# Dyspepsia in the young adult patient: Management strategies in the era of declining *Helicobacter pylori* prevalence and increasing antimicrobial resistance

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**Papers**

**1) "Test, Score and Scope": A selection strategy for safe reduction of upper gastrointestinal endoscopies in young dyspeptic patients referred from primary care.**

**2) Do young dyspeptic patients consider upper gastro-intestinal endoscopy useful**

**3) Managing dyspepsia in young adult patients: effects of different tests for Helicobacter pylori in a "test-and-scope" approach**

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## Populærvitenskapelig sammendrag

Bakterien Helicobacter pylori er den viktigste årsaken til sår i magesekk og tolvfingertarm. I tillegg vil bruk av betennelsesdempende medisiner kunne gi slike sår. Kreft i denne delen av mage-tarm systemet er uhyre sjelden i aldersgruppene under 45-50 år.
Den størst gruppen av pasienter med dyspepsi har imidlertid det vi kaller "funksjonelle" plager, som har svært sammensatte og bare delvis forståtte årsaksforhold. Kun 8-10 % av de med funksjonell dyspepsi som også har H. pylori vil bli bedre av sine plager dersom bakterien fjernes. Disse fakta har dannet grunnlaget for den herskende retningslinjen for hvordan disse pasientene handteres i USA og Europa, den såkalte Maastricht Consensus rapporten.
I Norge har man vært tilbakeholdne med å følge disse retningslinjene, dels pga. en tradisjonelt mer restriktiv holdning til bruk av antibiotika, dels fordi man har ment at de ikke-invasive testene ikke var gode nok til en slik screening. I vårt helsevesen har vi kunnet praktisere en

åpen tilgang til gastroskopi i den forstand at kun en liten prosent av henvisninger til denne undersøkelsen fra allmennlegene blir avvist. I de senere år har det imidlertid vært en glidning også i Norge i retning mot tankegangen uttrykt i Maastrichtrapporten.
Det er også en utbredt oppfatning at det å bli gastroskopert for en pasient med langvarig dyspepsi i seg selv er et gode som kan bidra til å øke pasientens akseptering av egne plager. Dagens norske praksis resulterer i et relativt høyt antall unge pasienter med normale funn ved gastroskopi, mens retningslinjene fra Maastricht kan kritiseres for at det fører til et høyt forbruk av bredspektrede antibiotika som pasienten har ingen eller marginal nytte av.
I den aktuelle studien ønsket vi å bruke eksisterende kunnskap til å teste om en kunne selektere ut de pasientene hvor en ikke ville forvente å finne noe ved gastroskopi, i den hensikt å unngå denne prosedyren. Studien er gjort på yngre pasienter med dyspepsi som er henvist til gastroskopi. I den første artikkelen viser vi at med noen enkle selekteringskritterier kan vi identifisere en gruppe pasienter hvor praktisk talt alle klinisk relevante funn som gjøres ved undersøkelsen finnes. Denne gruppen utgjorde omtrent 45 % av alle som ble henvist, men hadde over 90 % av de endoskopiske funn i gruppen. Seleksjonen ledet derfor til riktig behandling av disse. Hos de øvrige pasientene endret ikke gastroskopien på behandlingen, som uansett ville være symptomstyrt.
I vår studie ble imidlertid alle gastroskopert. De funn som likevel ville vært oversett skyldtes at vi brukte en serologisk test med kun 90 % sensitivitet. Dagens tester med monoklonalt antistoff mot H. pylori i en avføringsprøve vil være et klart bedre verktøy her.
En tilnærming til denne pasientgruppen med en god test på H. pylori og gastroskopi av kun selekterte pasienter ville gjøre det mulig å unngå mer enn halvparten av gastroskopiene som gjøres i denne aldersgruppen i dag. Samtidig ville vi beholde muligheten til å reservere antibiotikabehandling til den gruppen der effekten er størst.
I artikkel nummer to har vi sett på pasientene ett år etter undersøkelsen i lys av de fire hoveddiagnosene, peptisk sårsykdom, syrerefluks til spiserøret med og uten påvist betennelse samt funksjonell dyspepsi. Hensikten var bl.a. å undersøke hvor høy andel av pasientene i de forskjellige diagnosegruppene som var blitt bedre av sine plager, og i så fall hva de selv mente var viktigste årsaken til bedring. Vi var særlig interessert i gruppen med funksjonell dyspepsi og fant at kun 16 % oppga gastroskopien og den ledsagende informasjon som opplevd årsak til bedring. De største gruppene anga endring av livssituasjon og kosthold som de viktigste opplevde årsaker til bedring av sine plager.
I vår tredje artikkel har vi sett på de forskjellige non-invasive H. pylori testene og deres testegenskaper. Med utgangspunkt i komplett H. pylori status hos alle 341 pasienter og det at

samtlige var gastroskopert kunne vi beregne hvordan de forskjellige testene ville ha slått ut i det aktuelle materialet og med dette ytterligere kunne ha forbedret resultatene. Vi har også sett på de forskjellige testenes egenskaper i en setting med fallende H. pylori prevalens.
Vi konkluderer med at seleksjonsstrategien "Test, skår og skopér" er en velegnet strategi for å redusere antall unødvendige gastroskopier hos pasienter med dyspepsi under 45 år. Den kan samtidig bidra til å beholde en ønsket restrikttiv bruk av antibiotika. Dette bildet forsterkes ytterligere når prevalens av H. pylori faller.

## Summary

*Helicobacter pylori* (*H. pylori)* is the main cause of peptic ulcer disease, followed by regular consumption of non-steroidal anti-inflammatory drugs (NSAIDs). The occurrence of gastric cancer is very low below the age of 45-50 years and thus does not justify any kind of symptom-based endoscopic screening, especially in patients without anaemia, dysphagia or loss of weight. *H. pylori* also plays a well-documented, but minor role in functional dyspepsia (FD). These data form the base for the Maastricht convention report, implemented as the predominant guideline for managing young dyspeptic patients in Europe and USA. This is known as the "Test and Treat" strategy: Patients are tested for *H. pylori* at the general practitioners office and if positive treated directly without further examination. This strategy is supposed to save many upper gastro-intestinal (GI) endoscopies, while patients who have peptic ulcer disease (PUD) will receive the adequate treatment to terminate the disease. The small share of *H. pylori* positive patients with functional dyspepsia that will profit on *H. pylori* eradication (some 5%) will also be taken care of by this strategy.
However, this strategy leads to prescription of broad-spectrum antibiotics without contribution to improvement for most of the patients receiving them.
The Nordic countries have traditionally had a restrictive attitude towards use of antibiotics and in Norway the "Test and Treat" strategy has not been officially adopted. Instead there has been a more or less open access to endoscopy in the way that the individual practitioner together with the patients decide whether to refer to endoscopy or not. Rejections from the specialist centres seldom occur. This leads to a more individualized therapy based on the results from the endoscopy, in addition to case history and other tests. On the other hand, it also entails a significant number of negative endoscopies in a group of patients where serious pathology is infrequent. It has been the understanding that a negative endoscopy would contribute to diminish the patients' symptoms or at least their ability to deal with them.

The studied strategy concerning selection of young dyspeptic patients to upper-GI endoscopy shows that one can reduce the number of examinations by more than 50%, whilst only a small number of pathological conditions would be overlooked. At the same time, the use of antibiotics could be restricted to situations where it has an indisputable role, such as peptic ulcer disease (PUD), mucosa associated lymphoid tissue (MALT-) lymphomas and early stage gastric cancer
(Paper I).

After one-year follow-up we found that patients with PUD had a significantly higher score of symptom improvement. These patients recorded *H. pylori* eradication therapy as main reason for improvement. In the patients with functional dyspepsia who experienced improvement of symptoms, change of life situation and diets were recorded as main reason for improvement. Only 16% recorded the endoscopy and the subsequent information received as being of importance (Paper II).

In Paper III we have analysed the different non-invasive tests for *H. pylori* with regard to their test properties.

As we had complete data for *H. pylori* occurrence (true *H. pylori* status) in the 341 patients in the study, and all of them underwent endoscopy, we were able to re-calculate the results of the study as if we were using tests with better test properties. In the Western world the *H. pylori* prevalence is decreasing, and this will mean that screening strategies must be scrutinised. In Paper III we also have looked into this.

The dissertation discusses further the implications of the studied selection strategy in the contexts of functional dyspepsia, gastric cancer prevention and the consequences for microbiological resistance.

# List of papers

1. Valle PC, Breckan RK, Amin A, Kristiansen MG, Husebye E, Nordgard K, et al. "Test, score and scope": a selection strategy for safe reduction of upper gastrointestinal endoscopies in young dyspeptic patients referred from primary care. ScandJ Gastroenterol. 2006;41(2):161-9.

2. Valle PC, Breckan RK, Kildahl-Andersen O. Do young dyspeptic patients consider upper gastro-intestinal endoscopy useful? Hepatogastroenterology. 2010 Sep-Oct;57(102-103):1164-9.

3. Valle PC, Breckan RK, Mortensen L, Amin A, Kildahl-Andersen O, Paulssen E. Managing dyspepsia in the young adult patient: effects of different tests for Helicobacter pylori in a "test-and-scope" approach. Manuscript is submittet.

## Abbreviations as they occur

| | |
|---|---|
| *H. pylori* | *Helicobacter pylori* |
| PUD | Peptic ulcer disease |
| FD | Functional dyspepsia |
| NSAIDs | Non steroid anti-inflammatory drugs |
| G-I | Gastro-intestinal |
| MALT | Mucosa associated lymphoid tissue |
| GP | General Practitioner |
| GORD | Gastro oesophageal reflux disease (syn. GERD) |
| LR | Likelihood ratio |
| PPI | Proton pump inhibitor |
| ASA | Acetylsalicylic acid |
| NUD | Non ulcer dyspepsia |
| PDS | Postprandial distress syndrome |
| IBS | Irritable bowel syndrome |
| UEGW | United European Gastroenterology week |
| cagA+ Hp | Cytotoxin-associated gene positive *H. pylori* |
| S-M | Savary-Miller classification system for oesophagitis |
| LA | Los Angeles classification system for oesophagitis |
| CADET | Canadian Adult Dyspepsia Empiric Treatment- study |
| $H_2$ RA | Histamin 2 receptor antagonist |
| FDA | Food and Drug Administration (US) |
| ECL | Enterochromaffine-like cells |
| DDD | Defined daily doses |
| EIA | Enzyme immunoassay |

| | |
|---|---|
| UBT | Urea breath test |
| FSSG | Frequency scale of the symptoms of GERD |
| QUEST | Questionnaire for the diagnosis of reflux esophagitis |
| NNT | Number needed to treat |
| CI | Confidence interval (normally given as 95% CI) |

# 1. Introduction.

## 1.1 Background and general aspects

### 1.1.1 Dimension of the challenge.

Dyspepsia is a common condition accounting for a significant share of the consultations at the general practitioner (GP) with as many as 25% of people in the Western countries experiencing these symptoms regularly (1). Approximately 25% of these seek medical help, and dyspepsia is estimated to account for 2-5% of all consultations in general practice (2, 3).

### 1.1.2 Definitions

There are different definitions of dyspepsia; some of these include gastro-oesophageal reflux (GORD) related symptoms like heartburn and regurgitation (4, 5), while the Rome III definition excludes these by defining dyspepsia as 1 of 3 of the following symptoms: Postprandial fullness, early satiety and epigastric pain or burning in absence of structural diseases, likely to explain the symptoms (6). Dyspepsia has a great impact on quality of life. The reduction of quality of life for these patients is comparable to, and even greater than what is found in patients with other chronically diseases like diabetes and cancer (7, 8).
Regardless of the definitions used, there is a significant overlap between symptoms that origin from the oesophagus, stomach and upper gut (9, 10). When patients present with retrosternal, burning pain or discomfort and acid regurgitation as their only or principal symptoms, a diagnose of GORD is of relatively high confidence, but if these symptoms are mixed with symptoms listed in the Rome III criteria the diagnosis of the underlying condition is often more ambiguous.

### 1.1.3 Underlying conditions and their relation to the symptoms

Functional GI symptoms may coincide with many disorders, and this should be taken into consideration when making a strategy on how to address patients with dyspepsia.

Dyspepsia can be caused by PUD, GORD, a functional disorder often called non ulcer dyspepsia (NUD) and miscellaneous conditions like malignancy, biliary tract diseases, motoric disorders and others (11).

Many studies have been performed to identify symptom combinations and to make scoring systems able to indicate the underlying disorder at a useful and safe level. Prior to the discovery of the *H. pylori* bacterium the predictable value was too low to detect organic disease of significance and had a sensitivity level of approximately 70% (12). In an open access endoscopy policy the burden of young (<45 years) dyspeptic patients with negative or insignificant findings was, and still is, a matter of controversy. Scoring systems to predict negative endoscopies in order to avoid them rarely performed well enough to be applied in daily practice (13-16).

A systematic review performed by Moayyedi and colleagues in 2006 concluded that neither clinical impression nor computer models that incorporated demographic data, risk factors, history items and symptoms, adequately distinguished between organic and functional disease in patients referred to endoscopy because of dyspepsia. Positive likelihoods ratios (LR) to predict PUD by these factors were 2.2 (95% CI 1.9-2.6) (17).

### 1.1.4 Discovery of *H. pylori* – Beginning a new epoch in understanding dyspepsia?

The detection of *H. pylori* in 1982 by Marshall and Warren started a new era and changed both treatment options and diagnostic strategies in this group of patients, but also raised a lot of new questions (18, 19). Studies that compared different questionnaires to serologic testing of *H. pylori* concluded that testing was significantly superior to questionnaires and other clinical decision making systems (20, 21).

Since the discovery of *H. pylori* a huge number of papers concerning different strategies in the work-up of dyspeptic patients, mostly related to *H. pylori* in some way or another, have been produced. These can to some degree be divided into 3-4 groups:

Original studies testing and advocating a curtain selection strategy, studies comparing different strategies with respect of saved endoscopies, and analyses of economics, cost-benefit, patient satisfaction and detected pathology. In addition there are reviews, editorials and extended reports from working groups and finally, guidelines (1, 22-30).

## 1.2 Different strategies in the management of patients with dyspepsia

### 1.2.1 Elements to consider in a selection strategy to upper-GI endoscopy

Compared to a more or less open access to upper-GI endoscopy, the presented selection strategies intend to reduce the number of endoscopies by some kind of screening, or initiate therapeutic trials aimed at symptom relief. All the strategies are based on a set of statements about the diseases we have to take into account in this setting. These statements also have different levels of evidence and have therefore often been given different weight by the authors.

- *H. pylori* is a cause of PUD and account for 90-95% of duodenal ulcers and 60-100% of gastric ulcers (31).
- NSAIDs account for almost the entirety of the remaining gastric ulcers, especially in patients younger than 50 years (1).
- *H. pylori* is related to gastric cancer development. This is most strongly documented for MALT lymphoma, but also for adenocarcinomas of the stomach (30, 32-35). Gastric cancer occurrence is still increasing in developing countries, but decreasing in the developed part of the world.
- Gastric malignancy is very rare in patients younger than 45-50 years, and it is not necessary to take the risk of having cancer into account in a screening context like this (14, 34, 36).
- FD is positively but weakly related to *H. pylori*. Eradicating *H. pylori* in patients with NUD is approximately 8-10% better than placebo. There is no specific association between *H. pylori* and any specific symptom profile in NUD. This relation is controversial and epidemiologic data give little support for a causative connection between *H. pylori* and NUD (37, 38).
- There is no known causative association between *H. pylori* and GORD or oesophageal and cardiac cancer, but an inverse relation is observed (29).
- Young patients with symptoms suggesting GORD can be treated symptomatically. Grade of reflux oesophagitis seldom changes over years (39-41).
- Patients who present symptoms of reflux or dyspepsia after 50 years of age should be offered endoscopy directly and without unnecessary delay.

- Patients with alarm symptoms like unexplained weight loss, anaemia or dysphagia should be handled the same way regardless of age (1).

Additionally, other important elements should be taken into account:

- The health resources will never be sufficient to meet all needs, and both the health authorities and the single specialist must make cost-effect evaluations. To prioritise in the endoscopic laboratory means to evaluate the usefulness of endoscopy in one group of patients against another.
- An extended eradication policy for *H. pylori* will lead to a significant use of broad spectrum antibiotics. This will contribute to the increasing problem of multi-resistant bacteria (42).
- The deceasing prevalence of *H. pylori* in the Western countries will change the basis for some of the strategies and further increase the demand for proper screening tests (38, 43).
- The endoscopic examination together with the consultation by the specialist might have a positive influence on the patients even if no specific therapy is initiated.

Many of this "theses" are contradictory and the challenge is to weigh one against the others and evaluate their relative importance. This different weighting is then the basis of the different strategies for managing dyspeptic patients, and especially young dyspeptic patients.

### 1.2.2 The "Test and Treat" strategy.

"Test and Treat" is the predominant strategy according to the amount of papers advocating it, and the fact that it is implemented as the recommended guideline in most of Europe and North America (24, 29, 44-49). Dyspeptic patients younger than 50 years consulting their family physicians will be tested for *H. pylori* at the office, often with a rapid, full blood serological test giving the answer immediately. If positive, they will receive *H. pylori* eradication therapy without endoscopy.

This strategy is supposed to save a substantial number of endoscopies and thereby reduce costs. It will heal patients with PUD and give *H. pylori* positive patients with NUD the chance to respond to eradication. Those not improving symptomatically will then either be offered an empirical trial of acid suppression medication or endoscopy (50). However, in a 6-7 year follow-up study, a substantial number, up to 80%, of these patients , were sent to endoscopy after initial treatment (51).

### 1.2.3 The "Test and Scope" strategy.

This strategy also selects patients based on *H. pylori* testing of young dyspeptic patients. Contrary to the "Test and Treat" strategy, those who test positive are offered endoscopy (52-55). Additionally, dyspeptic patients using NSAIDs regularly will be referred to endoscopy, as will patients with alarm symptoms.

This strategy does not offer systematic *H. pylori* treatment to patients with FD.

A mix of these two strategies has also been tested. Patients testing *H. pylori* positive were offered eradication treatment; those who were negative went on to endoscopy (56-58).

### 1.2.4 Acid suppression trial

This strategy does not primarily focus on *H. pylori*, but rather towards the patients' symptoms. It offers a treatment trial with acid suppression medication as a first step. There is a substantial overlap between symptoms caused by PUD, FD and GORD and many patients do have elements of all these diagnoses. The rationale is that many patients both with organic and functional disorders would experience relief of symptoms immediately after a proton pump inhibitor (PPI) medication trial and a substantial share will not re-consult the physician (5, 59-62). Patients with recurrent symptoms or no relief at all should proceed to endoscopy and *H. pylori* testing followed by eradication treatment if indicated.

### 1.2.5 Direct endoscopy.

This strategy employs endoscopy as first choice with no prior testing or treatment trial. Testing for *H. pylori* is then often done during endoscopy. The general practitioners refer the patients more or less as an open access where the indication and threshold for reference will vary a lot (61, 63). The above-mentioned strategies have been compared to this one in different studies (46, 64). The strategy will lead to many negative examinations (14, 16). However, the usual argument supporting this strategy is the reassurance effect of a negative endoscopy because many of the dyspeptic patients might have an underlying fear of cancer as cause of their symptoms (65).

## 1.3 The statements behind the different management of dyspepsia are supported of data with variation in clarity.

Not all of these strategies have the same basis in convergent data. This in turn makes the choice of strategy a matter of great discussion, and the final understanding and conclusion are still not

at hand.

Indications for *H. pylori* eradication therapy can be divided into absolute and relative indications (66):

- Absolute indications:
    - Peptic ulcer disease (PUD), actual or previous
    - MALT lymphomas
    - Gastric cancer, presumptive curable
- Relative indications:
    - *H. pylori* as part of large scale eradication like the Test and Treat strategy
    - Functional dyspepsia (FD)
    - *H. pylori* positive first-degree relatives to patients with gastric cancer
    - *H. pylori* positive Patients in need of long term PPI treatment

While the absolute indications are beyond discussion, the relative ones are burdened by considerable doubt. When the underlying data is inconclusive and conflicting, and the consequences involve great numbers of patients, caution should always be taken with respect to side effects, over which we do not have the complete overview.

The effect of eradication in patients with FD and positive *H. pylori* test is well-documented (on level Ia in a system of Level of evidence). However, the effect is so small (8-10%) that this indication must be critically evaluated to balance to the potential harm of the treatment. On the other hand, the level of evidence for testing for, and eradication of, *H. pylori* in first degree relatives of patients having gastric cancer, especially siblings, is weaker (level III) but the number of treatments this implies is small.

We therefore have to look deeper into the different aspects implied by these management strategies.

### 1.3.1 *H. pylori*, the main cause of PUD and gastritis.

*H. pylori* is the cause of 95% of duodenal ulcers, and is considered to be the cause of approximately 70% of gastric ulcers. In accordance with a lower *H. pylori* prevalence, the incidence rate of PUD has also decreased. However, in the recent years some papers have reported a significantly lower prevalence of *H. pylori* in both of these conditions. The explanation for this is uncertain, but some theories can be proposed: The extended use of both antibiotics and PPIs may affect the performance of *H. pylori* tests, dependent on which kind of test is used. The use of NSAIDs and ASA is also increasing and if a patient with an upper-GI-ulcer has both used NSAIDs and was *H. pylori* positive, then the ulcer was probably defined as

a *H. pylori* ulcer. With a decreasing prevalence of *H. pylori* and an extended and increasing use of NSAIDs the relationship between *H. pylori* ulcer frequency and NSAID ulcer frequency may change.

*H. pylori* can give different patterns of gastritis, which in turn is associated with disease development. Gastritis located in the gastric antrum is associated with duodenal ulcers, while diffuse gastritis spread through the whole organ is associated with gastric ulcers, atrophic gastritis and in turn, gastric cancer (67).

### 1.3.2 NSAIDs and upper gastrointestinal ulcers.

The use of non-selective NSAIDs is associated with side effects in the upper GI-tract ranging from light afflictions to serious complications such as bleeding ulcers. Use of NSAIDs is an independent risk factor for ulcers, but the association with *H. pylori* has also been studied. Some degree of intolerance has been reported in 15-34% or more of patients using NSAIDs. This intolerance can account for approximately 10% of withdrawals from studies (68, 69). More serious complications like ulcer bleeding and/or perforations occurred with a RR of 4.4 (95% CI 3.7-5.3) compared to controls in a Spanish study (70).

There is also a significant variation in risk of bleeding between the different NSAIDs, with reported ORs ranging from 2.0 to 23.7, with ibuprofen at lowest risk and ketoprofen as the highest one reported in a study of Langman et al. (71). This fact, together with other well-known risk factors like advanced age and earlier bleeding ulcer, must be born in mind when risk stratification is performed before prescription of NSAID medication.

While the risk of GI complications seems to be equal during the whole time of exposure, the risk increases with the dose given. It is probably not possible to draw a secure limit of NSAID dose, but the infrequent, occasional consumption of low-dose, potent NSAIDs to relieve menstrual pain and headaches is hardly of relevance.

Preventative therapy seems to be best performed with PPI, as concluded in a review by Goldstein (68, 72), but *H. pylori* eradication if positive seems to be cost-effective (73). It seems reasonable at least to prescribe eradication of *H. pylori* as secondary prophylaxis after one bleeding episode if continued NSAID medication is strictly necessary.

### 1.3.3 Functional dyspepsia and *H. pylori*.

*Diversity in symptoms and definitions*

Management of the *H. pylori* positive patients having FD is in many ways a key issue in this discussion. The aim of a selection strategy managing young dyspeptic patients is to detect

patients in use of endoscopy and treatment based on well-documented indication. If it is concluded that all patients with dyspepsia and a positive *H. pylori* status should be offered eradication treatment, then further selection whether to perform endoscopy or not is of very little significance as there is not that much left to select.

Dyspepsia is often divided into un-investigated dyspepsia and investigated dyspepsia. Practically, the difference is whether the patients have been to endoscopy or not, and thus whether organic disease is excluded or not (6). The condition where organic defined diseases are excluded is called functional dyspepsia (FD) or non-ulcer dyspepsia (NUD). In fact, NUD might be a less precise term than functional dyspepsia because it gives an impression of symptoms identical to those accompanying ulcerous disease. This does not cover the symptom spectrum of FD, which is more complex and multifaceted. In the Rome III consensus, the terms "Epigastric pain syndrome" (EPS) and "Postprandial distress syndrome" (PDS) subgroups were introduced in order to distinguish between different clusters of syndromes observed in FD (74).

FD is very common, and there have been different definitions and suggested subdivisions (75). There is a great overlap between GORD related symptoms, and those related to dyspepsia thought to originate from the stomach and upper gut. Different definitions have either included or excluded the GORD related symptoms in FD. The Rome III diagnostic criteria are presented in Table X (Rome criteria).

Tack and colleagues performed a study to determine the significance of heartburn as part of the symptoms in a population with functional dyspepsia. 76% of patients with heartburn had pathological pH test vs. 26% of those without such symptoms. However, the last group tended to have more and stronger epigastric pain compared to the FD patients without a pathological test (75). This study like many others underlines the great overlap between those two conditions. Pathological gastro-oesophageal reflux is found in a high proportion (>30%) of FD patients without heartburn and regurgitation according to the Rome III criteria (76, 77)

These studies also illustrate the multifactorial aetiology underlying the condition.

*Diversity in pathophysiology*

Disturbed motility is considered to be of significance in the pathophysiology of FD. Both decreased and increased motility have been described related to FD, and motility disturbances may explain the symptoms during and after meals, eventually combined with hypersensitivity to gastric distension (78) (79).

Accommodation means the compliance of the stomach to meals in the sense of appropriate distension for the size of the meal, without increasing the pressure. Disturbance in

accommodation is associated with both meal related pain and early satiation. This have been demonstrated in ~~to~~ two studies using different methods: single photon emission computed tomography (SPECT), and fundic barostat, respectively (78, 80). In these studies almost half of the patients with FD had disturbed gastric accommodation in response to meals.
In a study by Sha et al., patients with severe symptoms of FD were tested with electrogastrography (EGG) and antral-duodenal manometry. More than two-thirds of the patients had abnormalities in both methods.
As in irritable bowel syndrome (IBS), visceral hypersensitivity plays an important role in FD. There is older data supporting this, but recently the relationship between symptoms, gastric emptying and gastric sensitivity were demonstrated. Patients with hypersensitivity had significantly higher scores for fullness and early satiety, while those with delayed emptying had higher scores for heartburn and regurgitation, nausea and vomiting, together with bloating (81).
The relationship between gastric acid and FD symptoms is unclear, but hypersensitivity to normal acid secretion might be an explanation. Many patients in the Rome III epigastric pain syndrome (EPS) group have pathological reflux when tested with 24-hour pH measuring.
There is growing data pointing out that the immunological response after gastro-intestinal infections like Salmonella and Giardia lamblia may be a factor in both IBS and FD.
FD is considered a condition with a complex pathogenesis and it is far from completely understood. These relationships can explain why only a proportion of the patients respond to the different treatment options.

*H. pylori* and Functional dyspepsia

*H. pylori* infection is also in some way related to FD, but data is conflicting. In the Sørreisa Gastrointestinal Disorder Study, the prevalence of dyspepsia in a community in Northern Norway was found to be stable at 25 to 30% between 1987 and 2004, in contrast to a marked decrease in *H. pylori* prevalence in the same time span (38). Many papers have been published concerning the effect of *H. pylori* eradication in patients with FD/NUD. Conflicting reviews and meta-analyses have been performed, but they seem to show a significant, but very small, effect of approximately 8-10% of *H. pylori* treatment in this group compared to placebo. A meta-analysis performed by Moayyedi et al. evaluated nine studies comparing *H. pylori* eradication to placebo in patients with FD. The absolute difference between the eradication and the placebo group was 8%.
These studies have calculated a number need to treat of 15 in FD (82). Other meta-analyses have come to the opposite conclusion and do not find support to recommend *H. pylori*

eradication to these patients (83).

In a large-scale Danish study more than 10 000 inhabitants (40-65 years) were traced and enrolled to either a *H. pylori* screen and treat group or controls. In a five year follow-up the authors found only a small, but insignificant decrease in dyspepsia score of 4%, but no improvement in quality of life. There was a modest effect on dyspepsia-related consultations and sick-leave days because of dyspepsia, but none on the prescription of what the authors call ulcer drugs. As expected a significant reduction in PUD rate was observed. The costs, however, were higher in the intervention group (84).

In contrast, other studies have not found any clinical benefit of *H. pylori* eradication in patients with FD (85, 86). In another Danish study of patients with uninvestigated dyspepsia comparing "*H. pylori* test and treat" strategy versus empiric PPI treatment, and a combination of the two strategies, the authors did not find any difference in symptoms resolution between the three groups. However, lower cost and endoscopy rates in the "test and treat" group were detected (87). A positive effect in the "test and treat" group should have been expected, as this strategy has the possibility to terminate PUD as would be assumed in approximately 20% of the *H. pylori* positive patients.

As *H. pylori* prevalence decreases the cost-effect ratio will become even more unfavourable.

*Wide scale screening of* H. pylori

As a consequence of data favouring eradication of *H. pylori* at wide indications, studies have been performed to evaluate the effect of a screening program.

A Danish study by Hansen including more than 10 000 patients in a randomized treat vs. control group over 5 years was previously mentioned (84). This study is now succeeded by a twelve year follow-up.

Additionally, there are at least two more comparable studies, both from UK. In Lane's study a significant reduction in dyspepsia related consultations was found, but there was no saving of costs or difference in quality of life between the *H. pylori* eradication group and controls after 2 years (88). This difference was sustained in a 7 years follow up of the same study population, a significant reduction in consultations, but not for dyspepsia-related medication consumption (89). Ford et al. presented a ten-year follow-up study where they found significant reduction in costs, but despite a tendency, no significant reduction in dyspeptic symptom score (90).

### 1.3.4 *H. pylori* and cancer.

The relationship between *H. pylori* and gastric cancer is a matter of concern when selection and eradication strategies are discussed. An age limit of 45 or even 50 years before we need to take detection of gastric cancer into account as discussed earlier and is widely accepted (Figure 1). The other aspect is *H. pylori* as a contributor to gastric cancer. If the consequence of the association between gastric cancer and *H. pylori* is worldwide prophylactic eradication, then the only management strategy we need is again the "screen and treat".

There is wide variation in the incidence of gastric cancer all over the world with an incidence range from 5.2 – 69.7 per 100 000. Russia and the Far East and parts of South America stand highest, while large areas in Western and Central Africa and India have the lowest incidence. A meta-analysis performed by the Helicobacter and Cancer collaborative Group found a combined odds ratio of 3.0 between being H. pylori positive and have gastric cancer. However, the OR increased to 5.9 when *H. pylori* serology collected 10 years earlier were analysed and taken into account. This indicates a delay in the *H. pylori* data of today and the data concerning the gastric cancer development ten years later (91). In a setting of an observed decreasing *H. pylori* prevalence this is a matter of interesting relevance.

For many countries there is a correlation between *H. pylori* prevalence and the age-standardized incidence rate of gastric cancer. We find an increasing incidence of gastric cancer going from US, UK, Italy, Portugal, China and further to Japan, and this correlates with an increasing prevalence of *H. pylori.* On the other hand, if we look at countries like India, Thailand and Gambia, which have high prevalence of *H. pylori*, we find a low incidence of gastric cancer.

The same is also found in other countries and forms a large paradox in the understanding of *H. pylori* as a main cause of gastric cancer. Furthermore, there is wide variance within individual countries; for instance in Malaysia we find a wide range in incidence of gastric cancer between Chinese and Indian population and the Malaysian natives despite the fact that the *H. pylori* prevalence rate is almost the same (92).

This illustrates what is called the African and Asian enigmas of *H. pylori* and gastric cancer, and this must be taken into consideration before too clear conclusions are drawn. Even if these data are burdened with defects, they still represent major objections to the complete understanding of the connection.

It is a challenge to explain the fact that 500 million people over the age of 60 years are infected by *H. pylori*, while "only" 900 000 develop gastric cancer. Less than 0.2% of people at "high risk" are affected by the disease. This is a problem in the context of prophylactic screening and eradication of a whole population in order to prevent gastric cancer. We obviously do not

understand the complexity of the disease, and the epidemiological relationships differ substantially.

One authority (P. Moayyedi, UEGW 2009) concluded that we only understand about 10% of the biology of the progression from *H. pylori* infection to gastric cancer.

Gastric cancer is associated with different risk factors. *H. pylori* plays an important role, but it does not explain the whole picture. Both environmental and genetic factors are of great importance in the aetiology of gastric cancer.

Having a first degree relative with gastric cancer is a risk factor in developing the disease, but the odds ratios vary with ethnic groups and countries, with a range from approximately 2 to 10 (93).

Fruit and vegetables as protective factors have been discussed and studied, but in a recent European study no risk reduction in gastric cancer was found by consumption of fruit and vegetables (94).

Salt consumption is documented to be related to gastric cancer, with an odds ratio >2 between those with highest and those with lowest intake (95). These observations were found regardless of *H. pylori* and smoking, another well-established risk factor. Smoking alone is found to have a hazard ratio of 6.2 (96).

There is no doubt that *H. pylori* are a risk factor for gastric cancer, but the consequence of this knowledge is conflicting and still open for debate.

Fukase et al. published a multi-centre study of 544 patients treated for early gastric cancer in Japan. They were all *H. pylori* positive. It was an open labelled study with two groups; one received *H. pylori* eradication treatment, and the other did not. During an observation period of three years they observed 9/272 patients with metachronous gastric cancer in the *H. pylori* eradicated group, vs 24/272 in the group where no such treatment was given (97). This underlines that *H. pylori* also play a role in later phases of the carcinogenesis and that eradication of *H. pylori* also matters when neoplasia is already detected.

On the other hand, eradicating *H. pylori* reduces the risk of cancer, but in no way eliminates it. A meta-analysis conducted by Foccio et al. of randomized controlled trials comparing eradication with placebo or an untreated group, provides data on the number of gastric cancers in the different groups. 1.1% in *H. pylori* eradication group developed gastric cancer compared with 1.6% in the control group. The risk reduction was significant (98). However, all these studies were performed in high prevalence areas and may not be applicable to others of low prevalence.

In another large multicentre prospective cohort study from Japan (also a high incidence country) PUD patients treated for *H. pylori* infection were compared to a control group not receiving *H. pylori* eradication. More than 4000 patients were followed over 5-6 years, and 56 cases of gastric cancers were identified. Though there was a tendency towards lower numbers of gastric cancers in the *H. pylori* eradicated group, no significant differences were observed (99).

In another study by Wong et al. from China, 1630 healthy carriers of *H. pylori* were randomly assigned to either receive *H. pylori* eradication therapy or placebo. Approximately 40% of participants had gastric changes such as atrophic gastritis, intestinal metaplasia or gastric dysplasia. During a follow-up period of 7.5 years they did not detect any difference in incidence of gastric cancers between the two groups. However, in a subgroup of patients with none of the precancerous lesions above mentioned, none of the *H. pylori* negative participants developed gastric cancer compared to the *H. pylori* positive group (0 vs. 6; p=0.02) (96).

These studies illuminate that this subject is conflicting and the answer in no way obvious even in regions with high prevalence of *H. pylori* and high incidence of gastric cancer.

Another important aspect that must be paid attention to is the inverse relation between *H. pylori* and cancer in the gastric cardia and distal oesophagus. This has been pointed out in many studies (100-102). The ATBC cohort study revealed that the risk of gastric cardia cancer among *H. pylori* infected individuals was about one-third of that among uninfected individuals. This association is also supported by the corresponding decrease of *H. pylori* prevalence while gastric cardia cancer and oesophageal cancer are increasing in Western countries. The mechanism for the inverse relationship is still unclear, but must be taken highly in to concern when the matter of prophylactic eradication of *H. pylori* in order to prevent gastric cancer is discussed.

CagA positivity in the *H. pylori* strains seems to increase the risk of developing gastric cancer. A meta-analysis of 16 studies found twice the risk of developing gastric cancer in individuals infected with a cagA-positive *H. pylori* strain compared to cagA-negative strains (103). The corresponding inverse effect on both gastric cardia cancer and oesophageal cancer and cagA-positivity *H. pylori* was found in a study from US and a case-control study from Sweden (102, 104). Further, in a large-scale study based on 78 985 gastric biopsy samples from USA, the authors concluded that *H. pylori* infection and associated disorders, such as chronic active gastritis and intestinal metaplasia, are inversely associated with Barrett´s metaplasia (105).

Cytotoxin-associated gene A (cagA gene) codes for a toxin (called CagA) which alters the structure of stomach cells and makes them more attachable to the *H. pylori* bacteria which in turn drives the development of more serious gastritis.
Despite the fact that there is a clear relationship between *H. pylori* and gastric cancer, there is today little evidence to support a population-based *H. pylori* eradication policy in order to prevent gastric cancer. Even though some of the studies from very high *H. pylori* prevalence areas support this approach, others do not. This approach would even be more hazardous in areas where both *H. pylori* prevalence and gastric cancer incidence is rapidly decreasing.
A more pragmatic approach with some more support is *H. pylori* eradication in groups and persons in high risk of developing gastric cancer, such as first degrees relatives of patients with gastric cancer and patients with detected dysplasia combined with a positive *H. pylori* status. Better markers to detect patients in high risk should be available and future research probably will bring this forth.
Differentiation between *H. pylori* positive patients with almost healthy gastric mucosa and mucosa with serious gastritis may be one of the key issues in the evaluation of risk of cancer. If the gastric mucosa is healthy the risk of serious gastric disease or PUD is extremely low, and authors have found biomarkers like the European GastroPanel (Pepsinogen I and II, Gastrin 17 and *H. pylori* antibodies) to be highly sensitive and suited to differentiate between healthy and non-healthy stomach in *H. pylori* positive patients (106).
However, in a "Test, Score and Scope" strategy all *H. pylori* positive patients would go further to endoscopy with the possibility to detect those with excessive gastritis, take biopsies and even in the future combine these with other biomarkers to allow individualized eradication therapy.

### 1.3.5 Gastro-oesophageal reflux disease

*Overlap of symptoms*

GORD has to be taken into account in this setting for two reasons: symptoms of GORD overlap with symptoms of dyspepsia and the observed relationship between GORD and *H. pylori.* Pathological reflux is shown to be an element in many patients suffering with FD even if they do not record heartburn as a symptom (75).
Symptoms suggesting reflux and empirical PPI trials are both useful in detecting GORD, but are of low specificity. On the other hand, oesophageal pH monitoring has good specificity, but is lacks in sensitivity (107).

*Endoscopy or PPI in the management of GORD*

An aspect in the natural course of GORD is that the degree of oesophagitis seems to be consistent over decades. A low-grade oesophagitis like Savary-Miller I-II or LA grades A and B are unlikely to develop complications like strictures and ulceration, leaving further endoscopic control unnecessary (39-41). Patients with high-grade oesophagitis, however, are often enrolled in control surveillance; even this is not stated in the Genval rapport. Patients with Barrett's oesophagus are most often detected by endoscopy in GORD patients. Therefore, many authors have advocated for the "once-in-the-lifetime-endoscopy" for patients with GORD, but there is a paucity of data supporting this (108).

Unless alarm symptoms such as dysphagia and unexplained weight-loss are present, it is not necessary to perform endoscopy in young patients with symptoms of reflux. This is now implemented in guidelines for managing GORD (109, 110). If we are going to perform the once-in-a-lifetime-endoscopy in patients with GORD, it would be more reasonable to do it in age groups were where we are more likely to find cancer in early stage, or precursors to cancer, rather than in younger patients.

GORD is now far more common than PUD in the western part of the world. In the Canadian CADET study 43% of patients with uninvestigated dyspepsia had oesophagitis in any degree, while only 5% had PUD (111).

Detection of oesophagitis by endoscopy does not seem to be useful before initiating treatment when the diagnosis is most likely to be GORD. The relief of symptoms is the primary goal of GORD treatment, and the endoscopy will not contribute to the indication.

Therefore, the use of a therapeutic trial of medication with a PPI or an $H_2$ receptor antagonist should be the first step in managing patients with GORD. This has also been addressed in many studies where for instance structured algorithms and questionnaires are compered to endoscopy (8, 112, 113)

This may also be a sensible option as a first step treatment in patients with FD, not least because many patients with FD have pathological gastro-oesophageal reflux as an important element in their condition.

Many papers have compared the "test and treat" strategy to empiric treatment using PPI in uninvestigated dyspeptic patients (62). First step empirical treatment also will include patients with PUD and positive *H. pylori* status. These patients will still have their disease, including the risk for complication it implies. This is unacceptable as long as we know both the aetiology to the disease and have a good treatment to terminate it.

To avoid this it is more favourable to test uninvestigated dyspeptic patients younger than 45 years for *H. pylori,* and to send those who are positive further to endoscopy. Those who are negative can receive empirical treatment with PPI or $H_2$ antagonist. This would also be an adequate option for all the patients with overlapping symptoms between GORD and FD.
As far as the aim of this treatment is relief of symptoms the treatment can be discontinuous and on-demand.

*GORD and H. pylori*

The relationship between *H. pylori* and GORD is of great interest. Many papers report a lower prevalence of *H. pylori* in patients with GORD, but the data are heterogenic and differ with geographic location.
Patients with GORD from the Far East had lower prevalence of *H. pylori* than patients from the Western countries, despite a much higher prevalence in the general population (114, 115). On the other hand, systematic review of the literature until 2003 found no evidence to indicate that *H. pylori* eradication in duodenal disease provokes reflux oesophagitis or worsens heartburn, so the data here are also conflicting (116, 117).
A possible pathophysiological explanation may be found in the different kinds of *H. pylori* gastritis. Gastritis located in the antrum is associated with higher acid output and may lead to duodenal ulcers and erosive duodenitis, while gastritis in the corpus, or general widespread gastritis, is associated with atrophic gastritis, dysplasia and a subnormal acid output.
This was illustrated in a study by Abe et al where they found *H. pylori* prevalence of 71% in the asymptomatic Japanese population, compared to 30%, 16% and 0 % in patients with oesophagitis, short segment Barrett's and long segment Barrett´s respectively (118). This is in good agreement with earlier reports both from the eastern and the Western part of the world (119-124). These studies suggest that it is not only the presence of *H. pylori*, but the severity and pattern of the gastritis following it, that determine the acid secretion and hence GORD (125).
While this data, together with epidemiological data, clearly suggests an inverse relationship between *H. pylori* and GORD, the question is still basically unsolved. However, like the same inverse relationship between *H. pylori* and cancer in oesophagus and gastric cardia, this possibility should call for caution before large-scale eradication of *H. pylori* is brought into practice.

*PPIs and* H. pylori *infection: a hazardous combination?*

Yet another conflicting question is whether we should eradicate *H. pylori* before long-term PPI treatment is instituted. PPIs and *H. pylori* infection interfere significantly with each other. The acid-reducing effects of PPIs differ significantly depending if the patients are *H. pylori* positive or not. For example, in a *H. pylori* infected subject, omeprazole 20 mg will lift the median intragastric pH to 5.5, while it will fall to 3.0 after eradication of *H. pylori* (126-131). The mechanism for this is thought either to be associated with the gastritis produced by *H. pylori,* or to acid neutralizing substances produced by the bacteria. This may play a role in the observed inverse relationship between oesophagitis and *H. pylori*. Studies have detected a negative effect of *H. pylori* eradication in patients with GORD and oesophagitis with respect to both symptoms and healing of oesophagitis (132, 133). *H. pylori* eradication seems to result in a more robust reflux disease.

Studies have found that eradication of *H. pylori* in patients with reflux oesophagitis treated with PPI reverses the gastritis and induces regression of gastric mucosal inflammation and atrophy (134). However, it seems as though *H. pylori* gastritis induced/worsened by PPI differs from the gastritis occurring spontaneously in *H. pylori* infected patients and which is associated with progression to gastric cancer. It may be that PPIs do not promote gastric metaplasia (134-139). In a review from Delaney and McColl published in 2005 the authors found no indication to test for or treat *H. pylori* infection in patients receiving treatment for GORD. They also found that the data concerning eradication before long term PPI treatment was unclear and stated that this could not be recommended (115).

Although PPIs affect - and may accelerate - the gastritis caused by *H. pylori,* and thus provoke atrophic gastritis (which can be a precursor to cancer), there is no proof that this really increases the risk of cancer (137, 140). The study of Kuipers et al. published in 1996 gave reason to worry about the danger of long-term use of PPI in *H. pylori* positive patients, because the authors reported an accelerated development to atrophic gastritis. This caused experts to recommend *H. pylori* eradication before long-term PPI therapy is instituted. However, this study has been widely criticized because of methodological problems in the study design: for instance, the FDA Gastrointestinal Drug Advisory Committee have invalidated the conclusion (FDC Report. 11 nov. 1996: Proton pump inhibitor relabeling for cancer risk not warranted). In a leading article in Gut in 2006, Kuipers also concluded that, by that time, there was no proof supporting that PPI use in *H. pylori* positive patients would increase the risk of gastric cancer (140).

On the other hand, continuous use of PPI leads to hypergastrinemia and its potential long-term dangerous consequences, such as ECL cell hyperplasia and its role in the carcinogenesis. This

has been supported by data detecting that that a higher proportion of gastric cancers seem to be of neuroendocrine origin than had been realized earlier (141, 142).

Unlike the oesophagus, the gastric cardia is an area where both *H. pylori* and pathological reflux may play a role in the development of inflammation and complications such as intestinal metaplasia. However, the role of intestinal metaplasia in the cardia is uncertain and it is difficult to directly compare it to intestinal metaplasia in the setting of Barrett's oesophagus. Its association with cardia cancer is uncertain, and estimates range from a very weak association up to a more robust risk, similar to that which is known for Barrett's oesophagus. Available data suggest it to be more likely as low as intestinal metaplasia in the rest of the stomach with an OR of 2-3 (143, 144).

In conclusion, there are data and arguments both for and against *H. pylori* eradication prior to long term PPI treatment. It is concerning that PPIs seem to provoke a proximal gastritis, which may have a higher risk of developing further to gastric cancer than atrophic gastritis and intestinal metaplasia do. Data supporting the development of cancer in this setting is still missing, and an eradication policy in this setting is not supported (145).

In a study by van Soest et al. concerning compliance in patients taking PPI over time, they found that one-year persistence was only 31% in patients using PPI for GORD. Highest adherence was found in patients with Barrett's oesophagus and high grade (LA) oesophagitis. Half of all patients used PPI on demand and lowest adherence was seen among those patients with GORD without endoscopic verified oesophagitis (146).

The use of PPIs in patients in need of NSAIDs but at risk of gastroduodenal complications due to this medication adds to the use of PPIs in addition to that of patients suffering from GORD. This seems to be an increasing indication for PPI consumption. In the study from the Netherlands, 21% of the PPI prescriptions were given as a gastric cytoprotection. However, approximately 75% of these patients did not continue the PPI medication (146). Both these observations of discontinued PPI consumption undermine the arguments for a systematic *H. pylori* eradication before long term PPI treatment.

If we should prescribe *H. pylori* eradication to all patients receiving long-term PPIs, a substantial number would then have been given to no effect.

### 1.3.6 Epidemiology of *H. pylori* and antibiotic resistance

As shown above, the only consistent indications for *H. pylori* eradication not burdened with divergent data are gastric and duodenal ulcers, MALT lymphomas and gastric cancer in the early stage. The rest of the widely used indications are based on conflicting data with divergent

conclusions. In a setting with such vague foundation all aspects need to be taken in to account. An aspect we especially need to look into in these discussions is the ecological effect of large scale antibiotic consumption. Patients with FD and GORD make up 30-40% of the population, and some 20% of these must be expected to be *H. pylori* positive. Adding the indication of gastric cancer prophylaxis and long-term PPI use to this list, we consequently end up with nearly all *H. pylori* positive persons. Where each cure consists of 2-3 broad spectrum antibiotics, and up to 20% fail to clear the bacterium after one cure, this will probably make a substantial contribution to the problem of multi-resistant bacteria.

*The history of* H. pylori

*H. pylori* seems to have been in symbiosis with humans for nearly 60 000 years, and like humans has been spread out from Africa to the rest of the world. *H. pylori* consists of many strains. Falush et al. assigned 370 *H. pylori* strains to four main population groups, with two being divided further into different subgroups, altogether making seven main groups. The geographical location of different subgroups corresponded to major events in the settlement history of humans, like the colonisation of America and Polynesia (147, 148).

This is different from the genetic diversity seen in humans, where the genetic differentiation increases with geographic distance from the origin. Migration from one area to another seems to increase genetic diversity in the "new" population while *H. pylori* seems to hold on to its original pattern (149). This will probably create many different bacteria-host constellations and might be of significance for some of the unexplained observations, for instance the variation between *H. pylori* and gastric cancer mentioned earlier**.** *H. pylori* may have played an important role for humans all through evolution, and may probably still do.

H. pylori- *a useful symbiosis.*

A distinctive property of the bacteria is the urease activity, the ability to break down urea and thereby re-circulate nitrogen in the body. This is a very important mechanism in protein production and of great impact in periods and areas with lack of food. The ability to take care of nitrogen has been estimated to make 6-7 g protein a day, which is 12% of minimum protein intake a day for human beings according to United World Food Program. In a population of one billion people suffering of malnutrition (2010) and most of them colonized by *H. pylori*, this ability can really make a difference and accounts for an estimated two million tons of protein (150).

The ability to break down urea is coded for by 9 different genes in *H. pylori*, which also shows

the phylogenetic importance of it (151). These sides of the story of *H. pylori* should also urge caution in the question of eradication.

H. pylori *prevalence and the socio-economical issues.*

As pointed out earlier and in Paper III the prevalence of *H. pylori* is decreasing in Western countries (38, 152). Prevalence studies in Japan ranging over 17 years have also found a fall in prevalence from 70% to 50% (43). However, worldwide there is an extreme variation in *H. pylori* prevalence, ranging from 90% in a study from east Siberia to 7.5% from a large-scale central laboratory, Caris Life Science, Irving, based on biopsies (105, 153). The decreasing prevalence is probably first of all a consequence of improved hygiene and sanitation, especially during childhood, and the socio-economic development allowing this, together with widespread eradication by antibiotics (154).

Even the transmission of *H. pylori* is not fully understood; human to human spread both through oral-oral and faecal-oral route seems plausible and is supported by different studies (155).

Studies in siblings have reported one *H. pylori* positive sibling to be a strong predictor for the other siblings to be positive (156, 157). In the study of Muhsen et al., Israeli Arab children from three different villages were followed up for 3-4 years. The authors found the same co-variation between siblings, but also found an increased probability to be infected during the follow-up period if one sibling was *H. pylori* positive. The latter study also found that *H. pylori* prevalence correlated with the socio-economic status of the village. This is also in accordance with several other studies that have detected a correlation between *H. pylori* prevalence and multiple parameters, all expressing socio-economic development of the examined society (158-161). These studies are also in accordance to the co-variation of *H. pylori* prevalence and the socio-economic axis of the world. Prevalence of *H. pylori* increases with large number of siblings, low education, number of people per room, the use of well water, housing in a street without pavements, and in houses without flushed toilets.

Conditions associated with poor sanitation and overcrowding are thus risk factors for *H. pylori* infection and express all aspects of poverty.

*Resistance development in* H. pylori

The usual first line eradication regime consists of a dual combination of metronidazole, clarithromycin or amoxicillin together with a PPI. Previously, the cure often contained bismuth, but this is now used mostly in second line quadruple treatment (162). However, *H. pylori*

resistance to the key antimicrobial drugs is a rising problem.

Resistance to metronidazole is the most common and well-known, with consistent reports of 35% of *H. pylori* strains being resistant (163). This is the situation for the industrialized countries, and has been stable for years, but in developing countries the resistance rate is much higher; in some areas nearly all *H. pylori* strains have developed metronidazole resistance. This is probably due to the extended use of the drug in treatment of parasites (162) as well as other indications.

Clarithromycin resistance has been considerably lower and has been reported as approximately 10% in Western countries, but recently Megraud et al. in a paper concerning *H. pylori* resistance in Europe, found clarithromycin resistance to be 17.5% overall, with a corresponding 14.1% resistance to levofloxacin (163). Again, the resistance rate to macrolides in the developing countries is much higher and seems to vary between 25-50%.

A very important observation in the paper from Megraud was the variation of clarithromycin and levofloxacin resistance rate between Western/Central and Southern Europe (>20%) and the Northern European countries, where it was found to be below 10%. The authors showed a significant positive association between outpatient antibiotic usage and the level of primary resistance observed in *H. pylori* to these key antimicrobial agents.

A study performed by McNulty and co-workers tested the antibiotic susceptibility of *H. pylori* from biopsy specimens from two endoscopic units with local laboratories performing *H. pylori* culture. Additionally, they collected data from the Helicobacter Reference Unit (HRU), a central laboratory receiving biopsy specimens from the whole of the UK. These three microbiological laboratories are in fact the only three undertaking *H. pylori* culture and represent 95% of the susceptibility data from England and Wales.

*H. pylori* samples were cultured in 6,4% of all 2063 patients from the two hospitals, indicating a low prevalence of *H. pylori* in those regions, and the authors conclude that *H. pylori* now is uncommon in dyspeptic patients (164). This is also in accordance with the observations performed by Asfeldt and co-workers in the Sørreisa II study (38). McNulty found a significant difference in *H. pylori* resistance to clarithromycin, metronidazole and quinolone, respectively, between the HRU (68%, 88%, 17%) and the cultures analysed at the two hospitals, (18%, 43%, 13% from Bangor hospital, and 3%, 22%, 1% from Gloucester). The specimens analysed in the HRU were mostly treatment failures, which was not the case in the local laboratories. The study correlated these to antibiotic histories taken in 132 patients from Bangor and Gloucester, and found that each earlier course of clarithromycin, metronidazole or quinolone increased the risk of resistance to 50%, 60% and 80%, respectively. This exemplifies both the vague

correlation between the dyspepsia and *H. pylori,* as well as the hazards of using broad spectrum antibiotics where the effect is dubious.

Clarithromycin has been widely recommended as first-line treatment together with metronidazole and PPI, and the eradication rate was initially 90%. With a resistance rate above 20% the success rate will be as low as 60-70% (165). This will again increase the numbers for second- and third-line therapies. The situation seems to be the same with quinolone, an often-suggested alternative to clarithromycin. Even for quadruple regimes the eradicating effects have been recorded to be to be approximately 80%.

### 1.3.7 Antimicrobial resistance as a health challenge.

*Association between consumption of antibiotics and microbial resistance*

During the recent years there has been a growing concern about antimicrobial resistance in general as a major health problem. Antibiotic consumption is increasingly recognized as the main reason for resistance (166).

The most useful indicator is probably "Consumption of antibiotics for systemic use" expressed in DID (Defined daily doses (DDD) of an antibiotic per 1000 inhabitants per day), since this parameter is most likely to indicate the size of pressure driving antibiotic resistance and in turn is highly relevant for public health (42). Despite methodological problems in estimating the total use of antimicrobial medication exactly over time, it clearly seems both to increase and change towards a pattern of extended use of broad-spectrum, modern drugs (166). In a report from the National Centre for Antimicrobials and Infection Control, Denmark, it was found that the combination of penicillins (including beta-lactamase inhibitors), cephalosporins, carbapenems and fluoroquinolones continued to increase both compared to earlier data (167) and in the period 2001 to 2007 from 19.2% to 38.2%. At the same time, an increasing resistance towards the same antibacterial agents was observed (168).

In the same way as *H. pylori* resistance seems to reflect previous antibiotic treatment (164), many papers report the same observations in the other areas of infectious disease medicine, like treatment of infections in the urinary and the respiratory tract. A systematic review and meta-analysis presented by Costello and co-workers and based on 24 studies provides strong evidence for the association between the prescription of antibiotics in primary care and microbial resistance at sites as different as the respiratory tract, the urinary tract and the skin. The effect is strongest the first months after an antibiotic course, but can be observed for up to one year. This effect represents a residual in the population, and is an important driver in the

high endemic levels of antimicrobial resistance in the community (169). The group also found evidence for a dose-response relationship between trimethoprim and amoxicillin, both much used in primary care and of high relevance in *H. pylori* discussion.

Theoretically, there can be a methodological problem in these kinds of studies with confounding and reverse causality. If bacterial samples are only taken if the infections do not respond to the first line treatment, then the retrospective case-control analysis will be strongly associated with the preceding antibiotic course that did not cure the disease and therefore does not reflect the naïve situation. However, the prospective studies in the meta-analysis eliminated reverse causality as an explanation for the observed increase in resistance after an antibiotic course, and the prospective results were in accordance with the other studies.

This meta-analysis and the underlying studies clearly underline that all use of antibiotics, regardless of indication, will increase the residual of resistant bacteria in a community, and hence also contribute to the need for increasing use of more broad-spectrum antibiotics in the communities observed in the entire industrialized world.

The authors concluded that the only way to avoid the vicious cycle of resistance leading to the ever greater use of more powerful broad spectrum antibiotics is to avoid their initial use whenever possible (169).

This review is also in agreement with the concern of the experts involved in this field.

In a paper from the European Surveillance of Antimicrobial Consumption (ESAC), participants in an expert consensus meeting from 12 countries were asked to score the relevance of 22 potential quality indicators with respect to antimicrobial resistance, patients health benefit, cost effectiveness and public health policy makers. 12 of the 22 indicators were found useful and relevant to evaluate quality of antibiotic usage and consumption (170). These indicators scored higher on the dimensions “Resistance reduction” and “Public health policy” than they did on “Patients health benefit” and “Cost effectiveness”. This tells that these experts were more preoccupied with the increasing consequences of antimicrobial resistance than they were with the individual patient’s health benefit.

In the context of *H. pylori* and the burden of papers concerning the effect of *H. pylori* eradication in patients suffering of FD, the focus has almost entirely been to “patient’s health benefit” and “cost effectiveness”. The aspect of microbial resistance has only been summary mentioned, and then, for the most with respect to resistance in *H. pylori*, not as a general, comprehensive problem. It may be necessary to revise this now in the context of the alarming levels of microbial resistance.

# 2. Aims of the study

In this project we wanted to explore if the theses about dyspepsia could be combined and taken into account in a way that could save endoscopies by excluding negative examinations and still avoid antibiotic overuse in a population of young dyspeptic patients.

## 2.1 Paper 1:

We wanted to explore a selection strategy where we also would take a Scandinavian restrictive attitude to antibiotic use into account. Because of this attitude the "Test and Treat" policy has not been adopted as an official guideline in Norway (171). On the other hand, the potential of *H. pylori* testing prior to endoscopy has not been exploited.

According to predefined selection criteria we intended to define risk groups prior to endoscopy in a way in which the vast majority of significant findings would be found in one group.

## 2.2 Paper 2:

In this part of the study we performed a one-year follow-up to investigate which elements in their management a year earlier the patients considered valuable and a reason to improvement, if any. A main point of interest was whether the patients diagnosed to have FD regarded the endoscopic procedure and the following information to be valuable if no medical treatment was prescribed.

## 2.3 Paper 3:

If *H. pylori* screening tests are used prior to endoscopy the test properties of sensitivity and specificity are of the greatest importance and should be properly validated before recommendation.

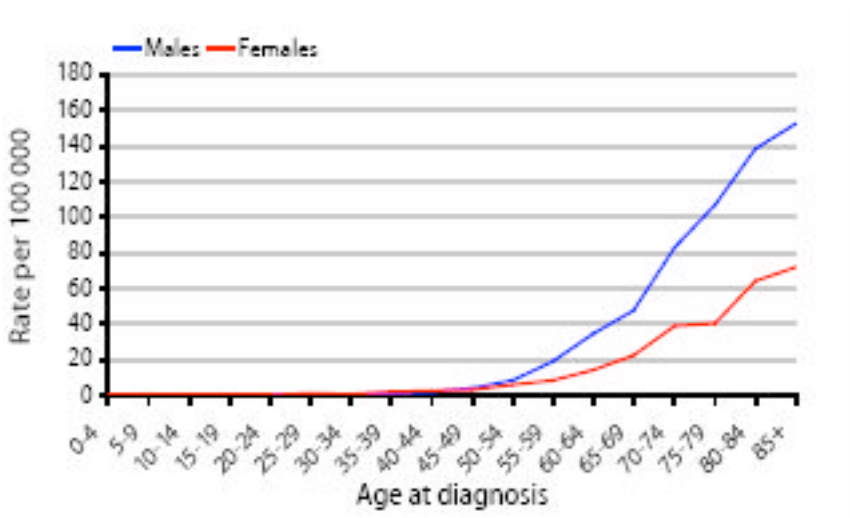
When the present study was initiated the test and treat strategy guidelines recommended the use of rapid serological tests. These are still recommended under that strategy. Therefore, we wanted to one compare one rapid test to a well-established EIA serological method, by using an accepted Gold standard defining *H. pylori* status (172). As all patients in the study proceeded to endoscopy, we also were able to make theoretic calculations of the results using other *H. pylori* tests. It was also desirable to perform these calculations in a setting of decreasing *H. pylori* prevalence.

# 3, Patients and methods

All patients between 18 and 45 years referred to upper-GI endoscopy in the endoscopy units either in Harstad County Hospital (Now University Hospital of North Norway, Harstad) or in Nordland central hospital in Bodø (now Nordland Hospital, Bodø) were considered for inclusion.

The age limit of 45 years was chosen to avoid the problem of gastric cancer.

Figure 1
The figure show age specific incidence of gastric cancer in men and women between 2000 - 2004 in Norway. Based on data from the Norwegian Cancer registry.




Data from the Norwegian Cancer Registry

Figure 1 shows age specific incidence of gastric cancer in Norway and is well in accordance with data from the western countries otherwise.

Approximately one week prior to endoscopy the patients received a letter with a request to participate in the study, written information describing the study, and a questionnaire.

In the endoscopic unit a study nurse addressing participation met the patients. If the patient agreed to be enrolled in the study, the nurse looked over the questionnaire and made sure it was complet. Blood samples for haemoglobin measurement and an EIA based serological test for *H. pylori* were collected. The Helicobacter Pyloriset EIA-G (Orion Diagnostica, Espoo, Finland) was used to analyze this. The study nurse also performed a whole blood rapid serological test using the “Pyloriset Screen” test (Orion Diagnostica, Espoo, Finland).

The exclusion criteria are presented in paper I.

After the pre-endoscopic examination the patients were sent on to the gastroenterology

consultants without any other information than the referral letter.
After an ordinary medical report, endoscopy was performed. All findings and treatment prescriptions were recorded. This set-up was as close up to normal daily practice as possible. Experienced consultants performed all endoscopic examinations.
Immediately after the examination the consultant recorded their clinical diagnose on the form and reported whether the patient suffered from PUD, GORD, NUD or something else, followed by a more detailed specification.
This differentiation was the basis for the one-year follow-up examination where we wanted to determine how useful the endoscopic examination was, as evaluated by the patients themselves in the different diagnose groups. The study also evaluated the therapeutic decisions that were a direct consequence of the endoscopic findings, defined as clinically relevant endoscopic findings.
As five different H. pylori tests were collected, including those forming the recommended gold standard, and all patients went through endoscopy, we also had the opportunity to both evaluate the two serological based tests, and also to recalculate the material if tests of better performance had been used.

## 3.1 The questionnaires:

We used two questionnaires in the study, one as part of the pre-endoscopic examination and the other at the one-year follow up.
The main purpose of the questionnaire was to collect information necessary to allocate the patients into the different risk groups. It recorded information about use of NSAIDs together with unintended and unexplainable weight loss, which is an alarm symptom.
It also contained questions about dyspeptic symptoms. These questions simulated the questions the general practitioners normally ask the patients during a consultation because of dyspepsia and a referral to endoscopy is considered. These simple questions should give information on whether the patients' symptoms indicated reflux or dyspepsia in the strict definition (Rome III). Questions to explore the duration of symptoms and their impact on daily life were included and further, if the patients worried about cancer as an underlying cause to their symptoms.
The questionnaire used at one-year follow-up (paper II) was based on that used at inclusion. It was modified to follow the symptom development and the patient's own evaluation of symptomatic improvement.
The most important subject addressed in this paper was to objectify the therapeutic

consequences of the endoscopic findings one year earlier. In which cases was the finding by endoscopy the clue to making the right therapeutic decisions?
Further, we also wanted to explore the reassurance value of a negative endoscopy, as evaluated by the patients themselves. Most interesting here was thought to be the score from the group diagnosed to have FD/NUD, where the examination did not lead to a specific treatment, like *H. pylori* eradication etc.

## 3.2 Criteria and definitions

In paper I the patients were allocated to three different risk groups based one the pre-endoscopic examination. The criteria were:
Group A: Positive *H. pylori* EIA test, use of NSAID by definition, weight loss or anaemia.
Group B: None of the group A criteria.
Group C: None of the group A criteria, but a reflux related dominating symptom
True *H pylori* positive status: *H pylori* culture positive, or a histological examination positive for *H pylori* and a positive rapid urea test.
Clinically relevant endoscopic finding: Conditions where endoscopy was mandatory to make the correct diagnosis and hence, was necessary to provide the appropriate treatment like *H. pylori* eradication to patients diagnosed to have ulcers.
Weight loss: 3 kg or more loss of weight during the last 3 months.
Regular NSAID use: 50% or more of DDD of an NSAID during one of the 4 last weeks.
PUD: Active ulcer in the stomach or the duodenum in an *H. pylori* positive patient, or erosive duodenitis or a deformed bulb combined with a positive *H. pylori* test.

## 3.3 Ethical aspects

The study was performed according to the Declaration of Helsinki and approved by the Regional Ethics Committee at the University of Tromsø.
In the European guidelines, H. pylori eradication is recommended when a patient with NUD is *H. pylori* positive. A positive *H. pylori* status is also associated with an increased OR to develop cancer. It is therefore problematic that the patients in this study were systematically screened for *H. pylori*, since most of those who were positive were not offered treatment during the study.
However, all patients diagnosed to have PUD received treatment against *H. pylori,* and all

patients were informed that their results were sent in full to their general practitioners. The well-documented indications to treatment used in daily practice in Norway at the time of enrolment were followed in the study.

We took six specimens from every patient. The direct risk of complication associated with the study procedures was low, but a potential harm is always connected with collecting biopsy specimens, even if this is very small (173).

However, biopsies were deemed absolutely necessary to obtain a true *H. pylori* status of the patients, and we considered the value of the specimens high enough to justify the potential risk. The patients were excluded if they had used anticoagulation medication prior to endoscopy or, if possible, medication was discontinued for some days before endoscopy.

Screening methods for selecting patients for further examination or treatment always imply an ethical aspect. No available test has 100% sensitivity and specificity and hence, will overlook some patients where indication for further treatment is present.

As all patients enrolled in the present study should proceed to endoscopy, this dilemma was avoided. However, when the selection strategy tested in the study is escalated into daily practice, it will be burdened with this problem.

The screening method used in any selection strategy must have excellent test abilities to keep the number of false negative and false positives as low as possible. This aspect is addressed in paper III.

The selection strategy used in this study is presented as an alternative to the "Test and Treat" strategy, which is currently in widespread use. "Test and Treat" can lead to overuse of antibiotics, which poses an ethical problem in addition to the medical and ecological problems previously discussed.

Another problem in the "Test, Score and Scope" strategy is that it is not designed to detect those few patients with high-grade oesophagitis and Barrett's oesophagus as well. However, the incidence of high grade oesophagitis is very low and, moreover, there are currently no established endoscopic surveillance programs neither to detect it nor to follow up these patients when the condition is detected (40). A strategy to screen all patients with any degree reflux symptoms with endoscopy in order to detect those with Barrett's oesophagus has not been proven to be worthwhile.

# 4. Results

## 4.1 Paper I

The applied selection strategy was able to detect nearly 90% of the clinically relevant endoscopic findings allocated to one of the predefined groups. This was found in group A, accounting for 45% of the patients. The prevalence of these findings in group A, B and C were 20.1%, 2.4% and 1.6% respectively. This means that 55% of endoscopies could be avoided with a modest number of pathology overlooked. Overlooked pathology in group B and C corresponded to the test abilities of the EIA serological test used in the study.
Because of the great overlap of symptoms between dyspepsia and GORD, defining a group based on the predominant reflux symptom (group C) does not seem to be useful. A therapeutic trial with PPI is a better approach than endoscopy in this group.

## 4.2 Paper II

Patients treated for PUD with *H. pylori* eradication was the group with the significantly highest score of complete relief or considerable improvement of symptoms, compared to patients with NUD or GORD with and without oesophagitis.
Among the NUD patients reporting symptom improvement, 50% recorded changes of lifestyle/life situation or change in diet as reason for improvement. Only 16% recorded the endoscopy and the following information about the benign nature of the condition to be of importance in improvement. The two GORD groups, with and without oesophagitis, recorded differently from the NUD and PUD groups, as use of acid reducing medication accounted for nearby 60% of reason for improvement. Interestingly, about 30% recorded change of life situation and diet as the main reason for improvement, despite prescription of acid reducing medication. However, the self-reports of the two GORD groups were almost identical.
This underlines the conclusion from the paper that the endoscopic presence or absence of oesophagitis is of negligible value to make the right therapeutic choices.

## 4.3 Paper III

Paper III compares different *H. pylori* tests and shows how tests with better test properties would have performed more favourable in the present study.
The sensitivity of the tested selection strategy could have been improved from the actual 89% to approximately 95% or even more by using a C-UBT or an *H. pylori* faecal test. The importance of these findinga increases when one considers populations with declining *H.pylori* prevalence.

# 5 Discussion

## 5.1. Methodological issues

The study was performed at two different centres. This may raise the question of conformity - whether the information to the patients, test procedures and indication for therapies were appropriately standardized between the two centres. In order to address this problem we arranged study meetings during planning, before study start, and early during the enrolment phase. The same supervisor educated the study nurses at both laboratories.

The strategy evaluated in the present study concerns patients with uninvestigated dyspepsia, and it may be a matter of discussion whether the patients in the algorithm should have been recruited from the general practitioners before a decision on referring the patients was made. In the present study we collected participants from patients referred to endoscopy. This design represents a selection based on a certain degree of symptoms and hence, does not include the dyspeptic patients not sent to endoscopy by the general practitioner. Therefore, it may be an objection to the study that it does not exactly examine the population it pretends to. On the other hand, collecting the patients from the general practitioners on the earlier level of the decision process is also from experience difficult both with respect to reliability of the enrolment of study subjects, and bias. Further, a measure in the study is endoscopies saved, and therefore, patients referred to endoscopy probably would be the most appropriate group to study.

### 5.1.1 Weakness of the questionnaires

In the very initial phase of the study we did a pilot evaluation and discovered two important problems in the questionnaire. Many patients recorded use of NSAIDs, but had consumed no more than a few tablets, weeks beforehand. Many studies avoid this problem by using the term “regular use of NSAIDs”, but without defining the term. We did not find a good definition or an established cut-off limit to categorize a patient as an NSAID user.

Therefore, we chose the definition presented and in paper I. However, it might be a matter of discussion which cut-off limit would be most appropriate in the context of dyspepsia. We analyzed the consequences of the chosen cut-off by looking at the two extreme situations: all patients recording any consumption of NSAIDs despite the number of tablets, and not to include NSAID users at all in the risk group A. The results are referred in paper I and indicate

that the chosen definition is reasonable. However, as a method this is dubious and should have been validated prior to the study and not during it.

It is probably not possible to draw a secure limit of NSAID dose, but the infrequent, sporadic consumption of low potency NSAIDs due to menstrual pain and headache is hardly of relevance. However, while the risk of GI complications related to use of NSAIDs seems to be equal during the time of exposure, the risk increases with the dose given. This might support the chosen cut-off limit in the present study (68, 72, 174, 175).

The other problem we had to address in the questionnaire was the definition of weight loss we had chosen. We defined it as unintended loss of more than 3 kg during the last 3 months. This definition was not related to the patients' normal weight and a patient of 55 kg would then in fact have twice the loss of weight related to normal as a patient of 110 kg would.

To avoid this problem the correct definition would be weight loss of 5% or more of initial body weight during the last 3 months.

We also found *unintended weight loss* to be insufficient as many of the patients recording weight loss by definition, had plausible explanations to it. This could be an ongoing divorce, illness in close family, or a number of other causes so obvious that they should hardly count as an indication to endoscopy. This problem should have been detected earlier and led to a follow-up question.

Although this lead to an overestimation of the group where endoscopy was recommended according to the definition, it did not contribute to falsely high numbers of endoscopies saved. On the contrary - the endoscopy group (group A) could have been further reduced by a more strict definition of unintended and unexplainable weight loss.

In 2010 Bai et al. published a paper addressing alarm symptoms, which utility and ability to detect malignancy has previously been uncertain. They compared endoscopic findings with alarm symptoms such as dysphagia, weight loss, GI bleeding and vomiting in a material of 100 000 consecutive patients who underwent upper-GI endoscopy.

The authors reported a pooled sensitivity of 13.4 % and specificity of 96.6 %. The sensitivity of weight loss predicting a serious condition was only 9%. The only feature that modestly suggested malignancy was dysphagia with a sensitivity of almost 30%. (176). This is strongly in accordance with the impression we had about weight loss during enrolment in our study and emphasises our considerations about recording weight loss.

A main objection to both questionnaires is their lack of validation, such as the validation of the Glasgow Dyspepsia Severity Score (177). To use a validated questionnaire is a prerequisite to compare different study populations and hence compare different results (178). The Glasgow

Dyspepsia Severity Score has as its main focus the severity of the symptoms and not their composition. It does not pretend to distinguish GORD from symptoms related to the stomach and upper gut.

Other scoring systems directed against GORD like FSSG and QUEST have appeared in recent years (179-181)

The reason why we used our own questionnaire instead of a validated set in the pre-examination was to make the study situation as close to the situation in the family physician's office as possible. The different questionnaires were made in collaboration with two general practitioners, and in fact do not differ much from those in the above-mentioned validated questionnaires.

GORD, dyspepsia and irritable bowel syndrome (IBS) are common conditions and therefore statistically will occur simultaneously in some patients. It is commonly observed in clinical practice that these syndromes overlap more often than prevalence alone would predict, and this is supported by recent studies (182-185).

The symptom questions in our questionnaire are presented in paper I. The first questions are typically connected to dyspepsia and ulcers while the 3 last are related to GORD and are the same questions defining GORD in a lot of papers.

Additionally, the patients were asked to record which one of these symptoms was most dominating.

This was thought to give a good indication of whether a patient suffered with dyspepsia because of PUD/NUD or because of GORD (40, 75, 186).

The results of the symptom questions did not influence the main results because it did not contribute to allocation of the patients to the high-risk group (group A) except for the questions concerning weight loss and NSAID consumption. The main aim of the study was to define the group where endoscopy should be recommended and would prove useful.

However, we wanted to address the question of symptom overlap and evaluate to what extent a clear group of patients with GORD could be defined, and whether this was useful at all.

The symptom questions should have been more precise in defining location of the pain and the questionnaire would have been more complete if it included questions about bloating and early satiety. By doing so, defining the FD group would have been more consistent and easier to compare to other studies. The group could have been defined according to the Rome III criteria.

The lack of definition related to symptoms is probably a more important disadvantage in paper II, where different diagnosis groups are examined in a one-year follow-up. The patients were asked about degrees of improvement and – if improvement had occurred - to attribute a reason

for it. In this part of the study it is a great deficiency that the NUD/FD group, being the main subject to study, is not defined by a validated scoring system. Our study defines NUD/FD by the clinical assessment made by an experienced senior consultant in gastroenterology, based on referral information, the case history told by the patients themselves, and a negative endoscopy. Again, this was done to create a study situation simulating the patients' flow through the system and the diagnostic process in daily practice as far as possible. A diffuse delineation between NUD and GORD can be a bias in the study because of the expected effect of medication in the GORD patients. However, this is a problem demonstrated in many studies (184, 187) and a significant portion of NUD patients will take advantage of PPI medication anyway.

In the NUD group in the follow-up study, 11 of 123 (9%) patients had recorded their main symptom in the pre- examination questionnaire to be heartburn, regurgitation or aggravation of symptoms when bending forward, thus suggesting GORD. According to study definition these patients were allocated to the GORD group, but after examination by the specialist were interpreted as having NUD. The reason for this is unclear, but they probably have weighted their symptoms in a different way in dialog with the gastroenterologist asking follow-up questions.

### 5.1.2 Use of scoring systems during endoscopy

A well-known problem in endoscopic studies is the inter-observer variation between gastroenterologists (188, 189). This emphasises the need for standardized scoring systems.

In the recording of gastritis the consultants reported whether gastritis was present or not.

It would have been far more precise and informative if the Sydney classification system had been used (190-192).

Two specimens were taken for histological examination during endoscopy, but these results were not systematically compared to the endoscopic diagnosis of gastritis, which could have given an estimate of the sensitivity and specificity of visual-based diagnosis.

On the other hand, the finding of gastritis was not a notable finding in the study procedures, reflecting its lack of notability in the daily routine (unless gastritis alone combined with a positive *H. pylori* status is considered as indication for eradication therapy).

However, in an evaluation of the Sydney classification system the authors concluded that the correlation between endoscopic based diagnosis of gastritis according to the Sydney classification, and the histological diagnosis of gastritis, was very low. The endoscopic diagnosis was given inappropriately, and the authors suggested that the term gastritis should be

reserved only for the results of histological examinations (191). This corresponds with the Sørreisa I study, where an overwhelming proportion of the persons without GI-symptoms were found to have gastritis by endoscopy.

This is also in good accordance with studies showing that approximately 50% of patients without dyspeptic symptoms do have gastritis while about the same share are found to have endoscopic gastritis in those recording symptoms (193, 194).

Hence, the significance of endoscopically diagnosed gastritis is unclear, and it should be considered with caution as an indication to any kind of treatment.

Another weakness of the study is the choice of the Savary Miller (S-M) scoring system. The S-M grading system was used to describe oesophagitis (195, 196). We used the modification of Little where grade I is defined solely as erythema (197, 198).

However, S-M grade I based on solely erythema is very subjective and in the present study the consultants recorded oesophagitis S-M grade I in more than one third of all included patients, despite risk groups and symptoms. We suppose that S-M grade I, according to Little has a specificity not suitable to studies. Therefore, we chose to exclude S-M grade I in the further analyses.

The extremely low sensitivity of S-M grade I is published in a recent study from Genta et al where endoscopic reported oesophagitis graded by S-M or LA systems were compared to histopathology findings. Erosive or ulcerative oesophagitis changes were detected by the pathologists in only 1.4% of the biopsies from patients reported by the endoscopic operator to have oesophagitis S-M grade I (199). Many authors have criticized the S-M grading system because of significant inter-observer variations and diversity in interpretation. Instead, they have suggested that the MUSE (metaplasia (M), ulceration (U), structuring (S) and erosions (E)) or the Los Angeles (LA) system should replace the S-M grading system (107, 189, 200, 201).

By leaving out grade I in the analyses we probably have reduced this problem.

## 5.2 Which selection strategy is then to be chosen?

The strategy we choose to follow will highly depend on how we weigh the different theses above against each other. If we draw the conclusion that eradication of H. pylori ought to be performed as gastric cancer prophylaxis, then we do not need a selection strategy; we need a screen-and-treat program. On the other hand, if the consequences of antibiotic overuse vs the

weak association between *H. pylori* and FD and the lack of data supporting *H. pylori* eradication to prevent gastric cancer are emphasized, a more complex approach will be needed. Traditionally the Scandinavian countries have wanted to follow restrictive indications for use of antibiotics, especially broad-spectrum drugs, and this is reflected in lower rates of microbial resistance than found in most other European countries (42).

General practitioners often have a more pragmatic attitude to the management of dyspepsia, and may initially prescribe PPI as a trial and then refer to endoscopy if the symptoms persist. The threshold for referral is probably affected by age at symptom debut, the patient's attitude and worry, the physicians' knowledge and interest in the field and of course the waiting list to endoscopy (202).

The choice of management strategy reflects which of the theses we emphasize. The connection between *H. pylori* and PUD is well documented, and the indication is beyond discussion. On the other hand *H. pylori* eradication therapy in patients with FD is far more controversial and based on a weak, but significant positive difference of approximately 8-10% compared to placebo. The consequence, however, will be that all dyspeptic patients with a positive *H. pylori* test will have to be treated. As pointed out earlier, we need to treat 12-15 patients with broad-spectrum antibiotics to achieve one cure. 20% of all eradication treatments do not lead to eradication of the bacterium and will have to be retreated with second line therapy.
However, if the rising problem of bacterial resistance to antibiotics is considered a growing problem, and one related to the overall use of the antibiotics in the population, it should lead to a more cautious attitude to *H. pylori* eradication.

The different definitions of dyspepsia also have an impact on which management strategy that will turn out to be most cost-effective. An illustrative example is that when dyspepsia is defined to also include both epigastric pain and heartburn, initial PPI medication trial is most cost-effective. In studies defining dyspepsia strictly according to Rome III criteria normally the "Test and Treat" strategy turns out to be preferable (5, 203-205).

The two extreme points of view are on the one hand the statement that "the only good *H. pylori* is a dead *H. pylori*", and on the other, an open access to endoscopy without any other pre-endoscopic criteria than dyspeptic symptoms. The first implies a first line detection and treatment of *H. pylori* at the general practitioners office and often a second medical trial with PPI for those who do not respond. This is often substantiated by data supporting that

eradicating *H. pylori* also has a cancer-preventive effect.

Many patients with *H. pylori* gastritis do not have dyspeptic symptoms at all. If *H. pylori* eradication should be put into effect as a health program, screening for *H. pylori* independent of dyspeptic symptoms is the only way to do it, just like it was done in the Danish screening study (84).

The open access strategy gives a more pragmatic management of the dyspeptic patients, involving more individualized therapy trials. The *H. pylori* eradication policy will, in this case, probably be more influenced by local recommendations and personal attitude, than it will be in international guidelines like the Maastricht III.

This is to some extent the situation in Norway, except that in the official health care system the patients have to be referred to endoscopy by primary physician. However, this leads to a lot of negative endoscopies in young patients and may not be the most cost-effective use of an important and expensive endoscopic unit.

The effect of a strategy will also be influenced by the prevalence of *H. pylori.* In low prevalence areas the "Test and Treat" strategy has been shown to be equivalent to a strategy based on empiric acid suppression in a cost-benefit perspective (62, 206, 207).

In a recent study comparing six strategies for *H. pylori* diagnosis and management in un-invested dyspeptic patients, no improvement in cost-effectiveness was found between empirical PPI trial and 5 different "test and treat" strategies based on five different *H. pylori* detection methods (208)

### 5.2.1 *H. pylori*, the main cause of PUD and gastritis

The present study of a "Test, Score and Scope" strategy is mainly addressed at detecting patients with actual or previous PUD and ulcers caused by NSAIDs. Combining the results from papers I and III, this selection strategy should be able to detect almost all PUD (>97%) in a dyspeptic population - even in a setting of decreasing *H. pylori* prevalence - by using *H. pylori* fecal test or C-UBT. This also implies that all not *H. pylori* positive patients will receive *H. pylori* treatment, and the decision of eradication can be individualized in the non-PUD group.

Many authors claim that every dyspeptic patient with a positive *H. pylori* test should automatically receive eradication. The dilemma is then not whether to treat or not, it is when to do tests. Not to treat is then reckoned as unethical.

In the "Test, Score and Scope" strategy the decision point is moved further out in the diagnostic chain; when the actual *H. pylori* infection has proven its pathogenic role, eradication is

indicated.
This should not be an ethical dilemma, but a pedagogic challenge and comparable to other situations where patients are carriers of presumptive pathogenic bacteria but without being ill themselves.

### 5.2.2 *H pylori* and cancer.

Dyspeptic and reflux symptoms debuting after the age of 45-50, should always receive endoscopy in order to exclude gastric cancer. But cancer may occur even in younger patients, even if it is extremely rare. As seen in paper I, we happen to detect one patient at the age of 43 with an early gastric cancer. This cancer would not have been detected in a "Test and Treat" strategy. He had no alarm symptoms and hence, in a "Test and Treat" setting, he would only have received eradication therapy, not endoscopy. This procedure would have been delayed probably for months, which could reduce the chances of a positive outcome of cancer treatment significantly.
If he had been *H. pylori* negative the same delay would have happen in the "Test, Score and Scope" strategy, but as *H. pylori* is associated with gastric cancer it has a five-fold higher chance of being detected immediately in this strategy.
Doing tests for *H. pylori* and prescribing direct eradication therapy if positive at the general practitioners, has also become more common in Norway. This has unfortunately led to the same treatment in older patients with dyspepsia. We have seen examples of patients older than 50 years who presented with a gastric cancer more than half a year after they received *H. pylori* eradication because of positive *H. pylori* and without further examinations. This could obviously have been discovered earlier if endoscopy had been done.

### 5.2.3 Functional dyspepsia and *H. pylori*.

The "Test, Score and Scope" strategy does not imply systematic treatment of *H. pylori* positive patients with FD.
In the present study we compared data from patients with a clinical diagnosis of NUD after endoscopy, (n= 122), combined with *H. pylori* infection - (n=23) or without it (n=99). *H. pylori* positive patients did not receive eradication treatment. They were compared with respect to significant improvement of their symptom in the one-year follow up. 35% of the *H. pylori*

positive patients recorded significant improvement or complete relief of their symptoms vs 26% in the *H. pylori* negative group. If *H. pylori* were the key causative factor and *H. pylori* eradication therapy was *not* prescribed, we might have expected the opposite result (unpublished data).

Considering the complexity of the phenotype of FD and the related dysfunctions and disturbances observed, therapy trials should be individualized. Use of PPI and $H_2$ receptor antagonists ($H_2RA$) has been shown to also have a small but significant effect in improvement of FD symptoms and found to be cost-effectiv equal to *H. pylori* "Test and Treat" in uninvestigated dyspepsia (62).

Extensive eradication treatment in this group of patients will lead to substantial contribution to antibiotic overuse. This is the definitively largest group of patients in this setting, and even where the effect of eradication is well documented, the NNT is too high to justify systematic treatment. The "Test, Score and Scope" strategy gives the opportunity to individualize the therapy of the FD patients and reserve eradication for the patients with serious and sustained symptoms, widespread gastritis and with no effect of PPI.

### 5.2.4 NSAIDs and upper-GI ulcer.

NSAID consumption is associated with upper-GI side effects like ulcers, complicated by perforations and ulcer bleeding. This is well known, but the limit of danger is not clarified. Sporadic use of NSAIDs is common in the general population and the impact of some few tablets a month to GI side effects is difficult to evaluate. Many authors use the term "regular NSAID users" without further definition.

Applying the definition used in the present study, 12 % of the patients in the endoscopy group were allocated to the high-risk group, solely because of NSAID consumption. These patients accounted for 7% of the significant endoscopic findings.

This underlines how important it is to take NSAID consumption into account as an independent selection criterion to endoscopy. This may be of increasing importance when a higher number of ulcers show up to be *H. pylori* negative. Regular use of NSAIDs may be an underestimated and contributing factor in this observation. As pointed out earlier, there is a need of a more precise definition of "regular NSAID use" and more dedicated studies addressing this problem.

A clinical problem in daily practise is to be able to do systematic risk stratification of single patients before prescription of NSAIDs, and subsequently offer the patients at high risk of GI side-effects prophylactic PPI treatment. An ongoing population study in Denmark (Odense) is investigating this problem. A study dealing with the problem outlined in the present study

would obviously contribute to a better risk stratification.

### 5.2.5 GORD

In the present study we defined group C, the GORD group, as patients recording a reflux related symptom as their dominant symptom (questions 12-14 in the pre-endoscopy questionnaire). However, only 47 of the 266 patients in group A and B recorded negative in all the reflux related symptoms.

The symptom questions and the answer profile in the three groups are shown in figure 2.

Figure 2

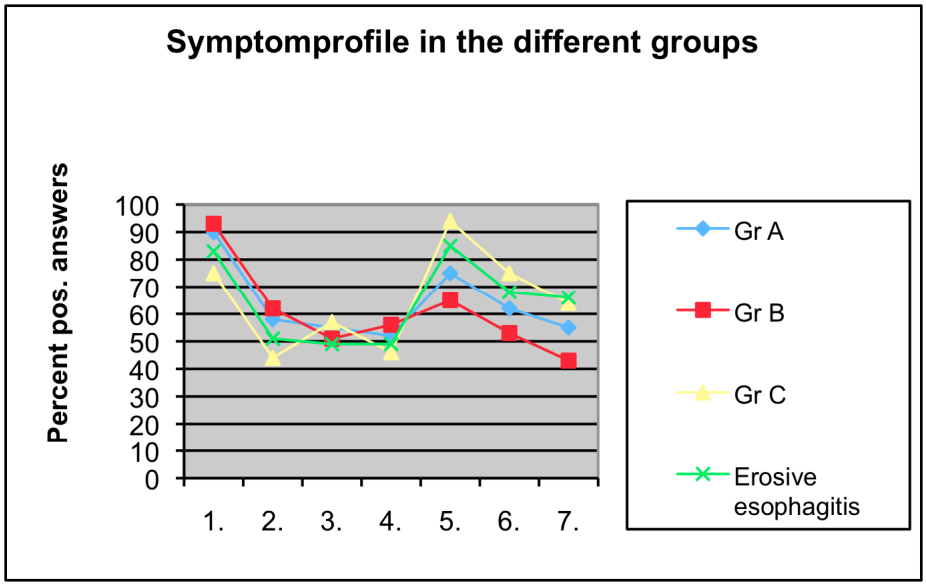



Figure 2 show the distribution of symptoms in the three different groups in paper I.

The numbers 1-7 refer to the questions in the questionnaire where questions 5-7 are mostly related to GERD.

1 Do you have pain in the upper part of the abdomen?

2 Do meals provoke or worsen the pain?

3 Does intake of food or acid-suppressing medication relieve the pain?

4 Does the pain disturb sleep during the night?
5 Do you experience regurgitation regularly?
6 Do you experience heartburn regularly?
7 Do these symptoms aggravate when you bend forward?

The questions and the distribution in number and percent are also presented in table II in paper I.

This illustrates the concurrence of symptoms between dyspepsia and GORD, and even if a validated questionnaire had been used this would not have eliminated this problem.
The division of patients having GORD, with- or without oesophagitis was not shown to be useful. It is now widely accepted that young patients with reflux symptoms do not need a routine endoscopy, and can be offered acid-reducing therapy directly.
As long as there is an extensive overlap of symptoms between dyspepsia and reflux, *H. pylori* testing may be convenient. This is so because ulcers can hide behind a set of symptoms that suggest both GORD and dyspepsia, even if a reflux related symptom is predominant.
This also underlines the rationale of giving PPI as a first line therapeutic trial to those who are *H. pylori* negative. This is also an obvious option for those who are positive but where no ulcers were detected by endoscopy.
An objection to this strategy when oesophagitis is the theme is that Barrett's oesophagus would be overlooked in the patients who are *H. pylori* negative.
This is true, but on the other hand, screening patients with GORD in order to detect Barrett's or oesophagus cancer has never been proven to be worth carrying out.
If endoscopy should be performed " once in a lifetime" in patients with reflux in order to detect these complications, it would make more sense to do it in an age group in which dysplasia and cancer have also to be taken into account.
In paper II we did not find any difference in the proportion of GORD patients with and without oesophagitis who report any degree of improvement in the one-year follow-up.
Detection of oesophagitis by endoscopy does not seem useful before initiating treatment when GORD is the most probable diagnosis. The relief of symptoms is the goal of the treatment anyhow, and the result of the endoscopy will neither confirm nor disqualify the treatment indication.

In the present study 12% of all patients had oesophagitis of S-M grade II. As expected the share in the GORD group (group C) were higher. 26% of the patients in this group had oesophagitis vs 8% in the other two groups combined.
However, in absolute numbers, this means that more than 50% of patients with oesophagitis did not record a GORD-related symptom as their predominant symptom. Two patients had high-grade oesophagitis and consequently, a higher potential for complications. One of them was allocated to the GORD group, the other not. This again underlines that symptoms alone are a poor marker for oesophagitis. But this may be of minimal importance. An overwhelming majority of patients with endoscopically detected oesophagitis have a low-grade oesophagitis. This is stable over decades and to a very low degree associated with serious complications. According to the results presented in paper II, the effect of the given treatment does not depend of whether the patient does have oesophagitis or not.

### 5.2.6 The antimicrobial resistance problem

The main purpose of this study was to obtain a safe reduction of the number of upper-GI endoscopies in young dyspeptic patients. This could spare endoscopic resources to be used in cost-effective way. It could also contribute to a more restrictive use of antibiotics in the *H. pylori* setting.
In this situation we need to counterbalance the data supporting the benefits of *H. pylori* eradication in, for instance, patients suffering from FD, with the problem of increasing antimicrobial resistance.
If we compare material in the present strategy to the "Test and Treat" strategy, we save nearly 75% of antibiotic courses, each consisting of two broad-spectrum antibiotics. In the presented material of 341 patients, approximately 75 double courses of antibiotics would have been prescribed based on vague and conflicting data.
A substantial reduction in the consumption of antibiotics in primary medicine is obviously necessary. Therefore, all areas of medicine must contribute to a critical evaluation of all indications to prescription; is the evidence for health benefit for the individual patients so convincing that it makes prescription of antibiotics mandatory? The advice from the Standing Medical Advisory Committee in their report "The Path of least resistance" was "the fewest number of antibiotic courses should be prescribed for the shortest period possible" (209).
*H. pylori* eradication have showed up not to be an exception.
The observation of antimicrobial resistance as a rising health problem, and the growing evidence of the total use of antibiotics as its cause, is also a major concern in gastroenterology.

This has to be taken in to account when we make guidelines and recommendations to eradicate *H. pylori* especially where the underlying data supporting the indication are vague and conflicting.

# 6. Conclusions

In Europe, the increasingly occurring microbiological resistance related to the overall use of antibiotics represents a challenge for the health care systems. *H. pylori* is associated with different conditions with varying evidence. On one hand, *H. pylori* is accepted as the main cause of gastric and duodenal ulcers, where eliminating the infection will heal the disease. On the other hand, *H. pylori* is only weakly associated to FD, with only a modest effect of eradication. Even more unclear and conflicting is the data showing a prophylactic effect on gastric cancer by large scale eradication of *H. pylori*. Both the treatment of *H. pylori* in functional dyspepsia, and the treatment of symptom-free individuals in order to reduce cancer risk, involve huge numbers people, and should consequently be considered in the context of bacterial resistance. The declining prevalence of *H. pylori* caused by better sanitary and general living standards is also of great importance. Last but not least, the problem of increasing bacterial resistance also affects *H. pylori* itself.

We therefore need to have strict and well-documented indications to recommend *H. pylori* eradication - such as gastric and duodenal ulcer disease.

In the earliest stage of MALT lymphomas (stage I), eradication of *H. pylori* will have the potential to reverse the disease in 80-90%, but close and frequent control is mandatory (210). Both gastric MALT lymphomas and early stage gastric cancer are well-established indications for *H. pylori* eradication. These are absolute indications and beyond discussion.

However, the relative indications should also be considered in contexts of cost-benefit, saved resources and patient satisfaction. Although this has been done in a huge number of papers, very few publications pay attention and concern to the problem of bacterial resistance.

First degrees relatives of young patients with gastric cancer, or those with frequent incidence of the disease in the family, are probably groups where *H. pylori* eradication might be useful and reasonable even with a lack of convincing data.

Eradication of the infection should also be offered to patients with detected dysplasia.

Data supporting this is weak and conflicting, but these indications involve a small number of people, and the individual indication to eradicate can be evaluated by a specialist in gastroenterology.

However, it is in the context of FD and cancer prevention that a large number of treatments are found.

There is data suggesting that wide scale *H. pylori* eradication may be cost-efficient, evaluated in a perspective of economic savings and symptomatic score. Likewise, wide scale eradication has been performed in order to prevent gastric cancer. In both these settings the data is conflicting whether it is useful or not.

Many studies concerning cost-benefit of the different strategies have given conflicting results. Therefore, there is a need for critical analysis of large scale treatment practices, such as the test and treat strategy, and programs for *H. pylori* eradication as cancer prevention, and to balance the discussion with the unwanted effects of increasing bacterial multi-resistance.

Patients presenting with dyspepsia should be tested for *H. pylori* by a non-invasive test with good accuracy (such as the *H. pylori* faecal test). If they test positive, endoscopy should be performed to exclude PUD. If PUD is excluded, or initial *H. pylori* status is negative, then a PPI or $H_2$ antagonist medical trial should be performed.

Together with the PPI prescription trial the patients with FD should receive exhaustive information from the family general practitioner explaining the benign nature of the condition.

Patients younger than 50 years of age with symptoms of GORD can have a PPI or H2 antagonist medication trial and do not need endoscopy unless combined with alarm symptoms.

Though data is conflicting, there is no support for prescribing *H. pylori* eradication to patients where long-term PPI therapy is instituted (115, 140, 145).

Test and treat is effective in reducing numbers of endoscopies, at least initially, but will lead to a significant overuse of antibiotic treatment.

The “Test, score and scope” strategy to manage young dyspeptic patients has the ability to reduce both the number of negative endoscopies and the use of antibiotics.

The right treatment to the right patient means treatment while minimizing harm.

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Paper 1

Paper 2

Paper 3

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