differenciate and classify the patient according to the following categories :
   1. Endoscopic negative GORD.
   2. Uncomplicated oesophagitis.
   3. Complicated oesophagitis (including Savary type III, Barrett oesophagus, stenosis and deep ulcers). It is agreed that only the complicated oesophagitis requires an endoscopic surveillance.

4. In case of endoscopic negative GORD and of uncomplicated oesophagitis, the treatment after initial endoscopy and medical assessment may be based only on symptomatic evolution.

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