PO Box 2345 Beijing 100023, China
Fax: +86-10-85381893
Email: wcjd@wjgnet.com www.wjgnet.com

World Chin J Digestol 2004 May;12(5):1100-1103
世界华人消化杂志 ISSN 1009-3079 CN 14-1260/R




# 胃食管反流病与幽门螺杆菌相关性胃炎及胃肠激素的关系

吴灵飞, 王炳周, 冯家琳, 郑宗茂, 张金池, 曾 哲

吴灵飞, 王炳周, 郑宗茂, 曾哲, 汕头大学医学院第二附属医院消化科 广东省汕头市 515041
冯家琳, 汕头大学医学院第二附属医院信息科 广东省汕头市 515041
张金池, 汕头大学医学院第二附属医院放免室 广东省汕头市 515041
吴灵飞, 男, 1964-09-26生, 汉族, 湖北省武汉市人. 1986年湖北医科大学毕业, 医学硕士, 副主任医师. 主要从事胃肠疾病研究.
广东省中医药管理局资助项目, No.99591
项目负责人: 吴灵飞, 515041, 广东省汕头市东厦北路69号, 汕头大学医学院第二附属医院消化科. lingfeiwu@21cn.com
电话: 0754-8355461 传真: 0754-8346543
收稿日期: 2003-12-12 接受日期: 2004-01-12

## Relationship of *Helicobacter pylori* related gastritis, gut hormones and gastroesophageal reflux disease

Ling-Fei Wu, Bing-Zhou Wang, Jia-Lin Feng, Zong-Mao Zheng, Jin-Chi Zhang, Zeng Zhe

Ling-Fei Wu, Bing-Zhou Wang, Zong-Mao Zheng, Zeng Zhe, Department of Gsatroenterology; Second Affiliated Hospital, Shantou University Medical College, Shantou 515041, Guangdong Province, China
Jia-Lin Feng, Department of Information; Second Affiliated Hospital, Shantou University Medical College, Shantou 515041, Guangdong Province, China
Jin-Chi Zhang, Department of Radioimmunoassay, Second Affiliated Hospital, Shantou University Medical College, Shantou 515041, Guangdong Province, China
Supported by Guangdong Chinese Traditional Medicine Management Agency, No.99591
Correspondence to: Dr. Ling-Fei Wu, Department of Gastroenterology, Second Affiliated Hospital, Shantou University Medical College, Shantou 515041, Guangdong Province, China. lingfeiwu@21cn.com
Received: 2003-12-12 Accepted: 2004-01-12

## Abstract

AIM: To evaluate the relationship of *H pylori* infection, *H pylori* -related gastritis, serum gastrin and motilin levels and esophageal lesions in gastroesophageal reflux disease (GERD).

METHODS: All 53 GERD patients were divided into non-erosive reflux disease (NERD group, 32 cases) and reflux esophagitis (RE group, 21 cases ) by endoscopy. The degrees of gastritis in antrum and body as well as esophagitis were evaluated by pathological examinations. Fasting serum gastrin and motilin concentrations were determined by radioimmunoassay. *H pylori* was examined by serum *H pylori*-antibody, Warthin-Starry stain, urease-dependent test (rapid urease test or $^{14}$C-breath test). *H pylori* infection was affirmed when at least two of three tests were positive. 20 normal persons were as controls. In NERD group, 18 were *H pylori* positive and 14 were negative. In RE group 12 were *H pylori* positive and 9 were negative. According to the classification of esophagitis, 11 were Class Ⅰ, 7 Class Ⅱ and 3 Class Ⅲ. There were 30 *H pylori* (+) and 23 *H pylori* (-) in 53 GERD patients.

RESULTS: As compared with healthy controls, fasting serum motilin levels in RE group were significantly lower (360±126 *vs* 440±110 μg/L, $^{a}P$ <0.05) and those in NERD group were similar ($P$ >0.05). No differences in gastrin levels were found between NERD or RE group and controls (both $P$ >0.05). The serum gastrin levels in *H pylori* (+) GERD were significantly higher than controls (35.8±11.6 *vs* 28.5±10.6 μg/L, $^{b}P$ <0.05). In *H pylori* (+) GERD patients, gastritis grades in the antrum and gastric body were significantly higher than that in *H pylori* (-) patients ($\chi^2$=32.97, $\chi^2$=15.67, both $P$ <0.005). The esophagitis grades were similar in *H pylori* (+) and *H pylori* (-) GERD ($\chi^2$ =0.82, $P$ >0.05). The gastritis grades were not associated with the esophagitis degrees, but with *H pylori* infection.

CONCLUSION: Motilin is involved in the pathogenesis of RE. *H pylori* can lead to hypergastrinemia and gastritis in the antrum and gastric body.

Wu LF, Wang BZ, Feng JL, Zheng ZM, Zhang JC, Zhe Z. Relationship of *Helicobacter pylori* related gastritis, gut hormones and gastroesophageal reflux disease. Shijie Huaren Xiaohua Zazhi 2004;12(5):1100-1103

## 摘要

**目的: 通过对胃食管反流病(GERD)患者幽门螺杆菌(*H pylori*)感染、*H pylori*相关性胃炎的程度及血清胃泌素(Gas)、胃动素(Mot)水平的检测, 探讨*H pylori*与GERD之间的关系.**

**方法: GERD患者53例按内镜表现分为非糜烂性反流病(NERD)和反流性食管炎(RE)2组, 结合病检评估胃窦、胃体黏膜炎症及食管黏膜损伤, 采用放免法检测空腹血Gas, Mot水平. *H pylori*检测采用血清抗体法, 组织银染及尿素酶依赖试验($^{14}$C-尿素呼气试验或快速尿素酶试验), 三项试验中二项阳性定为*H pylori*感染. 20名正常健康人作对照. 32例NERD患者18例*H pylori*阳性, 14例阴性; 21例RE患者12例*H pylori*阳性, 9例阴性. RE组Ⅰ级食管炎11例, Ⅱ级7例, Ⅲ级3例. 53例GERD中, *H pylori* (+)30例, *H pylori* (-)23例.**

**结果: RE组Mot水平显著低于对照组(360 ± 126 *vs* 440 ± 110 μg/L, $^{a}P$ <0.05). NERD组Mot水平与对照组相比差异无显著性($P$ >0.05). NERD和RE二组患者Gas水平与对照组相比均无显著性差异($P$ >0.05), *H pylori* (+) GERD患者Gas水平显著高于对照组(35.8 ± 11.6 *vs* 28.5 ± 10.6 μg/L, $^{b}P$ <0.05). *H pylori* (+) GERD患者与*H pylori* (-)组相比, 胃窦胃炎及胃体胃炎均有高度显著性差异($P$ <0.005), 但2组食管炎程度并无显著性差异($P$ >0.05), 胃炎的程度与*H pylori*感染有关但与食管炎的程度无关.**

**结论:** Mot与RE发病有关. *H pylori*(+)GERD患者有较高Gas水平及明显胃窦及胃体炎症,但*H pylori*性胃炎与食管病变分级无关.

吴灵飞, 王炳周, 冯家琳, 郑宗茂, 张金池, 曾哲. 胃食管反流病与幽门螺杆菌相关性胃炎及胃肠激素的关系. 世界华人消化杂志 2004;12(5):1100-1103
http://www.wjgnet.com/1009-3079/12/1100.asp

## 0 引言

胃食管反流病(gstroesophageal reflux disease, GERD)是一种临床常见疾病, 根据有无食管炎症状, 一般将之分为非糜烂性胃食管反流病(non-erosive reflux disease, NERD)、反流性食管炎(reflux esophagitis, RE)和Barrett食管三种类型[1], 其发病机制较复杂. 一般认为与食管下端扩约肌(LES)、膈肌功能异常[2-5]及酸突破[6-10]有关, 与幽门螺杆菌(*H pylori*)的关系争论颇多[11-17]. 我们通过观察NERD和RE患者血胃动素与胃泌素含量的变化, 并作*H pylori*阳性和阴性GERD患者胃炎与食管炎程度的相关性分析, 旨在探讨*H pylori*及其胃炎与GERD之间的关系.

## 1 材料和方法

**1.1 材料** 本院2001/10-2003/10门诊患者具有反酸、烧心、反食、胸痛等症状至少3 mo. 内镜诊断为RE者应排除消化性溃疡及肿瘤. 内镜检查阴性者经质子泵抑制剂(PPI)试验(Losec 20 mg bid × 7 d)明显减轻症状则诊断为NERD[18]. 由于Barrett食管仅3例, 故本组GERD剔除Barrett食管患者, 只包括NERD($n$=32)和RE ($n$=21)二类患者. 所有患者均无上消化道手术史及严重心、肝、肾等疾病, 近1 mo均无使用非甾体类消炎药、胃肠动力药及抗*H pylori*药物. 对诊断为NERD的患者回顾性分析PPI试验前的检测数据. 对照组20名健康志愿者, 均无GERD症状, 亦无近期服药史. RE分级参照2000全国《反流性食管病(炎)治疗及诊断方案(试行)》标准[19]. Ⅰ级: 食管黏膜点状或条状发红、糜烂, 无融合现象; Ⅱ级: 有条状发红, 糜烂, 并有融合, 但非全周性; Ⅲ级: 病变广泛、发红、糜烂, 融合呈全周性, 或有溃疡. 胃炎的诊断标准参照全国《慢性胃炎研讨会共识意见》标准[20], 分别按部位(胃窦、胃体及胃底贲门部)各取活检组织行HE染色及病理学检查, 根据炎症的程度分为无、轻度、中度及重度四级.

**1.2 方法** 采用WS染色、尿素酶依赖试验(快速尿素酶试验或$^{14}$C-呼气试验)及查血清*H pylori*抗体的方法, 三项试验中二项阳性诊断*H pylori*感染. 所有病例均于清晨空腹静脉采血, 按照说明书以放免法进行检测. Gas试剂盒购自北方生物技术研究所, Mot试剂盒购自301医院科技开发中心放免所.

**统计学处理** 计量资料采用mean±SD表示, 均数的检验采用$t$检验. 计数资料采用$\chi^2$检验或Radit分析, $P$<0.05认为差异有统计学意义.

## 2 结果

NERD组32例, 男19例, 女13例, 平均年龄43 ± 11岁, 其中*H pylori*(+)18例, *H pylori*(-)14例. RE组21例, 男14例, 女7例, 平均年龄47 ± 12岁, 其中*H pylori*(+)12例, *H pylori*(-)9例. 内镜分级: Ⅰ级11例, Ⅱ级7例, Ⅲ级3例. 二组患者*H pylori*感染率均为56%, 无统计学差异($P$>0.05). 二组年龄亦无显著性差异($P$>0.05). 对照组20例, 男12例, 女9例, 平均年龄35 ± 12岁, 胃镜检查阴性.

**2.1 血清Gas、Mot水平** GERD患者根据内镜下表现分为阴性(NERD)和阳性(RE)2组. 2组患者血Gas水平与对照组比较均无显著性差异($P$>0.05). NERD组Mot水平较低, 但与对照组比较无统计学意义($P$>0.05). RE组Mot含量与对照组相比, 有显著性差异($^aP$<0.05). 若根据*H pylori*情况分组, *H pylori*(+)组($n$=30)GERD患者Gas水平较高, 与对照组相比有显著性差异($^bP$<0.05), *H pylori*(-)组($n$=23) GERD患者Gas水平与对照组相比无显著性差异($P$>0.05). *H pylori*(+)/(-)组Mot水平均低于对照组, 但无统计学意义($P$>0.05, 表1).

表1 GERD患者血清Gas, Mot含量 (mean ± SD, μg/L)

| 分组 | | $n$ | Gas | Mot |
|---|---|---|---|---|
| 内镜表现 | NERD | 32 | 32.9 ± 12.1 | 405 ± 113 |
| | RE | 21 | 26.8 ± 9.8 | 360 ± 126[a] |
| *H pylori* | (+) | 30 | 35.8 ± 11.6[b] | 378 ± 10 |
| | (-) | 23 | 23.5 ± 10.7 | 300 ± 121 |
| 对照组 | | 20 | 28.5 ± 10.6 | 440 ± 110[a] |

[a]$P$<0.05, $t$=2.16 *vs* 对照组; [b]$P$<0.05, $t$=2.26 *vs* 对照组.

**2.2 *H pylori*(+)/(-) GERD患者胃食管炎** *H pylori*(+)胃窦胃炎、胃体胃炎均较明显. 30例*H pylori*(+)患者中

表2 GERD患者*H pylori*(+)/(-)组胃食管炎症分级 ($n$)

| | | 胃窦胃炎 | | | | 胃体胃炎 | | | | 食管炎 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *H pylori* | $n$ | 无 | 轻 | 中 | 重 | 无 | 轻 | 中 | 重 | 无 | 轻 | 中 | 重 |
| (+) | 30 | 0 | 19 | 8 | 3 | 3 | 18 | 5 | 4 | 18 | 7 | 4 | 1 |
| (-) | 23 | 17 | 4 | 2 | 0 | 14 | 5 | 2 | 2 | 14 | 4 | 3 | 2 |
| | | $\chi^2$=32.97 | | | | $\chi^2$=15.67 | | | | $\chi^2$=0.82 | | | |
| | | $P$<0.005 | | | | $P$<0.005 | | | | $P$>0.05 | | | |

有19例有轻度胃窦部炎症，8例中度炎症，3例重度炎症. 在胃体部炎症中，18例为轻度炎症，5例为中度炎症，4例重度炎症. 23例 *H pylori* (-)患者中胃炎均较少见. *H pylori* (+)/(-)组比较，胃窦胃炎及胃体胃炎均有高度显著性差异($P$<0.005). 二组患者食管炎程度的比较则无显著性差异($P$>0.05，表2). 胃窦炎症、胃体炎症的程度与食管病变的程度进行Radit分析，均未见显著性差异($P$>0.05). GERD患者食管病变的程度均不与胃窦、胃体炎症程度相关.

## 3 讨论

GERD的发生与多因素有关. 食管胃动力异常、食管对反流物清除机制缺陷或黏膜上皮防御机制损伤均可导致GERD发病[20-24]. 然而，影响LES压力及食管蠕动的因素颇多[2-5]. 研究表明，Mot水平降低可使胃排空延缓[24-27]，Gas则可使LES压力升高，但生理状态下Gas对LES的影响并不大[27]. 文献报道 *H pylori* 感染者常引起高Gas血症，根除 *H pylori* 后可使Gas水平恢复正常[24, 28]. *H pylori* (+) GERD患者是否亦有Gas异常未见报道. 本组中，*H pylori* (+)组Gas水平显著高于 *H pylori* (-)组，说明 *H pylori* 同样对GERD患者Gas有影响. Gisbert *et al* [28]对 *H pylori* (+)与 *H pylori* (-)GERD患者进行食管测压及24 h食管pH值测定，结果二组患者并无显著性差别. 本组中，GERD患者无论有无食管黏膜的损伤，其空腹血中Gas水平与对照组相比均无统计学意义. *H pylori* (+)GERD患者Gas较高但与Mot无相关，表明在GERD的发生过程中Gas对食管动力并未起重要作用. RE组Mot显著性低于正常值，表明Mot与GERD进展有关. GERD与 *H pylori* 的关系一直引人注目. 流行病学资料表明，GERD患者 *H pylori* 感染率低. 土耳其后裔的人群中 *H pylori* 感染率高(60.6%)而RE发生率低(9.7%)，荷兰人群中 *H pylori* 感染率低(18.5%)而RE发生率高(33.0%)，二者呈反比关系[29-30]. 但是，不同地区有不同的结果[31-35]. 在本组中，GERD主要为NERD及RE患者，Barrett食管少见，且二组 *H pylori* 感染率及年龄均无显著性差异，说明 *H pylori* 及年龄因素在GERD病变逐渐进展的过程中并不起作用. 我们认为GERD患者的这些特点可能与我国为 *H pylori* 高发区及种族差异有关.

本组患者 *H pylori* 感染与GERD食管炎病变程度无关，但与胃窦胃炎及胃体胃炎均有关. 在21例RE患者中，11例 *H pylori* (+)且病变程度较轻. 而在24例 *H pylori* (+)患者中，均有胃窦部炎症，部分患者胃体部炎症更为严重. 由于本组无近期服药病史，胃部炎症主要应为 *H pylori* 相关性胃炎[35]，但胃炎与食管黏膜损伤无关. 有学者认为不是 *H pylori* 而是胃炎对GERD有保护作用[10, 36-39]. 我们认为这应依具体情况而定. 本组患者中胃体胃炎较重者食管病变较轻，而胃体炎症较轻者GERD症状常较明显，其他学者亦观察到类似现象[16, 21]. 此外，我们注意到RE患者内镜下贲门炎不多见. 21例RE中仅6例出现贲门炎，为28.6%. 32例NERD患者中，只2例(6.2%)有贲门炎，并未见Csendes *et al* 报道GERD患者贲门肠上皮化生多见的情况[40]. 这些结果的差异可能与不同人群的遗传背景、*H pylori* 菌株的生物学特性、个体食管病前状态及对疾病的不同反应性有关[10-12, 41-47].

本项研究中，NERD的诊断是采用PPI试验和非24 h食管pH值检测金标准，毕竟pH检测、压力测定及核素法条件要求较高或患者依从性差，难于普及. 文献报道，PPI试验敏感性和特异性可达80%以上[18]. 我们认为对疑似NERD的病例采用此法方便简捷，值得推广. 然而，亦应注意到PPI对酸耐受力差，在胃中暴露于酸后易失效，因此对某些胃排空延缓的病例由于药物可能已在胃中失效或减效并未显出实际效果，因此本组应除外PPI无效的GERD病例. 此外，胆汁反流的病例亦不在此列. 寻找一种简便有效的诊断方法或筛选指标有助于更广泛地探讨GERD的发病机制[48].

## 4 参考文献


1 Wong WM, Lam KF, Lai KC, Hui WM, Hu WH, Lam CL, Wong NY, Xia HH, Huang JQ, Chan AO, Lam SK, Wong BC. Avaldated symptoms questionnaire (Chinese GERDQ) for the diagnosis of gastro-oesophageal reflux disease in the Chinese population. *Aliment Pharmacol Ther* 2003;17:1407-1413

2 Fritscher-Ravens A, Mosse CA, Mukherjee D, Yazaki E, ParkPO, Mills T, Swain P. Transgastric gastropexy and hiatal hernia repair for GERD under EUS control: a porcine model. *Gastrointest Endosc* 2004;59:89-95

3 Chrysos E, Prokopakis G, Athanasakis E, Pechlivanides G, Tsiaoussis J, Mantides A, Xynos E. Factors affecting esophageal motility in gastroesophageal reflux disease. *Arch Surg* 2003;138:241-246

4 Cheng WF, Yi CQ. The study on the motive function of esophagus in patients with reflux esophagitis. *Shijie Huaren Xiaohua Zazhi* 1999;7:444-445

5 Sarnelli G, Ierardi E, Grasso R, Verde C, Bottiglieri ME, Nardone G, Budillon G, Cuomo R. Acid exposure and altered acid clearance in GERD patients treated for *Helicobacter pylori* infection. *Dig Liver Dis* 2003;35:151-156

6 Lin JK, Hu PJ, Zhu XY, Zheng MH, Li CJ, Ren M. The value of esophageal manometry and 24 hour pH monitoring in diagnosis of GERD. *Huaren Xiaohua Zazhi* 1998;6:51-53

7 Pan LN, Zhao HQ. Reflux esophagitis: etiology and pH detection of esophagus and value of diagnosis of X-ray. *Shijie Huaren Xiaohua Zazhi* 2000;8:1135-1136

8 Freston JW, Triadafilopoulos G. Approaches to the long-term mnagement of adults with GERD-proton pump inhibitor therapy, laparoscopic fundoplication or endoscopic therapy? *Aliment Pharmacol Ther* 2004;19(Suppl 1):35-42

9 Manes G, Mosca S, Laccetti M, Lioniello M, Balzano A. *Helicobacter pylori* infection, pattern of gastritis, and symptoms in erosive and nonerosive gastroesophageal reflux disease. *Scand J Gastroenterol* 1999;34:658-662

10 Ackermark P, Kuipers EJ, Wolf C, Breumelhof R, Seldenrijk CA, Timmer R, Segeren KC, Kusters JG, Smout AJ. Colonization with cagA-positive *Helicobacter pylori* strains in intestinal metaplasia of the esophagus and the esophagogastric junction. *Am J Gastroenterol* 2003;98:1719-1724

11 Wang TY, Bi CS, Jiang JL, Wang ML, Liu B. Reflux esophagitis: a clinical analysis of 242 cases. *Shijie Huaren Xiaohua Zazhi* 2002;10:942-945

12 Manes G, Pieramico O, Uomo G, Mosca S, de Nucci C, Balzano A. Relationship of sliding hiatus hernia to gastroesophageal reflux disease: a possible role for *Helicobacter pylori* infection?

*Dig Dis Sci* 2003;48:303-307
13 Feng GJ, Hu FL, Wang HH, Liu JX. A study on the relationship of *Helicobacter pylori*, gastrin and gastroesophageal reflux disease. *CMJ* 2003;83:96-99
14 Graham DY. *Helicobacter pylori* is not and never was "protective" against anything, including GERD. *Dig Dis Sci* 2003;48: 629-630
15 McColl KE. Motion-*Helicobacter pylori* causes or worsens GERD: arguments against the motion. *Can J Gastroenterol* 2002;16:615-617
16 Cheng LG, Dong LH, Ge JR, Wang YP, Mao YL, Ma JH. A study on the relationship of *Helicobacter pylori* and reflux esophagitis. *Zhonghua Xiaohua Neijing Zazhi* 2003;20:47-48
17 Alonso Aquirre PA. PPI test and endoscopy in GERD. *Rev Esp Enferm Dig* 2002;94:88-97
18 Yu ZL. Diagnostic criterion and existing problems about reflux esophagitis. *Chinese J Internal* 2000;39:151-152
19 The association of Chinese digestive disease. The common opinions on chronic gastritis in China. *Chinese J Digestion* 2000; 20:117-118
20 Zhang WD, Xiao HD, Hu FL, Hu PJ, Xu ZM. The common opinions on *Helicobacter pylori*. *CMJ* 2000;80:394-395
21 Hirschowitz BI, Haber MM. *Helicobacter pylori* effects on gastritis, gastrin and enterochromaffin-like cells in Zollinger-Ellison syndrome and non-Zollinger-Ellison syndrome acid hypersecretors treated long-term with lansoprazole. *Aliment Pharmacol Ther* 2001;15:87-103
22 Xie Y, Zhou XJ, Lui LH, Huang DQ, Cheng J, Huang Y, Wang CW, Zhu JQ, Zhang KH. Role of nitric oxide in the oxidative damages on esophageal mucus in reflux esophagitis. *Shijie Huaren Xiaohua Zazhi* 2001;9:1213-1214
23 Liu WX, Hong G, Fu BY, Jiang RL, Liu ZY. Interdigestive serum motilin levels and Gut motility in functional dyspepsia. *Shijie Huaren Xiaohua Zazhi* 2001;9:722-724
24 Esposito S, Valente G, Zavallone A, Guidali P, Rapa A, Oderda G. Histological score for cells with irregular nuclear contours for the diagnosis of reflux esophagitis in children. *Hum Pathol* 2004;35:96-101
25 Wilson P, Welch NT, Hinder RA, Anselmino M, Herrington MK, DeMeester TR, Adrian TE. Abnormal plasma gut hormones in pathologic duodenogastric reflux and their response to surgery. *Am J Surg* 1993;165:169-176
26 Perdikis G, Wilson P, Hinder RA, Redmond EJ, Wetscher GJ, Saeki S, Adrian TE. Gastroesophageal reflux disease is associated with enteric hormone abnormalities. *Am J Surg* 1994; 167:186-191
27 Okamoto K, Iwakiri R, Mori M, Hara M, Oda K, Danjo A, Ootani A, Sakata H, Fujimoto K. Clinical symptoms in endoscopic reflux esophagitis: evaluation in 8031 adult subjects. *Dig Dis Sci* 2003;48:2237-2241
28 Gisbert JP, de Pedro A, Losa C, Barreiro A, Pajares JM. *Helicobacter pylori* and gastroesophageal reflux disease: lack of influence of infection on twenty-four-hour esophageal pH monitoring and endoscopic findings. *J Clin Gastroenterol* 2001; 32:210-214
29 Loffeld RJ. *H pylori* and reflux esophagitis in Turkish patients living in the Zaanstreek region in the Netherland. *Dig Dis Sci* 2003;48:1846-1849
30 Vinjirayer E, Gonzalez B, Brensinger C, Bracy N, Obelmejias R, Katzka DA, Metz DC. Ineffective motility is not a marker for gastroesophageal reflux disease. *Am J Gastroenterol* 2003; 98:771-776
31 Tack J, Fass R. Approaches to endoscopic-negative reflux disease: part of the GERD spectrum or a unique acid-related disorder? *Aliment Pharmacol Ther* 2004;19(Suppl 1):28-34
32 Fallone CA, Barkun AN, Friedman G, Mayrand S, Loo V, Beech R, Best L, Joseph L. Is *Helicobacter pylori* eradication associated with gastroesophageal reflux disease? *Am J Gastroenterol* 2000;95:914-920
33 Graham DY. The changing epidemiology of GERD: geography and *Helicobacter pylori*. *Am J Gastroenterol* 2003;98:1462-1470
34 Tefera S, Hatlebakk JG, Berstad AE, Berstad A. Eradication of *Helicobacter pylori* does not increase acid reflux in patients with mild to moderate reflux oesophagitis. *Scand J Gastroenterol* 2002;37:877-883
35 Wu LF, Zheng ZM, Li GP, Wang BZ, Zhan HY, Zeng Z, Zhou ZQ. Effect of weishusan on patients with functional dyspepsia and *H pylori* infection. *Shijie Huaren Xiaohua Zazhi* 2002; 10:275-278
36 Cremonini F, Di Caro S, Delgado-Aros S, Sepulveda A, Gasbarrini G, Gasbarrini A, Camilleri M. Meta-analysis: the relationship between *Helicobacter pylori* infection and gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2003;18:279-289
37 Fujiwara Y, Higuchi K, Shiba M, Watanabe T, Tominaga K, Oshitani N, Matsumoto T, Arakawa T. Association between gastroesophageal flap valve, reflux esophagitis, Barrett's epithelium, and atrophic gastritis assessed by endoscopy in Japanese patients. *J Gastroenterol* 2003;38:533-539
38 Wu LF, Li GP, Zheng ZM, Wang BZ, Zheng ZC, Zhou ZQ. Efficacy of Weishusan Combined with Furazolidone and Amoxycillin in the Eradication of *Helicobacter pylori* and Prevention of Recurrent Duodenal Ulcer. *Zhongguo Zhongxiyi Jiehe Zazhi* 2002;10:74-77
39 Ishaq S, Jankowski JA. Barrett's metaplasia: clinical implications. *World J Gastroenterol* 2001;7:563-565
40 Csendes A, Smok G, Quiroz J, Burdiles P, Rojas J, Castro C, Henriquez A. Clinical, endoscopic, and functional studies in 408 patients with Barrett's esophagus, compared to 174 cases of intestinal metaplasia of the cardia. *Am J Gastroenterol* 2002; 97:554-560
41 Goldblum JR, Vicari JJ, Falk GW, Rice TW, Peek RM, Easley K, Richter JE. Inflammation and intestinal metaplasia of the gastric cardia: the role of gastroesophageal reflux and *H pylori* infection. *Gastroenterology* 1998;114:633-639
42 Byrne PJ, Mulligan ED, O'Riordan J, Keeling PW, Reynolds JV. Impaired visceral sensitivity to acid reflux in patients with Barrett's esophagus. The role of esophageal motility. *Dis Esophagus* 2003;16:199-203
43 Dietz J, Meurer L, Maffazzoni DR, Furtado AD, Prolla JC. Intestinal metaplasia in the distal esophagus and correlation with symptoms of gastroesophageal reflux disease. *Dis Esophagus* 2003;16:29-32
44 Moss SF, Armstrong D, Arnold R, Ferenci P, Fock KM, Holtmann G, McCarthy DM, Moraes-Filho JP, Mutschler E, Playford R, Spechler SJ, Stanghellini V, Modlin IM. GERD 2003-a consensus on the way ahead. *Digestion* 2003;67:111-117
45 Kern M, Hofmann C, Hyde J, Shaker R. Characterization of the cerebral cortical representation of heartburn in GERD patients. *Am J Physiol Gastrointest Liver Physiol* 2004;286:G174-181
46 Urbach DR, Ungar WJ, Rabeneck L. Whither surgery in the treatment of gastroesophageal reflux disease (GERD)? *CMAJ* 2004;170:219-221
47 Nijevitch AA, Loguinovskaya VV, Tyrtyshnaya LV, Sataev VU, Ogorodnikova IN, Nuriakhmetova AN. *Helicobacter pylori* infection and reflux esophagitis in children with chronic asthma. *J Clin Gastroenterol* 2004;38:14-18
48 Kahrilas PJ. Diagnosis of symptomatic gastroesophageal reflux disease. *Am J Gastroenterol* 2003;98(3 Suppl):S15-23