



# Stomach Pain – Evidence-Based Methods in the Diagnosis and Treatment of Dyspepsia

## *Summary and Conclusions*

---

### **Introduction**

Following headache and fatigue, stomach problems represent one of the most common reasons for physician visits. Dyspepsia accounts for approximately 3% of all physician visits. Dyspepsia is a general term to describe prolonged (weeks to months) pain or discomfort localized to the upper abdomen. The word dyspepsia originates from the Greek and means poor (dys) digestion (pepsia).

Peptic ulcers, eg, ulcers located in the stomach or the duodenum, are one of the many causes behind dyspepsia. The discovery that peptic ulcers are related to a bacterial infection (*Helicobacter pylori* or *H. pylori*) and the development of effective drugs for treating peptic ulcers has substantially changed treatment strategies and improved the outcomes.

This has generated expectations that other causes of dyspepsia can be successfully treated in similar ways. Controversial opinions along these lines and the substantial increase in prescription of potent antacids are among the reasons for this report.

### **What causes dyspepsia?**

Dyspepsia has many causes that are either organically or functionally related. Organic dyspepsia includes mainly peptic ulcers, ie, ulcers in the duodenum or stomach, inflammation in the esophagus (esophagitis), and cancer in the esophagus and stomach. This report addresses only the association between *H. pylori* and stomach cancer. If organic changes cannot be found, the problem may be attributed to a reflux disorder or functional dyspepsia.

### **Peptic ulcers**

For many years, it has been known that the appearance of ulcers in the stomach and duodenum is related to an imbalance between aggressive (pepsin enzymes and gastric acid) and protective factors. Hence, treatment of peptic ulcers has been aimed mainly at counteracting the formation of gastric acid or neutralizing it. A common belief is that inappropriate diet, high coffee intake, and psychological stress have a major influence on the occurrence of peptic ulcers. However, scientific evidence is limited due to methodological problems. Smoking is shown to contribute to the occurrence of ulcers and prevents healing. Evidence concerning alcohol is inconsistent; both improvement and deterioration and healing have been reported.

Around 15 years ago an important discovery showed that most patients with peptic ulcers demonstrated inflammatory changes (gastritis) in the stomach caused by *H. pylori*. This bacterial infection is found worldwide and is much more common in western countries than in developing nations, suggesting that socioeconomic conditions are of importance for the spread of the disease. The infection pathway is not known. *H. pylori* appears more often at higher ages, and blood tests suggest that 40% to 50% of people aged 50 and older in Sweden are carriers.

### **Gastroesophageal reflux**

Typical symptoms in gastroesophageal reflux disease (GERD) include heartburn, "chest burn" (pain behind the sternum), and acid reflux, which appears from reflux of gastric acid and other stomach contents to the esophagus. In nearly half of the patients, parts of the esophagus become inflamed or become sites for further ulcer formation of varying severity.

### **Functional dyspepsia**

Functional dyspepsia is a diagnosis arrived at through the process of elimination, ie, thorough investigation of patients with dyspepsia does not show an organic cause or any disturbance in the function of the gastrointestinal tract, eg, reflux. The character of the disorder and the subjective experience demonstrate substantial individual variations.

### **Ulcers caused by NSAID drugs**

Drugs classified as NSAID (non-cortisone type anti-inflammatory agents) often cause dyspepsia and occasionally cause lesions that are usually localized to the stomach. They are used both for chronic joint and muscle disorders (eg, rheumatoid arthritis) and for acute pain in the joints and muscles. The symptoms correlate poorly with changes in the mucous membrane of the stomach, because of the pain relieving effects of NSAID drugs. Bleeding (life threatening in isolated cases) and anemia are not uncommon as the initial clinical findings for ulcers. Side effects are associated with drug-induced weakening of the protective mechanisms of the mucous membrane of the stomach, making it more vulnerable to external factors and factors within the body itself, eg, gastric acid. High doses of NSAIDs, high patient age, concurrent treatment with cortisones, and earlier ulcers are risk factors. Alarming findings on the high number of cases with fatal outcomes in the United States, where overuse of NSAID appears to be substantial, motivates the need for more information on the risks for side effects.

ASA (acetylsalicylic acid) at low doses has become widely used as secondary and tertiary prophylaxis in coronary vessel disease (angina, myocardial infarction, and stroke). The risks for stomach problems are low, but serious bleeding in the stomach may occur even in individuals who have not previously had peptic ulcers.

In Sweden, NSAID drugs have recently been registered which are substantially more active anti-inflammatory agents than those which depress the protective mechanisms of the mucous membranes. These drugs (Cox-2) are theoretically appealing. However, the scientific evidence is limited. Their position in the therapeutic arsenal, mainly for

chronic rheumatic diseases, is believed to depend on their cost in relation to their long-term effects and potential side effects.

## **Rates of dyspepsia**

Epidemiological studies of diseases included under the concept of dyspepsia are associated with methodological problems. These include, eg, the lack of objective findings in many patients and problems in resources needed for thorough methodology to study large, representative populations. What consistently appears in the studies is that the condition is common. During a 3-month period, nearly 30% of the adult population reported dyspepsia. Only a small share of these individuals had ulcers (1 in 10) or reflux disease (1 in 7), which means that functional dyspepsia dominates within the diagnostic group.

Certain gender differences have been found. Ulcers in the duodenum appear more frequently in men while functional dyspepsia appears more frequently in women. A limited population based study from Sweden showed that younger women had the highest rate of physician visits due to dyspepsia. Stomach cancer, which seldom appears below age 40, is approximately twice as common in men than in women.

## **Diagnosing dyspepsia**

### **Symptomatology (case history)**

As a rule, is it not possible to establish the cause of dyspepsia, with reasonable certainty, in a particular patient based only on the character of the stomach problem. However, the case history can make different diagnoses more or less probable and facilitate the choice of examinations to confirm or exclude the disease. Heartburn and acid reflux strongly suggest reflux disease. The duration of symptoms is also an important factor in investigating and treating patients with dyspepsia, as is the course of symptoms. The symptoms that speak for and against various diagnoses are included in the knowledge which physicians at all levels are assumed to have, however, application of this knowledge varies. Therefore, a need exists for clearer definitions of symptoms or symptom constellations which lead to a particular diagnostic or therapeutic action. In dyspepsia, one usually refers to alarm symptoms (eg, weight loss, dark feces, blood in vomit, difficulties in swallowing), which should always give examination a high priority. Another alarm symptom is the new debut of dyspepsia in patients over 45 years of age.

### **Gastroscopy and other diagnostic studies**

Gastroscopy holds a special place among the studies that can be performed to determine the underlying diagnosis of dyspepsia. A flexible instrument (gastroscope) can be introduced into the stomach to inspect the mucous membrane and detect organic changes such as ulcers and cancer. Between 10% and 20% of patients with more than occasional dyspepsia have ulcers, and approximately 10% have reflux esophagitis, while less than 1% have cancer. These three diagnoses can be established with high reliability through gastroscopy. Twenty-four-hour pH-measurement in the esophagus probably has the next highest information value in examining patients with dyspepsia

and is assumed to provide a basis for the diagnosis of gastroesophageal reflux disease in up to 70% of the patients with prolonged dyspepsia.

Ultrasound is of value to diagnose morbid processes in the bile ducts, pancreas, and abdomen, which occur in approximately 5% of patients with dyspepsia.

### **H. pylori, diagnosis**

As a rule, the routine methods used in primary care are non-invasive (do not require gastroscopy) and can, eg, consist of identifying antibodies against *H. pylori* in whole blood (quick-test = direct answer) or in serum that is sent to a medical laboratory. A more reliable test is the urease exhalation test, which is based on the knowledge that *H. pylori* has the ability to chemically break down urea with help of the urease enzyme. Corresponding examinations are often conducted on tissue samples that are obtained through biopsy in conjunction with gastroscopy (invasive examination). In gastroscopy, tissue samples can be resected for culture of *H. pylori* and for microscopic examination of the stomach mucous membrane and for a so-called quick-urease test.

## **Project methodology**

### **Literature review**

A critical review of the scientific literature was the most important step in summarizing the state of knowledge on treatment of dyspepsia related diseases. A literature review mainly involves randomized controlled studies (RCT) which attempt to isolate the treatment effects from the influence of irrelevant factors. A search in MEDLINE using the keywords in English language journals targeted the literature from 1966 through 1997. A subsequent literature search covered the period through March 1999. Using a structured format and various quality criteria, the working group identified studies for further review and evaluation.

References regarding stomach cancer in *H. pylori*-positive individuals were searched in MEDLINE for the period 1982 through March 1998 using the combination "*Helicobacter pylori* or *Campylobacter pyloridis*". Studies were selected that reported on *H. pylori* in stomach cancer patients in relation to a reference group. Further studies were selected that related the occurrence of *H. pylori* infection in population groups to the incidence or mortality from stomach cancer in the same groups. The studies identified were evaluated according to the validity of the study method and were thereafter categorized into four groups according to the weight of the evidence. Only the two groups judged to contain the best evidence, ie, specially qualified cohort studies and case control studies, were used as a basis for conclusions.

### **Decision analysis**

Decision analysis appears in medical-economic studies to clarify the consequences of different alternative methods for achieving a particular result. The report applies decision analysis by presenting a decision tree diagram. The analysis is based on

statistical probability theory (Bayes theorem on conditional probability). The purpose of the analysis is to assess the expected cost and the expected health consequences of various alternatives. Thereby, diagnostic and treatment alternatives can be compared with regard to the costs per achieved result, for example, the cost per quality adjusted life year.

### **Gastroscopy survey**

A national questionnaire survey of gastroscopy, eg, the number of examinations and waiting times, was conducted for 1997.

## **Result of literature review**

### **Peptic ulcers**

The major finding is that short-term treatment (1 to 2 weeks) with antacids heals at least 90% of the lesions in the duodenum without influencing *H. pylori* infection. If treatment is combined with antibiotics targeted at *H. pylori* infection, the risk for relapse declines substantially. The most favorable results were achieved with proton pump inhibitors in combination with amoxicillin, claritromycin and metronidazole (so-called triple therapy). The most common triple therapy reported in the literature includes a combination of proton pump inhibitors with amoxicillin and claritromycin or claritromycin and metronidazole.

The documentation is not as good in reference to ulcers in the stomach, as regards both healing and relapse. A consistent finding is that only antacids promote lesion healing within 6 to 8 weeks in approximately 80% of cases. Relapse during the first year can be reduced substantially from about 50% to 5% if treatment corresponds to that used for duodenum ulcers. The hemorrhage complications caused by superficial lesions and ulcers also appear to be reduced with the treatment strategy now being used.

The number of therapeutic failures in clinical practice tends to be greater than in clinical trials, which always include well-defined study populations. This can mainly be attributed to lower compliance with medication. Another reason may be that *H. pylori* is resistant to the antibiotics used. Studies have not addressed the value of different strategies in treating duodenal lesions which have not healed completely (approximately 5% to 10%).

In summary, the most effective treatment for *H. pylori*-positive patients with lesions in the duodenum or stomach is triple therapy, which consists of antacids in combination with two antibiotics. This finding agrees with the guidelines issued by the Medical Products Agency. Prescription of these drugs appears to adhere to the guidelines, but compliance has not been well surveyed.

### **Reflux disease**

With drugs that inhibit the formation of gastric acid, esophagitis can heal and the symptoms can be ameliorated. The therapeutic effects are related to the degree and duration of acid inhibition, which should be more effective than in ulcer therapy.

Since the diagnosis of esophagitis only can be determined through gastroscopy, and the symptom of heart burn is common, a treatment strategy is required for patients where diagnosis-based examination for various reasons should not or cannot be performed. Therefore, the literature review has focused especially on endoscopy-negative gastroesophageal reflux disease. Many studies revealed deficiencies regarding the characteristics of patients, symptom duration, and the degree of severity. The placebo effect is high, approximately 40%, and therefore the symptom ameliorating effects of agents that inhibit formation of gastric acid, mainly in the group of proton pump inhibitors, is limited to approximately 30%. In summary, antacids provide better symptom relief than placebo in reflux disease, even when esophagitis is not present.

### **Functional dyspepsia**

Generally, clinical studies cover a group of patients with different symptom complexes. Since objective findings from functional dyspepsia are lacking, the treatment effects are often assessed using scales for subjective estimation of stomach problems and quality of life.

The two principally different treatment strategies studied are: 1) eradication of *H. pylori* and 2) symptom relief using drugs aimed at disorders in stomach function. Only during the past 2 years have studies been published which are based on randomized controlled trials (RCT) and other well-designed studies with adequate numbers of patients. Only one of these studies suggests that treatment with antibiotics of *H. pylori* results in better symptom relief than placebo. In all four studies, only one in five patients who received active treatment were symptom free at the conclusion of the followup period. These results speak strongly against the argument that eradication of *H. pylori* has a place in treatment of functional dyspepsia.

This conclusion is supported by the knowledge that patients with functional dyspepsia carry *H. pylori* infection at the same or an insignificantly higher rate than individuals who do not have corresponding stomach problems. Furthermore, there is no correlation between the symptoms and the inflammatory changes in the stomach caused by *H. pylori*. Several controlled studies have assessed drugs such as different types of antacids and pharmaceuticals that impact on the movement patterns of the stomach or other stomach functions. In studies using antacids, mainly proton pump inhibitors, a large percentage of patients with heartburn were included, a symptom of reflux disease, which responds well to antacid treatment. Positive treatment results can therefore be completely or partially explained by the fact that patient selection has been inadequate (patient data not appropriate for the purpose). In the absence of well-designed studies and evidence-based information on disease cause, functional dyspepsia is not an indication for antacid treatment. Only isolated, scientifically unbiased studies have been conducted using drugs that probably have effects on different stomach functions, but where there is no evidence to support their significance in conjunction with functional dyspepsia.

The conclusion that can be drawn from these clinical studies is that no drugs have been more effective than placebo. The reason is mainly that our knowledge about the causes on functional dyspepsia – a heterogeneous symptom complex – is incomplete.

### **Peptic ulcers caused by NSAID drugs**

A key question is whether ulcers in connection with NSAID use becomes more severe when *H. pylori* infection is also present, in other words if eradication is a way to prevent the onset of ulcers. Three of the four studies which were found to be methodologically sound have different designs and differences in patient data. Nevertheless, they clearly show that the occurrence *H. pylori* infection does not influence the healing of ulcers or relapse of ulcers caused by NSAIDs, either in the stomach or the duodenum. In the fourth placebo controlled study eradication of *H. pylori* by triple therapy (which included bismuth) showed significantly lower ulcer onset during ongoing NSAID treatment. Generally, there is lack of support for eradication treatment in patients before or during NSAID use. When NSAID treatment is used, drugs with the lowest risk for side effects should be selected and the lowest effective dose should be used. In some chronic joint diseases, pain-relieving drugs outside of the NSAID group may be a suitable alternative.

Regardless of the choice of antacids, lesions heal better if NSAID treatment is discontinued. Hence, this should be the first step if possible. In many cases it is necessary considering the nature of the basic disease to continue NSAID treatment. Likewise, prophylactic treatment can be considered when patients are given NSAIDs or these drugs are given to patients at a higher risk for ulcers (primary prophylaxes) and patients who have developed ulcers during NSAID treatment (secondary prophylaxis).

Mainly, the drugs studied consist of two groups with a high capacity to inhibit the formation of gastric acid (histamine-2-receptor antagonists and proton pump inhibitors) and misoprostol, which protect the mucous membrane and have antacid effects. Unfortunately the latter agents are often associated with a high rate of diarrhea. Furthermore, misoprostol causes contractions in the uterus and therefore the drug should not be used during pregnancy or by women during their fertile years, as long as adequate anti-contraception is not used.

Findings in a few studies that were accepted for review in the report show that all treatment principles result in lesion healing. In two comparative studies, the proton pump inhibitor omeprazole has shown significantly better effects than misoprostol and the histamine-2-receptor antagonist, ranitidine. Prophylactic treatment should be considered in patients at high risk for NSAID side effects involving the stomach. In the primary and the secondary prophylactic studies, basically the same results were found as in the treatment studies, but they differ somewhat depending on the location of the lesion. Omeprazole has better protective effects than misoprostol as regards lesions in the duodenum and is superior to ranitidine as regards lesions in the stomach. Misoprostol prevents the occurrence of lesions in the stomach more effectively than ranitidine.

### **Stomach cancer and H. pylori**

Stomach cancer appears more often in people who carry H. pylori compared to non-infected individuals. This is associated with the fact that inflammatory changes in the mucous membrane of the stomach can constitute a preliminary stage for cancer. However, the increased risk is small which means that other currently unknown factors are involved. Certain H. pylori strains may be more predisposed than others. Currently it is not possible to identify what carriers of H. pylori infection are at risk for stomach cancer. Consequently, there are no grounds for screening for H. pylori infection to prevent cancer.

### **Survey of gastroscopy in Sweden**

A questionnaire survey showed that 1748 gastroscopies per 100 000 inhabitants were performed in 1997, which represents nearly a 40% increase compared to 10 years ago. A small percentage is assumed to result from acute conditions such as hemorrhaging. The reasons behind substantial geographic variations are not known. In other words the extent to which indications diverge, or other conditions exist, is not clear. Waiting time for cases that are not acute or otherwise not prioritized have been somewhat shortened. The median waiting time is currently 3.5 weeks, but varies widely.

### **Results of decision analysis**

Using decision analysis, a test-and-scope strategy (test first, and perform gastroscopy on those who are not improved after treatment) has been compared with a strategy that involves prompt gastroscopy and targeted treatment. This analysis covers individuals who seek care for dyspepsia for the first time, are 45 years of age or older, do not have acid reflux or heart burn as dominant symptoms, and have no alarming symptoms such as weight loss, hemorrhaging from the gastrointestinal canal, jaundice, or palpable tumors (tumors a physician can feel with the hands). In the decision model, patients are followed as regards investigation, treatment, treatment effects, and costs for 1 year from the first physician contact. Even if the decision analysis is only a mathematical analysis, certain conclusions may be drawn. The decisive question for the success of the test and scope strategy is how the patients, who are eliminated from further examination with the help of the H. pylori test, react. If more than 55% to 60% return and are subject to gastroscopy the gain of the test and scope strategy is lost. Another factor which is of importance for cost results is the extent to which "opportunity" H. pylori screening (ie, in conjunction with a physician visit for another reason) is done even among patients who initially were managed with prompt gastroscopy. Furthermore, the costs of the test-and-scope strategy become disadvantageous if the patients with functional dyspepsia who were found to be H. pylori positive in initial H. pylori testing become subject to eradication treatment.

### **Economic viewpoints**

The use of medication in patients with dyspepsia has changed in several respects. A dramatic increase has occurred in the use of antacids, mainly the rapid growth in proton pump inhibitors. This is due to a high rate of prescriptions for reflux disease and dysfunctional dyspepsia. The total sales volume of proton pump inhibitors for the group



of dyspepsia exceeded 1.3 billion in 1998. According to the diagnosis prescription study ulcers comprise approximately 20% of all cases of dyspepsia and functional dyspepsia approximately 50%. The diagnostic reliability has not been validated. With some probability, the percentage of ulcer patients is overestimated. The percentage probably is somewhat closer to 10% based on several epidemiological studies. The onset has been stable or the trend is declining in recent times. Prescription of ulcer medicine for functional dyspepsia can be estimated at approximately 1/2 billion SEK per year, which is noteworthy since the indications are not approved and the effectiveness of the drugs are not scientifically documented. The total cost to society, direct and indirect, for dyspepsia can be estimated at 3.7 to 4.4 billion SEK per year. A thorough comparison of cost trends over time is not possible since earlier studies did not include identical diagnostic groups. What has been shown, however, is that the costs for surgical intervention have declined rapidly, while the percentage of the costs for drugs has increased substantially, from 2%-3% to 25%-30%, of the total.

## Research needed

With the discovery of the relationship between *H. pylori* and ulcers, the question was raised why only a minority of the infection carriers were affected. Further knowledge is needed about the mechanisms that attack and protect the mucous membrane in the stomach and the duodenum. Prospective epidemiological studies should be seen as necessary to determine the role played by life style and environment. Available knowledge on bacteria genetic make-up can be expected to provide information about the capacity for various bacteria strains to cause disease, which is of importance to the occurrence not only of ulcers but also stomach cancer.

Research in the area of functional dyspepsia is less defined. The apparently heterogeneous condition carries less serious symptoms and consequences than ulcers. From the individual's perspective, a survey of symptom-producing mechanisms is urgent since new pharmacological pathways can be opened. Research can lead to a rational therapy of functional dyspepsia, which is of obvious socioeconomic interest.

## Conclusions

- ❑ Dyspepsia, a general term for pain or discomfort localized centrally in the upper abdomen, is common in the population. The most valuable information in investigating dyspepsia comes from gastroscopic examination, a gastroscope is a special, flexible instrument that can be slid down into the stomach. The number of examinations per year has increased substantially.
- ❑ The total cost to society for investigation and treatment of patients with dyspepsia is substantial. With modern drug treatment, the costs related to surgery have declined markedly in the past decades. On the other hand, the costs for drugs have increased rapidly. These costs could be reduced substantially if knowledge about their use for different conditions related to dyspepsia would be fully utilized in clinical practice.

- ❑ More than half of the patients with dyspepsia receive a diagnosis of functional dyspepsia, which means that a cause underlying the problem could not be objectively determined. Probably, the classification of functional dyspepsia is heterogeneous and consists of several sub-classifications. Knowledge on what evokes and causes the symptoms of functional dyspepsia is currently limited. It is essential to conduct research in the field so that effective, rational treatment can be offered.
- ❑ Symptom relief from functional dyspepsia can be achieved by antacids when the problems have a dominant element of reflux of acid to the esophagus. Prokinetik drugs, whose effects are to stimulate movement in the stomach, may relieve symptoms in some cases. The scientific evidence is, however, limited.
- ❑ Most of the patients with peptic ulcers (lesions in the stomach and duodenum) are chronic carriers of the bacteria *Helicobacter pylori* which causes inflammatory changes in the stomach. A large percentage of the population carry this infection without symptoms, but only 1 in 6 are affected by ulcers. It is therefore not meaningful to start mass screening to identify carriers of *Helicobacter pylori* infection. Knowledge on the factors related to various strains (types) of *Helicobacter pylori*, and on individual-related factors, represent urgent areas for research to increase understanding on the origins of ulcers.
- ❑ Only patients with peptic ulcers should be treated with antibiotics targeted against the bacteria *Helicobacter pylori*. Furthermore, it is well documented scientifically that treatment with drugs that inhibit the formation of gastric acid in the stomach, particularly the type of proton pump inhibitors, in combination with two antibiotics do not heal lesions in the duodenum but mainly reduce the risks for recurrence. This treatment strategy is well established both regarding lesions in the duodenum and the stomach, but less well documented regarding stomach lesions.
- ❑ Patients with reflux disease, ie, with recurring problems caused by reflux of stomach contents through the upper orifice of the stomach (cardia), are soon symptom free with antacids such as proton pump inhibitor.
- ❑ Drugs within the groups NSAIDs (anti-inflammatory agents, but not of the cortisone type) often have side effects such as dyspepsia, and are a common reason for ulcers, mainly in the stomach. They are used for acute and chronic joint and muscle diseases. In long-term use of NSAIDs, such as for chronic rheumatoid arthritis, prophylactic treatment should be considered in patients having risk factors. It is relatively well documented that proton pump inhibitors and misoprostol, with the capacity to both inhibit gastric acid formation and protect the mucous membrane of the stomach, are the most effective in treating lesions in the stomach, while the antacids proton pump inhibitors and histamine-H<sub>2</sub>-receptor blockers are the most effective in treating lesions in the duodenum.
- ❑ Severe and alarming stomach problems, eg, hemorrhaging, should lead to acute or speedy examination of the esophagus and the stomach by gastroscop, a

special instrument for direct inspection of these organs. In some cases, the existence of *Helicobacter pylori* is investigated to determine whether or not gastroscopy should be conducted. In the report, we have presented and discussed the advantages and disadvantages of different management strategies using a decision tree model. Clinical examinations using practical application of this and similar theoretical decision models would be valuable, both for the individual patient and for society's resources.

- Stomach cancer comprises less than 1% of all dyspepsia and seldom appears in people below 45 years of age. *Helicobacter pylori* infection is associated with a somewhat higher risk for stomach cancer. Presently, it would be irrational to conduct mass screening for this bacteria infection and to treat cancer preventively, since several other factors of importance exist. We do not have sufficient scientific knowledge about the virulence (capacity to cause disease) of various bacteria strains and about the receptivity of the individual – the prerequisites for preventive intervention.