

***Helicobacter Pylori* and Smoking: Two Additive Risk Factors for Organic Dyspepsia**

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The hopes to distinguish between organic and functional dyspepsia on the grounds of the patient's symptomatology have not been fulfilled due to the low specificity of the so-called sinister symptoms. There is increasing evidence accumulating that *Helicobacter pylori* status and other environmental factors such as smoking have a higher discriminant power. Studies performed in our laboratories testing *H. pylori* status on gastric biopsy samples have shown that preselection of patients according to smoking habits and *H. pylori* status has a higher potential in avoiding unnecessary endoscopies in primary care patients as compared to risk factors based on patient complaints. Out of a total population of 282 primary care patients, one out of 24 endoscopies revealed significant pathology such as peptic ulcer or reflux esophagitis in the non-smokers with a negative *H. pylori* status, but when both risk factors were positive, the percentage rose to one out of every two patients. These observation have largely been confirmed by recent studies where *H. pylori* status was prospectively assessed prior to endoscopy by highly specific *H. pylori* serology or ¹³C breath test analysis.

INTRODUCTION

Dyspepsia is defined as any pain, discomfort or nausea referable to the upper alimentary tract, which may be intermittent or continuous and has been present for at least one month [1]. Dyspepsia is a very common clinical problem accounting for two to three percent of primary care consultations and some 30 to 50 percent of cases of chronic upper abdominal complaints presented to the gastroenterologist [27]. A large proportion of these patients do not have recognizable organic disease and are commonly labelled as having functional dyspepsia. Although upper gastrointestinal endoscopy is the investigation of choice for the distinction between organic and functional dyspepsia, one must take into account that the percentage of relevant organic disease found by this invasive technique is in the range of 25 to 15 percent, whereby the lower limit refers to patients of the primary care setting [2-4].

The diseases most often diagnosed are peptic ulcer and reflux esophagitis; the possibility of underlying carcinoma exists but primarily in older patients. In adequately trained hands, ultrasonography is of special value in the search of extraintestinal organic disease, especially gallbladder pathology, which is relatively common in dyspeptic patients. Endoscopy is both unpleasant and costly, and many attempts have, therefore, been made in recent years to cut down the amount of unnecessary procedures [8]. The strategies employed are mainly based on screening for so-called clinical risk factors, also referred to as sinister symptoms, but their discriminant power is limited due to the overall low specificity of each individual factor, and it is generally recognized that no single symptom allows an unequivocal diagnosis by itself [9]. Simultaneous evaluation of specified symptoms with

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linear discriminant analysis as well as stepwise logistic regression analysis, however, appears to have the potential to distinguish between functional and organic dyspepsia in approximately 70 percent of the cases [4, 5]. The low prevalence of organic disease in dyspeptic patients generally results in low positive and high negative predictive values. Consequently, the main impact of the predictive models may be to reduce the number of negative endoscopies rather than to predict a precise diagnosis [5]. In a dyspepsia study aimed at establishing the clinical characteristics and prevalences of upper gastrointestinal lesions in a large, primary-care referral, Swiss multicenter study [7], a simplified questionnaire on "risk symptoms and factors" (adapted from that proposed by Talley et al. [5]) adequately identified as "patients at risk" almost two-thirds of the patients with peptic lesions, while reducing the endoscopic workload to about one-third of the patients. Although the clinical criteria used, therefore, had some discriminant power between organic and functional dyspepsia, up to one-third of clinically relevant findings may have been missed. In recent years, particular attention has been given to age, gender and environmental factors such as smoking, drug consumption and especially *Helicobacter pylori* infection as risk factors for organic dyspepsia.

GENETIC AND ACQUIRED RISK FACTORS

Role of age as risk factor

There is circumstantial evidence available from many epidemiological studies that age above 45 is a risk factor for peptic ulcer and gastric malignancy and, to a lesser degree, also for reflux esophagitis [5]. For the latter disease, this particularly applies to the severity of the condition. Gastric malignancy is particularly rare below the age of 45 [10].

Role of gender

Organic dyspepsia appears to be more common in male subjects. This relates particularly to duodenal ulcer and reflux esophagitis, but not to gastric ulcer, where a higher NSAID consumption is likely responsible for the increased prevalence in the elderly female population [10-12].

Role of tobacco smoking

Smoking is a well-established risk factor in duodenal ulcer disease [13-18], even though this has long been disputed [19]. The epidemiologic evidence in favor of an increased risk is weaker in reflux esophagitis [20] and is mostly based on observations on the deleterious effects smoking exerts on the esophageal motility, such as a decrease in LESP [13, 21, 22], an impairment of esophageal clearance and promotion of duodenogastric reflux [23, 24].

Similarly smoking is an established risk factor for esophageal carcinoma, including adenocarcinoma in Barrett esophagus [25] and probably also for gastric carcinoma.

*Role of *H. pylori**

There is a strong and uncontested association of *H. pylori* infection and peptic ulcer especially duodenal ulcer and to a lesser degree gastric ulcer [26, 27]. Similarly, *H. pylori* infection contributes to development of gastric cancer [28]. Nevertheless, more than 80 percent of patients infected with *H. pylori* never develop a peptic ulcer nor a gastric carcinoma, and this considerably reduces the discriminant power of *H. pylori* infection as a risk factor for organic dyspepsia. There is very little evidence suggesting any direct link between *H. pylori* infection and reflux esophagitis [10, 29]. Many patients with functional

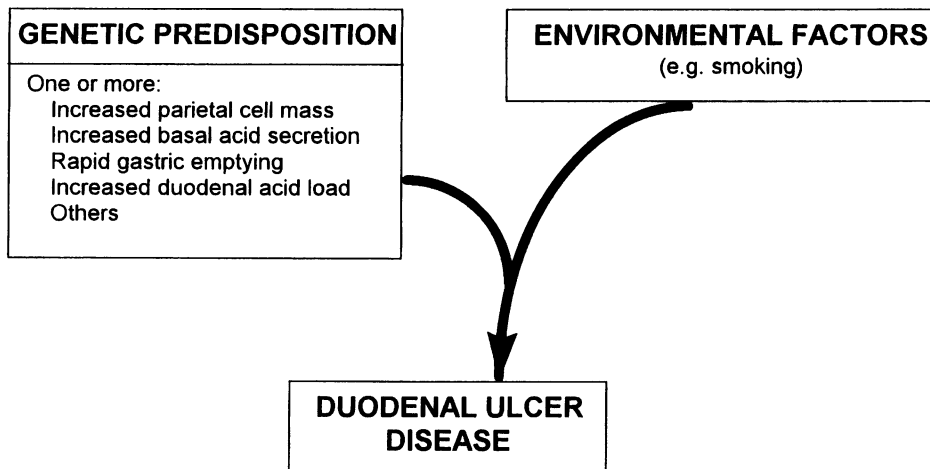


Figure 1. The sequence of genetic susceptibility combining with environmental factors to produce duodenal ulcer disease. (From [26] with permission.)

dyspepsia are infected with *H. pylori*, but the prevalence of this infective agent is only marginally higher than in healthy controls [30].

H. pylori induces chronic gastritis in all subjects infested, but additional genetic and acquired risk factors, especially smoking, have long been postulated to play a facilitating role in the promotion of organic disease, especially peptic ulcer disease [26] (Figure 1).

DISCRIMINANT VALUE OF GENETIC AND ACQUIRED RISK FACTORS FOR THE DISTINCTION BETWEEN ORGANIC AND FUNCTIONAL DYSPEPSIA

There are only limited data from the literature available to show to what degree the above discussed risk factors can be considered as guidelines in helping the primary care physician to preselect patients at risk for organic dyspepsia [10, 31] with a reasonable confidence, and thus to help reduce unnecessary endoscopies. Since there is a considerable overlap for each factor between patients suffering from organic and functional dyspepsia, it is of particular interest to evaluate the additive discriminant power of more than one risk factor. It is the aim of this review paper to discuss the results of a study of our group, where these parameters were analyzed retrospectively [32], and to compare them with the few published prospectively sampled data.

*Studies on combined risk of *H. pylori* and smoking*

Two hundred and eighty-two patients referred from their primary care physician were enrolled into our dyspepsia study [7] if they met the following criteria: symptoms for a minimum of one month, informed consent for drug trial, including upper gastrointestinal endoscopy and *H. pylori* status (based on CLO-urease test on three biopsy samples). All were prospectively screened for criteria suggesting an organic origin of the disorder such as nocturnal pain, severe pain, severe regurgitation or heartburn, loss of weight, pain relieved by food, age of more than 50 years, *H. pylori* status and nicotine abuse. Nonparametric data were given as absolute numbers or percentages. Comparisons were made with the chi-square method (with Yates correction where necessary) and the chi-squared test for trend

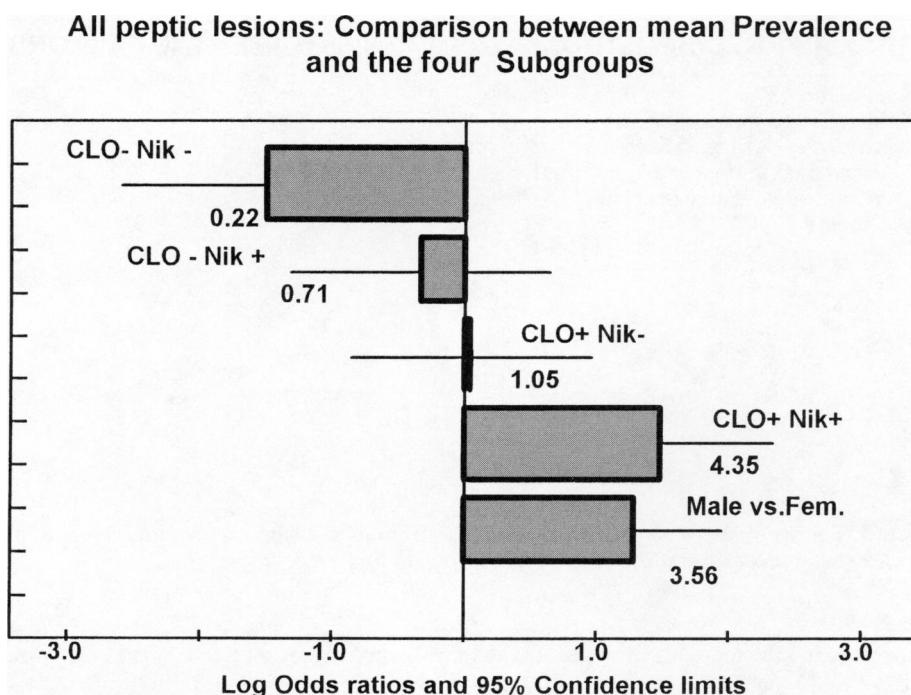


Figure 2. Prevalence of all lesions (reflux oesophagitis and/or peptic ulcers) in each subgroup (odds ratios calculated for both sexes pooled, each category vs. all others pooled). Intersection with Y axis = non-significant difference.

(for categories in natural order). Rate differences and odds ratios as a measure of relative risks were calculated by using the Mantel-Haentzel-Peto method.

Of the patients, 112/282 (39.5 percent) were *H. pylori* positive. Overall, 16 percent of patients had one or more relevant lesions: 7.8 percent esophagitis, 8.5 percent duodenal ulcers and 1.8 percent gastric ulcers. None of the above mentioned clinical criteria had an unequivocal discriminant power. However, three other factors appeared to be related to a higher prevalence of lesions in this population of dyspeptic patients. In decreasing order of discriminant power they were: a positive CLO-urease test (indicating *H. pylori* infection), smoking and male gender.

Consequently, the population—both genders individually and pooled—was stratified into four subgroups:

1. Patients who did not smoke and had a negative CLO-urease test (CLO-Nik-).
2. Patients who did smoke and had a negative CLO-urease test (CLO-Nik+).
3. Patients who did not smoke and had a positive CLO-urease test (CLO+Nik-).
4. Patients who did smoke and had a positive CLO-urease test (CLO+Nik+).

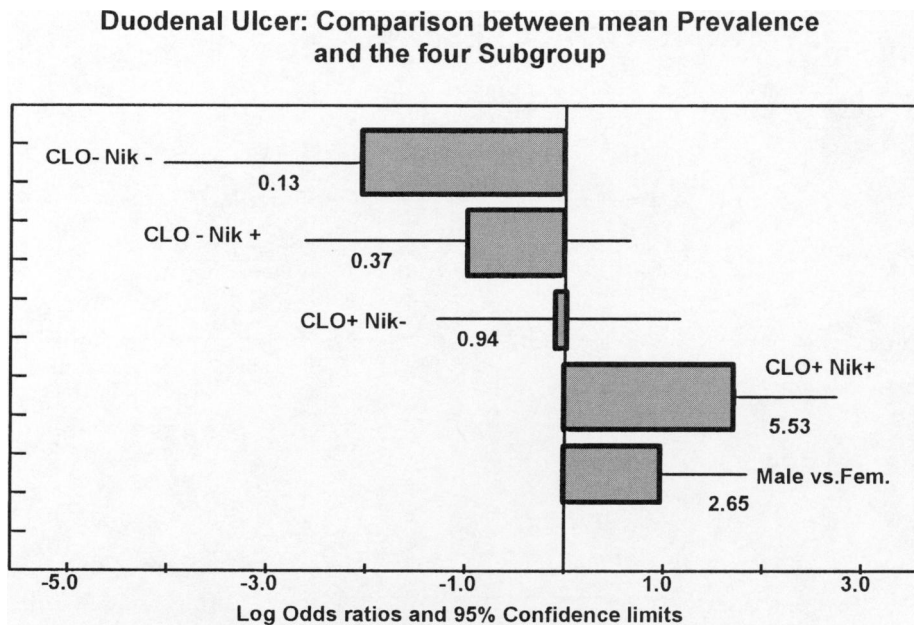


Figure 3. Prevalence of duodenal ulcer in each subgroup (odds ratios calculated for both sexes pooled, each category vs. all others pooled). Intersection with Y axis = non-significant difference.

Patients with both a positive CLO-urease test and who smoked accounted for only 16 percent of the population but for 46 percent of the lesions, but lesions were seen in only four percent of the 42 percent of the subjects who were non-smokers and had a negative CLO-urease test.

The odds ratios representing the discriminant power of these acquired factors are presented in Figures 2 and 3

Overall, and in particular for the duodenal ulcer subgroup, a negative *H. pylori* status in combination with non-smoking represented a highly significant negative discriminant factor for organic disease (odds ratio: 0.22 [0.07-0.67, 95 percent confidence interval], $p < .001$, and 0.13 [0.02-.93, 95 percent confidence interval], $p < .001$, respectively), while the reverse situation, namely a positive CLO test and smoking were reflected by a highly significant positive risk factor for organic disease (odds ratio: 4.35 [1.84-10.29, 95 percent confidence intervals], $p < .001$, and 5.53 [1.97-15.53, 95 percent confidence intervals], $p < .001$). Similarly, male sex had a high discriminant power for organic disease in the whole group (odds ratio: 3.56 [1.81-6.98, 95 percent confidence intervals], $p < 0.001$), as well as in the duodenal ulcer subgroup (odds ratio: 2.65 [1.12-6.28, 95 percent confidence intervals], $p < .05$).

In reflux esophagitis (data not shown), *H. pylori* status and smoking had a weaker discriminant power as compared to male sex. In all four groups, males had a higher prevalence for the latter disease (odds ratio corrected for smoking and *H. pylori* status: 4.54 [1.8-9.5, 95 percent, confidence intervals], $p < .001$). The CLO-Nik- group had a significantly lower probability of having an esophagitis (odds ratio: 0.46 [0.13-1.63, 95 percent confidence intervals], $p < .05$). Inversely, patients with a positive CLO-urease test and/or smoking taken as a group had a significantly higher probability of having an esophagitis than the *H. pylori*-negative non-smokers (combined odds ratio: 2.58 [1.01-7.27, 95 percent confidence intervals], $p < .05$).

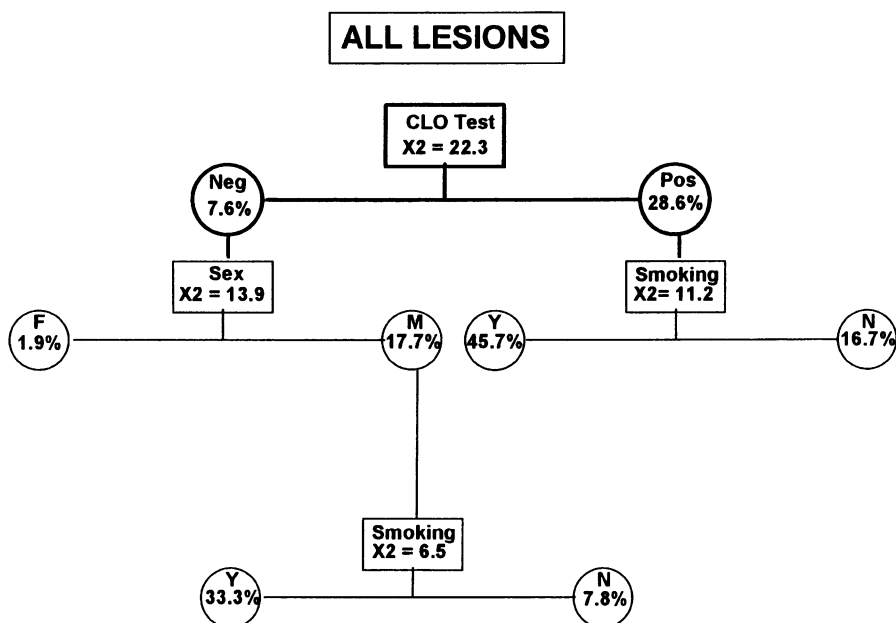


Figure 4. Stepwise chi-square test by highest value at each step. Data for all endoscopically found relevant lesions. CLO-test indicates urease test for *H. pylori* infection. All X2 values represent a factor with significant discriminant power within the stepwise chi-square test. F = female, M = male, Y = yes, N = no. Data given in percent indicate the percentage of the total number of patients included in the study (n = 282).

The data were further analyzed by sequential chi-square test (an analysis that allows weighing the independent contribution of each factor analogous to a stepwise regression analysis) in which each of the putative risk factors is tested and the population stratified for the most highly significant parameter. Each subpopulation is retested for the remaining risk factors, until no significant differences remain (Figures 4 and 5). The most important risk factor for all lesions taken together and in particular for duodenal ulcer disease tested separately was a positive CLO test, followed by smoking. Male gender followed by smoking were the two dominant risk factors in the CLO- ulcer group and similarly in patients with reflux esophagitis. *H. pylori* infection only marginally qualified as a risk factor in patients with reflux esophagitis, particularly in female patients ($p < .1$).

Analysis of the data in view of endoscopic yield revealed that 1:24 endoscopies were positive in the CLO-Nik-group, 1:6 if the patients had either a positive CLO-test or were smokers, and 1:2 in patients who were in the CLO+Nik+ group. Regarded separately, the corresponding positive yields were 1:30, 1:10 and 1:7 for reflux esophagitis and 1:119 (CLO-Nik-), 1:26 (smokers), 1:13 (CLO+) and 1:3 (CLO+Nik+) for duodenal ulcers.

Gender, positive *H. pylori* status and smoking, thus, had an important and additive discriminant value to distinguish between organic and functional dyspepsia. The results strongly suggest that preselection of patients according to smoking habits and *H. pylori* status is more helpful in avoiding unnecessary endoscopies in primary care patients as compared to clinical risk factors based on patient complaints. Since this statement is based on a retrospective analysis, and since *H. pylori* status was assessed at endoscopy, this observation needs to be further verified by prospective studies with the use of a highly sensitive non-invasive method for *H. pylori* screening, ideally with the help of the ^{13}C -urea breath test or one of the new highly specific serological tests. A prospective study partly

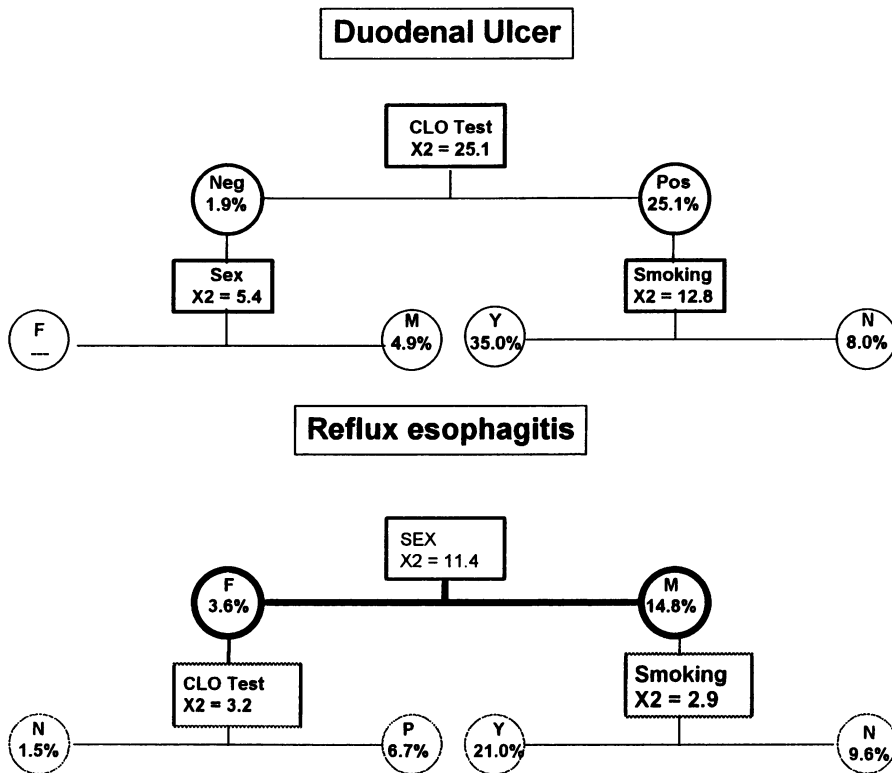


Figure 5. Data analyzed with the same analysis as in Figure 4 for patients with duodenal ulcers (5a, top) and patients with reflux esophagitis (5b, bottom).

fulfilling these requirements has recently been published [31]. Earlier data are also available from prospective studies where *H. pylori* status was assessed by serology [10]. The latter study revealed that, a positive *H. pylori* serology fulfills together with a history of sinister symptoms the criteria of an independent risk factor, helping considerably to cut down on unnecessary endoscopies.

In the study where *H. pylori* status was prospectively assessed with the ^{13}C urea breath test, 327 patients were referred for endoscopy [31]. Organic dyspepsia was found in 52 percent of those with a positive result. By contrast, less than 79 percent of those with a negative breath test had no abnormality at endoscopy. The stepwise logistic regression analysis identified smoking, previous upper gastrointestinal investigation and duration of symptoms as significant independent predictors of ulcer disease in the *H. pylori* positive subjects. The peptic ulcers prevalence was found to be almost two-fold as frequent in *H. pylori*-positive smokers as compared to *H. pylori*-negative smokers. Unfortunately, the data of that study are not fully comparable with those of our study. Their study was not performed on primary care patients, and the rate of relevant organic dyspepsia was considerably higher. Moreover, the *H. pylori* prevalence in their population was much higher (65 percent vs. 39 percent in our study), and the prevalence of peptic ulcers was even more unbalanced (32 percent vs. 10.3 percent in our study). No attention was given to the

question of whether reflux esophagitis is more frequent in *H. pylori*-infected smokers. Nevertheless, the data collected in a selective group confirm our findings collected among primary care patients that smoking is a prominent facilitator of organic dyspepsia in *H. pylori* positive subjects, particularly for duodenal ulcer disease.

The additive risk smoking plays in *H. pylori*-positive subjects in developing a peptic ulcer is indirectly confirmed by the observation of an Australian group that smoking is no longer a risk factor for ulcer recurrence once *H. pylori* is eradicated [33].

POSSIBLE REASON FOR INCREASED RISK OF SMOKING IN *H. PYLORI* POSITIVE SUBJECTS

It has been speculated that the excess of peptic ulcer disease in cigarette smokers may be explained by their increased susceptibility to *H. pylori* infection [33]. It is more likely that the mucosa of *H. pylori*-infected subjects is more susceptible to smoking-induced damage, e.g., by reducing blood flow as suggested by Taha et al. [35].

CONCLUSION

There is increasing evidence that smoking represents a very substantial additive risk for development of organic dyspepsia in *H. pylori*-positive subjects. This relates particularly to peptic ulcer disease, whereas its relation to reflux esophagitis needs further investigation. Similarly, male gender and advanced age are accompanied by a higher risk for organic dyspepsia. Clearly, absence of any of these risk factors does not fully exclude organic disease, but the likelihood of finding relevant pathology in young *H. pylori*-negative subjects who are non-smokers is an important argument against an early endoscopy in this group. Here, endoscopy should be reserved to those patients who do not respond to a simple probatory therapy within one to two months.

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