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AGA Technical Review: Evaluation of Dyspepsia

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The optimal management of the patient who presents with dyspepsia remains controversial. Empiric therapy is often prescribed, but is this the most cost-effective and safest approach, or is immediate investigation to reassure both patient and physician and treat specific disease (e.g., peptic ulcer, esophagitis, or *Helicobacter pylori* infection) a better option? Our aim was to review the available management strategies in the literature and critically evaluate their implications to help develop modern practice guidelines. A MEDLINE and Current Contents Search was performed up to April 1997 using the MeSH term dyspepsia. The papers that considered management of dyspepsia were retrieved and reviewed, and their reference lists were checked for additional citations. The authors met to review and synthesize the available data.

Definitions and Epidemiology

Upper abdominal pain or discomfort is remarkably common in the general population. The annual prevalence of recurrent upper abdominal pain or discomfort in the United States and other Western countries is approximately 25%; if frequent heartburn (defined as retrosternal burning pain or discomfort once a week or more often) is also considered, the prevalence approaches 40%.[1–11] When classic heartburn or acid regurgitation are the dominant symptoms, objective evidence of gastroesophageal reflux disease can often be identified.[12–14] The diagnosis and management in such cases is well established and will not be considered in this report.[15] The term dyspepsia here will be restricted to mean chronic or recurrent pain or discomfort centered in the upper abdomen (i.e., the epigastrium); reflux symptoms alone and acute abdominal conditions will not be included.[14] Because meal-related symptoms have poor discriminating value,[16–18] the relationship to meals will not be considered part of the definition. It is further assumed that the physician evaluating the patient, after taking the history and performing a physical examination, considers the symptoms to be likely to originate from the upper gastrointestinal tract and not from the abdominal wall muscles or elsewhere. A patient with dysphagia or bleeding would not be classified as having dyspepsia. A similar definition has been endorsed previously.[14,19,20]

The Problem: What Is the Optimal Management of Dyspepsia?

For many persons, the symptoms of dyspepsia are of short duration or mild severity[21] and are therefore self-managed. Less than half of dyspepsia sufferers seek medical care for their complaints in the United States and Europe.[7,9,10,22,23] Despite this, the management of dyspepsia represents a major issue in clinical practice; 2%–5% of all family practice consultations are accounted for by dyspepsia.[24] The factors that determine whether a patient consults a physician are poorly defined, but symptom severity, increasing age, lower social class, fear of serious disease, a family history of cancer, and possibly psychological distress and insurance status are important.[7,22,23,25] In this report, attention will be focused on management of those who consult a physician rather than on non-patients with dyspepsia.

Views differ on the optimal management strategy for the patient who presents with new-onset dyspepsia.[26–30] The major options currently are (1) empiric medical therapy (e.g., an antisecretory or prokinetic agent) with any subsequent investigation reserved for failures; (2) immediate diagnostic evaluation in all cases, applying either endoscopy or upper gastrointestinal radiography and targeting therapy based on the results; (3) testing for *H. pylori* infection and reserving endoscopy for positive cases to look for ulcer disease or cancer; and (4) testing for *H. pylori* by serology or a urea breath test and treating all positive cases with antibacterial therapy.

Only a minority of patients with dyspepsia have peptic ulcers and even fewer have cancer (Tables 1 and 2).[17,31–70] Therefore in 1985, the American College of Physicians (ACP) recommended, based on a literature review of outcomes and cost, that antisecretory medical therapy is preferable for patients without obvious organic disease <45 years of age.[26] The ACP further suggested that endoscopy (rather than a barium series) should be reserved for patients who have little or no response to therapy after 7–10 days or for patients whose symptoms have not resolved after 6–8 weeks.

Table 1. Findings on Esophagogastroduodenoscopy in Patients With Dyspepsia

Study (no. of patients)	Age composition	DU (%)	Deformity (%)	GU (%)	Esophagitis (%)	Cancer (%)	Normal (%)	Comments
Barnes et al.[31] (n = 50)	NA	22	24	6	2	2	40	
Møllman et al.[32] (n = 197)	28% <40 yr	25	NA	13	NA	1	55	
Fischer et al.[33] (n = 304)	Adults	14[a]	2	7	19[b]	1	39	[a]DU + prepyloric [b]and/or hiatus hernia
Beavis et al.[34] (n = 187)	54% <45 yr	6	20	5	17	1	50	
Holdstock et al.[35] (n = 1805)	NA	[a]	NA	[a]	9	2	46	[a]DU + GU = 14%
Gear et al.[36] (n = 346)	NA	12	12	6	8	2	48	
Gear et al.[37] (n = 968)	NA	1	9.3	5.5	2.7	2.2	58	
Greenlaw et al.[38] (n = 100)	19–87 yr	11	NA	14	NA	3	39	
Adami et al.[39] (n = 346)	58% <40 yr	2	9	1	NA	1	64	
Fedail et al.[40] (n = 2500)	Mean, 34 yr	17	2	0.7	8	1	42	
Nyrèn et al.[41] (n = 972)	Mean, 38 yr	2	1	2	3	0.2	72	
Lance et al.[42] (n = 100[b])	Mean, 40 yr	24[a]	NA	7[a]	2	1	63	[a]Two had both; [b]93 endoscopy, 7 barium meal
Edenholm et al.[43] (n = 167)	Mean, 40 yr	10	NA	5	NA	1.8	83	
Davenport et al.[44] (n = 1041)	NA	10	NA	5	NA	2.6	60	
Fjøsne et al.[45] (n = 1275)[a]	Mean, 57 yr	8	9	12	9	3.3	53	[a]Includes repeat and follow-up endoscopy
Saunders et al.[46] (n = 559)	Mean, 42 yr	23	21	6	29	0.2	31	
Hansen et al.[47] (n = 416)	24% <40 yr	9	NA	8	NA	2	63	
Forbat et al.[48] (n = 78)	Mean, 22 yr	15	13	2.5	5	0	62	
Williams et al.[49] (n = 686)	40% <45 yr	12	NA	8	14	2.5	49	
Capurso et al.[50] (n = 1153)	23–70; mean, 44 yr	[a]	NA	[a]	3	1	77	[a]DU + GU = 8%
Kagevi et al.[51] (n = 172)	<20–80+ yr	9	3	4[a]	6	1	69	[a]GU = 2%, prepyloric = 2%
Mansi et al.[52] (n = 2086)	NA	9	NA	4	3	1.5	62	
Hallisey et al.[53] (n = 2659)	All >40 yr	10	NA	6	19	4	32	
Johannessen et al.[54] (n = 930)	33% <40 yr	12[a]	NA	5	14	1	71	[a]DU = 9%; pyloric = 3%
Hansen et al.[55] (n = 436)	Median, 53 yr	6	5	6	16	0	59	
Bytzer et al.[56] (n = 878)	NA	7	NA	8	2	1.4	64	
Kiyota[57] (n = 106)	10–80+ yr	[a]	NA	[a]	4	7	53	[a]DU + GU = 18%
Klauser et al.[58] (n = 220)	Mean, 49 yr	10	NA	5	17	5	25	
Inoue et al.[59] (n = 240)	>18 yr	4[a]	3	5[a]	3	1	75	[a]Includes 1% with both
Talley et al.[17] (n = 820)	14–90; median, 62 yr	4	NA	8	14	3	60	
Bytzer et al.[60] (n = 208)	Mean, 45 yr	15	NA	1.4	11	1	67	
Heikkinen et al.[61] (n = 400)	77% >44 yr	9	NA	4	15	2	55	
Bianchi Porro et al.[62] (n = 2229)	Median, 48 yr	34	NA	8	20	2	56	
Hungin[63] (n = 6744)	67% >40 yr	[a]	NA	[a]	17	1	35	[a]DU + GU = 15%
Ayoola et al.[64] (n = 10112)	8–96 yr	12	NA	2[a]	9	1	27	[a]GU = 1.2%; prepyloric = 0.5%
Stanghellini et al.[65] (n = 1057)	Mean, 39 yr	[a]	NA	[a]	10	1	64	[a]DU + GU = 21%

NOTE. Results are percentage of all patients with dyspepsia undergoing endoscopy. Not all endoscopic findings are included; therefore, the percentages do not necessarily add up to 100%.
DU, duodenal ulcer; GU, gastric ulcer; deformity, deformed duodenal cap; NA, data not available; normal, No sign of present or past peptic ulcer disease, cancer, or esophagitis.

However, the empiric therapy approach has been criticized because it may promote inappropriate prolonged use of H_2-receptor antagonists (the most frequently prescribed medical therapy for uninvestigated dyspepsia), weaken the value of subsequent investigation, mask the symptoms of malignant ulcers (and even heal such ulcers temporarily), and result, albeit rarely, in serious side effects.[27] A further problem is that if there is a high likelihood of symptom recurrence, this might lead to investigation in most patients eventually; an empiric approach therefore would not save resources.[27] In past analyses it has also been assumed that knowledge of the underlying diagnosis of dyspepsia would be unlikely to alter treatment.[26] However, the recognition that eradica-

Table 2. Findings on Esophagogastroduodenoscopy in the General Population

Study (no. of patients, design)	Age composition	DU (%)	Deformity (%)	GU (%)	Esophagitis (%)	Cancer (%)	Normal (%)	Note
Ihamäki et al.[66] (n = 358, matched controls)	15–65+ yr	1	4[a]	<1	NA	<1	≥48	[a]Scar in duodenum, stomach + BI + BII
Khuroo et al.[67]								
(n = 193 with dyspepsia, random)	≥15 yr	37 + 16[a]	2	5 + 2[a]	5	<1	>18	[a]Chronic + healed ulcer
(n = 177 no dyspepsia, matched)	≥15 yr	1 + 5[a]	1	0	1	1	>77	
Johnsen et al.[68]								
(n = 273 with dyspepsia, by questionnaire)	20–69 yr	[a]	NA	[a]	0	12	54	[a]DU + GU = 8%
(n = 273 no dyspepsia, matched)	20–69 yr	[a]	NA	[a]	0	8	66	[a]DU + GU = 4%
Katelaris et al.[69] (n = 197, random)	Mean, 28 yr	6	7	2[a]	1	1	≥49	[a]Only prepyloric, no gastric
Lond et al.[70] (n = 500 with dyspepsia, random)	Adults	9	NA	4	NA	NA	NA	

NOTE. Results are percentage of all individuals undergoing endoscopy. Not all endoscopic findings are included; therefore, the percentages do not necessarily add up to 100%.
DU, duodenal ulcer; GU, gastric ulcer; Deformity, deformed duodenal cap; NA, no data available; Normal, no sign of present or past peptic ulcer disease, cancer, or esophagitis; BI, Bilroth I; BII, Bilroth II.

tion of *H. pylori* essentially abolishes, in most patients, relapse of duodenal and gastric ulcer disease[71] strongly suggests that management strategies need to be reexamined. Others have therefore proposed management policies in which only patients at high risk of ulcer or cancer based on age,[49,72] symptoms,[29,44,72,73] or *H. pylori* status by serology[73–79] are investigated by endoscopy, with the remainder being treated empirically.

Few randomized controlled trials exist comparing immediate investigation with empiric therapy for patients with dyspepsia.[60] In the absence of definitive data, decision analysis can be used to compare alternatives using information available about the natural history of conditions causing dyspepsia, response of these conditions to therapy, and costs. Decision analysis is a useful method of quantitatively weighing up the different options when evidence is not available from clinical trials.[80] After a review of the relevant literature, a critical analysis of all the available decision analyses and trials is presented to evaluate the major alternative approaches and identify optimal management.

Differential Diagnosis of Dyspepsia

In patients with dyspepsia who are investigated, four major causes can be identified for their complaints: chronic peptic ulcer disease, gastroesophageal reflux (with or without esophagitis), malignancy, and functional (or non-ulcer) dyspepsia (Tables 1 and 2).[17, 31–65]

Structural Disease

A peptic ulcer is found in approximately 15%–25% of cases. A chronic duodenal ulcer is usually caused by *H. pylori* (up to 95% of patients are infected but this varies geographically); chronic gastric ulcer commonly results from *H. pylori* (approximately 70% of cases) or use of nonsteroidal anti-inflammatory drugs (NSAIDs).[71,81,82] Reflux esophagitis (defined as the presence of mucosal breaks) will be identified at endoscopy in 5%–15% of cases. The absence of reflux esophagitis at endoscopy, on the other hand, does not exclude gastroesophageal reflux[83]; the role of 24-hour pH testing in the situation in which classic reflux symptoms are absent is uncertain, but the yield is probably modest.[13,14,84] Gastric or esophageal cancer is found in <2% of cases. Gallstones cause a pattern of pain (typically severe, prolonged in duration, and episodic) that generally can be distinguished from other diseases and should not be confused with functional dyspepsia.[85,86] Chronic pancreatitis or pancreatic cancer is rarely later found to be a cause of apparently unexplained dyspepsia,[61] and celiac disease is also a very rare cause of dyspepsia.[87,88] Lactose intolerance may coexist with dyspepsia but is uncommonly confused with functional dyspepsia.[61] Other relatively rare causes of dyspepsia include medications (e.g., digitalis, theophylline, erythromycin), infiltrative diseases of the stomach (e.g., eosinophilic gastritis, Crohn's disease, sarcoidosis), metabolic disturbances (e.g., hypothyroidism, hypercalcemia), hepatoma, and intestinal angina.[84]

Functional Dyspepsia

Functional dyspepsia is defined as at least a 3-month history of dyspepsia in which there is no definite structural or biochemical explanation for the patients'

symptoms.[14] This diagnostic category accounts for up to 60% of patients presenting with dyspepsia.

The pathophysiology of functional dyspepsia remains obscure.[14] Putative mechanisms include disordered motor function (e.g., delayed gastric emptying with or without small intestinal dysmotility),[65,89–94] altered visceral sensation (e.g., gastric hypersensitivity to mechanical distention[95,96] and small intestinal hypersensitivity[94]), altered intestinogastric reflexes,[90] gastric acid sensitivity (meal-stimulated gastric acid secretion is not increased except possibly in a subgroup with *H. pylori* infection[97]), and psychological distress including abuse.[98–100] The detection of physiological abnormalities is largely confined to research studies because direct clinical relevance has yet to be documented.

Between 30% and 60% of patients with documented functional dyspepsia have *H. pylori*–induced gastritis. However, this infection is also common in the background population, and the prevalence increases with age.[23,82,101,102] Although an increased prevalence of *H. pylori* in functional dyspepsia has been reported in a recent meta-analysis,[101] this may be largely accounted for by confounding factors such as age, socioeconomic status, and past ulcer history.[102] Moreover, there is no association between *H. pylori* and any specific symptom profile,[103] and a benefit of anti–*H. pylori* therapy in functional dyspepsia is not established.[104,105] Therefore, patients with *H. pylori* are not currently excluded from the functional dyspepsia category.

Diagnostic Tests

The yield from upper endoscopy in patients being investigated for dyspepsia increases with advancing age.[49,96,97] Once a single adequate endoscopy has been performed, the value of most additional tests is at best marginal based on the data available.[51,58,84,106–108] Gastric emptying testing may detect delayed solid or liquid emptying in 25%–50% of patients with functional dyspepsia, but this usually does not alter management.[89,92] Ultrasonography of the gallbladder in dyspepsia has a yield of only 1%–3%, and the finding of gallstones is usually incidental.[13,51,58,108]

Even though the yield of endoscopy is low, missing gastric cancer is often of greatest concern to the clinician contemplating empiric therapy, especially in an older patient. Early diagnosis of potentially curable cases is of most interest.[53,109] Hallissey et al.[53] showed that an invasive strategy of immediate investigation (mainly endoscopy) in patients ≥40 years old, and particular perseverance in cases with high-risk conditions, increased the proportion of curable early gastric cancer among all detected cancers from 1% to 26%. Similar figures were found by Sue-Ling et al.[110] in a retrospective review. Contrary to these findings, Holdstock and Bruce in 1981 were unable to confirm any effect on prognosis in gastric cancer when comparing three geographical areas with an almost tenfold variation in endoscopy rates.[111] The literature is consistent with gastric malignancy in Western nations being very rare in patients <45 years of age.[49,106,108] Gastric cancer detection and treatment and fear of gastric cancer has to be taken into account when planning the management of dyspepsia.

Endoscopy Versus Barium Meal to Exclude Ulcer and Cancer

In family practice, upper gastrointestinal radiographs are still commonly used to exclude peptic ulcer and other diseases in patients with dyspepsia. However, endoscopy has consistently been shown to provide superior diagnostic accuracy in detecting structural causes of dyspepsia than radiography (Table 3).[38,112–114] Dooley et al.[114] found that in only 39 of 98 patients (40%), the initial clinical diagnosis subsequently was shown to be correct. Double-contrast barium meal increased this figure to 65%, and endoscopy increased the figure to 88%.

Longstreth[115] compared long-term (6 months) costs after endoscopy and gastroenterological consultation vs. costs after barium radiography in patients referred by primary care physicians due to incomplete response to

Table 3. Sensitivity and Specificity of Endoscopy vs. Double-Contrast Radiography

		Barium meal		Upper endoscopy	
Study, yr (no. of patients)	Diagnosis	Sensitivity	Specificity	Sensitivity	Specificity
Martin et al.[112] (n = 100)	DU	0.50	0.97	1.00	1.00
	GU	0.22	0.97	0.83	1.00
Greenlaw et al.[38] (n = 100)	DU	0.63	1.0	1.0	1.0
	GU	0.50	1.0	1.0	1.0
Shaw et al.[113] (n = 385)	DU	0.50	0.99	0.99	1.00
	GU	0.91	0.99	0.85	0.98
Dooley et al.[114] (n = 100)	All	0.54	0.91	0.92	1.00

DU, duodenal ulcer; GU, gastric ulcer; All, all organic diagnoses.

empiric treatment. There was a statistically significant advantage for endoscopy and gastroenterological consultation with respect to subsequent physician visits (mean cost, $33 vs. $114) and total costs ($134 vs. $435). Endoscopy was also generally preferred by more patients than barium radiography when, after the procedures, they were directly compared.[116]

Another advantage of endoscopy is that gastric ulcers can be confirmed to be benign by performing biopsies; the prevalence of unsuspected cancer in gastric ulcer disease in Western nations, however, is now very low, ranging from 0% to 3%.[117,118] Endoscopy allows gastric biopsy specimens to be taken to document *H. pylori* status; rapid urease testing (e.g., the CLO test) is relatively inexpensive, and is sensitive (80%–95%) and highly specific (up to 100%).[119,120]

The risk of upper endoscopic complications reported in the literature is very low, varying between 1 in 330 to 1 in 2700.[121,122] Cardiopulmonary complications are most common, varying from 1/690 and 1/2600, followed by perforation (1/900 to 1/4200) and bleeding (1/3400 to 1/10,000). Deaths due to upper endoscopy occur with a rate ranging from 1/3300 to 1/40,000. There has been a trend for complication rates to fall with time; the lowest figures have been reported most recently. Moreover, the above mentioned figures refer to overall rates (including therapeutic endoscopies, which account for a disproportionate proportion of the complications). Therefore, it can safely be assumed that the risk of simple diagnostic endoscopy at present corresponds to the lowest figures given here.

Endoscopy is therefore a safe and accurate test. If a decision is made to investigate a patient with dyspepsia, endoscopy should be the first diagnostic test performed. This is consistent with current ACP guidelines.[26]

Stratifying for Patients at High and Low Risk of Structural Disease

Because resources are always limited in relation to needs, directing diagnostic tests only to those with a high probability of benefiting from having their diagnosis definitely established (e.g., those with peptic ulcer, gastric cancer) is valuable. One predictive factor is age[49,106,123]; Williams et al.[49] noted that abnormal findings were made much more often in older people compared with younger people. The frequency of abnormal findings in older people was 69% by endoscopy and 58% by barium meal in that study; the corresponding figures for people <45 years of age was 40% and 25%, respectively.

Mann et al.[72] devised a scoring system based on age, gender, smoking, previous history of organic causes, and vomiting that reduced the number of endoscopic examinations performed by 30%, yet still detected 98% of serious disease. Davenport et al.[44] reported that preliminary screening through interview allowed separation of patients into low-, medium-, and high-risk groups. Patients predicted to have a low risk had a 0.3% chance of having cancer and a 10% risk of having an ulcer.

However, the transferability of such scoring systems from one population to another has been disappointingly limited.[56, 107] In a Danish study,[56] the performance of the Mann et al. scoring system[72] was explored in detail. To obtain an acceptable detection rate of major pathological conditions (sensitivity, 97%) a cutoff point had to be chosen that corresponded to a specificity of 9%, and the reduction in endoscopic examinations was a mere 8%. These results are in line with data provided by Sutton,[124] who found that the accuracy of computer-aided systems based on symptoms lay only in the range of 48%–62%.

Dividing patients with uninvestigated dyspepsia into clusters of symptoms (ulcer-like, dysmotility-like, or reflux-like dyspepsia)[14,19] also does not seem to aid in identifying organic dyspepsia, in part because of the extensive overlap of the groupings.[7,11,14,125,126] Indeed, subjects with ulcer-like dyspepsia do not have a substantially higher prevalence of chronic peptic ulcer than those with dysmotility-like dyspepsia.[17,21,68,122] Further, patients with reflux-like dyspepsia, which has been presumed to be more sensitive for identifying gastroesophageal reflux disease,[14] have a substantial prevalence (approximately 10%) of peptic ulcer disease.[17,63,127,128] Adang et al.[18] found that the diagnostic accuracy of history taking was even lower for esophagitis than for peptic ulcer. Similarly, management based on symptom clusters derived from identifying the predominant symptom rather than groupings of symptoms has been proposed.[29] However, the ability to detect or exclude organic disease with any symptom-based approach has not been established to be sensitive or specific enough to date.[16,18,54,128–130] Because the approach to peptic ulcer disease must now include attempts to permanently cure concomitant *H. pylori* infection, lack of a definitive diagnosis is a major limitation of an empiric symptom-based approach to planning management.

An alternative approach has been proposed to identify high-risk patients with dyspepsia based on screening by serology for *H. pylori*.[108] This infection is strongly associated with chronic peptic ulcer and, to a somewhat lesser degree, with gastric cancer.[71,75,76] Sobala et al.[75] found that if patients with dyspepsia ≥45 years old all underwent endoscopy, but endoscopy was restricted to patients <45 years old with either positive *H. pylori*

serology (using a highly sensitive and specific test) or NSAID takers, then such a strategy would reduce the endoscopy workload by 23% and would miss no cancers while having a sensitivity for detection of peptic ulcer of 97%. A similar conclusion was drawn by Mendall et al.,[76] who found a sensitivity of 98% and a specificity of 75% for ulcer disease while reducing the endoscopy workload by 42%.

On the other hand, in a recent Swedish study, 38% of women and 17% of men with gastric cancer were seronegative for *H. pylori*.[131] Moreover, another study found that half of those *H. pylori* positive with a serological enzyme-linked immunosorbent assay (ELISA) kit were breath-test negative.[132] A recent meta-analysis of the accuracy of the commercial ELISA kits[133] found the test cutoffs for sensitivity and specificity to be on average 85% and 79%, respectively, with the low and high extremes for sensitivity, 49% and 99% and for specificity, 63% and 85%. The performance of the breath test is better with an average sensitivity and specificity ≥90%,[2,119,134] although it might be reduced after treatment.[135]

Natural History of Dyspepsia

Patients with functional dyspepsia typically have a relapsing condition.[8,11,21,22,136–139] In one report,[139] 65% of those with dyspepsia at study entry reported the same symptom 3 years later. A U.S. study[8] found that 86% still reported dyspepsia after 12–20 months, and a British study[22] found dyspepsia was present in 74% of the cases after 2 years. Chronic peptic ulcer is also a relapsing disease unless *H. pylori* is eradicated or maintenance therapy is given; symptomatic relapse occurs in 50%–80% of patients over 1 year in both duodenal and gastric ulcer disease.[140,141] Most cases of reflux esophagitis are also probably chronic and will relapse in approximately 50%–80% of cases over a year if medical treatment is ceased.[8,142,143] The relapse of functional dyspepsia, ulcer disease, and esophagitis must therefore be taken into account in any management guidelines.

Decision Analyses on Management of Dyspepsia

Many investigators have used decision analysis to evaluate alternate strategies for the diagnosis or management of patients with dyspepsia. A systematic review of all published decision analysis was undertaken.[109,144–155] These decision analyses differ in the clinical problem addressed (peptic ulcer disease or dyspepsia), the perspective of the analysis, the time frame considered, the underlying causes considered in the analysis, the patients to whom the analysis is applicable, and the outcomes analyzed. Clinicians need to appreciate the methodological aspects of decision analyses to critically evaluate the literature, and more importantly, determine if the results of the decision analyses are applicable to the clinical problems encountered in their own practice setting.

Decision analyses classically use decision trees to graphically represent explicit alternatives considered in the analysis. Decision analyses consider the probabilities of events or outcomes and the values attached to the occurrence of clinical events and outcomes. These values or "utilities" may include costs, or other measures, for example the duration of time a patient experiences a particular condition, such as time free of duodenal ulcer[149] or time without symptoms.[150,151] Several methods of analyses may use decision trees. In a cost-benefit analysis, all outcomes or utilities are expressed in a common measure, most often monetary units, and strategies are recommended if the net benefits minus net costs are positive.[154] Other studies may separately include analyses of two or more utilities, such as costs and life expectancy,[109,144,151] whereas still others may combine a cost measure and an effectiveness measure to report cost per year of life saved,[144] cost per ulcer cured,[145] or costs and number of endoscopies and number of courses of antibiotics.[155]

An important consideration in the evaluation of a decision analysis is the specific question being addressed and the explicit alternatives being analyzed. Some analyses have addressed the diagnostic evaluation and treatment, often with inclusion of a strategy of empirical treatment.[109,144–147,149,151,152,155] Other studies have focused mostly on comparison of specific treatment regimens, such as H_2-receptor antagonists vs. antibiotics[146,151,152] or regimens with proton pump inhibitors.[153] A few analyses have addressed the role of maintenance therapy.[109,149,152] Only one study has evaluated the role of a surgical procedure, highly selective vagotomy, in the management of patients with peptic ulcer disease.[149]

Several of the decision analyses addressed patients with suspected or diagnosed peptic ulcer disease,[146,149–153] whereas others were of more clinical relevance and addressed the broader problem of the patient with dyspepsia,[105,144,145,147,151,154] or only *H. pylori*–positive dyspeptic patients.[155] The perspective of the analyses has also varied from a payer's perspective[109,145,148,150,155] to the perspective of a national health service[151] or managed care.[153] Finally, studies have differed in the extent of analysis of the robustness of the conclusions to changes in underlying assumptions about the structure of the problem, the probabilities of events, and the costs or utilities

assigned to clinical events and outcomes (sensitivity analyses).

One well done early study of strategies for diagnosis and management of dyspepsia found that the choice of an optimal strategy depended on the relative value placed on the outcomes analyzed because the strategies ranked differently on different measures such as mortality, morbidity, or cost[144]; an ulcer therapy strategy produced less morbidity and lower mortality but was more expensive compared with a symptomatic therapy strategy. "These findings support an individualized approach to the management of dyspepsia. No particular strategy should be dogmatically prescribed," the investigators concluded.[144]

Silverstein et al.[109] compared a strategy of managing patients with specific therapy guided by the results of endoscopy with empiric therapy prescribing H_2-receptor antagonists over a 1-year time frame. The endoscopy strategy assumed that all patients would undergo initial endoscopy and a course of treatment based on the endoscopy findings. Failures of therapy early or late after endoscopy were presumed to result in a return visit and a change in medication, but no repeat endoscopy. Also analyzed were the diagnostic strategies with the addition of maintenance therapy with an H_2-receptor antagonist following the first episode of dyspepsia, and strategies where initial serological testing with an accurate locally validated test kit for the presence of *H. pylori* infection was undertaken, with endoscopy or anti–*H. pylori* therapy reserved for patients with serological evidence of *H. pylori* infection, and empiric antisecretory therapy for the remaining patients. The analysis indicated that the 1-year medical charges for the initial management of an incident episode of dyspepsia was $2123 for empiric therapy compared with $2163 for endoscopy, a difference of approximately $40, or 2%.[109] The analysis was applied to young adults (age 40), middle-aged adults (age 55), and older adults (age 75), and in each age strata were applied to subsets of patients taking NSAIDs or having *H. pylori* infection. The decision based on medical care charges was a toss-up across all age and clinical strata. Initial serological testing for *H. pylori* actually slightly increased charges by 3% if the patient was offered endoscopy when serological testing was positive. However, a strategy of antimicrobial treatment if serology was positive and empiric H_2-receptor antagonist treatment if negative decreased charges by 2.5% compared with a strategy of endoscoping all patients initially. A strategy of reassurance but no medication for patients with an endoscopically established diagnosis of functional dyspepsia also did not alter the results in any substantial way. The findings were also essentially unchanged by analyses in which the costs of visits, tests, and medications were varied over reasonable ranges and the probabilities of response to therapy, recurrent dyspepsia, and risk of delay in therapy were varied. The results were confirmed in a Monte Carlo simulation in which the costs and probabilities in the decision analysis were sampled from probability distributions and the analyses were repeated. The conclusions were unchanged when alternate strategies using maintenance therapy, initial testing for *H. pylori*, or avoiding the use of H_2-receptor antagonists for known functional dyspepsia were analyzed.

Other investigators have found that empirical *H. pylori* therapy was much less costly and have therefore recommended this approach. Fendrick et al.[145] developed a model limited to persons with symptoms suggesting peptic ulcer disease. They found that the predicted costs per patient treated were lowest for serological testing for *H. pylori* (and treating seropositive cases) at $894 and empiric antisecretory therapy combined with antibiotics (for all cases) at $818; the most expensive strategy was endoscopy and biopsy for *H. pylori* at $1584. If an upper endoscopy is <$500, Fendrick reported that an investigation strategy was generally favored.[145] When Silverstein's model was applied to the costs used by Fendrick et al.,[145] it was found that only one quarter of the differences were explained by the higher costs for the initial endoscopy, and the rest were mostly related to the lower probability estimates of symptom recurrence and therapeutic failure.[109]

Ofman et al.[155] compared empiric eradication with treatment depending on the results of endoscopy in otherwise uninvestigated *H. pylori*–positive patients with dyspepsia. They found that empiric treatment was less expensive ($820 vs. $1276) because of a reduced use of endoscopy (52%), but at the cost of an increased use of antibiotics (252%). Ofman et al.[155] concluded that endoscopy-related costs had to be reduced by 96% before initial endoscopy and *H. pylori* treatment were equally cost effective in infected cases. However, the prerequisites were not directly comparable with the analysis by Silverstein et al.[109] because the applied rates of failure were lower, the costs of initial and return physician visits were less than half (66% and 55% lower, respectively), and the endoscopy costs were more than twice as high ($1211 vs. $500, respectively). When Ofman's assumptions[155] were applied in the Silverstein model, essentially the same results reported by Offman et al. were found; almost half of the original difference was explained by the difference in assumptions about early or late failure of treatment and recurrent episodes (Silverstein and Talley, unpublished observations, 1997). For example, Ofman et al. assumed a recurrence rate per annum of 55% in func-

tional dyspepsia compared with 70% in Silverstein's model.

Other decision analyses have suggested that the outcome of a strategy of *H. pylori* eradication may not produce the immediate benefits expected. Sonnenberg concluded that a significant cost-benefit could accrue with screening and treatment for *H. pylori* if at least 8% of infected patients with functional dyspepsia were cured by anti–*H. pylori* therapy, but suggested that such an approach should not be recommended until it is established that cure of the infection does relieve symptoms in functional dyspepsia.[154] Briggs et al. emphasized in their model that it would take at least 5 and possibly up to 18 years for any benefit to the community to emerge with a strategy of test and treat for *H. pylori* in dyspepsia.[151]

It is concluded that the results of all decision analyses critically depend on the assumptions included. Because these may not reflect true clinical practice and will certainly differ from region to region, the results of the decision analyses must be viewed very cautiously.

Trials of Management Strategies

There is some, albeit limited, empiric evidence that the frequently recommended conservative strategy of an initial trial of empiric therapy in younger patients before investigation is nearly as costly as a strategy of initial investigation and may be less satisfying to the patient.[60,156] In a randomized study in a family physician setting, Goulston et al.[157] compared an "Australian strategy," which required a positive diagnosis of an ulcer or ulcerative esophagitis at endoscopy or radiography before an H_2-receptor antagonist may be prescribed, and a "British strategy," according to which the patients were treated freely at the discretion of their family physician without necessarily being investigated. Costs of consultations, radiology, endoscopy and other tests, drug costs, personal costs, and total cost per patient were measured during a 6-month period after the initial consultation. The cumulative total cost per patient was equivalent in the Australian ($392) and the British ($406) groups, although the follow-up period of 6 months may have been too short to detect ulcer relapse, for example.

Goodson et al.[158] carried out a randomized study comparing traditional management including early barium meal with a less invasive plan that included reassurance and empiric treatment with high-dose antacids. Of those allocated to empiric care without investigation, 15% underwent radiography within 26 weeks. Symptom alleviation was similar in the two groups, but there was decreased intake of antacids and increased intake of H_2-receptor antagonists in the reassurance group. There was no difference in improvement in the patients' functional status (measured by the Sickness Impact Profile), but there was a tendency toward greater improvement among patients given traditional care for all three variables studied. Further, patients a priori preferred early investigation, although the satisfaction scores were similar in the two groups.

A well-performed randomized trial in dyspeptic patients requiring treatment compared prompt endoscopy followed by a sound selective use of H_2-receptor antagonists, including reassurance without drug treatment in those with functional dyspepsia ($n = 187$) vs. empiric H_2-receptor antagonist treatment with diagnostic endoscopy reserved for those who failed therapy ($n = 186$).[60] It was found that 66% of those randomized to empiric treatment eventually underwent endoscopy anyway during the first year of follow-up. The diagnosis of two cases of esophageal cancer was delayed 1 month by empiric treatment. After 1 year, dyspeptic symptoms and functional status had improved similarly in the two groups, but a significantly greater number of patients in the empiric treatment group were dissatisfied with their management and had lost more time from work. Moreover, 40% of the peptic ulcers were not diagnosed, and subsequently not adequately treated, with the empiric strategy. They concluded that a strategy of prompt endoscopy may be preferable to empirical H_2-receptor antagonist treatment.

An often overlooked factor in studies comparing empiric therapy with treatment determined by the results of an upper endoscopy is the positive therapeutic effect of upper endoscopy per se, even when no underlying disease is found. Lydeard et al.[25] observed that fear of a fatal disease was significantly greater among consulters compared with nonconsulters despite similar symptomatology. Hungin et al.[156] compared the health care consumption 1 year before with 1 year after endoscopy. General practice consultations and specialist referrals were reduced the year after, and drug therapy became more rational; those with no or minor abnormalities on endoscopy decreased, and those with major abnormalities increased their use of medications. However, this was not a randomized trial, and the results must thereby be viewed very cautiously, although they support the findings of Bytzer et al.[60]

This does not rule out a noninvasive strategy having a reassurance value comparable to endoscopy. Patel et al.[79] found that a negative noninvasive *H. pylori* test provided significant reassurance and symptom relief in young dyspeptic patients, but comparative data are needed. On the other hand, Lassen et al. reported preliminary find-

ings from a randomized controlled management trial in 475 patients comparing a ^{13}C-urea breath test strategy (and eradication therapy in infected patients) with an endoscopic strategy; at the 1-month time point, the endoscopy group had significantly greater symptom improvement and were more satisfied than the breath test group, but long-term data are not yet available.[159]

Treat or Investigate: A Close Call

Based on the literature review and review of the available decision analyses and trials, noninvasive testing and empiric *H. pylori* treatment seems to represent an acceptable strategy and may be the least expensive approach. How much will be saved in the long term over a strategy of endoscoping all cases on presentation largely depends on the costs of endoscopy, the cost of physician visits, and the symptom recurrence rate.

Recommendations to manage patients with dyspepsia by empiric *H. pylori* therapy may not necessarily result in expected savings in medical care costs if patients who fail to respond to therapy or who have recurrent episodes eventually undergo endoscopy. These costs will rise even further in patients who "doctor shop" and are offered repeat endoscopic procedures. Clinicians are likely to judge that patients whose symptoms do not respond to empiric therapy and patients who experience recurrent episodes of dyspepsia should have endoscopy.[26] Unfortunately, because the natural history of the conditions that commonly cause dyspepsia are associated with failures to respond to empiric therapy and high rates of recurrent episodes of dyspepsia, actual savings in costs may be modest with an empiric therapy strategy. Indeed, even in peptic ulcer patients who are cured of *H. pylori* infection, upper gastrointestinal symptoms commonly recur, which may in part be explained by the development of reflux esophagitis.[160] The decision will also need to be reevaluated when new trials establish whether or not cure of *H. pylori* also cures a proportion of patients with functional dyspepsia.

Thus it is not established that strategies to avoid endoscopy, such as screening for *H. pylori* status, will actually produce substantial savings in the long-term. Randomized controlled trials in clinical practice of different management strategies are now needed to provide adequate empiric evidence to guide physicians and health policy.

Conclusions

While management must be individualized, based on the available evidence the following is concluded regarding strategies for management of new adult patients with chronic or recurrent dyspepsia in Western nations. Endoscopy remains the gold standard approach because it is still the optimal means of establishing a firm diagnosis, targeting therapy, and providing adequate reassurance. Prompt endoscopy is always indicated in older patients or in those with alarm features such as weight loss. This is not controversial, but more work is needed to identify optimal clinical predictors of serious underlying disease. Repeat endoscopy in those with an initially negative result must be avoided if costs are to be reasonably maintained. On the other hand, in patients without alarm features the role of prompt endoscopy remains in contention. Where endoscopy costs are high or endoscopy lists are long, a prompt endoscopy strategy is unlikely to be cost-effective or practical.

An alternative management strategy in young cases without alarm symptoms that has increasing empirical support is testing for *H. pylori* infection. The key issue then is whether to obtain endoscopic confirmation in patients who are *H. pylori*–positive based on noninvasive testing or treat all positive cases.

This alternative management strategy relies on accurate noninvasive *H. pylori* testing using a locally validated method, a background prevalence of *H. pylori* in the population that is not universally high, and adequate follow-up to investigate those with recurrent or continuing symptoms. The major advantage of treating rather than immediately undertaking endoscopy in infected cases is that the former approach is likely to be the most cost-effective and convenient because the ulcer pool will be removed and presumably fewer endoscopies in the long term will be required. Moreover, noninfected patients will have a high probability of being spared undergoing a normal endoscopy. Patients who know they are infected will also be more likely to request treatment regardless of the results of endoscopy, and physicians are most likely to prefer undertaking a treatment strategy initially. The disadvantages of this approach are also substantial. Increased levels of antibiotic resistance may occur in the community. Using current serology tests, there is a risk of both overtreatment because of false-positive results, and undertreatment because of false-negative test results. The benefits in functional dyspepsia are likely to be small or nonexistent. Furthermore, cancer and ulcer disease will occasionally be missed, and reflux esophagitis may be unmasked. The reassurance value of this approach also remains to be established. Moreover, the long-term outcome of treating all infected dyspeptic patients with anti–*H. pylori* therapy remains inadequately documented and needs close monitoring in the community.

The evidence does not favor an empiric *H. pylori*–

treatment approach without serological or breath testing. An approach of initial empiric antisecretory or prokinetic therapy for all patients is also probably less appropriate because this is likely to provide the least patient reassurance, may only delay diagnostic testing in the long term, and may promote inappropriate long-term medication use.

The decision to choose empiric therapy, *H. pylori* testing, or initial endoscopy should be based not only on cost, but also on other considerations such as patient and physician attitudes toward uncertainty, the ethics of not identifying a curable disease such as peptic ulcer or cancer, patient satisfaction, institutional or societal forces to restrain the use of diagnostic procedures, and the background prevalence of disease. Guidelines may therefore reasonably endorse any of these management approaches depending on the weight of circumstances in different regions. The results of community-based randomized controlled trials of management strategies may modify these conclusions.

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