# 行政院國家科學委員會專題究計畫成果報告

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| 計畫名稱：<br>(中、英文) | 幽門螺旋桿菌在非潰瘍性消化不良及慢性胃炎所扮演之角色 -- 前瞻性雙盲式長期追蹤研究<br>The role of *H. pylori* in the nonulcer dyspepsia and chronic gastritis – A prospective, double bline, long term follow-up study |

計畫類別：☑ 個別型計畫　☐ 整合型計畫

計畫編號：NSC 89 — 2314 — B002 — 085

執行期間：88 年 8 月 1 日至 89 年 7 月 31 日

個別型計畫：計畫主持人：王德宏
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註：整合型計畫總報告與子計畫成果報告請分開編印各成一冊，彙整一起繳送國科會。

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執行單位：國立台灣大學醫學院內科

中華民國　九十　年　　月　　日

計畫中文摘要：

關鍵詞：**幽門螺旋桿菌、非潰瘍性消化不良、清除治療**

越來越多的研究顯示幽門螺旋桿菌(Hp)在各種胃、十二指腸疾病中，包括胃炎、胃潰瘍、十二指腸潰瘍甚至胃癌的致病機轉均有密切之關係。Hp血清盛行率在臺灣一般人口約50%。然而，大多數感染Hp者，並未造成消化性潰瘍，卻以各種消化不良的症狀困擾許多病人，而被歸類為非潰瘍性消化不良(NUD)。這些病人因為長期反覆的檢查、治療及無法正常安心工作，消耗了大量的社會、經濟資源。雖有許多針對Hp感染和NUD相關性的研究，卻由於缺乏完美的設計，主要是病例數太少，缺少雙盲、隨機、安慰劑對照組、症狀反應和生活品質評估，及追蹤期不夠長，終致意見紛岐，無一致的結論。因此，不論就公共衛生政策、醫療或經濟效益角度，儘早釐清 Hp感染與NUD的關係及決定Hp根除療法在治療NUD的地位，乃當務之急。

我們設計了一個前瞻性、長期追蹤的雙盲試驗計劃，其目的乃以三年期間，前瞻性、大規模地探討：(1) Hp感染與NUD的關係; (2) Hp根除療法在治療NUD的角色; 是否使用 Hp根除療法大規模地來治療NUD，可以得到很好的效果; (3) NUD的症狀次分群是否與 Hp感染有關聯性。於前一年半期間，自門診因長期反覆上腹不適的病人中，收集四百位 Hp感染的NUD病人進入本研究。我們選擇了一個Hp清除率為50~60%的二合一組合，加上外貌相同安慰劑的雙盲式治療，預計將自然產生三組情況，即Hp根除成功者，Hp根除失敗者，和安慰劑組加以比較。治療後4~6週內接受上消化道內視鏡複檢及胃切片，每次胃切片檢查均包括(a) CLO test；(b) Hp培養；(c)特殊染色組織病理；及(d)Hp血清抗體測定四種檢查。其檢查結果將密封至追蹤一年後才公布，以避免和病人面談時，可能有預設

立場的偏差。每人治療前及一年後均接受完整的問卷，包括症狀量表和生活品質評估。進行統計分析，並採用症狀和生活品質改善程度做為治療結果評判的指標。

結果顯示在Hp清除成功組（A1組），Hp清除失敗組（A2組）及安慰劑對照組（P組）之間對於消化不良症狀的改善幅度，並沒有顯著的差異，同時對於生活品質評量的改變量也無明顯的差異。因此，對於多數的非潰瘍性消化不良的患者而言，以Hp根除法來治療，並未能使症狀有顯著的改善。

計畫英文摘要：

Keywords：***Helicobacter pylori*, non-ulcer dyspepsia, eradication therapy**

Since the successful culture of *Helicobacter pylori* by Marshall in 1983, many reports have demonstrated that *H. pylori* is strongly associated with gastritis, peptic ulcer, even gastric cancer. Nonulcer dyspepsia is defined as chronic or recurrent upper abdominal or retrosternal discomfort lasting for more than four weeks with symptoms unrelated to exertion and for which no cause can be found on investigation. Because the treatment of NUD remains unsatisfactory in many cases, there has been growing interests in the concept of targeting on the anti-*H. pylori* therapy for *H. pylori* positive NUD patients. However, the effects of empirical treatment with eradication therapy of *H. pylori* still be controversial and remains a public-health problem in the management of patients with NUD. The aims of this study were : 1) to explore the relationshiop between patients with *H. pylori* infection and nonulcer dyspepsia; 2) to explore the role of eradication of *H. pylori* in the treatment of NUD.

This was a prospective, large scale, double blind and long-term follow up study. We had applied PPI dual therapy with the combination of lansoplazole 30 mg qd and amoxicillin 250 mg qid for 14 days. It would create a control group with uneradicated *H. pylori* infection under this treatment course which was compatible with that requested in placebo control study. The results of *H. pylori* status and histologic examination were blinded to both patients and the medical members who interviewed the patients at OPD until final end point at 1 year to avoid any bias of evaluation of parameters during the follow-up period. It would predict that these patients were divided into three nearly equal arms at 4-6 weeks after eradication therapy according to whether the eradication of *H. pylori* was successful or not, i.e. *H. pylori* negative

(eradicated), positive (uneradicated) and placebo control. Rescue medicine, antacid, was taken by patients as necessary for symptom relief during 1 year follow-up period.

One hundred and forty patients were assigned to receive active therapy to eradication *H. pylori* (omeprazole and amoxicillin) (group A) and 70 were assigned to receive identical placebo (group P). The difference of change in the symptoms score was not significant. At one year, there was no significant difference among groups for the consumption of the antacid. There was no significant difference among groups in the change of quality of life evaluating by PAIS at one year.

In conclusions, we found no evidence that eradicating the infection leads to relief of symptoms 12 months after treatment.

# Introduction

Since the successful culture of *Helicobacter pylori* by Marshall in 1983, [1]many reports have demonstrated that *H. pylori* is strongly associated with gastritis, peptic ulcer, even gastric cancer [2-5]. In Taiwan, the prevalence rate of *H. pylori* is 50% in general population [6].

In contrast to peptic ulcer disease having a minor prevalence, only about 10 % or less, in general population., there has been a large portion of population, about 25%, [7] still suffering from upper abdominal discomfort, so called dyspepsia. Up to half the patients with recurrent dyspepsia do not have a peptic ulcer, esophagitis, gastric cancer or another definite structural abnormalities and cannot be found any biochemical explannation for the occurrence of their symptoms, i.e. nonulcer dyspepsia (NUD) [8-9]. Nonulcer dyspepsia is defined as chronic or recurrent upper abdominal or retrosternal discomfort lasting for more than four weeks with symptoms unrelated to exertion and for which no cause can be found on investigation [10]. These patients accounts for substantial healthcare costs because of attendant days lost from work, medication use and costly investigations [11-12]. Because the treatment of NUD remains unsatisfactory in many cases [13], there has been growing interests in the concept of targeting on the anti-*H. pylori* therapy for *H. pylori* positive NUD patients. However, the effects of empirical treatment with eradication therapy of *H. pylori* still be controversial and remains a public-health problem in the management of patients with NUD [14-16]. NUD has been further classified into various subgroups according to symptom clusters, including "ulcer-like", "reflux -like", dysmotility-like", and " non-specific like" dyspepsia [8]. Two recent studies have suggested that *H. pylori* is associated more with ulcer-like symptoms than with

dysmotility-like symptoms [17-18]. NUD patients are characterized by somatization and a negative assessment of their own health which differs to those of duodenal ulcer [19]. Psychopathology may not be the major explanation for functional gastrointestinal disorders [20]. It is mandatory to well evaluate the outcome of treatment with a reliable and valid scale. It will urgently need well designed trials to overcome all above debates. Moreover, the cost benefit has been appreciated for screening and eradication therapy of *H. pylori* infection in the management of NUD [21-22].

The aims of this study were : 1) to explore the relationship between patients with *H. pylori* infection and nonulcer dyspepsia; 2) to explore the role of eradication of *H. pylori* in the treatment of NUD.

# Materials & Methods

Overall study design

This was a prospective, large scale, double blind and long-term follow up study. We had applied PPI dual therapy with the combination of lansoplazole 30 mg qd and amoxicillin 250 mg qid for 14 days based on the fact that its *H. pylori* eradication rate was 50-60%[ Yang's observation ,unpublished data ]. It would create a control group with uneradicated *H. pylori* infection under this treatment course which was compatible with that requested in placebo control study. Actually, this double blind design possessed the spirit of randomized and placebo control internally. The results of *H. pylori* status and histologic examination were blinded to both patients and the medical members who interviewed the patients at OPD until final end point at 1 year to avoid any bias of evaluation of parameters during the follow-up period. It would predict that these patients were divided into three nearly equal arms at 4-6 weeks after eradication therapy according to whether the eradication of *H. pylori* was successful or not, i.e. *H. pylori* negative (eradicated), positive (uneradicated) and placebo control. Rescue medicine, antacid, was taken by patients as necessary for symptom relief during 1 year follow-up period.

**Subjects**

Four hundred consecutive patients, both sexes of any age, with NUD and *H. pylori* infection which were proved by panendoscopy and gastric biopsy with informed consent during one and a half years period in hospital were enrolled in.

Inclusion Criteria

Any patient presenting with dyspepsia who fulfilled the criteria of NUD were enrolled.

1. Symptoms of dyspepsia: upper abdominal pain or discomfort or bloating, early satiety, postprandial fullness, nausea, retching, vomiting, belching, heart burn, regurgitation.
2. Definition of nonulcer dyspepsia:

   chronic or recurrent upper abdominal or retrosternal discomfort lasting for more than four weeks with symptoms unrelated to exertion and for which no cause can be found on investigation.
3. Subgroups of NUD:

   Ulcer-like: epigastric pain, nocturnal pain, relief by food/antacids, remitting/relapsing disease.

   Reflux-like: heart burn, acid regurgitation.

   Dysmotility-like: nausea/vomiting, early satiety/anorexia, postprandial bloating/belching, upper abdominal discomfort.

   Non-specific: cannot be categorized into above

Exclusion Criteria

(1)A history of peptic ulcer disease, esophagitis, gastric malignancy, erosive duodenitis, gastric surgery and abdominal surgery;

(2)Patients with hiatal hernia who present symptomatic gastroesophageal reflux, frequent hearburn or acid regurgitation.

(3)Any person who had had serious illness or surgery.

(4)Biochemical or ultrasound shows concurrent hepato-pancreato-biliary disease or in the past history.

(5)Regular use of nonsteroid anti-inflammatory drug (NSAID), steroid.

(6)Current use of antibiotics, bismuth-containing drugs, propton pump inhibitors, $H_2$ receptor antagonist, tricyclic antidepressants, anticholinergics,

anticoagulant.

(7)Pregnant or nursing woman.

(8)A history of drug allergy to penicillin group.

**Questionnaire**

Each patient completed symptom questionnaire with GSRS [23] and a psychological adjustment to illness scale(PAIS) [24] by a trained interviewer. A complete medical history, in addition to gastrointestinal symptoms were obtained from each patient, including age, sex, ethnicity, residence area, education level, occupational history, marital status, cigarette and alcohol consumption, betnut quid, beverage of tea or coffee, use of antacids and antiulcer drugs, use of antimicrobial agents, aspirin and non-steroid anti-inflammatory drugs(NSAID), history of gynecologic problems in female, personal and family history of gastrointestinal and other major systemic diseases. Based on above detailed questionnaire, NUD patients were sorted out, subgrouped and enrolled in the main study.

**Endoscopy and biopsy**

All dyspepsia patients received regular panendoscopic examinations on the esophagus, stomach and deuodenal bulb. The subjects who fulfilled the criteria of NUD definition were suggested to undergo gastric biopsy for histology and culture of *H. pylori* with informed consent. Five sets of biopsy specimens were taken from prepyloric antrum and high body for histologic examination, culture and CLO test. The endoscope were disinfected with an automatic washing machine (Endo Thermod disinfector, Olympus Co., Tokyo, Japan). The biopsy forceps were sterilized with ethelyene oxide and disinfected as described above. Follow-up panendoscopy with gastric biopsy was performed at 4-6 weeks after eradication therapy and the 1 year end point.

**Microbiologic studies**

Two specimens were put into the BHI broth for transportation and, after grinding, streaked on the agar plate with selected medium. Plates were incubated at 37°C under microaerophilic condition for 3-7 days. *H. pylori* was identified by characteristic biotyping, being gram negative, oxidase, catalase and urease positive..

**Histologic studies**

Two biopsy specimens were processed with hematoxyline-eosin and Warthin-Starry silver stain. The presence of *H. Pylori* and gastritis were recorded and graded for evaluating the presence and density of mononuclear and polymorph nuclear cell infiltration according to the Sydney system.

**Rapid urease test (CLO test)**

One specimen was placed in rapid urease test agar. The result will be judged by color change within 24 hours.

**Serologic studies**

Blood samples were collected from all NUD patients for measurement of serological test for *H. pylori* infection.

**Evaluation of *H. pylori* status**

The amount of *H. pylori* was graded from 0 to 4: gr 0 negative; gr 1: suspicious (only at histology & CLO test); gr 2: mild but definite; gr 3: moderate; gr 4: severe. The *H. pylori* status was considered as positive when 1) at least two of four tests is positive; 2) if only one test(histology or CLO test) is positive, the amount of *H. pylori* must not be less than grade 2; 3) only culture positive. Eradication was considered to be successful if the culture, histology and CLO test all showed negative or $^{13}$C-urea breath test was negative.

**Treatment with anti-*H. pylori* regimens**

1.(1)PPI dual therapy: Lansoprazole 30mg qd.+Amoxicillin 250mg qid. x 14 days;

(2)Identical placebo.

2.Rescue medicine: antacid prn for relief of symptom after completion of eradication therapy.

**Evaluation of outcome**

1. *H pylori* infection status.
2. Symptom response: The post-treatment panendoscopy will be performed 4-6 weeks after completion of anti-*H. pylori* treatment. Patients will be followed up at OPD every two months thereafter. The follows will be obtained and recorded in special forms.
   1) symptom scale: severity(0-3: none, mild, moderate, severe), duration, frequency and symptom-free time every two months;
   2) consumption of rescue medicines and compliance;
   3) individual symptom status, total symptom-free time and global scale at the 1 year end point of the trial.
   4) PAIS: for evaluation of real quality of life to adjust the symptom response.

**Statistic analysis**

Statistical tests were performed using SAS system. The Chi-square test or Fisher's exact test was used for nominal scaled and between groups in sample. Two independent samples were compared by the Student's test or Mann-Whitney/ Wilcoxon rank sum test. The stepwise logistic regression analysis was performed with various items affecting the change of dyspepsia score or QoL score. P value of $< 0.05$ will be considered to be significant.

# Results

From November 1997 to August 1999, there were five hundred patient diagnosed of non-ulcer dyspepsia by panendoscopy. After checking with the inclusion and exclusion criteria, 400 cases were eligible. Of them, 210 cases were *H. pylori* positive and enrolled for anti-Hp therapy and long-term follow-up. After giving the informed consent. These patients were divided into each of two groups by a 2:1 randomization. One hundred and forty patients were assigned to receive active therapy to eradication *H. pylori* (omeprazole and amoxicillin) (group A) and 70 were assigned to receive identical placebo (group P). The two groups were well matched with respected to age, sex, initial dyspepsia score, previous medications and food habit. A total of 166 patients (80%) were reassessed one year after termination of anti *H. pylori* therapy. Of the 111 patients in the active group, 66 patients (59%) were considered as *H. pylori* negative. Of the 55 patients in the placebo group, none was considered as *H. pylori* negative.

The mean (±SD) dyspepsia score by modified GSRS (excluding bowel dysfunction syndrom, range 0~36) in the group A1, A2 and P at one year were 16.4±4.8, 17.0±5.2, and 16.8±5.0, respectively at one year. The difference of change in the symptoms score was not significant. The score in all group were lower than those at base line. (Table 1)

At base line, 90%, 93%, and 88% of patients in group A1, A2, and P respectively had been taking medications for dyspeptic symptoms during the preceding 3 month. At one year, there was no significant difference among groups for the consumption of the antacid.

There was no significant difference among groups in the change of quality of life

evaluating by PAIS at one year. (Table 2)

# Discussion

*H. pylori* infection is very common in Taiwan and strongly associated with gastritis, peptic ulcer, even gastric cancer. It has been proved that eradication of *H. pylori* can cure peptic ulcer and prevent its recurrence. However, a more large portion of population suffered from nonulcer dyspepsia. They consumed a lot of medical and economic resources for medications and investigation and loss of work.. It is extremely important to determine whether *H. pylori* infection play a role in the NUD and whether eradication will cure or diminish symptoms in the patients with NUD in two aspects: the first, if positive relationship is present, aggressive eradication therapy of *H. pylori* will be administered massively to NUD patients; and it will save the cost of loss of work and various medical investigation; the second, if negative relationship is proved, the vast cost of screening in patients with NUD and medicine payment in *H pylori* eradication treatment will be saved, and the researches for the management of NUD should be changed.

Although some trials which applying standard triple therapy to cure *H. pylori* infection in NUD patient have been reported. But, in all these studies one or more serious methodological weakness was identified, including nonrandomized, non-placebo-controlled designs [25-26], lack of maintenance of blindness, application of inadequate outcome measures, failure to eradicate infection and follow up patients after therapy, and inadequate study power [16]. Some unencouraging results were observed but lack of long-term follow up of symptom response [27-28]. In contrast, a sustained symptomatic improvement has been reported in children who have had their infection cured, but these studies have been nonrandomized, non-placebo controlled and non-blinded [29-30]. There was a significant and marked reduction noted in the

symptoms over a period of one year following eradication when compared with the *H. pylori* positive patients [31].

We design a prospective, double blind, randomized and well controlled study with long-term follow up to investigate whether *H. pylori* infection plays a major role in the NUD and whether eradication of *H. pylori* will effectively control or rescue the symptom and improve quality of life in these patients. We will apply PPI dual therapy with a borderline success of eradication rate (50~60%) to the NUD patients with H. pylori infection. Indeed, applying *H pylori* eradication therapy to the persons with negative *H. pylori* infection is unethical. In addition, the chronic inflammation can last even more than 6 months after successful eradication of *H. pylori* infection. However, most therapeutic trials to date have evaluated symptom status within 1-2 months of completion of treatment and this may be too soon to assess final outcome. Recent findings have shown that symptom reduction is more evident 1 year after eradication of *H. pylori* than after 4 weeks [32]. So, the optional end point of measuring the outcome of symptom response may should be more than 6 months and at best 1 year or more. Nearly 60% of the patients benefit from placebo treatment [33]. Neutralization or suppression of gastric acid with cimetidine or antacids is of no clinical value in he patients with NUD [34]. So, rescue antacids given as necessary for temporary symptom relief during 1 year follow-up period will not interfere the outcome of the long term effect of eradication of *H. pylori*. From the point of view, true placebo control may be only needed at short term post-treatment follow-up and not necessary at a long-term follow-up. Our design applying this borderline success (50~60% eradication rate) of eradicating *H. pylori* infection will divided blindly and naturally the treated patients into three nearly equal arms, that is *H. pylori* eradicated, *H. pylori* uneradicated and placebo control group. Another advantage of amoxicillin

in this combination is no resistant strain to antimicrobial till now. Based on this idea, we highly expect these results will avoid controversy and bias as other previous studies to obtain the facts whether *H. pylori* infection really play a major role in the symptoms of NUD and whether NUD is a curable disease under eradication therapy of *H. pylori* infection.

In conclusions, we assessed the clinical benefits of the eradication of *H. pylori* infection in patients with nonulcer dyspepsia in a randomized, double-blind, placebo-controlled study. We found no evidence that eradicating the infection leads to relief of symptoms 12 months after treatment.

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Table 1. Base-line characteristics of each study group.

| Characteristic | Group A1 (successful) | Group A2 (failed) | Group P (placebo) |
|---|---|---|---|
| Case no. | 66 | 45 | 55 |
| Male (%) | 42 | 45 | 40 |
| Age (mean±SD) | 40±10.4 | 42±9.6 | 41±11.0 |
| Dyspepsia score (mean±S.D.) | 18.5±5.3 | 19.3±4.9 | 19.1±5.6 |
| QoL score (mean±S.D.) | 25.3±12.3 | 24.5±12.1 | 25.1±12.6 |

Table 2. Outcome of the patient at one year

| Characteristic | Group A1 | Group A2 | Group P |
|---|---|---|---|
| *H. pylori* eradication (%) | 60 | 0 | 0 |
| Dyspepsia score (mean±S.D.) | 16.4±4.8 | 17.0±5.2 | 16.8±5.0 |
| QoL score (mean±S.D.) | 21.1±10.4 | 22.3±11.6 | 21.5±10.8 |