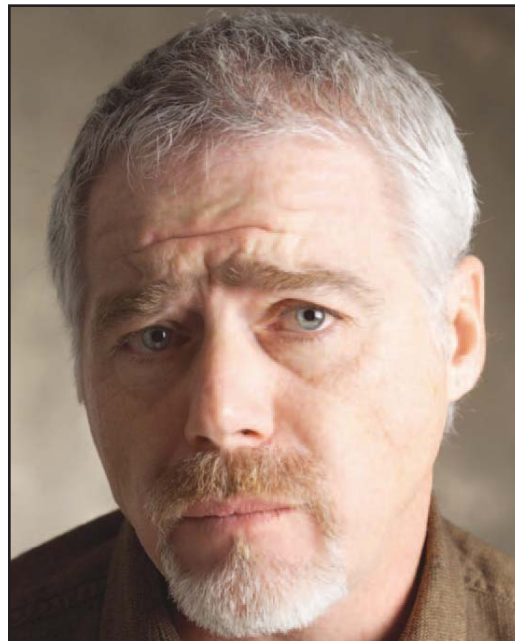




H. Pylori and Dyspepsia



**By Japie Louw, MB, ChB, FCP(SA),
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Since its rediscovery in the early 1980's, *Helicobacter pylori* (*H. Pylori*) has undoubtedly revolutionized the way we manage diseases of the foregut.

Idiopathic peptic ulcer disease has become an infectious disorder, cured in the vast majority of cases by a short course of antibiotics and acid suppression with or without bismuth. *H. pylori*'s association with gastric malignancy is also increasingly appreciated, although few will yet advocate a "search and destroy" policy for an organism which has, after all, been labelled a class 1 carcinogen.¹

Unfortunately, the organism may have become a victim of its own success. The amazing

The success of H. pylori eradication in peptic ulcer disease probably had an effect on the expectations for its role in other diseases of the foregut.

In this article:

1. What is dyspepsia?
2. What is the role of *H. pylori* in dyspepsia?
3. What are the management strategies for dyspepsia?

success achieved by *H. pylori* eradication in the case of peptic ulcer disease almost certainly had a spinoff effect with regard to expectations for the organism's role in other diseases of the foregut.

Dyspepsia is, at least for some, a case in point. It is a condition which means different things to different people, has a poorly understood pathophysiology in its functional form, and where the role of the organism is perhaps less than obvious. Dyspepsia also has considerable impact on individual quality of life, public health and health economics.²

What is dyspepsia?

Dyspepsia refers simply to "pain or discomfort centred in the upper abdomen."³ Any definition as

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It is essential to look for yet another defining element of dyspepsia: do authors refer to investigated or uninvestigated dyspepsia?

imprecise as this one requires a number of footnotes. “Discomfort” is intended to refer to a “subjective, negative feeling that the patient does not interpret as pain and which, if fully assessed, can include a number of specific symptoms.”³ These symptoms include abdominal fullness, early satiety, bloating, or nausea. The term “centred” implies that the pain is experienced in or around the midline; hypochondrial pain is not included in the definition of dyspepsia.

One important omission in the current definition of dyspepsia is heartburn. Heartburn is a topic which deserves discussion on its own merit, but for the purposes of this review, heartburn is considered a specific enough symptom (if correctly elicited and interpreted) to strongly suggest the presence of gastroesophageal reflux.⁴

When reading papers, especially those which address the role of *H. pylori* in dyspepsia, it is essential to look for yet another defining element of dyspepsia: do the authors indicate whether they have studied investigated or uninvestigated dyspepsia?

Put simply, if a patient with dyspepsia sits down for a consultation, that patient has uninvestigated dyspepsia. Once this patient has been evaluated, he or she will be categorized as having either organic dyspepsia [peptic ulcer disease, gastric carcinoma, nonsteroidal anti-inflammatory drug (NSAID) gastropathy, *etc.*] or “functional” or “non-ulcer dyspepsia.” This may seem self-evident, but it is worth thinking about for a moment. Clearly, the uninvestigated dyspeptic can have a number of conditions, amenable to defined therapy. Specifically, if you study a population of uninvestigated dyspeptics,

Table 1

Indications for immediate diagnostic workup in dyspeptic subjects

1. Recent onset/change in nature of symptoms in patients over a certain age (usually the 45-year threshold).
2. Alarm features at any time: unintentional weight loss, evidence of blood loss, dysphagia, and the use of nonsteroidal anti-inflammatory drugs.
3. Patients requiring long-term continuous or frequently intermittent therapy.
4. Patients with severe symptoms that have not responded to therapy.
5. Recurrent vomiting.
6. Family history of gastric cancer

with an appreciable background rate of peptic ulceration, *H. pylori* eradication strategies can reasonably be expected to have some success. Such results cannot, however, be generalized to a large group of patients with functional or non-ulcer dyspepsia.

How do you manage uninvestigated dyspepsia?

The management strategies for uninvestigated dyspepsia can be roughly divided into the pre-*H. pylori* and post-*H. pylori* eras.

What are the management choices in the pre-*H. pylori* era?

Options were essentially limited to empiric treatment or immediate investigation of those with dyspepsia. Given the nature of the beast, certain guidelines were developed to guide the clinician with regards to those that require immediate workup (Table 1). These guidelines also apply in the post-*H. pylori* era, and can be summarized as follows:^{5,6}

1. Recent onset/change in the nature of symp-

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toms in patients over a certain age. Age thresholds may vary, depending on the population incidence of disease (especially carcinoma), but it is interesting to note that, although there is pressure to increase the threshold age, many authoritative guidelines still advise a 45-year threshold.^{5,7} One is cognizant of a number of studies, including the locally conducted “C A D E T - P E” (Canadian Adult Dyspepsia Empiric Therapy-Prompt Endoscopy) study which may suggest an older threshold age.⁸ Quality data in this regard remains limited.

2. Alarm features at any time. Obvious factors are unintentional loss of weight, evidence of blood loss (whether overt or occult), dysphagia, and the use of NSAIDs. Physicians must keep in mind that evidence suggests that even the cyclooxygenase-2 selective agents may be associated with significant gastrointestinal (GI) side effects, and that even low dose acetylsalicylic acid is not exempt from causing serious GI side effects.⁹

3. Patients requiring long-term continuous or frequently intermittent therapy.

4. Patients with severe symptoms that have not responded to therapy.

5. Recurrent vomiting.

6. Family history of gastric cancer (included by some).

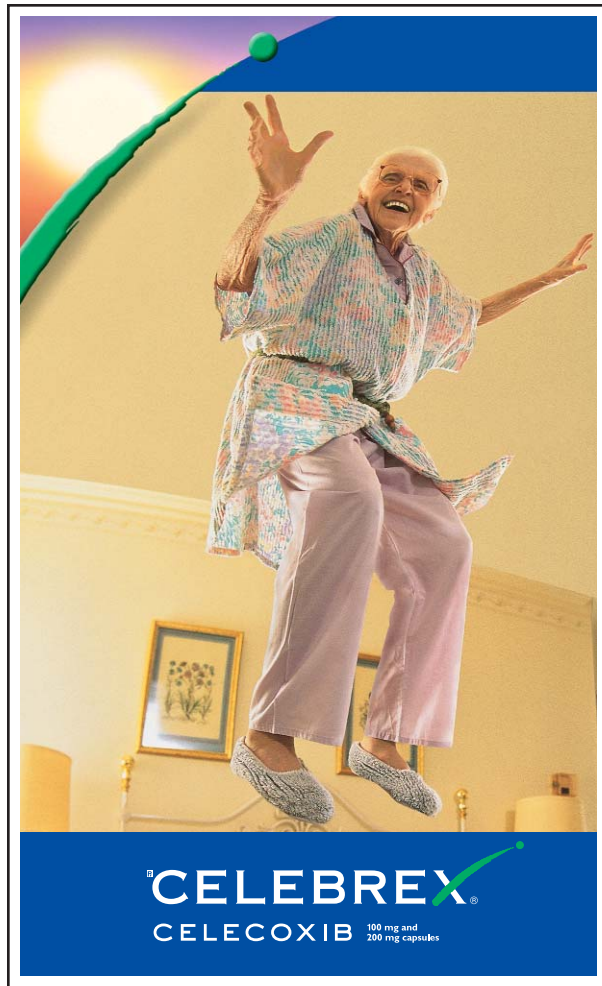
What are the management choices in the post-H. pylori era?

Two further management strategies have been developed to deal with dyspeptic patients in this era. These two strategies use *H. pylori* status to direct either therapy or the need for further investigation (“test and treat” or “test and investigate”). We will discuss the “test and treat” strategy, as it seems to have become the dominant approach.

Keep in mind that we are talking about uninvestigated dyspepsia. Intuitively, we may expect that *H. pylori* status will at least reliably identify those with peptic ulcer disease, a subgroup who will most definitely benefit from *H. pylori* eradication. Unfortunately, this may

not be the case in North America, where an appreciable percentage of patients with uncomplicated peptic ulcer disease are *H. pylori* negative.¹⁰

On the other hand, evidence linking *H. pylori* infection to the symptom of dyspepsia (uninvestigated) is also rather tenuous. Such is the nature of the work in this area that a number of studies can be cited and used to make a case for or against.



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The study of Moayyedi et al, reported in 2000, is a personal favourite.¹¹ This group used a validated questionnaire to interrogate 8,407 subjects. *H. pylori* status was determined by urea breath test. Dyspepsia was found in 44% of *H. pylori* positives and 36% of *H. pylori* negatives (Odds Ratio 1.2, 95% Confidence Interval 1.09-1.34); multiple logistic regression modelling suggested that *H. pylori* could be responsible for 5% of the dyspeptic symptoms in this community. Interestingly, a number of other factors, including the married state, low academic achievement, and living in rental accommodation, appeared to be almost equally important (and independent) risk factors for dyspepsia!

With *H. pylori*, however, the proof has always been in treating the infection in specific disorders. Once again studies abound, yet their quality vary considerably, as there is lack of uniformity with regard to the outcome measures used (especially with regard to the concept of cure versus improvement and the duration of followup). These studies allow us to make varying conclusions.

The CADET-HP study was conducted locally and makes most of the points we need to be familiar with.¹² This study, which has its potential problems with regards to inclusion criteria, involved 294 subjects, and “treatment success” was defined not as a cure, but as “no or mini-

mal” dyspepsia. Followup was over a one-year period. No matter what the analysis used (intention-to-treat [ITT] or “modified” ITT), and accepting the argument that patients with reflux symptoms should be included in the primary analysis, the authors report a significant benefit in outcome when eradication therapy is compared to symptomatic therapy with short-term acid suppression. However, in the era of evidence-based medicine, we are perhaps obligated

to interpret the results slightly differently. The overall therapeutic gain is approximately 15%, leaving us with a Number Needed To Treat of approximately 7 (that is, we will need to treat seven patients if one is to become asymptomatic or have minimal residual dyspepsia).

So what can we say about the “test and treat” strategy? Even the staunchest protagonist would have to agree that treatment is unlikely to relieve patient symptoms in most cases, and that we can expect success in only a small subset of patients who cannot be accurately identified pre-treatment. Expectations have been raised to such a level, however, that one remains astonished by the apparent reluctance of physicians to place the “test and treat” strategy in the proper context. More importantly, it is surprising that many physicians fail to advise patients that treatment for *H. pylori* is unlikely to rid them of their troubling symptoms. When one looks at this strategy soberly, it really is about trying to reduce management cost through lower utilization of endoscopy. On the plus side, it does at least appear to be safe in properly selected patients.

Many physicians fail to advise patients that treatment for H. pylori is unlikely to rid them of their troubling symptoms.

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What about *H. pylori* and nonulcer dyspepsia?

In this case, we are referring to: persistent dyspepsia in patients in whom organic causes have been excluded by an appropriate workup (this could include appropriate blood work, endoscopy/contrast studies, and ultrasound to exclude gallstones). To be considered problematic, this symptom should be persistent or recurrent for at least 12 weeks (not necessarily concurrent) over a 12-month period.³

Despite enormous enthusiasm for *H. pylori* eradication as a strategy for the management of nonulcer dyspepsia (a product of the disappointing outcome of standard therapeutic approaches, based on symptomatic treatment), review of the literature will provide little to support this strategy as being effective. Two meta-analyses inform this view.

The first analysis comes from Moayyedi et al; they published their interpretation of the facts in 2000.¹³ These authors performed a truly exhaustive review of the literature: identifying 5,146 articles considered appropriate on first searching the literature. Closer scrutiny whittled this number down to a more manageable 47 papers, but such is the nature of this literature

that they ended up with nine trials (2,541 patients) on which to base a conclusion. Analysis revealed an absolute difference in response rate of 8% (28% placebo, 36% eradication), with a relative risk reduction (by eradication) of 9%. Once again, a statistically significant finding, but one which in real terms means we have to treat 15 patients in order to “cure” a single subject.

But it gets worse. A second meta-analysis, conducted by Laine et al and published in 2001, could not demonstrate any benefit for an eradication strategy in patients with non-ulcer dyspepsia.¹⁴

With all this evidence, what do I do?

Although the pure and simple truth is rarely pure and never simple, the fact is that, at present, we do not have enough data to conclude that an *H. pylori* “test and treat” strategy is effective with regards to symptom control for the vast majority of patients presenting with this problem.

Does that mean that we can ignore a patient’s *H. pylori* status when confronted by a positive test result? Only at one’s peril. Once a physician has requested a test to determine *H. pylori* status, that practitioner is obligated to discuss the pros and cons of treatment with the patient if the



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Once a physician requests a H. pylori test, he/she is obligated to discuss the pros and cons of treatment with the patient, if the results indicate that the patient is infected.

results indicate that the patient is infected. The mistake would be to suggest that treatment is likely to result in improved symptom outcome.

However, there are other issues to consider, the most compelling probably being the organism's association with gastric carcinoma. Although the relationship is complicated, epidemiologic surveys have certainly established

H. Pylori & Dyspepsia (the ongoing controversy)

- The question still remains not whom to treat, but rather whom to test for *H. pylori* status.
- We should probably be a bit more honest with ourselves and our patients with regards to why we treat.
- The driving forces are cost reduction and anxiety with regards to ignoring the presence of an organism considered to be a carcinogen, and not necessarily symptom improvement.
- We, of course, have little prospective data to suggest that such an approach will be effective in preventing gastric cancer.

some relationship,¹⁵ and although we have no interventional trials on which to base treatment decisions, it's classified as a class 1 carcinogen.¹ Findings, such as those in the study by Uemura et al, make it very difficult not to offer treatment to patients known to be infected by *H. pylori*.¹⁶ In a nutshell, these Japanese workers studied 1,526 subjects and noted that gastric cancer developed in 2.9% of *H. pylori* infected subjects and in no uninfected subjects, over a modest eight-year period! CME

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