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REVIEW

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KEY WORDS: *Helicobacter pylori; immune response; virulence factors; peptic ulcer; stomach cancer*

Pathogenesis of Helicobacter Pylori Infection: Colonization, Virulence Factors of the Bacterium and Immune and Non-immune Host Response

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ABSTRACT

Helicobacter pylori (Hp), a gram-negative, spiral-shaped bacterium is one of the most widely spread pathogens in humans, as it concerns half of the world population. Mechanisms that allow Hp to cause a life-long infection involve modulation of the immune response and host cellular processes which include activation of the innate immune response, resistance to phagocytosis, modulation of dendritic cell activity and regulatory T cells, and production of proinflammatory cytokines. This is accomplished via virulence factors such as colonization factors (a variety of adhesins), factors that allow it to evade host defence (flagella and motility, urease system, induction of hypochlorhydria) and factors that are responsible for tissue injury (heat shock proteins A and B, vacuolating cytotoxin A, neutrophil activating protein of Hp, and cytotoxin-associated gene A). The interaction between bacterial effectors, environmental factors (genetic susceptibility to infection) and factors that modulate the host's response, such as polymorphisms in genes encoding cytokines or cytokine receptors, have been shown to influence the clinical outcome of Hp infection either towards peptic ulcer and/or cancer. Future studies, directed toward understanding interactions between Hp and immune cells in vivo, may lead to the development of novel therapeutic approaches for eradication of Hp.

List of Abbreviations
AP-1 = activator protein 1
BabA = blood group antigen-binding A
cag = cytotoxin associated genes
cag-PAI = cag pathogenicity island (a foreign DNA region in Hp)
cAMP = cyclic adenosine monophosphate
CARD4 = Caspase-activating domain 4
CpG = (DNA molecules that contain a) cytosine "C" followed by a guanine "G" dinucleotide ("p" refers to the phosphodiester backbone of DNA)
CREB-1 = cAMP response element-binding protein 1
FOXP3 = forkhead box P3 protein
GECs = gastric epithelial cells
Hops = helicobacter outer membrane proteins
Hp = Helicobacter pylori
HSP = heat shock protein
IFN-γ = interferon gamma
IL = interleukin
LPS = lipopolysaccharide
MALT = mucosa-associated lymphoid tissue
NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells
Nod = nucleotide-binding oligomerization domain
OipA = outmembrane inflammatory protein A
PAMPs = pathogen-associated molecular patterns
SabA&B = sialic acid-binding adhesin A&B
Th1 = T helper cell type 1
TLR = Toll-like receptor
TNF = tumor necrosis factor
Treg = regulatory T cell
VacA = vacuolating toxin A

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Conflict of Interest: none declared

INTRODUCTION

Helicobacter pylori (Hp) is a gram-negative, spiral-shaped pathogenic bacterium that colonizes the gastric epithelium and causes chronic gastritis, peptic ulcer and/or gastric malignancies including mucosa-associated lymphoid tissue (MALT) lymphomas, while most infected people remain asymptomatic.[1] These diseases are determined by the relationship between virulence factors of bacteria, host factors such as genetic predisposition and immune response.[1,2] Regarding genetic predisposition, polymorphism in the promoter region of interleukin (IL)-1 and IL-8 receptor have been associated with an increased incidence of atrophic gastritis and gastric cancer.[3,4] Prevalence among adults is 70–90% in many developing countries and 25-50% in industrialized countries.[5]

Takagi 2013

Abs. from
Digestive Disease Week 2013

Gastroenterology 2013; 144(5): S-679.

H pylori
? L. gasseri

No full publication until 2017

Mo1868 Abstract #.

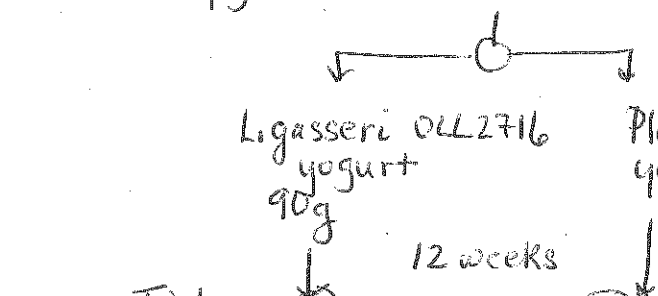
Effect of *L. Gasseri* on Dyspeptic Symptoms in Subjects With *H. pylori* Infection

Atsushi Takagi, Naomi Uemura, Kazuhiko Inoue, Shigemi Nakajima, Takashi Kawai, Toshihiro Ohtsu, Yasuhiro Koga

Objective: Probiotics, live microbiologic organisms found in foods and supplements, are a novel therapeutic class gaining popularity for the treatment of multiple gastrointestinal disorders including inflammatory bowel disease. To determine the clinical usefulness of *Lactobacillus* strains for functional dyspepsia in subjects with *H. pylori* infection, we conducted a multicenter, double-blind, controlled clinical trial in volunteers with *H. pylori* infection. Methods: Overall, 154 volunteers aged > 30 years were evaluated by ^{13}C -UBT and *H. pylori* stool testing (Wakamoto Pharmaceutical Co., Japan). *H. pylori* was detected in 131 volunteers (47 men, 84 women; mean age: 49.1 years). The 131 volunteers were randomized to receive either yogurt containing *L. gasseri* OLL2716 (90 g) or placebo (control) yogurt for 12 weeks. Gastrointestinal symptoms were assessed using the visual analogue scale (VAS). During test product consumption, each participant kept a diary, including compliance and gastrointestinal symptoms (epigastric pain, bloating, postprandial fullness, nausea, heartburn). Serum pepsinogen (PG), ^{13}C-UBT, *H. pylori* stool antigen OD were then determined. Results: There were no significant differences between the two groups in the *H. pylori* stool antigen OD value, ^{13}C-UBT and serum PG I/II. No side effects occurred in either group. Interestingly, after consumption, the VAS score for postprandial fullness decreased significantly in the *L. gasseri* group compared with before consumption($p<0.05$). Furthermore, the VAS score for bloating in *L. gasseri* group was significantly lower than that in placebo groups ($p<0.05$). Conclusion : *L. gasseri* may be useful for suppressing symptoms in dyspeptic subjects with *H. pylori*.

Mo1869

154 adults > 30 years old screened.
H. pylori ⊕ (n = 131) $\bar{x}$ = 49.1 yrs old.



Saggioro 2005

Helicobacter pylori eradication with *Lactobacillus reuteri*. A double-blind placebo-controlled study.

A. Saggioro, M. Caroli, L. Girardi, G. Chiozzini, M. Pasini
GI & Hepatology Department
Umberto I Hospital. Venice

Introduction

The need for alternative treatment strategies for *Helicobacter pylori* infections has created an interest to control this pathogen with probiotics. Indeed, some lactobacilli have been shown to possess antagonistic activity against *H. pylori* both *in vitro* and *in vivo*. Colonising the stomach, which could depend on adhesion and pH tolerance, a probiotic devoted to control of *H. pylori* needs to possess antagonistic activity against this organism. *L. reuteri* is known to produce the antimicrobial compound 3-hydroxy propionaldehyde (reuterin), trough the metabolism of glycerol, and in many studies *L. reuteri* showed much better survival than most of the strains isolated from stomach biopsies. We tested the effect of *L. reuteri* on the eradication of *H. pylori*.

Methods

30 patients, aged 25-56, suffering from dyspepsia, and positive to UBT (urea breath test), were randomly and blindly located on either omeprazole 20 mg plus *L. reuteri* (ATC 55730) 10^8 cfu b.i.d. before breakfast and dinner or omeprazole 20 mg plus placebo b.i.d. for 30 days, after the infection with *Helicobacter pylori* was confirmed by endoscopy and CLO-test plus histology. 4 weeks after the end of therapy all patients were again controlled with all the three tests.

Results

Patients receiving omeprazole plus *L. reuteri* were eradicated (3 negative tests) in 9 out 15 treated patients (60%), while no eradication occurred in the control population (omeprazole alone). Data were significant with $p<0.0001$

Conclusions

The gastric pathogen *Helicobacter pylori* is the principal cause of peptic ulcers and the major risk factor for gastric cancers in humans. From this study, it seems that probiotic supplementation by *L. reuteri* has a beneficial effect on *H. pylori* infections in humans being by itself able to eradicate the bacteria. It was demonstrated, in fact, that *L. reuteri* possesses the cell surface protein that inhibits *in vitro* the binding of *H. pylori* to glycolipids receptor and *in vivo L. reuteri* strains might be an effective competitor to *H. pylori* at the receptor site.

Poster presented to SIGE (Italian Society of Gastroenterology and Endoscopy) Congress. March 12-16 2005

Published in Dig Liver Dise 2005; 37(Suppl 1): A88

*Note - no antibiotic exposure

n=30 adults with dyspepsia (25-56 years old)

L. reuteri ATCC 55730 2×10^8/day Omeprazole (20mg) → 4 wks → 4 wks Followup → Hp⊖ 9/15 (60%)*

Placebo + Omeprazole → 4 wks → 4 wks → 0/15 (0%)

p=0.001

HOSPITAL CHRONICLES 2013, 8(3): 127–133

ORIGINAL ARTICLE

A Lyophilized Form of *Saccharomyces Boulardii* Enhances the *Helicobacter pylori* Eradication Rates of Omeprazole-Triple Therapy in Patients With Peptic Ulcer Disease or Functional Dyspepsia

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KEY WORDS: *Saccharomyces boulardii; Helicobater pylori infection; classic triple therapy; omeprazole; clarithromycin; amoxicillin.*

ABBREVIATIONS
ARR = absolute risk reduction
CLO = campylobacter-like organism test
CTT = classic triple therapy
GERD = gastro-esophageal reflux disease
ITT = intention-to-treat
MALT = mucosa-associated lymphoid tissue
NNT = number needed to treat
NSAID = non-steroidal anti-inflammatory drugs
OAC = omeprazole, amoxicillin, clarithromycin
PP = per protocol
PPI = proton-pump inhibitor
RR = relative risk

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Conflict of Interest: none declared

ABSTRACT

BACKGROUND: *Saccharomyces boulardii* prevents antibiotic-induced diarrhea and exerts anti-*H.pylori* effects *in vitro* and *in vivo*.

AIM: To assess whether *S. boulardii* enhances the efficacy of classic triple therapy in eradicating *H. pylori*.

METHODS: Seventy patients with peptic ulcer or functional dyspepsia according to Rome III criteria and *H. pylori* infection were treated with omeprazole 20 mg bid, clarithromycin 500 mg bid and amoxicillin 1 g bid for 14 days. A total of 36 out of 70 (51%) patients were randomized to *S. boulardii* [Ultralevure®, two capsules tid for 14 days (group A) and 34 (49%) on no intervention (group B). *H. pylori* eradication was assessed by a ^{13}C-Urea Breath Test.

RESULTS: At baseline there were no significant differences between the two groups in any patient or disease characteristics. *H. pylori* was eradicated in 30/36 (83.4%) patients in group A vs 20/34 (58.8%) in group B (P=0.034, 95% CI 4.4% to 43.6%). Seven patients in group B (20.6%) and 1 patient in group A stopped treatment because of diarrhea (95% CI 3.3% to 32.7%, P=0.026). Multi-factorial analysis did not reveal any patient or disease related parameter linked to treatment outcome except for the use of the probiotic.

CONCLUSION: *S. boulardii* enhanced the effect of classic triple therapy mainly by preventing antibiotic- and/or proton pump inhibitor-induced diarrhea.

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection affects 70-90% of the population in developing countries and 25–50% in developed countries.[1] In the majority of the cases *H.*

维普资讯 http://www.cqvip.com

Guo 2004

酪酸菌在幽门螺杆菌治疗中的应用

郭继兵 杨蒲芳 汪明涛 陆国义

【摘要】 目的 研究酪酸菌在幽门螺杆菌治疗中的价值。方法 病人随机分为治疗组和对照组，治疗组使用酪酸菌(米雅 BM)及三联疗法，对照组使用三联疗法，分别观察副反应发生率及幽门螺杆菌的根除率。结果 治疗组的幽门螺杆菌根除率为 93.6%，副反应发生率为 12.8%；对照组的幽门螺杆菌根除率为 88%，副反应发生率为 30%，两组相比副反应发生率有显著差异($P<0.05$)，幽门螺杆菌的根除率无显著差异($P>0.05$)。结论 酪酸菌能显著减少 Hp 根治中副反应的发生率，且能提高幽门螺杆菌的根治疗效，具有临床应用价值。

【关键词】 幽门螺杆菌；酪酸菌；治疗；副反应
中图分类号：R573.6 文献标识码：A 文章编号：1530－566(2004)03－0163－03

The application of clostridium butyricum to the eradication of Helicobacter pylori.

GUO Ji－bing, YANG Pu－fang, WANG Ming－tao, et al. *The People's Hospital of Putuo District*, 200060, *Shanghai*, *China*.

【Abstract】 AIM To assess the therapeutic value of clostridium butyricum in the treatment of infection caused by Helicobacter pylori(Hp). METHODS Hp－positive patients with chronicgastritis were allocated randomly into two groups receiving Triple Therapy (omeprazole + amoxicillin + furazolidone) with (n＝47) or without (n＝50) clostridium butyricum (MIYAIRI) for one week. RESULTS Four weeks after the end of thetreatment, Hp eradication rates were 93.6% and 88% ($P>0.05$), side effect incidence rates were 12.8% and 30% ($P<0.05$), respectively forclostridium butyricum－treated group and the control group. CONCLUSIONS Triple Therapy combined with clostridium butyricum yields high efficacy and lower incidence rate of side effects in the treatment of Hp－positive chronic gastritis.

【Key words】 Helicobacter pylori; Clostridium butyricum; Therapy; Side effect
CLC Number: R573.6 Document code: A Article ID: 1530－566(2004)03－0163－03

自 1983 年 Warren 和 Marshell 成功地分离出幽门螺杆菌(Helicobacter pylori，Hp)以来，随着人们认识的不断发展，大量研究已经证明 Hp 与慢性胃炎，消化性溃疡，胃粘膜相关淋巴组织(MALT)淋巴瘤及胃癌等密切相关，1994 年，国际癌症研究机构已将 Hp 列为 I 类致癌原，随着研究不断地深入，逐步认清了 Hp 的致病机制，并且对 Hp 的根除治疗亦有了一定的共识，多种药物联合治疗取得了较满意的疗效，但目前所推荐的治疗方案距离理想的方案仍有一定的差距，且三联及四联治疗使病人的副反应较多，Hp 感染的治疗仍是胃肠病领域研究的热门课题。本文应用酪酸菌(商品名为米雅 BM，日本米雅利桑制药株式会社生产)，联合含质子泵抑制剂在内的三联疗法治疗 Hp 的感染，进行效果评判。

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1 对象与方法

1.1 对象选择 本研究所选择病例均为本院门诊病人，均经胃镜检查为慢性胃炎病人且病理及快速尿素酶检查均证实为 Hp 感染者，随机分为治疗组和对照组，其中治疗组 47 例：男性 27 例，女性 20 例；年龄为 19～68 岁，平均 41.3 岁。对照组 50 例：男性 26 例，女性 24 例；年龄 21～70 岁，平均 43.2 岁。均经肝肾功能检查及三大常规检查无明显异常，且治疗前 2 周内未服用相关药物。

1.2 治疗方法 治疗组：分别给予米雅 BM 片 40mg，每天 3 次，奥美拉唑胶囊 20mg、阿莫西林胶囊 500mg、痢特灵片 100mg，每天 2 次，疗程 7 天；对照组：给予奥美拉唑胶囊 20mg、阿莫西林胶囊 500mg、痢特灵片 100mg，每天 2 次，疗程 7 天，疗程结束后，停药至少 4 周，期间不服用相关药物，再行 C^{13} 尿素呼气试验检查。

not full article
not published in final ed.
as of 2014

L casei DG
H pylori

Giovannone 2007

Final ID: T2067

Lactobacillus casei DG effectiveness on Helicobacter pylori eradication treatment-side effects: a placebo- controlled, double-blind randomized pilot study

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Abstract Body: BACKGROUND: Helicobacter pylori (HP) plays an important role in chronic active gastritis, peptic ulcer, gastric cancer and low-grade mucosa associated lymphoid tissue (MALT – lymphoma) development. Occurrences of antibiotics resistance and/or side effects induce eradication treatment failure in about 20% of patients. Probiotic supplementation has been demonstrated to improve patient tolerance. AIM: To investigate effects of probiotic supplementation (Lactobacillus Casei DG – ENTEROLACTIS - Sofar S.p.A.) on the tolerance and efficacy of HP eradication treatment in a randomized, double-blind, placebo-controlled trial. METHODS: 60 HP positive patients by the 13C-urea breath test were randomly screened to receive: a) a standard 7 days week eradication triple therapy with esomeprazole 40 mg. o.d., clarithromycin 500 mg. b.d. and amoxicillin 1 gr. b.d. supplemented with Lactobacillus casei DG (16 billions of alive cells) o.d. for 28 days starting from 7 days before the beginning and finishing 14 days after the end of eradication treatment; b) the same 7 days eradication therapy supplemented with placebo o.d. with the same dosage and frequency of the probiotics. Side effects were assessed using a validated questionnaire and were recorded for 6 week from the start therapy with probiotics or placebo. RESULTS: No differences in adherence to treatment or drop out were registered; cumulative HP eradication rate was 72% with no significative differences in the two groups. No differences were found between the two groups for diarrhoea, taste modification, oral burning and inappetence. Otherwise the probiotic group showed less nausea, bloating and epigastric pain only when evaluated at the end of eradication week and 7 days after, even if these differences were not statistically significant. Patient global opinion about eradication treatment tolerability was better in the probiotic group at the same time points. CONCLUSIONS: In this pilot study, even if probiotic supplementation did not significantly reduce the frequency of symptoms during HP eradication, improves nausea, bloating and epigastric pain during and immediately after eradication treatment. Cumulative HP eradication rate was 72%, showing an increasing clarithromycin-resistence in Europe, not statistically modified by probiotic supplementation anyway able to improve patients' compliance.

60 Hp⊕ ITALY Single site RCT

↓ d

L casei DG → 7d → n = 30 → 4 wks → 6 wk f/up

Placebo → 7 days → n = 30

1.6 x 10⁹/d All had triple Therapy

7 days { Amox Clarith Eso

	L casei DG	Placebo	
Hp⊖	22/30 (73%)	21/30 (70%)	Total Hp⊖ 43/60 (72%) NS
AE	NS	NS	— no data collected during meeting.

PRESENTED AT THE ANNUAL MEETING OF THE AMERICAN GASTROENTERLOGICAL ASSOCIATION INSTITUTE AND DIGESTIVE DISEASE WEEK *May 19-24, 2007 Washington, D.C.*
Published Gastroenterol 2007; 132:

(4 Supp 2) A614