Helicobacter Pylori

Conventional and complementary treatments for eradication and optimal management.

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HELICOBACTER PYLORI: BACKGROUND AND TRANSMISSION ROUTES

Helicobacter pylori (H.pylori) is a curved, Gram-negative bacillus. It is microaerophilic, as well as oxidase, catalase and urease positive. It is implicated in the pathogenesis of non-atrophic and multifocal atrophic gastritis, as well as in the development of gastric cancer (Parsonnett 1994) and gastric lymphoma (Parsonnett 1991); therefore, it has been included by the World Health Organization among the type I carcinogens. There are two phenotypically distinct H. pylori groups:

- Type I bacteria, which express the cytotoxin-associated gene antigen (CagA) and the vacuolating cytotoxin-associated gene antigen.
- Type II bacteria, which do not express these gene antigens.

The type I bacteria are more pathogenic than the type II, and induce a more intense inflammatory response (Xiang 1995). Common risk factors include crowding, type of drinking water, lack of toilet facilities during childhood, lower family income and educational levels, and previous gastrointestinal endoscopy (Zaterka 2007).

Humans are the only known host of H. pylori, and the transmission route is not yet clearly understood. The human stomach is considered the reservoir, and accepted routes of transmission are:

- Fecal-oral route in developing countries.
- Gastro-oral route in developed countries, whereby water could be a vehicle (Das 2007).

Water as a transmission route has not been of concern in North America; however, for those travelling from North America to South-Asian countries, the type of water consumption may contribute to infection. In a South Indian population study, 76% of male patients and 73.5% of female patients who consumed municipal water were H. pylori positive, compared to 12.6% of those who consumed boiled or filtered water (Ahmed 2006).

In North America, H. pylori has been cultured from vomitus, diarrheal stools and saliva, demonstrating that the bacterium is potentially transmissible by these routes. Exposure to an H. pylori-infected person with gastroenteritis and vomiting presents an increased risk for infection. In a study of households in northern California, Perry et al. found that exposure to an infected household member with gastroenteritis was associated with a 4.8-fold increased risk of H. pylori infection among others in the household; vomiting being a greater risk factor than diarrhea alone (Perry 2006).

CLINICAL TESTING FOR H. PYLORI

The urea breath test (UBT) is a non-endoscopic test which, like a biopsy-based evaluation, reflects the bacterial load. Sensitivities and specificities have been reported to be 90 to 95% (Loy 2006). Evaluation with endoscopy or UBT should not be performed within four weeks of therapy involving bismuth compounds or antibiotics that might temporarily diminish bacterial density. Proton pump inhibitor (PPI) drugs also suppress H. pylori and, therefore, cessation of PPI therapy for two to three weeks prior to evaluation is considered adequate and appropriate (Laine 1998).

Clinicians should be aware that antibody tests do not necessarily reflect current bacterial load, and their presence may indicate prior rather than current infection. A recent meta-analysis of antibody tests reported a sensitivity of 85% and a specificity of 79%, significantly less accurate than endoscopy or the UBT outlined above (Loy 2006).

Any effect of PPIs or H2-antagonists on the UBT is clinically relevant, as these agents are being increasingly used in the control of acid peptic diseases. As a consequence, the UBT is often performed on patients who are either currently receiving anti-secretors or have only recently suspended these drugs. Furthermore, these patients are frequently reluctant to discontinue this therapy. False-negative UBT results have been reported in a considerable percentage of individuals taking PPIs. The proportion of patients with false-negative effects of PPIs has ranged from 10 to 56% (Connor 1999, Gatta 2004, Perri 1995).

H. PYLORI: IS THERE A LINK TO CARDIOVASCULAR DISEASE?

Since approximately 1995, researchers have described a higher prevalence of serological H.pylori infection in patients with coronary artery disease (CAD) than in healthy controls (Mendall 1995, Whincup 1996). Many subsequent investigations have been performed to examine this relationship (Ossei-Gerning 1997, Pasceri 1998, Koenig 1999, Quinn 1999, Brenner 1999, Murray 2000).

Various theories have been proposed to explain the atherosclerotic process induced by infectious agents. The "plaque instability theory" suggests that the CagA gene of

H. pylori plays a role in the acute infection of patients who have one or more vascular risk factors (Shmuely 2005).

Shmuely et al. suggest that upon reaching the vascular wall, H. pylori is directly involved in the development of atheromatous plaque in that region. H. pylori and C. pneumoniae are capable of intracellular penetration and can reach the aortic wall from distant sites hidden inside macrophages. They can then initiate an inflammatory process causing irreversible changes in the vascular wall (Shmuely 2005).

Further, H. pylori's presence in the coronary arteries may contribute to plaque instability and to the development of acute coronary syndrome (Shmuely 2005). Finally, it has been suggested that H. pylori infection causes a reduction in coronary artery lumen perfusion. Eradication of H. pylori significantly attenuates the reduction in coronary artery lumen in CAD patients after percutaneous transluminal coronary angioplasty, possibly due to the elimination of chronic inflammation and the decline in pro-inflammatory cytokine release (Kowalski 2001).

ERADICATION STRATEGIES; THERAPEUTIC AGENTS AND H. PYLORI; TRIPLE THERAPY PLUS BOVINE LACTOFERRIN

Treatment of H.pylori with triple therapy (three drugs twice a day for one week; PPI, amoxicillin and clarithromycin) shows eradication rates of approximately 80% (Ford 2004). Increasing problems with drug resistance, side effects and expense of antimicrobial therapy have stimulated a search for new treatments. Primary resistance to clarithromycin, for example, has been reported to be approximately 23% (Heep 2000, Tankovic 2001, Toracchino 1998-2002).

Bovine lactoferrin (bLf) is a glycoprotein of the transferrin family constituted by a single polypeptidic chain. BLf possesses antibiotic, anti-inflammatory and immune-modulating properties. Its extensive antimicrobial activities are related to its ability to sequester essential iron (bacteriostatic effect) and to bind the outer membrane of Gram-negative bacteria (bactericidal effect) (Dial 1998).

To determine if bLf was effective, 950 consecutive H. pylori-positive patients suffering from dyspeptic symptoms were evaluated in a seven-day triple therapy open randomized single-centre study; patients received rabeprazole, clarithromycin, tinidazole and bLf. Table 2 shows how the groups were organized.

H. pylori status was assessed after eight weeks by means of a C-UBT or H. pylori stool antigen test. The efficacy of triple therapy augmented with bLf was significantly higher than the other two regimens, both upon intention

Table 1: Conditions Associated With H. pylori Infection

Condition	Association or Finding	References
Alterations in lipids; high-density lipoprotein (HDL) and lipoprotein (a)	H. pylori seropositivity is associated with reduced HDL cholesterol levels. Successful eradication of H. pylori significantly improves lipid profile disturbances.	Scharnagl 2004, Chimienti 2003, Hoffmeister 2001
Elevated homocysteine levels and slowed coronary blood flow	H. pylori is capable of inducing malabsorption of folate and vitamin B12 from dietary consumption, thereby increasing circulating levels of homocysteine.	Sung 1996, Markle 1997, Harun 2007
Chronic urticaria	Immunological stimulation induced by chronic infection might (through mediator release) cause a non-specific increase of skin vessel sensitivity to agents that increase vascular permeability.	Bohmeyer 1996, Tebbe 1996, Wustlich 1999, Wedi 1998, Di Campli 1998
Schonleinhenoch purpura and idiopathic thrombocytopenic purpura (ITP)	Clearing of H. pylori eliminated the purpuric manifestations after eradication therapy. It has also been shown that eradication of H. pylori can increase platelet counts in patients with ITP.	Reinauer 1995, Cecchi 1998, Machet 1997, Mozrzymas 1997, Sato 2004, Stasi 2005, Inaba 2005
Acne rosacea	In H. pylori-positive rosacea patients, triple-therapy achieved significant improvement.	Rebora 1994, Mini 2005, Utas 1999
Migraine headaches	In those with migraines and concomitant H.pylori infection, long-term migraine remission occurs following H. pylori eradication.	Gasbarrini 1998, Pinessi 2000
Hereditary angioedema	Successful eradication of H. pylori is followed by a significant reduction in the number of attacks in patients with hereditary angioedema.	Rais 1999, Farkas 1999, Farkas 2001

Table 2: Group Assignments of DiMario 2003.

Group	Treatment	Eradication Rate
A	Rabeprazole, clarithromycin, tinidazole, bovine lactoferrin.	92.2% PP 95.9% ITT
B	Seven-day therapy with rabeprazole, clarithromycin, tinidazole.	71.2% PP 72.5% ITT
C	10-day therapy with rabeprazole, clarithromycin and tinidazole.	70.2% PP 75% ITT

to treat (ITT) and per protocol (PP) analysis. PP analysis was based on patients who completed the study, and ITT was a restrictive analysis that considered all drop outs as a "failure" of the given treatment (Di Mario 2003).

A second study with bLf and triple therapy was open-labelled, and involved 14 centres in Italy (Di Mario 2006). A total of 402 H. pylori-positive patients suffering from dyspeptic symptoms, gastritis and peptic ulcer disease were randomized into one of three treatment groups. Table 3 highlights treatment group assignments.

In this prospective, multi-centred randomized study, the bLf added to the standard one-week triple therapy for H. pylori infection significantly increased its eradication rate with respect to that of the non-supplemented regimen using both ITT and PP analyses. Conversely, a one-week administration of bLf previous to the one week of standard triple therapy (Group B) did not improve eradication rates and were comparable to those previously reported with standard triple therapy regimens.

TRIPLE THERAPY PLUS bLf AND PROBIOTICS

A recent clinical trial (Debortoli 2007) examined whether adding bLf and probiotics (Pbs) to the standard triple therapy for H. pylori infection could improve the eradication rate and reduce side effects. Successful eradication therapy (Table 4) was defined as a negative C13 UBT eight weeks after completion of the treatment. Like the previous trials, evaluation was conducted by ITT and PP analysis. The patients were randomized into two groups (see Table 4).

The results of this trial indicated that the addition of bLf and Pbs could improve standard eradication therapy for H. pylori infection; bLf serving to increase the eradication rate and Pbs to reduce the side effects of antibiotic therapy.

In addition to significant differences in eradication rates, there were significant differences in the side effects experienced by patients in the two treatment groups: 41/101 (40.6%) patients in group A, but only 10/105 (9.5%) patients in group B reported adverse effects due to therapy. More patients in group A than in group B complained of nausea, diarrhea, a metallic taste in the mouth, glossitis and abdominal pain. These differences were statistically significant (de Bortoli 2007).

CRANBERRY (VACCINIUM MACROCARPON)

Inhibition of H. pylori adhesion to the human gastric mucosa by a high-molecular weight constituent of cranberry juice has been demonstrated in vitro (Burger 2000). Cranberry juice has been shown to inhibit the adhesion of H. pylori strains to immobilized human mucus, human erythrocytes and cultured gastric epithelial cells. It may also prevent H. pylori-induced stomach ulcers by preventing the adhesion of the bacteria to the stomach lining (Burger 2002). Animal data have also demonstrated that cranberry juice fed to infected mice can clear H. pylori at a rate of 80%, 24 hours after the treatment and at an eradication rate of 20%, four weeks following treatment (Xiao 2003).

The evidence of anti-H. pylori activity in humans has also been elucidated in a prospective, randomized, double-blind, placebo-controlled trial in Linqu County of Shandong Province, China. Linqu County is a rural area and has one of the world's highest prevalence rates of gastric cancer. Furthermore, approximately 52% of children three to four years of age and 72% of adults are infected with H. pylori (Zhang 2005). One hundred and eighty-nine H. pylori-positive adult subjects were randomized to receive 90-day treatment with two 250ml doses of either cranberry juice or a placebo daily. At day 35 and day 90, results of the breath test for H. pylori were negative in 14 of the 97 (14.43%) subjects who consumed cranberry

Table 3: Group Assignments of DiMario 2006.

Group	Treatment	Eradication Rate
A	Esomeprazole 20mg b.d., clarithromycin 500mg b.d. and tinidazole 500mg b.d. for seven days.	77% (105/136)
B	Lactoferrin 200mg b.d. for seven days followed by the same schedule as group A.	73% (97/132)
C	Esomeprazole 20mg b.d., clarithromycin 500mg b.d. and tinidazole 500mg b.d. plus lactoferrin 200mg b.d. for seven days.	90% (120/134)

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Table 4: Group assignments of Debortoli 2007

Group	Patients	Treatment	Eradication Rate
A	101	Standard triple eradication therapy: esomeprazole, clarithromycin, amoxicillin	72% (73/101)
B	105	Modified eradication therapy (standard triple eradication therapy plus bLf (200mg BID) and Pb Lactobacillus plantarum, L. Reuteii, L. casei subsp. Rhamnosus, Bifidobacterium infantis andB. Longum, L. salivarius, L. acidophilus, Streptococcus thermophilus, L. sporogenes	89% (93/105)

juice and five of the 92 (5.44%) subjects who consumed placebo. Among 14 negative subjects in the treatment group, 11 subjects were negative at 35 and 90 days, whereas only two subjects were negative both at 35 and 90 days from the placebo group. The authors suggested that regular consumption of cranberry juice could suppress H. pylori infection in endemically infected populations (Zhang 2005).

Additional research on cranberry has revealed positive results. In a recent trial, 191 patients received triple therapy with omeprazole, amoxicillin and clarithromycin (OAC) for one week, with the addition of either cranberry juice or a placebo beverage. The results displayed no significant difference in eradication rate among the groups (82.0, 84.2 and 84.1% in the non-placebo OAC, cranberry OAC and placebo OAC groups, respectively), suggesting that the addition of a cranberry beverage to the triple therapy group did not affect the outcome. Interestingly, further analysis by gender yielded a significant 15% difference in eradication rate between female patients in the cranberry OAC group (95.2%) and female patients in the non-placebo OAC group (80.0%). The study for the first time presented a gender-associated outcome of triple therapy and supplemental cranberry juice (Shmuely 2007).

CURCUMIN

The clinical relevance of curcumin has been demonstrated both in vitro and in vivo for healing peptic ulcer by inhibiting nuclear factor-kappaB, cyclooxygenase-2 and lipooxygenase, inducible nitric oxide synthase, as well as inhibiting H. pylori growth (Bengmark 2006, Foryst-Ludwig 2004, Prucksunand 2001, Swarnakar 2005). Curcumin is an extract of the spice root turmeric and approximately 2% to 3% of pure tumeric powder is curcumin.

In a study to access a new triple therapy without antibiotics, researchers administered a seven-day treatment of curcumin 30mg bid, bLf 100mg bid, N-acetylcysteine 600mg bid and pantoprazole 20mg bid in 25 H. pylori-positive patients with functional dyspepsia. H. pylori status and upper gastrointestinal symptoms were assessed. After seven days of treatment, all dyspeptic symptoms showed a statistically significant reduction in severity scores (Di Mario 2007). Three patients achieved eradication following seven days of treatment, and eradication as well as symptom resolution were maintained at the two-month follow-up.

The effect of turmeric on the healing of peptic ulcers was studied by endoscopy in 25 patients (17 men, eight women). Only patients who had 0.5-2cm diameter ulcers were selected. There were 20 cases with duodenal ulcers and five cases with gastric ulcers. Nineteen of 25 patients (76%) experienced ulcer resolution after turmeric treatment for four to 12 weeks. Two 300mg capsules of turmeric were taken five times per day, 30 to 60 minutes prior to meals (Prucksunand 2001).

MASTIC – PESTACIA LENTISCUS

Mastic is a resinous exudate from the Pestacia lentiscus plant. It belongs to the family Anacardiaceae, which is cultivated in Mediterranean countries. Thus far, one trial using mastic as monotherapy demonstrated efficacy in healing of duodenal ulcers. Sixty patients aged 22-62 with symptomatic and endoscopically proven duodenal ulcers were entered in a double-blind clinical trial. Endoscopy revealed healing in 70% of the patients on mastic (1g daily) compared to patients on a placebo (Al Habbal 1984). However, it was not established if these patients were positive for H. pylori. Regardless, the healing effects on gastric and duodenal mucosa are impressive.

Inhibition of H. pylori has been verified through in vitro and in animal models (Bona 2001, Marone 2001). Conflicting data regarding the efficacy of mastic exists, and the likely explanation centres upon differing dosage forms utilized. The crude resin used in most published in vitro and animal trials contains a high percentage (30%) of an insoluble and sticky polymer (poly-myrcene). This polymer hinders oral administration and reduces the bioavailability of active compounds (Tassu 1995). This crude mastic resin has been shown to have no effect on H. pylori eradication (Bebb 2003, Loughlin 2003). In the future, total mastic extract without the sticky polymer may provide greater results. Newer in vitro data suggests that the major triterpenic acid extract has the greatest inhibition on H. pylori and may be effective in reducing H. pylori colonization (Paraschos 2007).

Table 5: Probiotic Strains for Co-Administration With Triple Therapy

Group	Treatment (Effective Dose 5-20 Billion CFU)	References
Adults and Children	Lactobacillus johnsonii La1	Cruchet 2003
Children	L. casei DN-114 001	Sykora 2005
Adults	L. johnsonii La1	Michetti 2001, Gotteland 2003
Adults	L. reuteri	Mukai 2002
Adults	S. boulardi	Cindoruk 2007

PROBIOTICS AND H. PYLORI: STRAINS OF PROBIOTICS TO BE USED WITH TRIPLE THERAPY TO INCREASE EFFICACY

The Lactobacillus species have been the focus of many clinical trials as they have the ability to tolerate low pH and transiently reside in the stomach. Several animal trials have displayed a variety of mechanisms by which Lactobacilli inhibit H. pylori. They include induction of cell autolysis, lactic acid-mediated suppression and inhibition of H. pylori binding to the glycolipid receptors in gastric mucosa. Probiotics have not been shown to eradicate H. pylori; however, certain strains listed have achieved outcomes of decreased gastric H. pylori load.

OTHER NOTEABLE INTERVENTIONS

Zinc carnosine, known as polaprezinc, is approved in Japan as a prescription medication for treating ulcers (Matsukura 2000). Zinc carnosine does not appear to contribute to eradication of H pylori. It does, however, neutralize monochloramine, a toxin produced by H. pylori, responsible for inducing inflammation of the gastric lining (Ishihara 2002, Suzuki 2001). Deglycyrrhizinated licorice, likewise, does not have direct evidence of H pylori eradication. However, several well-controlled human trails have demonstrated impressive efficacy for resolving gastric ulcers (Bennett 1980, Enggvist 1973, Feldman 1971). It is very unfortunate that these studies failed to objectively assess for the presence of H. pylori infection.

CLINICAL APPLICATIONS: NEW FIRST-LINE INTEGRATED THERAPY WITH HIGHEST EFFICACY FOR H. PYLORI ERADICATION

It appears appropriate to establish triple therapy with lactoferrin, probiotics and vaccinium as new first-line therapy for management of patients with confirmed H. pylori infection. The addition of Lactoferrin, a specific selection of probiotic strains, and vaccinium to standard triple therapy is capable of enhancing eradication rates, while simultaneously achieving significant reduction in therapy-induced adverse effects. Furthermore, the addition of the complementary agents appears capable of directly enhancing the ability of the gastric mucosa to heal injury induced from long-standing H. pylori infection and sequelae thereof. A selection of agents has shown promise as adjunct treatments for H. pylori eradication therapy; however, for the time being, they remain in preliminary stages of research.

Table 6: Complementary Medicines for Treatment of Functional Dyspepsia or Gastritis: H. pylori positive or negative.

Therapy - All agents must be utilized on an empty stomach	Dose	References
Iberogast*	30 drops tid	Melzer 2004, Rosch 2002, Von Arnim 2007
Zinc carnosine	50-100mg qd	Fuji 2000, Katayama 2000, Kato 2001, Mahmood 2006, Shimada 1999, Watanabe 1998
DGL	500-700mg tid	Bennett 1980, Enggvist 1973, Feldman 1971, Rees 1979
Curcumin	Extract with 95% Curcuminoids 500mg tid	Di Mario 2007, Prucksunand 2001

*Botanical formula: Iberis amara, Angelica, Chamomile, Caraway Fruit, St. Mary's Thistle, Balm Leaves, Peppermint Leaves, Celandine and Licorice Root.

Such agents include essential fatty acids (EPA and GLA) (Frieri 2000, Thompson 1994), garlic (Aydin 2000, Ernst 1999), vitamin C (Jarosz 1998, Zhang 1997) and berberine (Hu 1993).

A long list of botanical medicines has been evaluated for in vitro ability to inhibit H. pylori growth (O'Mahony 2005). Botanicals demonstrating anti-H. pylori activity, in order of highest to lowest activity, include turmeric, cumin, ginger, chilli, borage, black caraway, oregano and licorice.

FIRST-LINE THERAPY FOR TREATMENT OF SYMPTOMS ASSOCIATED WITH H. PYLORI-POSITIVE AND SERO-NEGATIVE GASTRITIS AND FUNCTIONAL DYSPEPSIA

Functional dyspepsia may be concomitant with H. pylori infection; however, the eradication of H. pylori may not ameliorate the dyspeptic symptoms (Koelz 2003). Similarly, patients with gastritis may be found to be H. pylori positive or sero-negative. Typically sero-negative cases of gastritis are caused by ASA, indomethacin, other NSAIDs or alcohol. Symptoms of gastritis in both H. pylori-positive and negative cases may include ache or burning pain in the abdomen, change in appetite with weight loss, nausea, vomitting, frequent burping and bloating. A selection of complementary medicines have demonstrated significant clinical efficacy for the management of functional dyspepsia and gastritis, irrespective of H. pylori status (Table 6).

CONCLUSION

Based on human clinical data, the integration of convention therapy with natural agents should serve as the new clinical standard in the eradication of H. pylori. The increased eradication rates and minimization of side effects warrants this implementation. Other natural agents for dyspeptic symptoms also show high rates of clinical efficacy.

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