HENK BOO'T
BABS G. TAAL
Departments of Pathology and Gastroenterology
The Netherlands Cancer Institute
Amsterdam, The Netherlands


Reply. We appreciate the stimulating discussion by de Jong et al. to our recently published article. In the study of de Jong, 2 in which in vitro–cultured H. pylori strains for the analysis of the CagA status were used, the following steps of strain selection may have occurred. First, by PCR assay, only the CagA status of single H. pylori colonies was tested. However, a high percentage of patients is infected simultaneously with two or more strains having different CagA genotypes. Second, as discussed by Cover et al., H. pylori can spontaneously lose the CagA gene during in vitro passage. Third, the low culture rate of H. pylori from patients with gastric MALT-type lymphoma (the bacterium was successfully cultured in only 12 of 30 patients) may additionally contribute to a strain selection. Fourth, further selection of H. pylori strains may be favored by treatment with chemotherapy or radiotherapy, which was performed in the study of de Jong et al. in about one third of the patients with MALT-type lymphoma before testing the CagA status.

In contrast to PCR analysis of in vitro cultured strains, serological testing permits the detection of an antibody response to all infecting H. pylori strains regardless of their relative concentration in the stomach. Therefore, serology is generally thought to be the more accurate method for the detection of the CagA status.

One of the two articles cited by de Jong et al. lack controls for validating the CagA enzyme-linked immunosorbent assay 3 and the other is a review article without original data. Witherell et al. found a moderately increased risk for gastric lymphoma in CagA+–infected individuals and concluded that CagA+ strains may be at higher risk than CagA− ones.

Additionally, geographical differences in the prevalence of circulating H. pylori strains may be responsible for discrepant results of the CagA status, a phenomenon already presumed for the lack of correlation of CagA+ strains with peptic ulcer disease and gastric carcinoma in some studies.

We agree with de Jong et al. that a positive serology indicates that infection with a CagA-positive strain has occurred in the patient during his lifetime and does not necessarily reflect the present CagA status. Studying the mucosal immune response in the stomach may be a better approach for testing the present CagA status. Therefore, we investigated in a new study the humoral immune response of the gastric mucosa by microculture of gastric tissue. In 9 patients tested so far, who were all part of our former study, mucosal and serological immune response to CagA were identical (8 CagA-positive patients, 1 CagA-negative patient).

Nevertheless, the presence of CagA in a high percentage of patients with gastric MALT-type lymphoma is not evidence for a role of CagA in the pathogenesis of this disease. However, D’Ellios et al. recently found that even at T-cell level, CagA is an immunodominant antigen in patients with H. pylori–induced gastritis. They have shown that CagA-positive T-cell clones act as potent helper cells for B-cell proliferation. This may represent an important mechanism leading to an uncontrolled B-cell proliferation and neoplastic transformation as hypothesized by the authors. These data underline that CagA+ strains of H. pylori may, together with additional up to now unknown factors, play a role in the development of gastric MALT-type lymphoma.

MATTHIAS ECK
BERND SCHMAUßer
AXEL GREINER
HANS KONRAD MÜLLER-HERMELINK
Institut für Pathologie
Universität Würzburg
Würzburg, Germany

Cost of Endoscopy in Economic Evaluation

Dear Sir:

We read with great interest the study by Heudebert et al. 1 in the April 1997 issue of Gastroenterology in which different treatment strategies were compared in patients with severe esophagitis. It was of special interest because we have also carried out an economic evaluation to compare different treatment strategies in patients with dyspeptic symptoms reported at the 1997 Digestive Week in Washington. In comparing the results, we noticed the high price ($1105) used by Heudebert et al. 1 for upper gastrointestinal endoscopy in the
cost-utility analysis. A review of the literature showed that in economic evaluations, the cost for upper gastrointestinal endoscopy varies substantially between studies. For example, in the January 1996 issue of GASTROENTEROLOGY, Silverstein et al.\(^1\) used a charge of $500 for endoscopy, whereas the cost for an upper endoscopy in the study by Ofman et al.\(^1\) was $555.61.

Because the cost used in economic evaluations may have a major influence on the results, uniformity is required. In the studies mentioned above, the third-party payer perspective was used implicitly. This means that reimbursement charges were used for the analyses. However, these charges can deviate from the real cost, which is relevant in the case of a societal perspective.\(^4\) In our study, we analyzed the real cost for upper gastrointestinal endoscopy at the University Hospital Nijmegen in 1993. The real cost for upper gastrointestinal endoscopy without hospital overheads was $103, which is only 29% of the reimbursement charge ($355).\(^5\)

We used the following concept for calculating the real cost,\(^6\) which can be broken down into three categories: fees, hospital charges, and overhead. First, upper gastrointestinal endoscopy normally takes half an hour and requires one physician ($43) and one supporting nurse ($10).

Second, the cost of equipment and materials used, administrative staff, and maintenance were calculated on the basis of the total cost of the endoscopy department divided by the total number of procedures performed in 1 year; the different types of endoscopy were weighted according to time needed to do each one ($50). In another study we have recently calculated a figure for hospital overheads, such as housing, energy, and a general department ($22). This figure was partly based on the hospital expenditure per square meter for housing and energy. In addition, the cost of personnel at nonmedical departments was used to calculate the cost per full-time equivalent employee at the endoscopy department. This $22 should be added to the previous categories.

Cost used in economic evaluations should approximate opportunity cost. Thus, in general, calculating the real cost or adjusting the figures should be considered instead of using the charges as they are.\(^6\) There will always be differences in the cost of diagnostic or therapeutic interventions between countries and even hospitals. Methods used to calculate cost should be clearly reported in a standardized way and broken down into cost categories (hospital charges, fees, overheads). This will make it easier to compare the results of cost analyses and provide more information on which to base cost estimates.\(^6\)

R. J. F. LAHEIJ
Department of Gastroenterology
University Hospital Nijmegen

J. L. SEVERENS
Department of Medical Informatics, Epidemiology, and Statistics
University of Nijmegen
The Netherlands


**Reply.** We read with interest the comments by Laheij and Severens. Although we agree with their overall comments, several of their statements require clarification and explanation.

We wish to make clear that our cost-effectiveness analysis was explicitly, not implicitly as the authors suggested, modeled from the perspective of the third-party payer. In contrast to many European countries in which the general population is covered through a National Health Care Plan, most individuals in the United States are under either traditional indemnity, capitated, or government-sponsored (Medicare/Medicaid) coverage. Because patients with severe gastroesophageal reflux disease are usually in their fourth or fifth decade of life (base case analysis considered 45-year-old otherwise healthy male), it is very likely that the health care coverage in the United States of such individuals would be carried by nongovernment sources. As such, we felt the third-party perspective was the most pragmatic for generalizability purposes.

Four major issues with the cost estimate for esophagogastroduodenoscopy (EGD) used in our model deserve explanation. First, the authors of the letter are correct in pointing out the differences between our model and that of Silverstein et al.\(^1\) However, applying our institution cost per charge ratio of 0.42, the revised figure is approximately US$450, much more in accordance to the Silverstein et al. cost estimate of US$500.

Second, from the third-party perspective, the "true" cost estimate does not reflect the actual cost incurred in the management of insured individuals who required an EGD. Third, attempts to reconcile EGD costs from Silverstein et al. and our model to the cost estimate presented in the letter (US$103) would be irrelevant because their estimate reflects salaries and going purchasing prices for supplies at their institution that are not comparable to true resource use in the United States. Finally, and more importantly, EGD was not a sensitive parameter in our model. In our sensitivity analysis, we considered an EGD cost as low as US$700, which did not alter the results of the analysis; decreasing the cost of EGD further to $400 had similarly negligible effects on the cost estimates of both the surgical and medical strategies. Our model, however, was sensitive to medication cost, which can only be estimated by using published average wholesale prices (i.e., Red Book) or surveying retailers, which without a doubt are not reflective of true resource consumption.

The recently convened Panel in Cost-effectiveness Analysis\(^5\) has recommended using the societal perspective in what they have defined the Reference Case and then including updated cost-effectiveness and marginal cost-effectiveness figures based on the authors' preferred perspective. Although we understand the arguments for such recommendation, we believe that the third-party payer perspective captures the best audience for our model.

GUSTAVO HEUDEBERT
Division of General Internal Medicine
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama


Correction


In the Correspondence section, the corrected author list should have appeared in the format and order as follows:

Douglas A. Corley, M.D., Warren M. Gold, M.D., Bruce F. Scharschmidt, M.D., Kenneth A Somberg, M.D., and Nathan M. Bass, M.D., Ph.D.
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Image of the Month Answer

Answer to Image of the Month Question (page 1822): The EGD image shows mucosal thickening and a polypoid mucosal surface. Similar findings were seen in the duodenum and colon, especially the rectum. Mucosal biopsy of the gastric antrum (not shown) showed a polypoid mucosal surface with basal cystically dilated glands, varying degrees of foveolar hyperplasia, mild nonspecific inflammation, but marked lamina propria edema and expansion. Interpreted in the proper clinical context, the histological findings were suggestive of Cronkhite-Canada syndrome (CCS). This led to repeat examination of the patient. She had hyperpigmentation of the palms, face, and dorsa of her fingers, as well as variable onycholysis and onychodystrophy of all her nails. She also had thin, sparse scalp hair. A diagnosis of Cronkhite-Canada syndrome was made.

CCS is a rare, sporadic disorder, with a 3:2 male to female ratio. Although not emphasized in the literature, 75% of reported cases are from Japan. Patients with CCS present in later adult life, at a mean age of 60 years. The most common gastrointestinal symptoms are nonbloody, protein-losing diarrhea, pain, and weight loss. Patients may have melena or hematochezia depending on the degree of erosive lesions. Gastrointestinal polyps are seen in 52%-96% of patients and have overlapping histological features with hyperplastic and juvenile retention-type polyps. Basal cystically dilated glands/crypts with marked lamina propria edema and expansion are characteristic. Hyperpigmentation (hypermelanosis) is usually diffuse with accentuation over the face, neck, and extremities (85%). Mucous membranes are spared, and there is mucosal pigmentation of the dorsum of hands. Alopecia (95%) is initially patchy with thin, sparse hair resembling alopecia areata, but can progress to complete baldness. It usually occurs parallel with onychodystrophy/onycholysis (90%). These cutaneous changes often resolve with treatment and may do so spontaneously despite ongoing gastrointestinal disease. Hypoalbuminemia is common and is accompanied by peripheral edema.

Death is generally caused by malnutrition. Dysplastic change or malignant degeneration is reported and may occur in up to 15% of patients. Surgery is harmful and corticosteroids are of little to no benefit. Total parenteral nutrition has led to complete resolution, and the current mainstay of therapy for CCS is aggressive nutritional support. Our patient was treated with protein infusions, followed by maintenance on a high-protein diet and Imodium (2 mg orally four times daily). The patient’s gastrointestinal symptoms, hypoalbuminemia, and edema have all resolved.

For submission instructions, please fax the Editorial Office at (301) 951-0757, or write to: Editorial Office, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814-3015.