

## Outcomes research in *Helicobacter pylori* infection

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### SUMMARY

While the medical community has accepted the role of *H. pylori* in the pathogenesis of peptic ulcer disease, confusion persists among clinicians regarding when and on which patients to attempt *H. pylori* eradication. Thus, the objective for outcomes research in *H. pylori* is to help clinicians identify which patients benefit from *H. pylori* eradication and to determine the cost-effective strategies for their diagnosis, treatment and follow-up care.

Economic evaluation of the impact of *H. pylori* infection has focused primarily on assessment of patient with documented peptic ulcer disease, with particular attention to costs of pharmaceuticals. However, drug costs are only one portion of the total costs of management for patients with acid-related disorders and therefore must be put in the appropriate context. Additional aspects of patient benefit (e.g. patient satisfaction) and health-care expenditures (e.g. over-the-counter medications, specialist visits,

hospitalizations) must be included in an evaluation of the value of a particular diagnostic test, treatment, clinical guideline or disease management strategy.

As a result of the high quality and quantity of data emerging, it can be safely said that *H. pylori* eradication is cost-effective in selected patient populations: newly documented peptic ulcer disease; history of peptic ulcer disease and taking maintenance therapy; and suspected peptic ulcer disease using a serological test to guide initial treatment. The role of eradication in other areas, for example, patients with non-ulcer dyspepsia and screening to prevent gastric cancer, remains to be seen. In addition to the performance of rigorous studies, researchers must respond to the 'information overload' on busy clinicians, by effectively disseminating their findings. If data generated from outcomes research are not integrated into everyday clinical practice, the enormous benefits associated with *H. pylori* eradication will not be achieved.

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### INTEREST IN OUTCOMES RESEARCH

Concerns over escalating health care expenditures have led to increased scrutiny over the clinical and economic impact of medical interventions.<sup>1</sup> While there is little debate that patients, physicians and payers are interested in health-care services that provide improved clinical outcomes, there remains some controversy on the role of cost in the allocation of health-care resources.<sup>2,3</sup> As part of a concerted effort to constrain cost growth, a number of managerial tools such as formularies to control the use

of pharmaceuticals and practice guidelines to standardize care are being employed to insure more appropriate use of medical services. Despite the widespread use of these and other processes, their impact on clinical outcomes and resource use have yet to be determined.<sup>4</sup>

A minority of medical interventions commonly used in clinical practice have been demonstrated to be beneficial in a controlled clinical trial. This paucity of data makes it difficult for decision makers to make informed conclusions regarding the usefulness of many health-care services in several clinical situations.<sup>5</sup> As a result, the 'effectiveness' or 'outcomes' movement has emerged to determine which of the many interventions are 'valuable', through the use of rigorous and standardized methods.<sup>6</sup> This may

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be achieved through the evaluation of medical practices integrating the best available safety and effectiveness—not efficacy—information with attention focused on those endpoints that matter to patients. Easily measured, surrogate endpoints (e.g. blood pressure measurements, urea breath test results) which may have little relevance to the patient are being substituted by symptoms or clinical outcomes (e.g. fatigue, abdominal symptoms) to which patients can directly relate—irrespective of their cause.

### OUTCOMES RESEARCH METHODS

A spectrum of research methods are available to produce the information necessary to improve both clinical decision making and health-care resource allocation.<sup>7</sup> Outcomes research differs from traditional clinical research in that resource use is frequently captured in addition to clinical endpoints. The collection of both clinical and cost data allow the comparisons of medical services using cost-effectiveness analysis.<sup>8</sup> These studies answer the question, How much more does it cost to achieve the extra clinical benefit gained?

From a study design perspective, outcomes researchers use randomized controlled trials less frequently than those who perform traditional clinical research. When randomized controlled trials are used, efforts are made to relax entry criteria to enroll a more diverse patient population. Data collection requirements tend to be less detailed to encourage the involvement of community-based patients and clinicians who were frequently excluded in the past. By broadening the scope of the randomized controlled trials, concerns over study generalizability are likely to be reduced. In the place of prospective clinical trials, outcomes researchers utilize alternative methods including epidemiological research designs and retrospective database studies.

### DECISION ANALYTIC MODELLING

In many instances, clinical questions arise that require data from numerous aspects of clinical medicine, e.g. epidemiology, natural history and intervention trials. In order to incorporate this information in a standardized way, various synthesis methods may be helpful. Literature review, meta-analyses, and decision analytic modelling are commonly used methods that allow data from numerous published and unpublished sources to be incorporated into a single study.

Decision analysis is an appropriate evaluative methodology when high-quality data are available, serious levels of uncertainty exist, and changes in practice patterns are expected. Its main strength is the flexibility it allows when there is inconsistency or uncertainty regarding the available data. Sensitivity analysis permits testing of a wide range of input values and assesses the impact of these changes on the model's results. However, it should be pointed out that the results generated by decision analytic models are limited by the quality of the data inputs entered into them. In most instances, the clinical probabilities and cost estimates are drawn from secondary sources.

### OUTCOMES RESEARCH AND *H. PYLORI*

A relationship between *Helicobacter pylori* infection and peptic ulcer disease is now well established and is viewed as a major advance in the management of acid-related disorders.<sup>9</sup> While the medical community has accepted that *H. pylori* plays a role in the pathogenesis of peptic ulcer disease, confusion persists among gastroenterologists and primary care physicians regarding when and in which patients to attempt *H. pylori* eradication.<sup>10</sup> This uncertainty is of particular interest in view of the fact that patients with acid-related disorders are increasingly cared for by primary care physicians. Thus, the objective of outcomes research efforts in the field of *H. pylori* and peptic ulcer disease is to help clinicians identify which patients benefit from *H. pylori* eradication and to determine the cost-effective strategies for their diagnosis, treatment and follow-up care.

*H. pylori* infection has many significant attributes that make it an important clinical condition for a series of outcomes research studies:

- infection is common worldwide; infection rates tend to increase with age and are independently associated with race and socioeconomic status;<sup>11</sup>
- the infection is chronic; in the absence of specific attempts at eradication, infection is assumed to be lifelong;
- the field is in a state of flux; information on the microbiology, pathophysiology and clinical manifestations of disease are emerging rapidly causing confusion among clinicians;
- the direct and indirect effects of this infection on resource use are substantial;
- maybe most important is that many questions remain about the diagnosis and treatment of *H. pylori* on patient

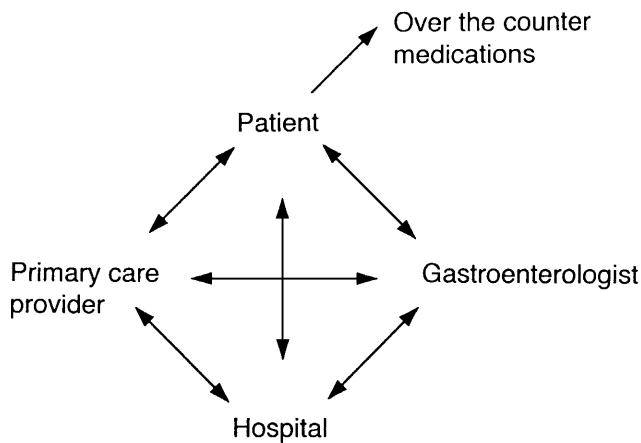


Figure 1. Conceptual model of the episode of care for patients with upper gastrointestinal symptoms.

outcomes in many clinical situations (e.g. non-ulcer dyspepsia). For example, clear consensus has not emerged regarding several key clinical areas including: optimal initial diagnostic strategy (is endoscopy necessary?); treatment (which regimen?); and follow-up care (must we confirm eradication?).

Economic evaluation of the impact of *H. pylori* infection has focused primarily on assessment of patients with documented peptic ulcer disease, with particular attention to costs of pharmaceuticals.<sup>12,13</sup> Because of their volume of use, anti-secretory agents have been subject to intense scrutiny. However, drug costs are only one portion of the total costs of management for patients with acid-related disorders. The role of drugs on the total costs of the episode of care of these patients must be put in the appropriate context. Additional aspects of patient benefit, (e.g. patient satisfaction), and health-care expenditures, (e.g. over-the counter medications, specialist visits, hospitalizations), must be included in an evaluation of the value of a particular diagnostic test, treatment, clinical guideline or disease management strategy. A schematic demonstrating a broader view of the 'episode of care' for a patient with upper gastrointestinal symptoms can be seen in Figure 1. To approach reality, all aspects of this conceptual model must be carefully considered.

#### ASSESSING *H. PYLORI* OUTCOMES RESEARCH

The availability of high-quality data from carefully controlled clinical trials allow the performance of decision analytic modeling of *H. pylori* and peptic ulcer disease in

specified patient populations. However, for these simulations to accurately mimic clinical practice, attention must be paid to the subtle differences between traditional clinical research and patient-based outcomes evaluations. Some of the important parameters on which to assess *H. pylori* outcomes assessments follow.

#### *Establishing the diagnosis*

Most published investigations in the peptic ulcer disease literature begin with a homogeneous cohort of patients who have been carefully investigated prior to study entry. Thus, patients consistently carry an objectively determined diagnosis when the study begins. This requirement of diagnostic certainty is an important difference between traditional clinical research and outcomes studies. As the cost of diagnosis (e.g. endoscopy) may be high and patient signs and symptoms are not predictive of objective findings, it is critical to include all diagnostic and treatment costs for patients with and without the disease under investigation. It is important when interpreting economic evaluations of *H. pylori* to consider if initial diagnostic and treatment costs have been included.

#### *Relationship of symptoms to diagnosis*

Patients tend to go to their physician if their symptoms are severe enough to warrant a visit. This decision is usually independent of any underlying diagnoses that may be the cause of the discomfort. In contrast to this symptoms-based approach, many peptic ulcer disease studies report objectively determined outcomes related to the presence or absence of ulcers, irrespective of the patients' symptom status. In reality, asymptomatic ulcer recurrences (a relatively common occurrence), may not cause patient morbidity or incur any health-care costs. In contrast, a significant amount of resources are devoted to symptomatic episodes for reasons other than peptic ulcer disease in those same patients. These non-ulcer episodes of care have been shown to be an important variable in certain economic evaluations.<sup>14</sup>

This 'symptom-driven' management approach attempts to mirror actual medical care delivery and allow a realistic estimate of resources utilization in the episode of care. Within an economic evaluation that accurately measures resource use, asymptomatic patients do not incur costs in addition to drug use. It should be understood that protocol-induced expenditures for

patients in research studies may either decrease or increase the total cost of care, depending on the intensity of the study design. While objectively determined disease has been used to estimate clinical outcomes and resource use in earlier published economic evaluations, a trend is to measure care as driven by patients' symptoms, not objective findings revealed by diagnostic evaluations.

#### *Defining the patient population and management strategies*

After a diagnosis of peptic ulcer disease and *H. pylori* infection is established, the impact of eradication therapy is well known. A number of decision analytic models demonstrated the clinical and economic superiority of *H. pylori* eradication in patients with newly diagnosed peptic ulcer disease when compared to a strategy of maintenance anti-secretory therapy that did not incorporate *H. pylori* treatment.<sup>12,13</sup> The available evidence of the profound effect of *H. pylori* eradication on reducing ulcer recurrence rates in newly diagnosed peptic ulcer disease patients should preclude the inclusion of a strategy that does not allow *H. pylori* eradication at some point in time. While it is important to choose appropriate comparisons, it is also essential that the clinical evidence exists before extrapolating the clinical benefits found in one population (e.g. newly diagnosed peptic ulcer disease) to others (e.g. peptic ulcer disease diagnosed in the past).

#### CHANGING PHYSICIAN BEHAVIOUR REGARDING *H. PYLORI*

Studies of physician adoption of medical innovation reveal that the performance of outcomes studies are not enough to insure that physicians change their practices appropriately.<sup>15</sup> Thus, an additional challenge arises to educate providers of the research findings so that they are applied to clinical practice. Despite the broad media (medical and lay press) attention to the discovery of *H. pylori* and its link to peptic ulcer disease, it is unknown how physicians have adapted their practice patterns to emerging information of the role of *H. pylori*.

A recent survey of US primary care physicians and gastroenterologists revealed that gastroenterologists were more certain about key advances in the treatment of peptic ulcer disease than were primary care physicians.<sup>10</sup> In addition, the responding gastroenterologists adopted *H. pylori* eradication therapy earlier than primary care physicians. This is of particular import given the expanding role of primary care physicians in

the management of acid-related disorders. However, practice patterns regarding *H. pylori* eradication were suboptimal for both primary care physicians and gastroenterologists.

This survey infers that at the end of 1994, the *H. pylori* message had not been universally delivered to or accepted by practicing physicians. The implications of this work suggest that the improved dissemination of information to physicians is needed so that lessons from research regarding *H. pylori* eradication are applied to clinical practice in an appropriate and timely manner.

#### ECONOMICS OF *H. PYLORI*

A National Institute of Health (NIH) consensus panel concluded that the major benefit of *H. pylori* eradication is a substantial reduction in the risk of ulcer recurrence.<sup>9</sup> Therefore, when *H. pylori* eradication is prescribed to appropriate patients there is potential to practically eliminate ulcer recurrences not related to non-steroidal anti-inflammatory drug (NSAID) use. The economic effects of *H. pylori* treatment are likely to be equally dramatic, through the reduction in ulcer recurrence costs and the fact that a significant number of patients with peptic ulcer disease would no longer require chronic anti-secretory therapy.

The NIH panel recommended that eradication therapy should be prescribed for patients with documented *H. pylori* infection and a documented active duodenal ulcer or ongoing maintenance anti-secretory therapy for ulcer disease. These recommendations, which require complete diagnostic certainty, tend to depart from earlier guidelines which endorsed an initial course of empiric anti-secretory therapy in patients with suspected peptic ulcer disease prior to diagnostic study.<sup>16</sup> The issue of diagnostic certainty is germane to this discussion in that individuals with peptic ulcer disease are difficult to distinguish from those with non-ulcer causes of symptoms in whom *H. pylori* eradication provides no clinical benefit. How to best incorporate the role of *H. pylori* into diagnostic and treatment practices has raised uncertainty among physicians.

#### NEWLY DIAGNOSED PEPTIC ULCER DISEASE

The dramatic reduction in the risk of ulcer recurrence in newly diagnosed peptic ulcer disease patients (from greater than 80% to less than 10%) after eradication of *H. pylori* infection translates to a marked decrease in the

need for medical services. Additional savings can be achieved in non-medical costs (e.g. work days lost as a result of peptic ulcer disease). Published decision analytic models have demonstrated the clinical and economic superiority of *H. pylori* eradication in patients with newly diagnosed peptic ulcer disease when compared to a strategy of maintenance or intermittent anti-secretory therapy that did not incorporate *H. pylori* treatment.<sup>12,13</sup>

#### PREVIOUSLY DOCUMENTED ULCER DISEASE, BUT UNKNOWN *H. PYLORI* STATUS

While the advantages of *H. pylori* eradication are clear in patients with newly diagnosed peptic ulcer disease, the impact of *H. pylori* eradication to the health-care system is likely to be small because of their relatively low incidence. A large cohort of people exists with peptic ulcer disease documented by endoscopy or upper GI series in whom the diagnosis of *H. pylori* was never established. Given the high rate of *H. pylori* infection in these patients, eradication therapy would practically eliminate ulcer recurrences significantly and reduce the number of peptic ulcer disease patients requiring chronic anti-secretory therapy. Hence, *H. pylori* eradication for peptic ulcer disease patients on maintenance anti-secretory therapy has the potential to reduce ulcer-related morbidity and lower health-care expenditures.

Patients who have a history of uncomplicated peptic ulcer disease unrelated to NSAID use, but who have received neither a diagnostic test for *H. pylori* nor *H. pylori* eradication therapy are excellent candidates for eradication. However, uncertainty remains whether all of these individuals be treated or eradication reserved for only those patients with persistent symptoms. One decision analysis estimated that patients with ulcers taking maintenance therapy who received immediate *H. pylori* treatment had fewer days with ulcers and lower health-care costs when compared to patients who were kept on regular anti-secretory therapy and eradication therapy when symptoms recurred.<sup>17</sup> However, since symptoms from non-peptic ulcer disease causes were also measured, the model estimated that the cessation of maintenance therapy after *H. pylori* eradication led to a slight increase in symptoms from non-ulcer causes. Timing of treatment aside, based on clinical and economic outcomes, patients with documented peptic ulcer disease not previously evaluated for *H. pylori* infection should be promptly treated.

#### SYMPTOMS SUGGESTIVE OF PEPTIC ULCER DISEASE

Symptoms suggestive of peptic ulcer disease are one of the most common reasons for an individual to visit a physician. As individuals with active peptic ulcer disease are difficult to distinguish from those with non-ulcer causes of symptoms, whether or not to document peptic ulcer disease and/or *H. pylori* infection remains unresolved. The trade-offs between diagnostic certainty and empirical therapy tend not to be clinical, but are economic, in that resources are devoted either to relatively expensive invasive tests or unnecessary therapy is prescribed to individuals who are unlikely to benefit.

Decision analysis was used to estimate the clinical and economic effects of likely initial treatment strategies for patients with suspected peptic ulcer disease. The details of this study have been published in detail elsewhere.<sup>14</sup> Outcomes were compared with strategies that employed immediate endoscopy and rapid urease testing (eradication therapy reserved only for patients with both peptic ulcer disease and *H. pylori* infection), and qualitative serological testing for *H. pylori* (eradication therapy was prescribed for all patients with a positive serological test).

During each symptomatic period over the episode of care, the presence or absence of symptoms, presence or absence of ulcer disease, the sequence of diagnostic testing and the therapeutic success or failure was measured. Patients were modelled to experience symptoms caused by both ulcer and non-ulcer causes. Under a broad range of clinical inputs and cost estimates, the safety and effectiveness of lower cost, less invasive treatment strategies support the initial non-invasive management in patients with suspected peptic ulcer disease. The economic advantage of the non-invasive strategies were sensitive to the cost of endoscopy and the likelihood of recurrent symptoms in non-ulcer patients who would eventually require endoscopy. If the cost of endoscopy were to fall below \$500, a recommendation that a diagnosis precede eradication would be justified on both clinical and economic grounds.

#### SCREENING TO PREVENT GASTRIC CANCER

There remain no data from controlled investigations which clearly show a role for *H. pylori* diagnosis and treatment in patients without peptic ulcer disease. Despite this, there is intense interest in better understanding the

role of *H. pylori* in different patient cohorts. Epidemiological investigations have demonstrated an increased risk of gastric cancer in individuals infected with *H. pylori*.<sup>18</sup> Unfortunately, the extent to which *H. pylori* eradication decreases gastric cancer risk remains unknown. The availability of accurate, low-cost diagnostic tests for *H. pylori* infection and effective *H. pylori* eradication therapy mandate that this question be addressed. Because a controlled trial would take decades to complete, decision analysis is a useful methodological tool to determine whether screening and treatment of *H. pylori* infection is a cost-effective way to prevent gastric cancer.

A number of investigations are underway to estimate the impact of *H. pylori* infection and subsequent eradication on the incidence of gastric cancer. Using clinical inputs derived from a review of the published medical and epidemiology literature and appropriate economic figures from health-care payers, 'ballpark' estimates of cost-effectiveness for varying rates of gastric cancer risk reduction can be generated. If, using optimistic estimates of the effects of eradication on gastric cancer risk, *H. pylori* screening is cost-effective, there is little choice but to perform controlled investigations to determine if and to what extent the cure of *H. pylori* infection alters the incidence of gastric cancer. A recent decision analytic model revealed that even at moderate rates of gastric cancer risk reduction that *H. pylori* screening and treatment was a cost-effective intervention.<sup>19</sup>

## CONCLUSIONS

The unfolding of the *H. pylori* story coupled with the high prevalence and economic burden associated with upper gastrointestinal symptoms, make acid-related disorders an ideal candidate for outcomes research. As a result of the high quality and quantity of data emerging, it can be safely said that *H. pylori* eradication is cost-effective in selected peptic ulcer disease populations. The role of eradication in other areas, e.g. patients with non-ulcer dyspepsia and screening to prevent gastric cancer, remains to be seen. Some clinicians are frustrated in that it appears impossible to keep up with every aspect of this innovation. Researchers must respond to this 'information overload' through the effective dissemination of their findings. If data generated from outcomes research are not integrated into everyday clinical practice, the enormous benefits associated with *H. pylori* eradication will not be achieved.

The tendency of clinicians not to pay attention to outcomes research results, particularly economic evaluations, may lead to missed clinical benefits and unnecessary expenditures. Whether or not physicians begin to use the information produced from these innovative studies, there is little doubt that outcomes research is here to stay. Those physicians who have been reluctant to join the outcomes bandwagon must understand what other stakeholders in health-care delivery have already accepted: that the rational basis for outcomes research is the overall improvement in the quality of health-care services—not simply a tool to reduce health-care costs.

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