

# Nutritional Management of *Helicobacter Pylori* Overgrowth

## Research Abstracts

### MASTIC GUM

**1. Al-Habbal MJ, Al-Habbal Z, Huwez FU. A double-blind controlled clinical trial of mastic and placebo in the treatment of duodenal ulcer. *Clin Exp Pharmacol Physiol* 1984 Sep-Oct;11(5):541-4.**

A double-blind clinical trial was carried out on thirty-eight patients with symptomatic and endoscopically proven duodenal ulcer to compare the therapeutic responses to mastic (1 g daily, twenty patients) and placebo (lactose, 1 g daily, eighteen patients) given orally over a period of 2 weeks. Symptomatic relief was obtained in sixteen (80%) patients on mastic and in nine (50%) patients on placebo, while endoscopically proven healing occurred in fourteen (70%) patients on mastic and four (22%) patients on placebo. The differences between treatments were highly significant (P less than 0.01). Mastic was well tolerated and did not produce side effects. It is concluded that mastic has an ulcer healing effect, but further studies are needed to establish its role in treating peptic ulcer.

PMID: 6395994 [PubMed - indexed for MEDLINE]

**2. Al-Said MS, Ageel AM, Parmar NS, Tariq M. Evaluation of mastic, a crude drug obtained from *Pistacia lentiscus* for gastric and duodenal anti-ulcer activity. *J Ethnopharmacol* 1986 Mar;15(3): 271-8.**

The effect of mastic, a concrete resinous exudate obtained from the stem of the tree *Pistacia lentiscus*, has been studied on experimentally-induced gastric and duodenal ulcers in rats. Mastic at an oral dose of 500 mg/kg produced a significant reduction in the intensity of gastric mucosal damage induced by pyloric ligation, aspirin, phenylbutazone, reserpine and restraint + cold stress. It produced a significant decrease of free acidity in 6-*H. pylorus*-ligated rats and a marked cytoprotective effect against 50% ethanol in rats which could be reversed by prior treatment with indomethacin. The protective effect was not seen when it was given intraperitoneally in phenylbutazone and restraint + cold stress models. The reduction in the intensity of ulceration in

cysteamine-induced duodenal ulcers was not found to be statistically significant in mastic-pretreated rats. The results suggest that mild antisecretory and a localized adaptive cytoprotectant action may be responsible for its anti-ulcer activity. These observations support the results of an earlier study on the clinical effectiveness of mastic in the therapy of duodenal ulcer.

PMID: 3724207 [PubMed - indexed for MEDLINE]

**3. Magiatis P, Melliou E, Skaltsounis AL, Chinou IB, Mitaku S. Chemical composition and antimicrobial activity of the essential oils of *Pistacia lentiscus* var. chia. *Planta Med* 1999 Dec;65(8):749-52.**

The chemical composition of the three essential oils obtained by steam distillation of the mastic gum, leaves and twigs of *Pistacia lentiscus* var. chia, was studied by GC/MS. Sixty nine constituents were identified from the oils. alpha-Pinene, myrcene, trans-caryophyllene and germacrene D were found to be the major components. The *in vitro* antimicrobial activity of the three essential oils and of the resin (total, acid and neutral fraction) against six bacteria and three fungi is reported.

PMID: 10630120 [PubMed - indexed for MEDLINE]

**4. Iauk L, Ragusa S, Rapisarda A, Franco S, Nicolosi VM. *In vitro* antimicrobial activity of *Pistacia lentiscus* L. extracts: preliminary report. *J Chemother* 1996 Jun;8(3):207-9.**

*Institute of Microbiology, University of Catania, Italy.*

The *in vitro* antimicrobial activity of *Pistacia lentiscus* L. extracts was determined. *Pistacia lentiscus* L. extracts were tested on bacteria (*Sarcina lutea*, *Staphylococcus aureus* and *Escherichia coli*) and fungi (*Candida albicans*, *Candida parapsilosis*, *Torulopsis glabrata* and *Cryptococcus neoformans*). Of the different plant extractions, decoctions showed the best antibacterial activity, but the activity against fungal cells appears to be much more interesting.

PMID: 8808717 [PubMed - indexed for MEDLINE]

Continued on page 2

## Nutritional Management of *Helicobacter Pylori* Overgrowth (Continued from front)

### GARLIC

**1. O'Gara EA, Hill DJ, Maslin DJ. Activities of garlic oil, garlic powder, and their diallyl constituents against *Helicobacter pylori*. *Appl Environ Microbiol* 2000 May;66(5):2269-73.**

*School of Health Sciences, University of Wolverhampton, Wolverhampton WV1 1DJ, United Kingdom.*

Chronic *Helicobacter pylori* disease is reduced with Allium vegetable intake. This study was designed to assess the *in vivo* anti-*H. pylori* potential of a variety of garlic substances. The garlic materials all showed substantial but widely differing anti-*H. pylori* effects against all strains and isolates tested. The MICs (range, 8 to 32 microg/ml) and minimum bactericidal concentrations (MBCs) (range, 16 to 32 microg/ml) of undiluted garlic oil (GO) were smaller than those of garlic powder (GP) (MIC range, 250 to 500 microg/ml; MBC range, 250 to 500 microg/ml) but greater than the MIC of allicin (4.0 microg/ml) (Table 2) present in GP. Allicin (MIC, 6 microg/ml; MBC, 6 microg/ml) was more potent than diallyl disulfide (MIC range, 100 to 200 microg/ml; MBC range, 100 to 200 microg/ml), its corresponding sulfide, but of a strength similar to that of diallyl tetrasulfide (MIC range, 3 to 6 microg/ml; MBC range, 3 to 6 microg/ml). Antimicrobial activity of the diallyl sulfides increased with the number of sulfur atoms. Time course viability studies and microscopy showed dose-dependent anti-*H. pylori* effects with undiluted GO, GP, allicin, and diallyl trisulfide after a lag phase of ca. 1 to 2 h. Substantial *in vitro* anti-*H. pylori* effects of pure GO and GP and their diallyl sulfur components exist, suggesting their potential for *in vivo* clinical use against *H. pylori* infections.

PMID: 10788416 [PubMed - indexed for MEDLINE]

**2. Jonkers D, van den Broek E, van Dooren I, Thijs C, Dorant E, Hageman G, Stobberingh E. Antibacterial effect of garlic and omeprazole on *Helicobacter pylori*. *J Antimicrob Chemother* 1999 Jun;43(6):837-9.**

*Department of Medical Microbiology, University Hospital Maastricht, The Netherlands.*

The antibacterial effect of a homemade raw garlic extract and commercial garlic tablets alone and in combination with antibiotics or omeprazole was determined against clinical isolates of *Helicobacter pylori*. MIC values of raw garlic extract and three types of commercial garlic tablets ranged from 10,000 to 17,500 mg/L. When MIC values of the commercial tablets were based on the allicin content, no differences between the three types were observed. The combination of garlic and omeprazole, studied with killing curves, showed a synergic effect which was concentration dependent. Further clinical evaluation of garlic in combination with the conventional agents for *H. pylori* treatment seems warranted.

PMID: 10404325 [PubMed - indexed for MEDLINE]

**3. Chung JG, Chen GW, Wu LT, Chang HL, Lin JG, Yeh CC, Wang TF. Effects of garlic compounds diallyl sulfide and diallyl disulfide on arylamine N-acetyltransferase activity in strains of *Helicobacter pylori* from peptic ulcer patients. *Am J Chin Med* 1998;26(3-4):353-64.**

*Department of Medicine, China Medical College, Taichung, Taiwan.*

Arylamine N-acetyltransferase (NAT) activities with p-aminobenzoic acid (PABA) and 2-aminofluorene (2-AF) were determined in the bacterium *Helicobacter pylori* collected from peptic ulcer patients. Two assay systems were performed, one with cellular cytosols, the other with intact cell suspensions. Cytosols or suspensions of *H. pylori* with or without specific concentrations of diallyl sulfide (DAS) or diallyl disulfide (DADS) co-treatment showed different percentages of 2-AF and PABA acetylation. The data indicated that there was decreased NAT activity associated with increased levels of DAS or DADS in *H. pylori* cytosols and suspensions. Viability studies on *H. pylori* demonstrated that DAS or DADS elicited dose-dependent bactericidal effects on *H. pylori* cultures. The data also indicated that DAS and DADS decreased the apparent values of  $K(m)$  and  $V_{max}$  of NAT enzyme from *H. pylori* in both systems examined. This report is the first demonstration that garlic components can affect *H. pylori* growth and NAT activity.

PMID: 9862023 [PubMed - indexed for MEDLINE]

**4. Zhou ZF, Zhang YS, Wang YM. [Seroprevalence of *Helicobacter pylori* infection among Yi and Han nationalities in Yunxian County, Yunnan Province]. [Article in Chinese] *Zhonghua Liu Xing Bing Xue Za Zhi* 1997 Feb;18(1):18-21.**

*Department of Digestion, First Affiliated Hospital of Kunming Medical College.*

Under cluster sampling, an early serum assay of *Helicobacter pylori* (Hp) infection among 1084 healthy people, was carried out. Out of them, 325 among the Yi and Han Nationalities at Yunxian County of Yunnan Province were given a simultaneous test of anti-HAV IgG. The results were as follows: overall Hp infection rate was 51.1%; no difference of the infection was observed between the Yis and the Hans; the prevalence of Hp antibody went up with age; higher rates were detected among those who drank river water or unboiled water than among those who drank tap water, well water or boiled water, from poultry raisers than from non-poultry raisers and with drug abusers than with non-drug abusers. Hp infection showed a parallel relation to HAV infection. Finally, seven main epidemic factors were sifted from multi-factor logistic analysis namely source of drinking water, drinking habit, chicken-raising, pig-keeping, dog-breeding, drug-abusing and consumption of garlic. All these findings suggested that drinking water was an important vehicle of Hp infection. Our research data seems to have lend support to both fecal-oral transmission

## Nutritional Management of *Helicobacter Pylori* Overgrowth (Continued from page 2)

viewpoint and the hypothesis that Hp infection derives from animals. Frequent intake of garlic may serve as an agent in long-term prevention of Hp infection among people in this area.

PMID: 9812475 [PubMed - indexed for MEDLINE]

### 5. Cellini L, Di Campi E, Masulli M, Di Bartolomeo S, Allocati N. Inhibition of *Helicobacter pylori* by garlic extract (*Allium sativum*). *FEMS Immunol Med Microbiol* 1996 Apr;13(4):273-7.

*Instituto di Medicina Sperimentale, Facolta di Medicina e Chirurgia, Universita G.D'Annunzio, Chieti, Italy. CELLINI@IMS.UNICH.IT*

The antibacterial effect of aqueous garlic extract (AGE) was investigated against *Helicobacter pylori*. Sixteen clinical isolates and three reference strains of *H. pylori* were studied. Two different varieties of garlic were used. The concentration of AGE required to inhibit the bacterial growth was between 2-5 mg ml<sup>-1</sup>. The concentration, for both AGE types, to inhibit 90% (MIC90) of isolates was 5 mg ml<sup>-1</sup>. The minimum bactericidal concentration (MBC) was usually equal to, or two-fold higher than, minimum inhibitory concentration (MIC). Heat treatment of extracts reduced the inhibitory or bactericidal activity against *H. pylori*; the boiled garlic extract showed a loss of efficacy from two- to four-fold the values of MIC and the MBC obtained with fresh AGE. The antibacterial activity of garlic was also studied after combination with a proton pump-inhibitor (omeprazole) in a ratio of 250:1. A synergistic effect was found in 47% of strains studied; an antagonistic effect was not observed.

PMID: 8739190 [PubMed - indexed for MEDLINE]

### 6. Sivam GP, Lampe JW, Ulness B, Swanzy SR, Potter JD. *Helicobacter pylori*—in vitro susceptibility to garlic (*Allium sativum*) extract. *Nutr Cancer* 1997;27(2):118-21.

*Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, Seattle, WA 98104, USA.*

Gastric cancer is the major cancer in the developing world and one of the top two worldwide. *Helicobacter pylori* is a bacterium implicated in the etiology of stomach cancer. The incidence of stomach cancer is lower in individuals and populations with high *Allium* vegetable intakes. *Allium* vegetables, particularly garlic, have antibiotic activity. Standard antibiotic regimens against *H. pylori* are frequently ineffective in high-risk populations. As part of our study of the role of *Allium* vegetable intake on cancer prevention, we wished to investigate its antimicrobial activity against *H. pylori*. An aqueous extract of garlic cloves was standardized for its thiosulfinate concentration and tested for its antimicrobial activity on *H. pylori* grown on chocolate agar plates. Minimum inhibitory concentration was 40 micrograms thiosulfinate per milliliter. *Staphylococcus aureus* tested under the same

conditions was not susceptible to garlic extract up to the maximum thiosulfinate concentration tested (160 micrograms/ml). To our knowledge, this is the first report of *H. pylori*'s susceptibility to garlic extract of known thiosulfinate concentration. It is plausible that the sensitivity of *H. pylori* to garlic extract at such low concentration may be related to the reported lower risk of stomach cancer in those with a high *Allium* vegetable intake. Furthermore, it may identify a strategy for a low-cost intervention, with few side effects, in populations at high risk for stomach cancer, particularly where antibiotic resistance and the risk of reinfection are high.

PMID: 9121937 [PubMed - indexed for MEDLINE]

### 7. You WC, Zhang L, Gail MH, Ma JL, Chang YS, Blot WJ, Li JY, Zhao CL, Liu WD, Li HQ, Hu YR, Bravo JC, Correa P, Xu GW, Fraumeni JF Jr. *Helicobacter pylori* infection, garlic intake and precancerous lesions in a Chinese population at low risk of gastric cancer. *Int J Epidemiol* 1998 Dec;27(6):941-4.

*National Cancer Institute, Bethesda, MD 20892, USA.*

**BACKGROUND:** Cangshan County of Shandong Province has one of the lowest rates of gastric cancer (GC) in China. While intestinal metaplasia (IM) and dysplasia (DYS) are less common in Cangshan than in areas of Shandong at high risk of GC, these precursor lesions nevertheless affect about 20% of adults age > or = 55. **SUBJECTS AND SETTING:** In order to evaluate determinants of IM and DYS in Cangshan County, a low risk area of GC a survey was conducted among 214 adults who participated in a gastroscopic screening survey in Cangshan County in 1994. **METHOD:** A dietary interview and measurement of serum *Helicobacter pylori* antibodies were performed. **RESULTS:** The prevalence of *H. pylori* was lowest (19%) among those with normal gastric mucosa, rising steadily to 35% for superficial gastritis (SG), 56% for chronic atrophic gastritis (CAG), 80% for IM, and 100% for DYS. The prevalence odds of precancerous lesions were compared with the odds of normal histology or SG. The odds ratio (OR) or CAG associated with *H. pylori* positivity was 4.2 (95% confidence interval [CI] : 1.7-10.0), while the OR of IM/DYS associated with *H. pylori* positivity was 31.5 (95% CI: 5.2-187). After adjusting for *H. pylori* infection, drinking alcohol was a risk factor for CAG (OR = 3.2, 95% CI: 1.1-9.2) and IM/DYS (OR = 7.8, 95% CI: 1.3-47.7). On the other hand, consumption of garlic showed non-significant protective effects and an inverse association with *H. pylori* infection. **CONCLUSIONS:** The findings of this study suggest that infection with *H. pylori* is a risk factor and garlic may be protective, in the development and progression of advanced precancerous gastric lesions in an area of China at relatively low risk of GC.

PMID: 10024185 [PubMed - indexed for MEDLINE]

## Nutritional Management of *Helicobacter Pylori* Overgrowth (Continued from page 3)

### LACTOFERRIN

#### 1. Dial EJ, Hall LR, Serna H, Romero JJ, Fox JG, Lichtenberger LM. Antibiotic properties of bovine lactoferrin on *Helicobacter pylori*. *Dig Dis Sci* 1998 Dec;43(12):2750-6.

Department of Integrative Biology, The University of Texas-Houston Medical School, 77225, USA.

To investigate a potential new treatment for gastric *Helicobacter pylori* infection, we have examined the use of the natural antibiotic lactoferrin, found in bovine milk, for activity against *Helicobacter* species both *in vitro* and *in vivo*. Lactoferrin was bacteriostatic to *H. pylori* when cultured at concentrations  $\geq 0.5$  mg/ml. Growth of *H. pylori* was not inhibited by another milk constituent, lysozyme, or by a metabolite of lactoferrin, lactoferricin B, but growth was inhibited by the iron chelator deferoxamine mesylate. Lactoferrin inhibition of growth could be reversed by addition of excess iron to the medium. Lactoferrin in retail dairy milk was found to be more stable intragastrically than unbuffered, purified lactoferrin. Treatment of *H. felis*-infected mice with lactoferrin partially reversed mucosal disease manifestations. It is concluded that bovine lactoferrin has significant antimicrobial activity against *Helicobacter* species *in vitro* and *in vivo*. Bovine lactoferrin should be further investigated for possible use in *H. pylori* infections in man.

PMID: 9881510 [PubMed - indexed for MEDLINE]

#### 2. Wada T, Aiba Y, Shimizu K, Takagi A, Miwa T, Koga Y. The therapeutic effect of bovine lactoferrin in the host infected with *Helicobacter pylori*. *Scand J Gastroenterol* 1999 Mar;34(3):238-43.

Dept. of Infectious Diseases, Tokai University School of Medicine, Kanagawa, Japan.

**BACKGROUND:** It remains unclarified whether bovine lactoferrin (bLF) can exert a therapeutic effect on the host infected with *Helicobacter pylori*. **METHODS:** Germfree BALB/c mice were orally inoculated with *H. pylori* to induce infection. Three weeks after infection the mice were given bLF orally once daily for 2 or 4 weeks and were then killed to examine the bacterial number in the stomach and the serum antibody titer to *H. pylori*. To count the number of epithelium-bound *H. pylori*, the resected stomach was agitated in phosphate-buffered saline to remove non-bound *H. pylori* before bacterial enumeration. **RESULTS:** The administration of 10 mg bLF for 3 to 4 weeks decreased the number of *H. pylori* in the stomach to one-tenth and also exerted a significant inhibitory effect on the attachment of *H. pylori* to the stomach. As a result, the serum antibody titer to *H. pylori*, whose level is presumed to represent the size of the immune response by the host, thereby reflecting the degree of bacterial attack, decreased to an undetectable level. **CONCLUSIONS:** These findings suggest that bLF exerts an inhibitory effect on colonizing *H. pylori* by detaching the bacterium from the gastric epithelium and by exerting a direct anti-bacterial effect.

PMID: 10232866 [PubMed - indexed for MEDLINE]

#### 3. Hamosh M. Protective function of proteins and lipids in human milk. *Biol Neonate* 1998;74(2):163-76.

Department of Pediatrics, Georgetown University Medical Center, Washington, DC 20007, USA. hamoshp@medlib.georgetown.edu

Human milk provides the infant with protection against infectious diseases. This protection is conferred through several mechanisms: specific antibody targeted protection against pathogens in the infant's environment (through milk IgA, IgG, and IgM) and broad-spectrum, nonspecific protection provided through several distinct mechanisms. These are: bactericidal effects (lactoferrin), bacteriostatic action (lactoferrin, lysozyme), lysis of microorganisms (lysozyme), antiviral effects (lactoferrin, products of milk fat digestion), antiprotozoan activity (free fatty acids produced during gastric and intestinal digestion of milk fat), and ligand action (inhibition of *Helicobacter pylori* adhesion to gastric mucosa by kappa-casein). In addition to these protective functions of the proteins and lipids of human milk, several enzymes present in human milk might provide protection by generating components that are bactericidal (bile salt dependent lipase, peroxidase), prevent inflammatory reactions (platelet-activating factor acetylhydrolase), or protect the integrity of milk proteins (antiproteases).

PMID: 9691157 [PubMed - indexed for MEDLINE]

#### 4. Dhaenens L, Szczebara F, Husson MO. Identification, characterization, and immunogenicity of the lactoferrin-binding protein from *Helicobacter pylori*. *Infect Immun* 1997 Feb;65(2):514-8.

Laboratoire de Bacteriologie-Hygiene, Faculte de Medecine Henri Warembourg, Lille, France.

Iron acquisition plays an important role in bacterial virulence. Different studies have been initiated to define the mechanism by which *Helicobacter pylori* acquires iron. We had previously demonstrated that human lactoferrin (HLf) supported full growth of the bacteria in media lacking other iron sources. The ability of *H. pylori* to use HLf as an iron source had been found to be dependent on cell-to-protein contact. Since lactoferrin has been found in significant amounts in human stomach resection specimens from patients with superficial or atrophic gastritis, the iron uptake of *H. pylori* via a specific HLf receptor may play a major role in the virulence of *H. pylori* infection. In this study, by using affinity chromatography with biotinylated HLf and streptavidin-agarose, we identified a 70-kDa lactoferrin-binding protein (Lbp) from outer membrane proteins of *H. pylori*. This Lbp was only present when *H. pylori* was grown in an iron-starved medium, suggesting that it serves in iron uptake. Direct binding assays with increasing concentrations of biotinylated HLf demonstrated that the lactoferrin interaction with the outer membrane of *H. pylori* grown in iron-restricted medium was saturable. Competitive binding experiments with bovine and human lactoferrin and with transferrin of horse, bovine, and human origin indicated that this Lbp appeared highly specific for HLf. A number of other studies have focused on the importance of transferrin and lactoferrin receptors in pathogenic bacteria and their specificity with the host species. This observation might explain the very strict human specificity of *H. pylori*.

PMID: 9009306 [PubMed - indexed for MEDLINE]