Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice

EDITOR,—I was interested to read the paper by Eggleston et al (Gut 1998;42:13–16) purporting to show that a “step up” approach using prokinetics and H2 receptor antagonists in the management of gastro-oesophageal reflux disease (GORD) is more cost effective than omeprazole in a general practice setting. I do not think the conclusions drawn are supported by data presented.

The MediPlus database does not permit systematic evaluation of the severity of GORD symptoms and so there is no certainty that the three patient groups (who received omeprazole, ranitidine or cisapride) were comparable. Patients were excluded from the study if they had initially been referred to hospital (<13%) because they were regarded as suffering from “more complicated GORD”. No evidence is presented for this assertion. It is well recognised that there is no correlation between the severity of a patient’s symptoms and the extent of any oesophagitis.1,2 The fact that patients on omeprazole received more prescriptions in the six month study period (2.96) than those on cisapride (1.83) is further evidence that the groups were not clinically comparable. Cisapride (1.85) is further evidence that the validity of findings on drug therapy appears to be a particular problem with...omeprazole and ranitidine, and represents a rationality of the decision to intervene, treating of this powerful drug on a highly selected population of patients with an additional benefit with a diagnosis of dysphagia or complicated gastro-oesophageal reflux disease (GORD). In studies of the effects of treatments, non-randomised comparisons can be affected by confounding factors and in our opinion this has resulted in the wrong conclusions being drawn from this study. Therapeutic interventions are commonly prompted by an indication. Primary care physicians selectively treat patients exhibiting more severe GORD with omeprazole and less severe symptoms with cisapride or ranitidine. Thus, by the very rationality of the decision to intervene, treatment differs between patients with GORD with respect to reducing...quality of life and heals the underlying pathology, preventing the development of complications such as stricture, and reducing hospital referrals.

The paper makes no evaluation of clinical success, basing the evaluation entirely on cost with the implicit assumption of equivalence in clinical efficacy between omeprazole, ranitidine and cisapride, which many other controlled studies have shown not to be the case.

The conclusions drawn by the authors are also flawed. The authors have provided no evidence that the “stepped approach” is appropriate in GORD. Many studies have confirmed that omeprazole is more cost effective.3 The recent reduction in the price of omeprazole makes this cost advantage even greater.

The conclusion, “such chronic dependence on drug therapy appears to be a particular problem with...omeprazole and represents a further argument in favour of a step up approach aimed at initially targeting prescribing...” is not supported by the evidence from the study nor by references. Moreover, the keenness of patients to take omeprazole is a reflection of its effectiveness. Given the central role of gastric acid in GORD reducing oesophageal exposure to this corrosive agent is a rational approach to the management of this disease. Antacid/alginate combinations provide short lived symptom relief. The H2 receptor antagonists and cisapride have some efficacy in treating GORD but there is now abundant evidence in the literature to show that proton pump inhibitors are the most effective agents in this disease. Unlike the H2 receptor antagonists, proton pump inhibition does not suffer from the drawback of tolerance, and omeprazole heals regardless of the grade of oesophagitis on endoscopy. Successful resolution with omeprazole is a better indicator of healing of any underlying oesophagitis than with H2 receptor antagonists.

In conclusion, treatment with proton pump inhibitors provides cost effective management across the GORD spectrum, resolves patients symptoms, improves their quality of life, reflects an underlying pathology, preventing the development of complications such as stricture, and reducing hospital referrals.

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REFERENCES

Cost effectiveness of treatment for gastro-oesophageal reflux

EDITOR,—Eggleston et al (Gut 1998;42:13–16) concluded from their observational study that the “step up” approach, starting with a prokinetic or H2 receptor antagonist, represents the most cost effective initial therapeutic strategy for the treatment of patients with a diagnosis of uncomplicated gastro-oesophageal reflux disease (GORD). In studies of the effects of treatments, non-randomised comparisons can be affected by confounding factors and in our opinion this has resulted in the wrong conclusions being drawn from this study. Therapeutic interventions are commonly prompted by an indication. Primary care physicians selectively treat patients exhibiting more severe GORD with omeprazole and less severe symptoms with cisapride or ranitidine. Thus, by the very rationality of the decision to intervene, treatment differs between patients with GORD with respect to the outcome criterion in efficacy assessment.

The authors minimised confounding by indication by excluding 511 of 790 patients with a diagnosis of dysphagia or complicated GORD or whose condition was sufficiently complex to require immediate specialist referral. Restricting subject selection indeed prevents confounding by indication, but introduces a change in the magnitude of the effect measured, which is called effect modification. By only evaluating patients with uncomplicated GORD, the difference in the effect measured between cisapride, ranitidine and omeprazole treatment will decrease. Many randomised clinical trials have shown that in patients with GORD omeprazole provides more rapid and complete healing of associated symptoms than ranitidine or cisapride.1 Therefore, it is misleading to minimise confounding by restricting subject selection, unless it can be assumed that there are no differences in treatment effect between patients. To control for confounding, several other options are available. However, even when confounding factors are taken into account, the validity of findings on drug benefits in non-randomised studies may still be questionable.

Besides confounding by indication and effect modification, the authors misused the term cost effectiveness.2 Cost effectiveness analysis is one form of full economic evaluation in which both the cost and consequences of treatments are examined.3 Eggleston et al assumed equivalence in therapeutic outcome between the cisapride, ranitidine and omeprazole therapies on the basis of retrospective analysis of prescription data. If this assumption is correct then the design of their study should be called a cost minimisation analysis. The term cost effectiveness should be restricted to studies in which the result can be described as having an additional benefit worth the additional cost. To determine which treatment strategy has additional benefit worth the financial effort, more information is required about symptom relief. Furthermore, the clinical differences in cost cannot be verified without the use of statistical testing. Although statistical testing of cost and cost effectiveness ratios is not as obvious as statistical testing of outcomes, methods are currently being developed to overcome these limitations.4

In conclusion, the study by Eggleston et al has several methodological shortcomings which have led to unfounded and therefore incorrect conclusions. To avoid the limitations of this study, a prospective randomised trial with representative patients must be carried out to determine which treatment approach, “step up” or “step down”, is best for treating patients with GORD and dyspeptic symptoms in general.

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Cost effectiveness of treatment for gastro-oesophageal reflux disease

EDITOR,—A reading of the recent article by Eggleston et al (Gut 1998;42:13–16) left several unanswered questions and concerns. The first issue was the authors’ statement that clinical equivalence between cisapride, ranitidine, and omeprazole had been established for uncomplicated gastro-oesophageal reflux disease (GERD). Standard practice, to my knowledge, there are no published studies which have reported a similar finding of clinical equivalence of omeprazole to either cisapride or ranitidine. A quick review of the literature revealed 11 studies in which omeprazole was statistically significantly better than cisapride or ranitidine in GORD.1–11

In a review of the reference abstract12 in which the case for clinical equivalence is postulated, the conclusion of equivalence was highly dependent upon the authors’ definition of treatment failure. I take exception to the authors’ definition that use of medication for longer than three months was a therapy failure. In the databases analyzed this does not have the ability to distinguish between continuing a medication in order to maintain successfully achieved symptom resolution and continued use of medication due to uncertainty of symptom resolution. Initiation of maintenance therapy after successful symptom resolution would not require any change in dosage in the case of omeprazole as 20 mg once daily is the recommended dose for long-term maintenance. Defining success as any use of medication for less than three months that did not involve a change in drug also opens up the possibility of misclassification. Those patients who stop using a drug as a result of treatment failure and who do not return for further care would not only be misclassified in this retrospective analysis as a success but could erroneously contribute to a lower economic burden in the therapy groups. As the selection methods, the authors stated that case records for a total of 257 patients were evaluated. However, there is a discrepancy between the abstract and the manuscript on the number of eligible patients. The abstract tells us that 257 patients and the manuscript refers to 257 patients. Additionally, why do the authors, with a database like MediPlusTM UK, which has more than one million patients, end up with a sample size of only 257 patients?

In the Discussion, the authors state that if more severely affected patients were selectively treated with omeprazole, one would expect to see increased non-drug resource use in this group. Since this did not occur, the authors consider this as supportive evidence that they had effectively controlled for this selection bias. An alternative explanation for the finding is that patients taking omeprazole were more severely ill due to physician selection bias but omeprazole has superior clinical efficacy in GORD compared with ranitidine and cisapride thus the omeprazole patients resource utilisation level is a reflection of a reduced proportion of patients that would be the case with any other treatment.

The authors do not state whether the general practitioner (GP) consultations attributed to the drug treatment groups were all specifically for GORD. No information was provided as to how the authors have separated our GORD related GP consultations from visits for other illnesses. Such a process should be accomplished by a reviewer blinded to treatment allocation, if under taken. The absence of information leads to a conclusion that the amount of GP consultations in table 1 represents visits for all health reasons. As treatment would have had a positive effect on reducing GORD related visits over the period of observing any difference between treatment groups would be diminished, resulting in the finding displayed in table 1.

The authors have based their analysis on an assumption of clinical equivalence which, in this case, is beyond the power of retrospective analysis to prove. Even if the three medications were clinically equivalent, there are a number of other unanswered questions from the manuscript that make it difficult for an unqualified acceptance of the authors’ conclusions.

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Reply

EDITOR,—We welcome the quantity and nature of the feedback but disappointment at the quality of the comments. The Nijmegen group question the “inappropriate” use of the term “cost effectiveness analysis” which is often used to refer to all forms of economic evaluation. The term, however, more properly refers to a particular type of evaluation in which costs are defined and measured in natural units and
costs are measured in monetary terms. Our analysis is structured in a manner that facilitates a direct comparison of the costs per patient relieved of symptoms. Such a structure enables outcome variations to be directly incorporated into the analysis as and when sufficient evidence is generated. Information about cost is useful only when considered jointly with information about clinical outcomes and further research concerning the long term cost and outcome of treatment is currently in progress.

The Nijmegen group’s reference to “effect modification” and its potential effect of diluting variations between the therapeutic options is irrelevant in the context of our paper. The aim of good prescribing is to select the most general population of patients to ensure that the therapeutic requirements of individual patients are optimally met by the prescriber. Obviously, in their day to day workload primary care physicians also frequently encounter patients with recurrent GORD as well as with H$_2$ refractory and complicated GORD. Cost effectiveness calculations on “undefined” GORD would inevitably favour omeprazole given that it causes the greatest suppression of acid secretion in patients with severe disease. We make no claims concerning the applicability of the analysis to undefined GORD but simply assert that the extent of acid suppression generated by omeprazole may not be necessary for first episodes of uncomplicated GORD. If this is the case, then hard pressed clinicians will be able to conserve their scarce health care resources for investment elsewhere.

Dr Crawley questions the numerical basis for the analysis. Our sample was generated as a random selection from the entire eligible Mediplus database for 1995 using the software random number based sample selection function. The sample chosen was selected on the basis of manageability given that an individual review of each patient record was required. The reduction from 279 to 257 patients was simply to increase the level of patient homogeneity as outlined in the original paper. Both Crawley and Bate also refer to a large body of evidence supporting the clinical and economic superiority of omeprazole. Unfortunately, for our purposes the vast majority of such evidence is irrelevant given that it does not specifically analyse prescribing in practice for new patients at the primary care level with mild to moderate GORD. Dr Crawley’s belief in the superiori of omeprazole due to the lack of need for dose titration is puzzling. The British National Formulary’s recommendation for GORD is for 20 mg daily for four weeks, followed by 40 mg for four to eight weeks as required, reduced to 10 mg for long term management, increased to 20 mg if symptoms recur. Dr Crawley’s further belief that patients may respond to treatment failure by simply doing nothing also is difficult to substantiate. It is reasonable to assume that individual patients exhibit a personal threshold of tolerance to the symptoms of GORD above which they seek professional advice. Such a threshold will vary significantly between patients but is likely to be fairly stable within the same patient. In such circumstances it is difficult to see why a patient would not seek further professional advice in cases where the initial prescription did not reduce symptomatology below their personal threshold.

Many of the issues raised reflect the fact that many gastroenterologists only come into contact with the tip of the iceberg with regard to GORD. By supporting 95% of patients without recourse to specialist advice, primary care physicians ensure gastroenterologists encounter a very thin slice of reality with regard to the overall management of GORD. The vast majority of treatments are initiated without prior investigation and where empiricism is successful such patients do not come to the attention of gastroenterologists. Although this may be appreciated intellectually by gastroenterologists, our paper provides powerful re-enforcement of the nature of the division of labour between primary care physicians and gastroenterologists in the treatment of reflux disease.

Diagnostic value of T cell reactivity in drug induced hepatatitis

Borron, I read with interest Maria and Victorino’s work (Gut 1997;41:534–40) on the diagnostic value of specific T cell reactivity to drugs in 95 cases of drug induced liver injury. They are to be congratulated on assembling the largest group of patients with suspected drug induced hepatotoxicity and attempting to assess causality using their lymphocyte test. In their discussion, when referring to the clinical significance of the presence of prosta
glandin producing suppressor cells in vitro, they state that, “patients in which this phenomenon was detected had a less severe disease, as assessed by aminotransferase concentrations and more rapid cure.” There is another potential clinical significance to the interpretation of our in vitro results and that is that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepato
toxicity, is a very interesting possibility. Our own epidemiological data are consistent with the results of the epidemiological study presented by him, showing that patients taking NSAIDs have an increased risk of developing liver injury induced by other drugs. In fact, we compared the frequency of NSAID consumption in our population with drug induced liver injury with two different adult populations integrated into prospective studies, one consisting of patients admitted to our internal medicine unit in the University Hospital and the other consisting of patients followed in the primary care setting (table 1). Patients with drug induced hepatitis took significantly more NSAIDs than the control populations (x$^2$ test, p<0.0001). Although all epidemiological evidence suggests that NSAIDs increase the risk of hepatotoxicity from other drugs, the possibility that this could have an immunological basis

<table>
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<th>NSAID</th>
<th>Hepatotoxic</th>
<th>Controls</th>
<th>Cases</th>
<th>Odds ratio</th>
<th>95% CI</th>
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<td>7</td>
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<td>99</td>
<td>5</td>
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<td>6.9</td>
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<td>11.6</td>
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CI, confidence interval.

Table 1 Risk of admission to hospital with drug induced liver injury in those taking NSAIDs plus one other drug known to cause sporadic liver injury

Patients with drug induced hepatitis | Patients admitted to hospital | Population of a health centre |
---|---|---|
Number of cases | 136 | 277 | 1723 |
Mean age | 46.7 | 63.9 | 44.6 |
Number taking NSAIDs | 43 | 40* | 206 |
Percentage | 32 | 14 | 12 |

* Took NSAID in the 15 days prior to admission.

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Reply

Editor,—We showed that the in vitro phenomenon of putative prostaglandin producing suppressor cells demonstrated in patients with drug induced hepatitis was significantly associated with a less severe form of disease and a more rapid cure. It is possible to speculate that this in vitro phenomenon could also occur in vivo and play a part in the down regulation of the immune response triggered by the drug or its metabolites.

We think that Dr Bartle’s point suggesting that there is another potential clinical significance to the interpretation of our in vitro results, namely that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity, is a very interesting possibility. Our own epidemiological data are consistent with the results of the epidemiological study presented by him, showing that patients taking NSAIDs have an increased risk of developing liver injury induced by other drugs. In fact, we compared the frequency of NSAID consumption in our population with drug induced liver injury with two different adult populations integrated into prospective studies, one consisting of patients admitted to our internal medicine unit in the University Hospital and the other consisting of patients followed in the primary care setting (table 1). Patients with drug induced hepatitis took significantly more NSAIDs than the control populations (x$^2$ test, p<0.0001). Although all epidemiological evidence suggests that NSAIDs increase the risk of hepatotoxicity from other drugs, the possibility that this could have an immunological basis

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has to be viewed with caution. In fact, it has been shown that prostaglandin E, has a protective effect in cases of hepaticosis induced by hepatotoxic agents and cytotoxic viruses, both in animal models and in humans, suggesting that a non-immunological mechanism may also be involved in this association.

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Supporting evidence. "...pylori eradication is strongly recommended in..." A sentence based on "unequivocal evidence such as functional dyspepsia..."


Guidance for trials in Helicobacter pylori infection

EDITOR—Your prestigious journal has recently published a supplement on guidelines for clinical trials in Helicobacter pylori infection (Gut 1997;41(suppl 2):S1-23). We welcome these guidelines, and as it would be expected from the authors’ experience and background, the term excellent would surely be adequate to describe the three different papers contained in the supplement. There are, however, at least two key points that merit discussion before these guidelines are generally applied by the scientific community.

Firstly, a methodological point. Double blind, randomised, controlled, well planned and developed trials do provide very sound and solid scientific evidence for evaluating efficacy. However, other types of trials, even uncritical, can give very valuable data on effectiveness, and cannot be discarded as long as methods and analysis are correct. In fact, some of the most cited articles are uncontrolled but very elegant studies and some are even not randomised. Sometimes the methodological rules are avoided but good science is produced.

Secondly, an ethical point. In the guidelines the following sentence is included, “In phase III studies, aiming at regulatory approval of a new drug regimen, one of two..." This sentence is clearly in conflict with the Declaration of Helsinki, mentioned as an ethical reference by the authors on the same page. As recently pointed by Angell, the Declaration of Helsinki states, “In any medical study, every patient—incuding those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.” If prospective study subjects have peptic ulcer disease, current recommendations are mandatory. H pylori eradication therapy should be..." In fact, the same group of authors have very recently stated in Gut that, “...H pylori eradication is strongly recommended in all infected patients with a diagnosis of duodenal or gastric ulcer disease, past or present... a sentence based on “unequivocal supporting evidence.” I think that patients should come first and methodology second, and strongly suggest that this sentence should be removed from the guidelines, or at least limited to pathologies with “equivocal” evidence such as functional dyspepsia.

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Figure 1 Predictive value of a positive serological test for Helicobacter pylori infection in patients with duodenal ulcer. Positive predictive value = 72/(72+2) × 100 = 97.2%. Patients with duodenal ulcer are assumed to have a 90% prevalence of H pylori infection. Data have been calculated for sensitivity and specificity of 80% for the serological test.

Clinical trials in Helicobacter pylori infection

EDITOR—We read with great interest the excellent guidelines for clinical trials in Helicobacter pylori infection published last September (Gut 1997;41(suppl 2):S1-23). The recommendations almost without exception, are extremely useful. We feel, however, that one or two points might be expanded, or deserve extra comment.

As the working party states, most of the studies published on eradication therapy are non-comparative or are not large enough to reach a definite conclusion. This is because the sample size required to rule out a 10% difference between treatment groups for a two-branch comparative study is nearly 600 patients. To our knowledge no studies of this size have been published to date and, therefore, the length and composition of ideal eradication therapy has to be determined in large multicentre trials.

Inclusion criteria should follow a model including, in phase II studies, aims at evaluating the safety of the drug regimen, in phase III studies, aims at determining the efficacy of the drug regimen.

In more than one place, the guidelines call for two positive diagnostic tests for a patient to be considered reliably infected by H pylori and included in a treatment study. However, the reliability of diagnostic tests largely depends on the prevalence of H pylori infection in the population studied. When studying a population known to harbour a very high prevalence of infection, such as patients with duodenal ulcer, two diagnostic tests are not necessary. A simple statistic calculation applying the Bayes theorem will show that in these patients a single diagnostic test—even serology—will be enough to confirm the diagnosis of H pylori infection. In brief, if we assume that the prevalence of infection is at least 90-95% in patients with duodenal ulcer, even assuming an exceptionally low sensitivity and specificity of 80% for the diagnostic technique, the predictive value of a positive result ranges between 97 and 99%. This is shown graphically in fig 1. Using more sensitive and specific tests such as histology for the urea breath test (UBT), the predictive value of a positive result will rise to almost 100%. Therefore, a second test will only add cost to the study, and will lead to the exclusion of a valuable percentage of patients with false negative results in the second test.

Similar reasoning can be applied to the post-treatment controls. If we compare treatments with an effectivity of over 80% and perform a six week UBT (assuming a sensitivity and specificity of 90% for the technique) the predictive value of a positive test result is over 97% (fig 2). This predictive value increases when the efficacy of the treatment and the specificity of the test increase. Therefore, a second test is probably unnecessary. We agree that patients with a positive UBT after treatment should undergo endoscopy, but for different reasons: the predictive value of a positive UBT after treatment is low, and nearly one third of patients will be cured despite a negative test result. The possibility of performing a single test after 3-4 months should therefore be considered.

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Figure 2 Value of a negative UBT to evaluate cure of Helicobacter pylori infection after treatment. Negative predictive value = 72/(72+2) × 100 = 97.2%. The eradication rate is assumed to be 80%. Data have been calculated for sensitivity and specificity of 90% for the UBT.
Dermatitis herpetiformis and cigarette smoking

Editor,—Some time ago a study by Snook and colleagues (Gut 1996;39:60–2) found cigarette smoking to be less prevalent among those with coeliac disease. This prompted Lear and colleagues (Gut 1997;40:289) to evaluate smoking status in patients with dermatitis herpetiformis (DH), an autoimmune blistering skin disease that also presents with a gluten sensitive enteropathy. They found that 29 patients with DH were significantly less likely to be smokers than matched and unmatched controls.

As we also have a large population of patients with DH, we did a preliminary review of our existing database to evaluate smoking status in these patients. A review of over 200 patient charts with biopsy confirmed DH (granular IgA in papillary dermis) revealed smoking information on 105 patients. Fifteen of these patients were less than 20 years of age at disease onset and thus were eliminated from the study, leaving 90 evaluable patients. Of these patients eight (8.9%) were smokers, whereas 17.1% of the Utah population aged 20 years or older are smokers,

How do we explain this apparent beneficial effect of smoking when it comes to DH? It is likely that the immunosuppressive effects of smoking play a role in this autoimmune disease, yet there are other autoimmune skin diseases, such as psoriasis, which are made worse and not better by smoking.

Editor,—It was with great interest that we read Periera and William's article (Gut 1998;42:883–5) reviewing the problem of the great imbalance between the limited number of donor livers versus the increasing need for transplantation in the UK and possible remedies to this tragic situation: strategies to increase the number of actual donations from the annual pool of potential donors. This great imbalance between allograft supply and demand is a challenging problem which confronts transplant centres everywhere. Furthermore, as medical science advances and clinical epidemiological analysis of post-transplant outcomes become clearer, we find that diseases that were previously either absolutely or relatively contraindicated for transplantation, such as chronic hepatic B and alcoholic cirrhosis, are now conditions potentially treatable by transplantation, further widening the differential between those in need of a transplant and number of available organs.

Clearly, Periera and Williams point out, there is a need to increase the numerator side of the organ supply:demad ratio and use every available organ. It must be emphasised, however, that the need to reduce the denominator side of this ratio—that is, reduce the need for transplantation, is equally as great. Currently, alcoholic cirrhosis and chronic hepatitis C (HCV) infection are the two most common indications for transplantation for liver disease in British Columbia, comprising 15 and 22% of all transplants as of 1997. These proportions are comparable to other centres across Canada and the United States. When one also considers that many of those infected with HCV acquired the infection from intravenous drug misuse and that alcohol consumption is reported to be an exacerbating factor in the progression of HCV towards cirrhosis,


NOTE

Sir Francis Avery Jones BSG Research Award 1999

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1999 Award. Applications (TWENTY COPIES) should include:

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A bibliography of relevant personal publications

An outline of the proposed content of the lecture, including title

A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 1998 but need not be a member of the BSG. The recipient will be required to deliver a 40 minute lecture at the Annual Meeting of the Society in March 1999. Applications (TWENTY COPIES) should be made to the Honorary Secretary, BSG, 3 St Andrews Place, London NW1 4LB, by 1 December 1998.
Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice
C M BATE

Gut 1998 43: 728-732
doi: 10.1136/gut.43.5.728

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