Current Management Strategies in Acid-Related Disorders
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Acid-related disorders include not only reflux esophagitis and peptic ulcer, but also a subset of patients with endoscopy-negative dyspepsia. The management strategy differs between these diseases and therefore a precise diagnosis is important. The unaided clinical diagnosis is of limited value in patients with pain or discomfort in the upper abdomen, and endoscopy is therefore an important and cost-effective diagnostic tool.

Duodenal ulcer is caused by an interplay between gastric acid and Helicobacter pylori. The treatment is aimed at rapid symptom relief and healing and at the same time eradication of H. pylori. At present the best choice is the combination of a proton pump inhibitor and two effective antimicrobial drugs, e.g., clarithromycin and metronidazole. The proton pump inhibitor has dual effect in this combination it provides optimal symptom relief and healing, and it increases the anti-H. pylori-effect of the antimicrobial drugs. The risk of reinfection varies geographically; in Europe it is around 1 percent per year, and cure of the infection provides long-term, maybe life-long, cure of the ulcer disease. Some gastric ulcers are not H. pylori-related and the treatment strategy therefore includes a diagnostic test for this infection. If positive, treatment is similar to that in duodenal ulcer, while H. pylori-negative gastric ulcer patients are treated with antisecretory drugs alone.

Reflux esophagitis correlates with the degree of acid exposure to the esophagus, and intensive acid inhibition is the most effective non-surgical therapy. In most cases the disease is chronic and needs continuous long-term therapy to prevent relapse. A staged reduction in dosage of the acid inhibitory drug may be attempted when the esophagitis is healed and the patient has become symptom free, but full dose therapy is often needed.

Patients with endoscopy-negative dyspepsia are a heterogeneous group and a more precise identification of the cause of the symptoms is a prerequisite for rational treatment. Empiric treatment can be tried in patients without alarm symptoms like bleeding or a palpable abdominal mass, and often an acid inhibitory drug is used. A more precise identification of those patients who have acid-related symptoms is possible using placebo controlled single-subject trials with an effective acid inhibitory drug, but in daily routine these drugs are simply given for a short period of time, and in case symptomatic relief is observed, the symptoms may be regarded as being acid-related and treated accordingly.

INTRODUCTION

The term acid-related disorder refers traditionally to two distinct diseases: peptic ulcer and reflux esophagitis. Recent studies of patients with endoscopy-negative dyspepsia have, however, clearly shown that gastric acid may cause pain and discomfort also in patients with no visible mucosal lesion in the esophagus, stomach or duodenum [1-4]. In some of these cases, an abnormal high acid exposure to the esophagus can be demon-
strated, but in many cases the results of pH-metry falls within the normal range, even in the group of patients with heartburn-predominant dyspepsia [1, 3].

The subgroups of patients with pain or discomfort in the upper abdomen are listed in Table 1, and it should be emphasized that the role of Helicobacter pylori-gastritis in dyspepsia is still unknown.

A rational management strategy presupposes a diagnostic strategy. Considering the NIH recommendations that routine antimicrobial therapy against H. pylori should be restricted to those patients with an H. pylori-related peptic ulcer [5], a precise diagnosis is important, now more than ever. Unfortunately, unaided clinical diagnosis based on

| Table 1. Subsets of patients with pain or discomfort in the upper abdomen. |
|-----------------------------|-----------------------------|-----------------------------|
| **Acid related:**           |                             |                             |
| Peptic ulcer disease        |                             |                             |
| Gastro-esophageal reflux disease |                   |                             |
| Reflux esophagitis          |                             |                             |
| Endoscopy-negative reflux disease with abnormal acid exposure | | |
| Endoscopy-negative reflux disease with normal acid exposure | | |
| Endoscopy-negative, non-reflux dyspepsia? | | |
| **H. pylori related:**      |                             |                             |
| Peptic ulcer disease        |                             |                             |
| Gastric cancer              |                             |                             |
| Endoscopy-negative dyspepsia? |                   |                             |
| **Dysmotility related:**    |                             |                             |
| Gastro-esophageal reflux disease |                   |                             |
| Endoscopy-negative, non-reflux dyspepsia? | | |

symptoms and demographic data is of limited value in patients with pain or discomfort in the upper abdomen. Every second dyspeptic patient with endoscopically confirmed active peptic ulcer is missed by clinical diagnosis even in situations with a high susceptibility of ulcer leading to a poor predictive value of that clinical diagnosis (Table 2) [6]. Furthermore, approximately one-third of patients with organic disease are misclassified as having functional dyspepsia [6-8]. Even patients with malignant disease can be hard to diagnose clinically, apart from those with advanced disease in whom the exact diagnosis will have no therapeutic implications. Fortunately, gastric and esophageal cancers are rare

| Table 2. Validity of clinical judgement as predictor of peptic ulcer: results from a clinical experiment in 1024 dyspeptic patients referred for a diagnostic endoscopy. Adapted from [8]. |
|-------------------|-------------------|-------------------|
|                   | Endoscopy         |                   |
|                   | Ulcer             | No ulcer          | Total |
| Clinical judgement| Ulcer             | 76                | 151   | 227   |
|                   | No ulcer          | 71                | 726   | 797   |
| Total             | 147               | 877               | 1024  |
findings in dyspeptic patients, and malignancy is found almost exclusively in older patients. As a consequence most authorities have recommended that endoscopy be reserved for those older than 40-45 years of age with new onset of dyspeptic symptoms [9]. On the other hand, recent studies have demonstrated the superiority of prompt endoscopy compared to a strategy based on empirical H₂-blocker treatment, both in terms of patient satisfaction, health care related costs [10, 11], and detection rates of early gastric cancer [12]. This view has been challenged by others [13-16], and particularly the possibility of screening dyspeptic patients for endoscopy according to their H. pylori status may be promising [16]. However, we still need randomized clinical trials in unselected patients to substantiate the suggestions of a clinical and economic benefit by using this strategy. These studies are under way and will be reported in the near future.

The importance of a precise diagnosis for obtaining optimal therapeutic gain should be balanced against cost and availability of endoscopy, and the strategy therefore varies geographically as well as with time. This decision is a complex one and it should encompass economic and clinical considerations as well as patient factors like anxiety, distress, and preferences.

MANAGEMENT STRATEGY IN PEPTIC ULCER DISEASE

Duodenal ulcer

The most important novelty in gastroenterology during the recent years is the discovery of H. pylori and its role in peptic ulcer disease. It is now well documented that the annual relapse rate of duodenal ulcer is reduced to a few percent after cure of H. pylori infection [17], and eradication of H. pylori has therefore become a primary goal in duodenal ulcer disease. When a duodenal ulcer is diagnosed the treatment strategy should be aimed at providing rapid pain relief, rapid healing, and at the same time cure of the infection. Although prostaglandin analogues are effective in healing duodenal ulcers, they show low efficacy with regard to ulcer pain relief and high incidence of diarrhea [18, 19], and a combination of a proton pump inhibitor and two antimicrobial drugs seems the optimal choice at present, because effective acid inhibition not only gives maximal symptom relief and healing, but also improves the anti-Helicobacter efficacy of antimicrobial drugs [20]. Alternative treatment regimens include the original triple therapy of bismuth, tetracycline, and metronidazole and combinations of H₂-blockers with two antibiotics. The original triple therapy is less expensive but may have significant compliance problems and a high incidence of side-effects. The duration of the antimicrobial regimen is one to two weeks, and if the patient is free of ulcer symptoms at this time, also the acid inhibitory drug may be stopped since the ulcer healing process will continue, provided the infection is cured [21]. There is no reason to perform repeat endoscopy unless the patient continues to have symptoms, or in case the ulcer was complicated with bleeding. In that case, the anti-secretory treatment should be prolonged some weeks and endoscopy repeated to ensure ulcer healing. It is important to emphasize that eradication of H. pylori also reduce recurrence of bleeding ulcers.

It is debated whether or not a diagnostic test for H. pylori is needed when a duodenal ulcer is diagnosed. The very high prevalence (greater than 90 percent) of H. pylori infection in this disease, together with a considerable risk of false negative results of the biopsy-based tests are the arguments for not performing a diagnostic test. The argument for testing is to avoid unnecessary antimicrobial treatment in H. pylori-negative patients. The battery of diagnostic tests of H. pylori infection differ with respect to sensitivity, specificity, invasiveness, cost, and to what additional information they provide, such as degree of gastritis and susceptibility of the bacteria to antimicrobial drugs. There is no “gold standard” for the detection of the bacterium, and the choice of test depends upon the clinical
situation. Both non-invasive urea breath testing and serology as well as biopsy-based histology and rapid urease tests are reliable indicators of *H. pylori* infection and a single test is sufficient [22]. In clinical situations where an endoscopy is indicated for other reasons a biopsy-based test is convenient, and in most cases a rapid urease test is the method of choice. Histology should be chosen when a histopathological assessment is wanted, for instance to exclude malignancy in a gastric ulcer. In cases of treatment failure biopsies should be cultured and antibiotic sensitivity profiles should guide further therapy. In most patients the clinical response is sufficient evidence of treatment success. If treatment failure is suspected urea breath tests, when available, and not serology should be used to document eradication. To avoid false negative results the breath test should be performed 4-6 weeks after end of treatment.

**Previously verified duodenal ulcer disease and recurrence of dyspeptic symptoms**

This patient will not need repeated endoscopy to confirm relapse of a duodenal ulcer, provided the symptoms are “ulcer like” and there are no additional alarm symptoms. It is very likely that the patient will benefit from anti-*H. pylori* therapy, and it is reasonable to confirm *H. pylori* infection with a non-invasive test, e.g., urea breath test or serology. If the patient is infected, eradication therapy should be given, also in case the patient is taking aspirin or NSAIDs, since it is much more likely that the duodenal ulcer is *H. pylori*-related and not NSAID-related, and there is no test which can determine whether an ulcer is caused by NSAIDs.

**Gastric ulcer**

The treatment strategy when a gastric ulcer is found differs for several reasons from that recommended in patients with a duodenal ulcer. There is a lower prevalence of *H. pylori* infection in patients with gastric ulcer and therefore a diagnostic test should be carried out, most convenient as a biopsy-based test at the time of endoscopy. If the patient is infected eradication therapy is given, including an effective acid inhibitory drug, which should be continued for 4 weeks after the antibiotics are stopped. The reason for this, is that the gastric ulcer might not be *H. pylori*-related and consequently needs the usual time for healing with an antisecretory agent.

In case the patient is not infected, monotherapy with an antisecretory drug is given. Repeat endoscopy is recommended in gastric ulcer until complete healing to exclude malignancy [23]. The optimal time for this second endoscopy is shortly after the ulcer is expected to be healed, and therefore it depends on the size of ulcer. Small gastric ulcers heal within 4 weeks, while larger ulcers may take 6-8 weeks [24].

In patients who are NSAID-users, long-term treatment with a mucosal protective agent or an antisecretory drug may be useful as prophylaxis against recurrence of the ulcer, in case the NSAID-therapy can not be discontinued.

**Recurrence of dyspeptic symptoms in patients with a previously diagnosed gastric ulcer**

The recurrence rate of gastric ulcers is lower than it is for duodenal ulcers, and when the risk of malignancy is also taken into account, endoscopy is recommended in this case to confirm ulcer recurrence and to exclude gastric cancer. In case a benign gastric ulcer is found, it is relevant to test whether or not the patient is *H. pylori* infected, and a biopsy-based test should be performed. If the patient is found positive eradication therapy should be given, including an antisecretory drug.

**MANAGEMENT OF GASTRO-ESOPHAGEAL REFLUX DISEASE**

Symptoms of gastro-esophageal reflux are very common in the general population, and also in primary and secondary care. The prevalence of reflux symptoms was found to
be around 37 percent in a study from North America [25] and a study from Sweden reported a six-month prevalence of 26 percent [26]. An estimated 25 percent of patients with heartburn seek medical advice, while most patients are self-medicating with antacids, alginates, or acid inhibitory drugs.

As shown in Table 1 only some patients with acid reflux have endoscopic esophagitis, since some have abnormal acid exposure to the esophagus without visible mucosal lesions, and some have reflux symptoms with esophageal pH monitoring within the normal range. Increasing severity of symptoms correlates with the duration of time with esophageal pH above 4 [27] and symptom-related reflux episodes last longer than those not perceived by the patient. Therefore acid contact time seems to be a contributing factor to esophageal sensitivity [28].

The rational treatment of reflux disease would be to improve the competence of the lower esophageal sphincter, but surgery is still the only effective treatment in this respect. Therefore acid suppressive drugs become the key-stone in the management of reflux, in addition to lifestyle advice. Prokinetic drugs like cisapride modify esophageal function by increasing lower esophageal sphincter pressure and the amplitude of esophageal contractions. They promote gastric emptying by increasing antral contractions and enhancing antro-duodenal coordination. Prokinetics can be used to control reflux symptoms, but they are less effective compared to proton pump inhibitors in healing the more severe grades of esophagitis [29], and the most satisfactory results in the treatment of erosive esophagitis have been seen with proton pump inhibitors [30].

In most patients, gastro-esophageal reflux is a chronic disease, with rapid relapse after withdrawal of treatment and with long lasting consequences for quality of life and morbidity [31]. A recurrence rate about 80 percent during the first six months is a common finding [32], and therefore continuous long-term therapy is usually required. A staged reduction in dosage of the acid inhibitory drug may be attempted when the esophagitis is healed and the patient has become symptom free, but full dose therapy is often necessary [33].

IDENTIFICATION OF PATIENTS WITH ENDOSCOPY-NEGATIVE ACID-RELATED DYSPESIA

 Patients presenting with dyspepsia are a heterogenous group and a more precise identification of the cause of the symptoms is a prerequisite for a rational treatment. When endoscopy has found no visible abnormality in the esophagus, stomach, or duodenum, empiric symptomatic treatment can be tried in patients without alarm symptoms. The rationale for prescribing an acid inhibitor in this situation is, of course, the assumption that the symptoms are acid-related, but this is only the case in a subgroup of these patients. Some symptoms such as heartburn are usually taken as a symptom of gastroesophageal reflux, but the diagnostic value of the clinical judgement is generally low. A more precise identification of those patients who have acid-related symptoms is possible using placebo-controlled single-subject trials with either an H₂-receptor antagonist [34] or omeprazole [35], but in daily clinical routine these drugs are simply given for a short period of a few weeks, and in case adequate symptom relief is obtained, the symptoms might be acid related. It is important to keep in mind, though, the very high placebo response in these patients, usually approaching 50-70 percent in most trials. Thus, the validity of the response to acid inhibition is supported if the symptoms recur shortly after stop of treatment, and especially if the successful response can be repeated.
REFERENCES

1. Trimble, K.C., Douglas, S., Pryde, A., and Heading, R.C. Clinical characteristics and natural history of symptomatic but not excess gastroesophageal reflux. Dig. Dis. Sci. 40:1098-1104, 1995.
2. Trimble, K.C., Pryde, A., and Heading, R.C. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. Gut 37:7-12, 1995.
3. Lind, T., Havelund, T., Carlsson, R., Eriksson, G., Glise, H., Junghard, O., Lauritsen, K., Lundell, L., and Pedersen, S.A. The effect of omeprazole 20 mg and 10 mg daily on heartburn in patients with endoscopy negative reflux disease (ENRD) treated on an on-demand basis. Gastroenterol. 110:AI78, 1996.
4. Bate, C.M., Griffin, S.M., Keeling, P.W.N., Axon, A.T.R., Dronfield, M.W., Chapman, R.W.G., O'Donoghue, D., Calam, J., Crowe, J., Mountford, R.A., Watts, D.A., Taylor, M.D., and Richardson, P.D.I. Reflux symptom relief with omeprazole in patients without unequivocal oesophagitis. Aliment. Pharmacol. Therap. 10:547-555, 1996.
5. NIH Consensus Development Panel. Helicobacter pylori in peptic ulcer disease. JAMA 272:65-69, 1994.
6. Bytzer, P., Hansen, J.M., Havelund, T., Malchow-Moller, A., and Schaffalitzky de Muckadell, O.B. Predicting endoscopic diagnosis in the dyspeptic patient. The value of clinical judgement. Eur. J. Gastroenterol. Hepatol. 8:359-363, 1996.
7. Hallissey, M.T., Jewkes, A.J., Allum, W.H., Ellis, D.J., and Fielding, J.W.L. Clinical diagnosis in dyspepsia: a valueless exercise. Gut 30:A709, 1989.
8. Bytzer, P. Strategies for the management of patients with dyspepsia of unknown cause (thesis). Odense University, Denmark; 1993, pp. 1-132.
9. Health and Public Policy Committee, American College of Physicians. Endoscopy in the evaluation of dyspepsia. Ann. Intern. Med. 102:266-269, 1985.
10. Bytzer, P., Hansen, J.M., and Schaffalitzky de Muckadell, O.B. Empirical H2-blocker therapy or prompt endoscopy in the management of dyspepsia. Lancet 343:811-816, 1994.
11. Silverstein, M.D., Petterson, T., and Talley, N.J. Initial endoscopy or empiric therapy with or without testing for Helicobacter pylori for dyspepsia: a decision analysis. Gastroenterol. 110:72-83, 1996.
12. Hallissey, M.T., Allum, W.H., Jewkes, A.J., Ellis, D.J., and Fielding, J.W.L. Early detection of gastric cancer. BMJ 301:513-515, 1990.
13. Rabeneck, L. Managing dyspepsia: is prompt endoscopy the way to go? Gastroenterology 108:1324-1325, 1995.
14. Fendrick, A.M., Chernew, M.E., Hirth, R.A., and Bloom, B.S. Alternative treatment strategies for patients with suspected peptic ulcer disease. Ann. Intern. Med. 123:260-268, 1995.
15. Perri, F., Clemente, R., Latiano, A., Villani, M.R., Bisceglia, M., Li Bergoif, M., Annese, V., and Andriulli, A. Urea breath test as first choice test in dyspepsia: a money and time sparing approach. Gut 37(suppl 2):A203, 1995.
16. Patel, P., Khulusi, S., Mendall, M.A., Lloyd, R., Jazrawi, R., Maxwell, J.D., and Northfield, T.C. Prospective screening of dyspeptic patients by Helicobacter pylori serology. Lancet 346:1315-1318, 1995.
17. Forbes, G.M., Glaser, M.E., Cullen, D.J.E., Warren, J.R., Christiansen, K.J., Marshall, B.J., and Collins, B.J. Duodenal ulcer treated with Helicobacter pylori eradication: seven-year follow-up. Lancet 343:258-260, 1994.
18. Lauritsen, K., Laursen, L.S., Havelund, T., Bytzer, P., Svendsen, L.B., and Rask-Madsen, J. Enprostil and ranitidine in duodenal ulcer healing: double-blind comparative trial. BMJ 292:864-866, 1986.
19. Ching, C.K., and Lam, S.K. A comparison of two prostaglandin analogues in the treatment of acute duodenal ulcer disease. Scand. J. Gastroenterol. 30:607-614, 1995.
20. Moayyedi, P., Sahay, P., Tompkins, D.S., and Axon, A.T.R. Efficacy and optimum dose of omeprazole in a new 1-week triple therapy regimen to eradicate Helicobacter pylori. Eur. J. Gastroenterol. Hepatol. 7:835-840, 1995.
21. Hosking, S.W., Ling, T.K.W., Chung, S.C.S., Yung, M.Y., Cheng, A.F.B., Sung, J.J.Y., and Li, A.K.C. Duodenal ulcer healing by eradication of Helicobacter pylori without anti-acid treatment: randomized controlled trial. Lancet 343:508-510, 1994.
22. Peura, D.A. Helicobacter pylori: a diagnostic dilemma and a dilemma of diagnosis. Gastroenterology 109:313-315, 1995.
23. Bytzer, P. Endoscopic follow-up study of gastric ulcer to detect malignancy: Is it worthwhile? Scand. J. Gastroenterol. 26:1193-1199, 1991.
24. Rune, S.J. and Walan, A. Healing characteristics: comparison of gastric and duodenal ulcers. In: F. Halter, A. Garner and G.N.J. Tytgat, eds., Mechanism of peptic ulcer healing. Dordrecht, Boston, London: Kluwer Academic Publishers; 1991, pp. 259-264.

25. Nebel, O.T., Fornes, M.F., and Castell, D.O. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Am. J. Dig. Dis. 21:953-6, 1976.

26. Ruth, M., Månsson, I., and Sandberg, N. The prevalence of symptoms suggestive of esophageal disorders. Scand. J. Gastroenterol. 26:73-81, 1991.

27. Mattioli, S., Pilotti, V., and Spangaro, M. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Am. J. Dig. Dis. 21:953-6, 1976.

28. Nebel, O.T., Fornes, M.F., and Castell, D.O. Healing characteristics: comparison of gastric and duodenal ulcers. In: F. Halter, A. Garner and G.N.J. Tytgat, eds., Mechanism of peptic ulcer healing. Dordrecht, Boston, London: Kluwer Academic Publishers; 1991, pp. 259-264.

29. Ruth, M., Månsson, I., and Sandberg, N. The prevalence of symptoms suggestive of esophageal disorders. Scand. J. Gastroenterol. 26:73-81, 1991.

30. Mattioli, S., Pilotti, V., and Spangaro, M. Reliability of 24-hour home esophageal pH monitoring in diagnosis of gastroesophageal reflux. Dig. Dis. Sci. 34:71-8, 1989.

31. Shi, G., Bruley des Varannes, S., Scarpignato, C., Le Rhun, M., and Galmiche, J.-P. Reflux-related symptoms in patients with normal esophageal exposure to acid. Gut 37:457-464, 1995.

32. Tytgat, G.N.J., Janssens, J., Reynolds, J.C., and Wienbeck, M. Update on the pathophysiology and management of gastro-oesophageal reflux disease: The role of prokinetic therapy. Eur. J. Gastroenterol. Hepatol. 8:603-611, 1996.

33. Boeckxstaens, G.E., and Tytgat, G.N.J. Pathophysiology, diagnosis, and treatment of gastroesophageal reflux disease. Curr. Opin. Gastroenterol. 12:365-372, 1996.

34. McDoigall, N.J., Johnston, B.T., Kee, F., Collins, J.S.A., McFarland, R.J., and Love, A.H.G. Natural history of reflux oesophagitis: a 10 year follow up of its effect on patient symptomatology and quality of life. Gut 38:481-486, 1996.

35. Tytgat, G.N.J., Anker Hansen, O.J., Carling, L., de Groot, G.H., Geldof, H., Glise, H., Efskind, P., Elsborg, L., Karltonen, A-L., Ohlin, B., Solhaug, O.H., Vermeersch, B., and other SCANED-CIS Trialists. Effect of cisapride on relapse of reflux oesophagitis, healed with an antisecretory drug. Scand. J. Gastroenterol. 27:175-183, 1992.

36. Vigani, S., Cerroni, R., Leandro, G., Badalamenta, S., Pantalena, M., Savarino, V., di Mario, F., Battaglia, G., Sandro Mela, G., Pilotto, A., Plebani, M., and Davi, G. A comparison of five maintenance therapies for reflux oesophagitis. N Engl. J. Med. 333:1106-1110, 1995.

37. Johannessen, T., Fjøsne, U., Kleveland, P.M., Halvorsen, T., Kristensen, P., Loge, I., Hafstad, P.E., Sandbakken, P., and Petersen, H. Cimetidine responders in non-ulcer dyspepsia. Scand. J. Gastroenterol. 23:327-336, 1988.

38. Staun, M., and rune, S.J. Controlled single subject trial to identify patients with acid related dyspepsia. Scand. J. Gastroenterol. 27(suppl 190):34, 1992.