

Helicobacter pylori management: How to improve the therapeutic confusion in practice

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There appears to be a disconnect between current guidelines for *Helicobacter pylori* testing and treatment, and clinical practice, including physician beliefs and actual prescribing patterns. In particular, there are markedly different approaches in primary and secondary care, and country-specific differences in eradication therapy for *H pylori* infection. Although most physicians do not believe that *H pylori* causes nonulcer dyspepsia, the majority appear to prescribe eradication. Less information is available on the management of *H pylori* infection and gastroesophageal reflux disease, and more marked differences in attitudes and practice occur in this condition. Even in peptic ulcer disease, where most clinicians both in primary and in secondary care believe *H pylori* should be eradicated, there is often a breakdown in the translation of this belief into practice. There is also confusion in terms of treatment regimens applied for *H pylori* eradication. Eradication regimens are less successful in practice than in clinical trials. Furthermore, a sizable proportion of patients with peptic ulcer remain symptomatic despite cure of the ulcer diathesis, which may undermine confidence. Therapeutic confusion about what to prescribe, side effects limiting compliance, bacterial resistance, and socioeconomic factors may all impair therapeutic success with eradication therapy in practice. Unfortunately, it has been well documented that guidelines alone are likely to have little or no impact in practice. Publication in a journal is unlikely to lead to effective implementation in primary care. On the basis of available evidence, clinical behaviour is most likely changed when guidelines are developed by the peer group of clinicians for whom they were intended, are disseminated through a specific educational program, and are implemented by applying, preferably during the consultation, specific reminders.

Key Words: *Clinical practice; Guidelines; H pylori; Nonulcer dyspepsia; Peptic ulcer; Therapy*

Helicobacter pylori infection is an important cause of dyspepsia in practice, and 'test and treat' has been established as the standard of care in the absence of red flags to cost effectively eliminate the ulcer diathesis (1). Efficacious combination therapies for eradication of *H pylori* infection have been tested in clinical trials, leading to treatment recommendations by international and national consensus conferences (2-4). However, a disconnect between guidelines and clinical practice is evident based on surveys of practice over the past decade (5-20). Here, the issue of therapeutic confusion in clinical practice is reviewed and practical recommendations are presented to try to overcome this problem.

L'Helicobacter pylori : Les mécanismes fondamentaux d'une guérison clinique

Il semble exister une dichotomie entre les directives actuelles relativement aux tests et au traitement de l'*Helicobacter pylori* et la pratique clinique, y compris les opinions des médecins et les modèles posologiques. Plus particulièrement, on remarque des démarches fort différentes dans les soins de première et de deuxième ligne, ainsi que des différences selon le pays dans la thérapie d'éradication de l'infection au *H pylori*. Bien que la plupart des médecins ne croient pas que le *H pylori* soit responsable de la dyspepsie non nucléaire, la majorité semblent prescrire l'éradication. On possède moins d'information sur la prise en charge de l'infection au *H pylori* et du reflux gastro-œsophagien pathologique, et des différences plus marquées d'attitudes et de pratique s'observent alors. Même en cas d'ulcère peptique, alors que les cliniciens de première et de deuxième ligne pensent que le *H pylori* devrait être éradiqué, on remarque souvent une rupture au moment de transposer cette opinion dans la pratique. Il existe également une confusion pour ce qui est des posologies de traitement appliquées à l'éradication du *H pylori*. Les posologies d'éradication sont moins efficaces en pratique que dans le cadre des essais cliniques. De plus, une proportion appréciable de patients atteints d'ulcère peptique demeure symptomatique malgré le traitement curatif de la diathèse ulcéreuse, ce qui peut miner la confiance du médecin. La confusion thérapeutique quant à ce qu'il faut prescrire, aux effets secondaires limitant le respect de l'ordonnance, à la bactériorésistance et aux facteurs socioéconomiques pourrait nuire au succès de la thérapie d'éradication dans la pratique. Malheureusement, il est bien documenté que les seules directives cliniques sont peu susceptibles d'avoir des répercussions dans la pratique. La publication dans un journal donne rarement lieu à l'implantation efficace d'un traitement de première ligne. D'après les analyses systématiques, le comportement clinique peut être modifié lorsque des directives sont élaborées à l'intention des cliniciens, sont diffusées par l'entremise d'un programme d'éducation spécifique et sont implantées par l'application, de préférence pendant la consultation, de rappels destinés aux patients.

EVIDENCE FOR THERAPEUTIC CONFUSION BY DISEASE INDICATION

The best evidence suggests that eradication of *H pylori* in nonulcer dyspepsia (NUD) results in a small benefit; the number needed to treat is around one in 15, although it may be even less in clinical practice (21,22). Understandably, the place of treatment of *H pylori* in NUD remains confusing because clinical trials have most frequently reported negative results, albeit with a small, usually nonsignificant trend in favour of eradication in many (21). Indeed, meta-analyses have also reported conflicting conclusions, and the experts disagree (21,23-27). No wonder opinion and

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TABLE 1
Surveys of physicians' attitudes to *Helicobacter pylori* infection

Author (reference)	Physicians surveyed, n	Physician speciality	Response rate (%)	Location and year of survey	Proportion (%) of respondents supporting treatment of <i>H pylori</i>										
					Duodenal ulcer		Gastric ulcer		Nonulcer dyspepsia		GERD		PPI triple therapy as first choice		
					PCP	GE	PCP	GE	PCP	GE	PCP	GE	PCP	GE	
Christensen et al (7)	636	PCP, GE	63	Europe 1992	73	87									
Milne et al (8)	1037	GE	65	UK 1993		80		38		69					
Hirth et al (9)	1119	PCP, GE, HI	30	USA 1994	65	99									
Fendrick et al (10)	4500	PCP, GE	30	USA 1994	64	99									
Boekema et al (11)	422	GE	54	Netherlands 1995		98		91		32		30			40
Breuer et al (12)	2394	PCP, GE	32	Germany 1995	74	86	84	85	41	27					
Breuer et al (13)	5994	PCP, GE, HI	52	USA 1996	95	100	97	99	66	43		50	16		40
Martinez-Sanchez et al (14)	359	PCP	79	Spain 1997	96		96		15						99
Binek et al (15)	363	GE	48	Switzerland 1997		100		100		79					53
Martin et al (16)	1832	PCP, GE	67	Scandinavia 1997	99	99	90	90	57	41					
Sharma et al (17)	1000	GE	31	USA 1998		100		100				54			69
Olafsson (18) and Berstad (18)	1718	GE	36	Scandinavia 1998		99		99		16		11			94
Zoorob et al (19)	1500	PCP	49	USA 1998	48										27
Maconi et al (20)	100	PCP	100	Italy 1998	64					66					88

GE Gastroenterologists; GERD Gastroesophageal reflux disease; HI Hospital internists; PCP Primary care physicians; PPI Proton pump inhibitor. From reference 5 with permission

practice differ widely in this indication. It is striking that the majority of primary care physicians and gastroenterologists in the surveys reviewed by O'Connor (5) did not believe that *H pylori* infection caused NUD, but unexpectedly 41% to 66% of primary care physicians and 27% to 43% of gastroenterologists prescribed *H pylori* eradication treatment. This is a striking example of the disconnect between belief and practice, and it probably reflects the frustration that clinicians experience in treating NUD with other therapies such as acid suppression (28,29).

Even more controversial is the association of *H pylori* infection and gastroesophageal reflux disease (GERD) (5,30). Therefore, it would be expected that clinicians would be perplexed here, and indeed gastroenterologists have reported widely differing views (Table 1). There is an ongoing debate in the literature about whether to offer eradication treatment in the setting of GERD symptoms, and also whether to eradicate infection before prescribing proton pump inhibitors long term to prevent progression of atrophic gastritis (4,30). There remain concerns that *H pylori* eradication may be associated with an increased risk of esophagitis (30), and indeed in those predisposed to GERD with more severe fundic inflammation causing acid suppression, it seems likely that these concerns are justified (31). On the other hand, eradication of *H pylori* infection, even in this setting, appears not to lead to severe esophagitis, and eradication therapy does not significantly increase reflux symptoms (32,33). O'Connor (5) noted that there were widespread country-specific differences in attitudes here (Table 1), but clinician beliefs and practice in terms of this indication have been understudied.

In contrast to NUD and GERD, it might be expected that treatment of *H pylori*-positive peptic ulcer disease, for which the evidence is unassailable and has been widely disseminated for over a decade (3), would be a different proposition in terms of a uniform treatment approach. Indeed, based on the surveys reviewed by O'Connor (5), most clinicians state that they would offer therapy to a patient with duodenal ulcer. However, surprisingly, a sizable minority of gastroenterologists and primary care physicians appeared not to believe that *H pylori* infection is a cause of gastric ulcer, although most reported that they would offer eradication therapy anyway; this may reflect the controversy over the interaction of *H pylori* and nonsteroidal anti-inflammatory drugs in gastric ulcer (34,35). Notably, it has taken over 10 years for clinicians to accept the proposition that *H pylori*

treatment is indicated in ulcer disease, reflecting a relatively slow diffusion of the evidence base to the bedside.

Other evidence suggests that despite the survey responses, there is a disconnect between what happens in practice and what clinicians say they do. In ulcer bleeding, where testing and treating *H pylori* infection is universally considered mandatory (3,4), Tytgat (36) reported that *H pylori* was only tested for in one-third of patients, and of those testing positive, only one-third were successfully treated. Arguably, this reflects a breakdown in the follow-up of bleeders post hospital discharge because control of bleeding rather than diagnosis of *H pylori* infection has traditionally been the focus of emergency care. However, the findings remain disturbing because others have observed similar dismal results, although admittedly the surveys all originated in the early 1990s and might not reflect current practice (37,38). A study from Leeds documented that only 30% of patients with dyspepsia and a proven history of peptic ulcer disease received *H pylori* eradication therapy in primary care (39). Other data support the underprescribing of eradication therapy for ulcer disease in primary and secondary care, and they have led to the concept of search and treat in clinical practice (40).

EVIDENCE FOR THERAPEUTIC CONFUSION IN TREATMENT REGIMENS

Another area of potential confusion relates to what should be optimally prescribed as first-line eradication therapy. The guidelines here have been consistent. For example, the Maastricht 2-2000 Consensus Report (4) recommends a proton pump inhibitor or ranitidine bismuth citrate combined with clarithromycin and amoxicillin as first-line primary care treatment; it is further recommended that patients for whom this treatment fails receive bismuth, metronidazole, tetracycline, and a proton pump inhibitor. Studies from the United States indicate that by the late 1990s, proton pump inhibitor combinations were most often prescribed by gastroenterologists but not primary care physicians, in contrast to Europe where both gastroenterologists and primary care physicians used proton pump inhibitors often (18-20). On the basis of a survey of pharmacies, Lee et al (6) reported that eradication regimens in Ireland varied markedly in terms of the acid suppression agent used; one in five patients was prescribed a different regimen. Other serious anomalies remain; for example, the elderly are less likely to receive eradication

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therapy, although ulcer complications in this age group are often devastating (41,42).

Notably, after eradication therapy, many patients continue to be prescribed acid suppression agents. Data suggest that approximately 50% will receive antisecretory therapy after eradication (43-45). What is less clear is why. Failure to successfully eradicate is one possibility. How often clinicians routinely confirm that *H pylori* infection has been cured is poorly documented and the guideline recommendations vary (2-4). In primary care, follow-up of ulcer disease to ensure cure is likely to be low. Less well recognized in practice is that a sizable proportion of patients with ulcers, despite cure of the infection, remain symptomatic (presumably due to NUD) (46). In NUD, it is expected that the majority of patients will fail to obtain long term relief after successful eradication, although this, too, may often be underappreciated (47).

The success rates of even optimal therapeutic regimens in practice is less than ideal. In trials, it has been accepted that less than an 80% eradication rate is unacceptable based on an intention-to-treat analysis (4). Unfortunately, even optimal therapy prescribed in practice provides less success than is seen in clinical trials. For example, Moayyedi et al (48) in the Leeds Help study randomized 1161 community subjects to triple therapy and 1163 subjects to placebo; the intent-to-treat eradication rate was only 61%, although this rose to 84% in a subanalysis of those who took all the medication.

REASONS STANDARD THERAPY MAY FAIL IN PRACTICE

There are many potential explanations for disappointing results in terms of *H pylori* eradication in practice. Inaccurate diagnosis should not be an issue if undertaken, unless testing is done only applying inadequate serology assays or the background prevalence of *H pylori* infection is very low, leading to more false positives even with the best tests (4). Despite the availability of accurate noninvasive tests, in primary care, empiric treatment of *H pylori* infection without testing in dyspepsia remains a widespread practice (44). This is likely to lead to unsatisfactory outcomes that may bias the clinician against future prescription of *H pylori* therapy and to overtreatment of true noninfected individuals.

Inappropriate choice of therapy does appear to be a barrier, reflecting clinician confusion (6). There may be country-specific issues that contribute to the confusion. For example, in the United States, each drug has to be written separately on a prescription multiplying the chance for error and requiring clinicians to remember the optimal choice and dose. On the other hand, in many countries, *H pylori* infection packs are available that enable the clinician simply to remember a brand name, which is presumably easier for the prescriber and reduces dosing errors. To complicate matters, some key drugs are unavailable in certain countries; for example, bismuth is no longer available in Australia because of market forces.

Side effects limit compliance in practice, and the incidence of side effects is probably underestimated if only controlled trial data are considered. In the Leeds Help study (48), 45% of patients had adverse events in the triple therapy group, and this was much higher than was observed in the placebo group.

Bacterial resistance is an issue that can lead to failure. Metronidazole resistance is a major problem ranging from 20% to 70% across the world, while clarithromycin resistance is increasing and ranges from 1% to 13%; amoxicillin resistance remains rare (49,50). However, the exact role of resistance in treatment failure may be more complex than has initially been appreciated because it is now recognized that there can be multiple bacterial strains in the stomach comprising resistant and sensitive bacteria (51).

Low socioeconomic status may drive poorer results in practice. Lane et al (52) in Bristol found that rates of participation in an

adult population being offered *H pylori* therapy as part of a community randomized-controlled trial were significantly lower in those from lower socioeconomic strata.

VALUE OF GUIDELINES AND STRATEGIES TO IMPROVE THEIR IMPACT

Much effort has been expended in creating national and international guidelines for dyspepsia and *H pylori* infection management, but the impact has been far less than was hoped. Guidelines need to be simple and firmly evidence based. Arguably, opinion at times has swayed the consensus groups as experts grapple with incomplete and flawed data. The guidelines themselves often disagree on specific issues, generating more confusion and mistrust (2-4). Many factors may influence the uptake of guidelines in various ways, including fear of litigation (that may promote use) versus financial incentives, colleagues' recommendations, and personal experience (that may hinder use) (53). It would be interesting to know if gastroenterologists suffering with dyspepsia follow their specialist societies' guidelines on management.

Publication in a journal or simply mailing guidelines to primary care doctors is highly unlikely to significantly alter practice (54). Grol et al (55) evaluated the attributes of clinical guidelines that influenced their use in general practice; this was based on an observational study of the use of 47 different recommendations from 10 national clinical guidelines. It was found that compliance was significantly impaired when the recommendations were controversial and not compatible with current values, were vague and not precisely defined, and demanded changes to fixed routines (55). Hence, guidelines need to specifically ensure that they include an explicit description of the scientific evidence in support, address how to manage negative reactions in patients (such as may occur with side effects of *H pylori* eradication treatment), and emphasize why the management recommendations are important both for doctors and for patients.

Often, guidelines do not alter practice (56). Grimshaw and Russell (57,58) performed a systematic review of 91 studies. They noted that the best chance of altering clinical behaviour would occur when the guidelines were developed by clinicians for whom they were intended (eg, by primary care doctors for primary care doctors), were disseminated using a specific educational program approach and employed patient-specific reminders during consultations. It was suggested by Meineche-Schmidt et al (59) that algorithms applying a reductionist approach often lose relevance in primary care. Indeed, the diffusion of guidelines developed by specialist societies to primary care often seem to be overlooked or even viewed with suspicion. The development of guidelines by primary care groups and the facilitation of local guideline development must be a priority. If guidelines can be effectively brought to the attention of the doctor during a consultation or are part of the order process, adoption appears to be increased (60). O'Connor (5) suggested that face-to-face education of the physician should be encouraged and described a method of academically based detailing that might be useful. However, such an approach is not likely to be possible because of cost constraints.

THE FUTURE

Despite the best evidence, ulcer disease currently remains under-recognized and undertreated in many parts of the world, while NUD, a more controversial indication, is frequently a target of *H pylori* infection therapy. Who to treat and what to treat with continues to confuse too many clinicians at the coal face. Strategies that may improve intervention for *H pylori* infection outcomes in primary and secondary care include ensuring that *H pylori* management guidelines are clear, succinct, authoritative

and avoid very controversial recommendations; promoting the local development of guidelines; and involving patients directly in the implementation of them.

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