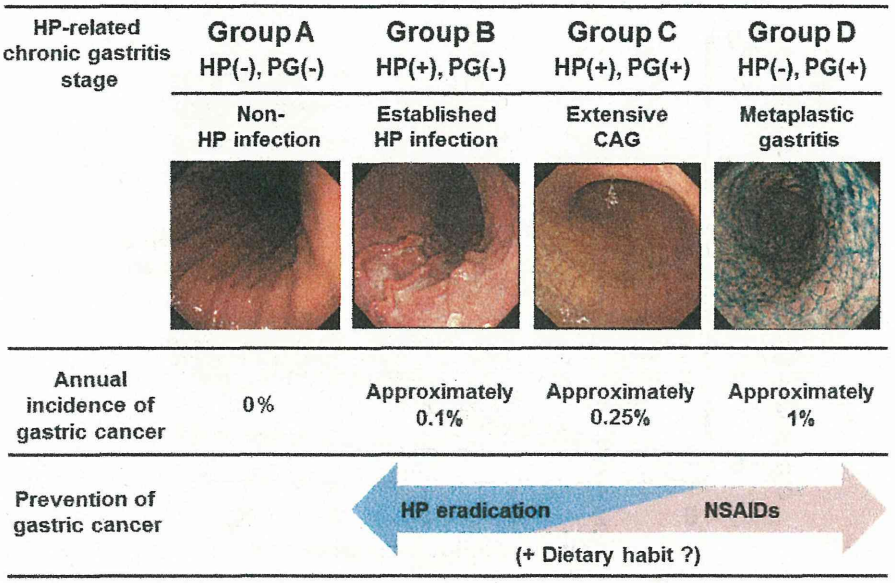

Fig. 3. Gastric cancer risk and prevention of gastric cancer based on *Helicobacter pylori* (HP)-related chronic gastritis stage. This shows the stage classification for HP-related chronic gastritis based on the serum pepsinogen (PG) test and HP antibodies. Among middle-aged healthy men, the annual incidence of gastric cancer showed a significant stepwise increase from Group A to Group D according to stage progression. Regarding gastric cancer prevention based on stage, in Group B, with mild atrophy, prevention of gastric cancer mainly by HP eradication can be expected. In Group D, with progression of atrophy and metaplastic gastritis, prevention of gastric cancer mainly by administration of non-steroidal anti-inflammatory drugs (e.g., cyclooxygenase 2 inhibitors) can be expected. In addition, prevention of gastric cancer may be possible with dietary habits.

2.5 Points in the diagnosis of GC risk using the serum PG test

The serum PG test is clearly a highly useful test for a GC risk marker. However, the occurrence of GC (particularly diffuse-type GC) in PG test-negative groups (group B in the stage classification for HP-related chronic gastritis) cannot be ignored. In our study, even when using the PG test criteria considered as the most balanced in terms of test accuracy (PG index 1+), the fact remains that about 40% of GC cases are PG test-negative. When diagnosing GC risk using the serum PG test, this fact must be carefully considered.

We therefore carefully investigated GC occurrence in a PG test-negative group. Specifically, to evaluate GC incidence, we subdivided the PG test-negative group into 3 groups: α group (serum PGI ≤70 ng/ml and PGI/II >3); β group (serum PGI >70 ng/ml and PGI/II >3), and γ group (serum PGI >70 ng/ml and PGI/II ≤3). The results identified a new group at high risk of GC, with GC incidence in the γ group (high serum PGII levels and severe inflammation of the gastric mucosa) reaching 0.2%, predominantly involving undifferentiated GC (Yanaoka et al, 2008a). This rate in the γ group, although not necessarily high among the PG test-negative group, still indicates a subgroup that deserves

particular attention. In addition, a group with high HP antibody titer (a marker that, like serum PGII level, reflects severity of inflammation) showed higher incidence of GC compared to a low-titer group (Yanaoka et al, 2008b).

Among PG test-negative groups, in group A of the stage classification for HP-related chronic gastritis (PG test-negative and HP-negative), we observed no occurrence of GC over a 10-year follow-up period. However, some cautionary points must be considered in a confirmatory diagnosis of Group A status. First, with HP antibody assay kits showing low sensitivity, antibody titers may be negative despite prior HP infection. Second, in HP-negative cases after eradication therapy, it should be kept in mind that "although HP is negative, the risk of GC is not zero." Third, risk assessment by the serum PG test cannot be applied in subjects with post-gastrectomy ,with renal insufficiency, using proton pump inhibitors, or showing an acute gastric mucosal lesion (AGML). In addition, we have reported that in subjects with a PGI/II ratio ≤3.0, serum PGI ≤30 ng/ml, or serum PGII >30 ng/ml, the risk of GC is significantly higher (Yanaoka et al, 2008b). Based on these data, even among group A patients, if the PGI/II ratio is ≤3.0 or serum PGI is ≤30 ng/ml, endoscopy should be performed once to evaluate the possible presence of CAG.

3. Prevention of GC based on the natural history of HP-related chronic gastritis

The evaluation of HP-related chronic gastritis is especially important in the analysis of GC prevention. However, previous studies have not assessed the extent of coexisting CAG or have assessed it only with endoscopic findings and/or histopathology on endoscopic biopsy. In this section, we discuss the strategy of GC prevention according to the evaluation of HP-related chronic gastritis based on the serum PG test.

3.1 Prevention of GC by HP eradication

Many previous studies have been conducted on the inhibition of GC by eradication therapy for HP, a major factor in gastric carcinogenesis. HP eradication therapy has recently been shown to prevent metachronous cancer after endoscopic resection of early GC (Fukase et al., 2008). However, in several reports to date, the effects on prevention of GC have not been as clear-cut as the effects of HP eradication on prevention of peptic ulcers. The studies that found inhibitory effects on gastric carcinogenesis were often non-randomized studies with a short observation period of ≤5 years (Fuccio et al., 2007). Moreover, results have been mixed. For example, in studies of GC occurrence after HP eradication in groups with or without precancerous lesions (CAG or intestinal metaplasia), significant inhibition of GC in the without-precancerous-lesion group was reported (Take et al., 2007; Wong et al., 2004). On the other hand, absence of inhibition of GC, regardless of the presence or absence of precancerous lesions, has also been reported (You et al., 2006). In contrast, in an animal study using HP-infected Mongolian gerbils, inhibition of gastric carcinogenesis by HP eradication was clearly demonstrated (Tatematsu et al., 2007).

These study results suggest several points. First, inhibition of gastric carcinogenesis by HP eradication is not complete, and even after eradication, more than a few GC cases have been observed. Second, the earlier during infection that eradication therapy is started, the greater the inhibitory effect on GC. Third, after a duration has elapsed, irreversible changes due to HP infection develop, representing a "point of no return". This suggests an attenuated

eradication effect. Fourth, HP infection promotes the proliferation and growth of cancer cells that have already developed (promoter effect). During long-term observation, clear-cut inhibition of gastric carcinogenesis by HP eradication is not seen, but eradication groups with shorter observation periods may display apparent inhibition of GC, with slower growth rates, and without growth of cancer that can be clinically diagnosed. Fifth, besides promoter effects on GC, HP infection, as previously described in detail, is also involved in gastric carcinogenesis mediated through the development and progression of CAG and intestinal metaplasia. To achieve a reduction in GC risk by eradication, in addition to HP elimination, improvement of CAG and intestinal metaplasia is necessary.

Based on these points, when evaluating the prevention of GC by HP eradication, evaluation of the equivalence of GC risk in the eradication group and non-eradication group (control) is necessary. With regard to this point, in almost all previous studies, either evaluation of CAG progression has been lacking, or even if evaluated, endoscopic or histopathologic findings, with strong subjective elements, were used. We therefore conducted a 10-year follow-up study in middle-aged healthy adults in whom progression of atrophic gastritis was monitored by serum PG (Yanaoka et al., 2009). In that study, although non-randomized, both the HP eradication and control groups showed equivalence with regard to CAG progression (an important risk factor), in addition to major risk factors for GC such as age, gender, and smoking. In this study, no significant inhibition of GC was observed even with HP eradication. However, with assessment by the PG test, evaluation in the PG test-positive (extensive CAG) and PG test-negative (non-extensive CAG) groups showed that HP eradication in the PG test-positive group did not prevent GC, whereas HP eradication in the PG test-negative group only achieved significant inhibition of GC (**Fig. 4**). These results confirm the

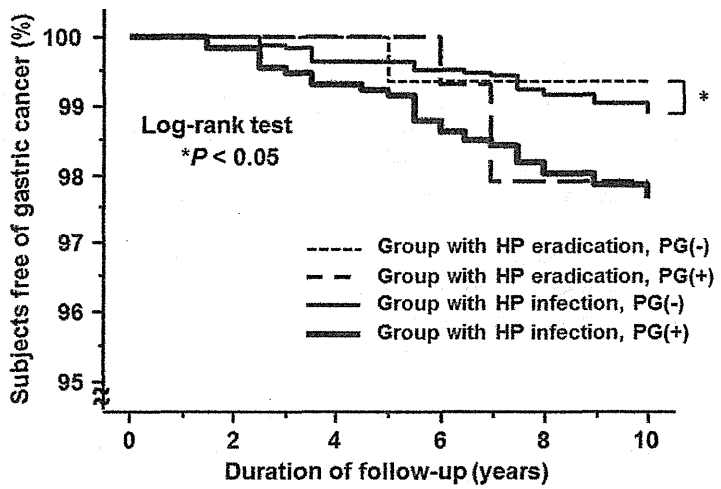

Fig. 4. Kaplan-Meier analysis of the proportion of subjects free of gastric cancer in the serum pepsinogen (PG) test-positive group and the PG test-negative group according to *Helicobacter pylori* (HP) infection status. In the serum PG test-positive group (extensive chronic atrophic gastritis (CAG)), no reduction in gastric cancer incidence was observed with HP eradication. Only the PG test- negative group (non-extensive CAG) showed a reduction in gastric cancer incidence with HP eradication.

previously mentioned results that assumed that no significant prevention of GC by HP eradication was achieved due to advanced CAG. This strongly suggests that in the majority of PG test-positive subjects, the stomach is past the "point of no return." The significance of HP eradication thus lies in achieving: 1) a decrease in GC proliferation and growth rates by inhibiting the GC-promoting effects of HP; 2) inhibition of carcinogenesis by halting progression of CAG; and 3) inhibition of inflammation-based gastric carcinogenesis (particularly diffuse-type GC) by healing chronic active gastritis. In fact, our study also showed that diffuse-type GC can be significantly inhibited by HP eradication.

3.2 Chemoprevention of GC by NSAIDs

Although prevention of GC by HP eradication can be expected, from a more realistic perspective, the effectiveness may be somewhat limited. In particular, among patients with advanced CAG, the chemopreventive effects of HP eradication therapy alone are unlikely to be sufficient. In populations where inhibition of gastric carcinogenesis cannot be achieved by HP eradication therapy alone, chemoprevention with the use of non-steroidal anti-inflammatory drugs (NSAIDs) is promising as a treatment strategy. Cyclooxygenase (COX) is a rate-limiting enzyme of prostaglandin synthesis in the arachidonic acid cascade. Among COX isozymes, attention has been focused on inducible COX-2, which is expressed in inflammatory responses and cancer proliferation (Kujubu et al., 1991). COX-2 expression has been reported in many gastrointestinal cancers, including colorectal cancer (Eberhart et al., 1994), and research has been undertaken into the prevention of carcinogenesis by COX-2 regulation (Giardiello et al., 1993; Kawamori et al., 1998; Kune et al., 1988; Thun et al., 1991). With regard to COX-2 expression in the gastric mucosa, not only a high rate of COX-2 expression in GC cells, but also COX-2 expression in precancerous lesions such as CAG, intestinal metaplasia, and dysplasia has been reported (Sung et al., 2000). In a study of GC tissue types, a high rate of COX-2 expression was found in intestinal-type GC (Saukkonen et al., 2001). In a study of GC according to site, cancers of the gastric cardia showed decreased COX-2 expression compared to cancers of other gastric areas (Ratnasinghe et al., 1999). In epidemiologic and animal studies, long-term use of aspirin or other NSAIDs has been reported to decrease GC risk in a dose-dependent manner (Duan et al., 2008; Hu et al., 2004; Wang et al., 2003).

In a Mongolian gerbil model of chronic active gastritis, which closely resembles HP-related chronic gastritis in humans, we evaluated the effects of etodolac, a selective COX-2 inhibitor, after initiation with a low dose of N-methyl-N-nitrosourea, a chemical carcinogen (Magari et al., 2005). The results confirmed that treatment with etodolac early in HP infection completely inhibited gastric carcinogenesis, which usually occurs at a high rate. In this model, we confirmed that proliferation of gastric mucosal epithelial tissue was significantly inhibited by etodolac, and that the development of intestinal metaplasia, thought to be a precancerous lesion, was significantly inhibited. In addition, we conducted a clinical study of GC chemoprevention using a COX-2 inhibitor in patients with metaplastic gastritis (Yanaoka et al., 2010). This study, although non-randomized, included patients who had undergone endoscopic resection of intestinal-type GC with a background of metaplastic gastritis. The incidence of metachronous cancer was evaluated in etodolac and non-treatment groups during a mean observation period of 4.2 years. The diagnosis of metaplastic gastritis was based on serum testing, as previously described. Regarding HP-related chronic gastritis stage, these patients were classified as Group D [HP(-), PG(+)]. In this study, long-term treatment with etodolac as a selective COX-2 inhibitor effectively inhibited metachronous cancer development in curatively treated, early GC patients with

metaplastic gastritis. These results are in line with the results of our previous animal experiment using HP-infected Mongolian gerbils, indicating that etodolac can prevent stomach carcinogenesis involving the CAG-metaplasia-dysplasia-cancer sequence. Serious cardiovascular events, depending on the drug, have been reported with long-term administration of COX-2 inhibitors. Whether etodolac is the best choice requires further investigation. However, particularly among patients with extensive CAG, in addition to HP eradication therapy, aggressive chemoprevention using NSAIDs such as selective COX-2 inhibitors may effectively inhibit gastric carcinogenesis (Fig. 3).

3.3 Possible GC prevention by dietary habits

On the other hand, HP eradication therapy and chemoprevention using NSAIDs were not carried out in all subjects, as problems exist with adverse effects of HP eradication or chemoprevention, drug-resistant bacteria, and medical economics. Research into HP-related chronic gastritis and promoters and inhibitors of gastric carcinogenesis, and studies of alternative therapies, primarily in the form of functional foods, has thus been conducted. In the progression of HP-related chronic gastritis, besides HP virulence factors such as VacA and CagA (Hatakeyama, 2004), and host factors such as cytokine polymorphisms (El-Omar et al., 2000), environmental factors such as lifestyle and dietary habits have been shown to be involved. In particular, dietary factors have been highly implicated as the factors to which the gastric mucosa is most frequently and directly exposed. For example, high sodium intake increases gastric mucosal inflammation and the risk of gastric cancer (Nozaki et al., 2002; Shikata et al., 2006) and cigarette smoking is considered to be deeply involved in the transition of CAG to intestinal metaplasia and dysplasia (Kneller et al., 1992; Tredaniel et al., 1997), which are precancerous conditions, in a model of gastric carcinogenesis postulated by Correa (Correa and Houghton, 2007). On the other hand, epidemiologic and animal studies have found that vegetables, fruits, and green tea can inhibit gastritis and reduce gastric carcinogenesis (Kobayashi et al., 2002; Yu et al., 1995).

The Japanese apricot (JA) (*ume* in Japanese; *Prunus mume* Siebold et Zucc.), in extracted or pickled form, has long been empirically used in Japan as a folk remedy for gastrointestinal infections such as gastroenteritis. In an in vitro study, Fujita et al. reported that JA extract displayed bactericidal activity against HP (Fujita et al., 2002). In addition, in an animal study using Mongolian gerbils, Otsuka et al. showed in vivo anti-HP effects of JA extract, demonstrating inhibition of chronic gastritis in HP-infected Mongolian gerbils (Otsuka et al., 2005). Based on these reports, because of the presumably potent anti-HP effects of JA, we conducted a study on associations between regular consumption of JA and HP-related chronic gastritis (Enomoto et al., 2010b; Jones, 2010). As a result, we found that consumption of JA is effective in inhibiting HP-related active inflammation of the stomach and CAG progression, and that development of GC may be inhibited by JA intake. Of course, because dietary habits are greatly influenced by other lifestyle factors, depending on the population being studied, the effectiveness achieved in preventing GC may differ. However, promoting dietary habits that protect against GC, including JA intake, may be an ideal alternative strategy for GC prevention (Fig. 3).

4. Conclusion

In conclusion, based on the natural history of HP-related chronic gastritis from blood test data, including the serum PG test and HP antibodies, specific prediction of the risk of GC in

each individual is now possible. With this information, more effective strategies to prevent GC are becoming possible. These are anticipated to have clinical applications such as in more effective GC screening, and in establishing appropriate GC prevention.

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Mutual correlation between gastric flora and *Helicobacter pylori* in gastric mucosa of Mongolian gerbil

Cynthia Zaman, Takako Osaki, Tomoko Hanawa, Hideo Yonezawa,
Satoshi Kurata and Shigeru Kamiya

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Mutual correlation between gastric flora and *Helicobacter pylori* in gastric mucosa of Mongolian gerbil

Cynthia Zaman, Takako Osaki, Tomoko Hanawa, Hideo Yonezawa, Satoshi Kurata and Shigeru Kamiya

Department of Infectious Diseases, Kyorin University School of Medicine, Mitaka

To compare the reciprocal correlation between gastric flora and *H. pylori* in gastric mucosa of Mongolian gerbil, gastric microflora of Mongolian gerbil were analyzed at first after infected with *H. pylori* T.K 1402.On the basis of the results of PCR of the extracted DNA from the fecal samples, *H. pylori* positive and *H. pylori* negative gerbils were differentiated whose gastric samples were used in the next experiment. *Actinomyces* spp., *Lactobacillus* spp. and *Bifidobacterium* spp. in *H. pylori* negative gerbil and *Actinomyces* israeli and *Eubacterium limosum* were identified. In this result, the gastric flora of the *H. pylori* (-) gerbil [No.4] were considered as the suitable microflora against the *H. pylori* colonization and so using the gastric sample of that gerbil in the next experiment, the mutual correlation between gastric flora and *H. pylori* were analyzed. *H. pylori* (-) by the real time-PCR among 5 *H. pylori* (-) gerbils which were clarified. The *Lactobacillus* spp. was also clarified by the real time-PCR among all of the gerbils.

Keywords: *H. pylori,* gastric flora, Mongolian gerbil

I Objective

To find out the mutual correlation between gastric flora and *Helicobacter pylori*, microflora were analyzed in *H. pylori* infected Mongolian gerbil's stomach and also their interaction with *H. pylori* was observed.

II Materials and Methods

Twelve Mongolian gerbils (5 wks old) were inoculated with *H. pylori* (1.04×10^7 cfu). Nested PCR using *ureA* gene primer was done using extracted DNA from collected fecal samples. Gastric mucus samples were obtained from gerbils sacrificing after eight wks of inoculation for the detection of *H. pylori* culture and PCR.On the basis of the results of PCR , gerbils were selected as high frequency, variable and low frequency groups and according to the highest and the lowest density of *H. pylori, H. pylori* positive and *H. pylori* negative gerbils were differentiated.

The gastric samples of the *H. pylori* (+) gerbil and the *H. pylori* (-) gerbil were inoculated into another twelve Mongolian gerbils (5 wks old) dividing them into two groups. One wk after this inoculation, all of the gerbils were inoculated with *H. pylori* ($1x\ 10^9$ cfu) twice. Bacterial numbers of gastric flora and *H. pylori* were compared between two groups.

III Results and discussion

After using the extracted DNA of the gastric samples, gerbil (No.5) was shown as positive in the result of nested PCR (Table 1). It was shown that in high frequency group number of *H. pylori* in gastric sample was higher than other groups. It was necessary to compare the stomach flora between gerbil No.4 (low frequency group) and No.5 (high frequency group) as *H. pylori* negative and positive. In this result, in the stomach of No. 4 and No. 5 gerbils, same aerobic bacteria (*E. coli* and *Kluyvera* spp.) were found. However, different species of anaerobes *(Lactobacillus* spp., *Actinomyces* spp. */ Bifidobacterium* spp. in gerbil No. 4 and *Actinomyces israeli* and *Eubacterium limosum* in gerbil No. 5) were found respectively.

In this result, the gastric flora of the *H. pylori* (-) gerbil [No.4] were considered as the suitable

Table 1. Isolation of *H. pylori* in fecal and gastric samples

Term	Gerbils No	PCR* (No. of positive/Total)	No. of *H. pylori* CFU / g mucus
High frequency	#2	4/6	8.8×10^2
	#5	5/6	1.3×10^4
	#11	5/6	5.4×10^3
Variable	#7	3/6	1.2×10^3
	#8	3/6	2.0×10^3
	#9	3/6	<200
	#10	3/6	4.0×10^3
Low frequency	#1	1/6	2.0×10^3
	#3	1/6	9.6×10^2
	#4	1/6	$<2.0\times10^3$
	#6	0/6	8.6×10^2

*Fecal samples were used for PCR

Table 2. Detection of *H. pylori* and *Lactobacillus* spp. by real time PCR in both *H. pylori* (+) and *H. pylori* (-) groups

	H. pylori (-) group					*H. pylori* (+) group					
Gerbil No	1	2	3	4	5	6	7	8	9	10	11
pH	2.5	3.0	3.0	3.0	3.0	3.0	3.0	4.5	4.5	4.5	3.0
No. of *H. pylori* (Real time PCR)	5.31	(-)	4.31	(-)	(-)	-/4.00	9.56	4.42	4.54	(-)	4.79
No. of *Lactobacillus* spp./g mucus	10.58	12.18	10.76	(-)	10.80	8.78	10.65	11.40	10.97	11.18	9.77

microflora against the *H. pylori* colonization and so using the gastric sample of that gerbil in the next experiment, the mutual correlation between gastric flora and *H. pylori* were analyzed. *H. pylori* (-) by the real time-PCR among 5 *H. pylori* (-) gerbils which were clarified. The *Lactobacillus* spp. was also clarified by the real time-PCR among all of the gerbils.

On the day of sacrificing the gerbils (4 wks after the inoculation), the stomach weight as well as the body weight of gerbils having *H . pylori* was observed relatively higher than those of *H. pylori* (-) group gerbils. The variations of pH in the stomach was also observed, lower pH in *H. pylori* (-) group gerbils than that in *H. pylori* (+) group gerbils was shown (Table 2).

These results suggest that some gastric flora such as *Lactobacillus* spp. may inhibit colonization by *H. pylori*. It is slso possible that gastric acidity detected in *H. pylori* (-) group gerbils is related to elimination of *H. pylori*.

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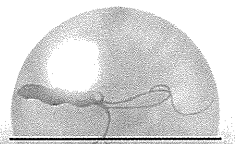

特集

Helicobacter Year Book—Annual Review 2009—

Helicobacter 研究の年間レビュー

感染ルートはどこまで明らかになったか

奥田真珠美*,** 福田修久* 栄谷直美* 山田英智**
小野淳一郎** 山本憲康* 福田能啓*

2009年に報告された*Helicobacter pylori*（*H. pylori*）の感染ルートに関する研究を中心にレビューした．ヒト-ヒト感染が主であり，家族内感染，とくに母-子感染が重要であることはこれまでも多くの報告があり確定的な感染ルートのひとつと考えられる．唾液や扁桃，嘔吐物から*H. pylori*が検出されたという報告も集積しており，口-口感染や嘔吐物を介した感染経路も重要であろう．一方，疫学研究では水からの感染を支持する報告が多いが，生活水や飲料水の解析では*H. pylori*を検出するのは困難であるとの報告も多く今後の検討課題である．新生児期に便から*H. pylori*が検出されるという報告も散見され，産道感染について大いに関心があるが，持続感染したという報告はほとんどなく，新生児ではなぜ定着しないのか“謎”のひとつである．

KEY WORDS

Helicobacter pylori，感染経路，新生児

はじめに

Helicobacter pylori（*H. pylori*）感染ルートは少しずつ解明されてきたが，予防策を講じるのはいまだ困難である．本稿では2009年に報告された感染ルートに関する論文を中心に関連する過去の論文も含めて紹介する．

1．家族内感染

家族内感染ではとくに母-子がおもな感染経路であるということは多くの論文が示している．Weyermann[1]らはドイツの検討で母，父，同胞について個別に検討したところ，感染している母親が子供への主たる感染源となっていることを疫学的に示した．家族内をPCR-based random amplified polymorphic DNA fingerprinting（RAPD）法で検討したバングラデシュの報告[2]でも母子の菌のタイプが一致し，母子感染がおもな感染経路であると報告した．Konnoら[3]も日本の家族の検討で*H. pylori*感染小児の約70%は母親の菌株と一致していることを示しており，現在の感染経路として母から子への感染が重要であることは明らかである．スナネズミで母子感染について検討した報告[4]であるが，4週齢のメスのスナネズミに*H. pylori*を感染させ，2ヵ月後に感染してい

＊OKUDA Masumi，FUKUDA Norihisa，SAKAEDANI Naomi，YAMAMOTO Noriyasu，FUKUDA Yoshihiro/兵庫医科大学地域総合医療学
＊＊OKUDA Masumi，YAMADA Hidetomo，ONO Jyunichirou/兵庫医科大学ささやま医療センター小児科

表❶ 生後1ヵ月以下の便中抗原陽性率の報告

報告者	検査時期	対象数	便中抗原陽性（%）	PCR法陽性（%）	備考
Baldassarre ME ら[8]	生後1ヵ月	172	5（2.9）	施行せず	陽性5名中3名の母親は *H. pylori* 抗体陰性 追跡では全例便中抗原陰性となった
Stray-Pedersen A ら[9]	生後7日未満	69	36（52.2）		陽性のうち26名にPCR法施行し，陽性9名（35%）
	生後7日～1ヵ月未満	46	7（15.2）		
Fujimura S ら[10]	生後3日	50	1（2.0）	15（30）	PCR法陽性15名のうち8名を24ヵ月で追跡したが陰転

ないオスとつがいにした．生まれた仔スナネズミは生後1週から1週間ごとに検討し，胃を矢状断で二分し培養，RT-PCR法，その他の免疫染色に供した．また血清と胃内にある母乳中の抗 *H. pylori* 抗体を測定した．仔の *H. pylori* は生後4週目から検出されるようになった．抗 *H. pylori* 抗体は生後3週で最高値となり，急激に低下した．これらの結果から，スナネズミの仔は感染している母から糞-口感染したことが示唆された．この動物実験では産道感染はしなかったということ，抗体が低下したころに感染しており，母乳中の抗体などの予防効果のため感染時期が遅くなったと推察できる．

夫婦間感染経路に関する報告はさまざまである．十二指腸潰瘍患者のパートナーの検討では44%が同じ菌株を保有していた[5]，Indexとなった子供の14組の両親をRAPD法で検討したところ，6組（42%）の両親の菌株が一致していた[3]などがある一方，夫婦とも陽性の21組で一致したのはわずか1組という報告[6]もある．Dasanu ら[7]はあいついで胃癌が発症したルーマニアから移住した夫婦を報告した．まず妻に胃癌がみつかり，3年後，55歳の夫も胃癌と診断された．ともに *H. pylori* 関連の活動性胃炎があり，胃癌患者の家族は *H. pylori* を共有するため同じ疾患の発症のリスクとなりうる．このような家族では発癌前に *H. pylori* 感染診断と除菌治療をおこなうことが適切であると述べている．

2．新生時期，乳児期早期の感染（表❶）

家族外，医療スタッフからの感染の可能性を示唆する周産期感染を検討したイタリアからの報告[8]である．180名の母親から出生した小児を対象とし，母親は産後4日までに血清抗体あるいは便中抗原を検査し，陽性のものは尿素呼気試験（UBT）で確認した．出生児は生後1，6，12，18ヵ月に検査した．同時に新生児室のスタッフの *H. pylori* 感染状況も検討した．母親の感染率は34.4%，スタッフは34.8%であった．生後1ヵ月で172名中5名（2.9%）が便中抗原陽性となったが，3名の母親は *H. pylori* が陰性であった．人工乳と中間リスクの新生児ユニットへの入院が感染のリスク因子となった．追跡では5名ともに自然消失（便中抗原陰性化）した．新生時期に便中抗原あるいはPCR法で *H. pylori* が検出された報告が散見される．ノルウェーの新生児の検討[9]では，249名の乳幼児の *H. pylori* 便中抗原を検討し，生後7日未満の児は69名中36名（52.2%）が便中抗原陽性であったが，生後1ヵ月以降は3.7%と低くなり，新生時期は一過性の感染が多いと述べられている．生後7日未満の新生児では経腟分娩で陽性率58.8%，帝王切開では10%であった．Fujimura ら[10]は生後3日目の新生児50名の便を検討したところ15名（30%）でPCR法の *H. pylori* DNAが陽性であったが，便中抗原陽性はわずか1名であった．母親の尿中 *H. pylori* 抗体が陽性であると児の *H. pylori* DNA陽性率が高くなったが母親の抗体が陰性でも陽性者がいた．陽性15名のうち生後24ヵ月時に8名の検査をおこなったが，PCR法，便中抗原ともに陰性であった．新生時期早期に *H. pylori* が検出されることは産道での曝露あるいはスタッフからの感染などが示唆されるが，いずれの報告でも一過性の検出であり持続感染にならないのは“謎”である．前出のスナネズミの実験[4]でも生後早期には定着しておらず，母親からの抗体による防御も考えられるが，イタリアからの報告[8]

では *H. pylori* 陰性の母親から出生したにもかかわらず便中抗原陽性が確認された乳児でも定着せずに後に消失していた．ただし，注意すべきは乳児における便中抗原の有用性で，UBT が施行できず，*H. pylori* 抗体も有用性が低いのでスタンダードが取れないため十分な検討がされていないことである．感染ルート研究のためにも生後早期の乳児における便中抗原の精度を検証する必要性を感じる．われわれはポリクロナール抗体を用いた便中抗原は乳児で偽陽性になりやすいという印象をもっている．

3．感染時期

イスラエルの保育所で便中 *H. pylori* 抗原を検討した[11]ものであるが，対象となったのは 316 名でこのうち 24.7%が便中抗原陽性であった．生後 3〜12 ヵ月は 98 名中陽性はわずか 7 名（7.1%）で，13〜60 ヵ月は 218 名中陽性 71 名で陽性率は 32.5%であり，多くの感染は 1 歳以降に生じると報告している．一般的に途上国は先進国より抗体陽転年齢が低い[12]と報告されているが，この検討ではドイツの便中抗原陽転時期[13]と類似していた．日本の報告[14][15]からは 5 歳ごろまでの感染が多いと考えている．

4．感染を媒介するもの

1）耳鼻咽喉科，口腔外科領域から

耳鼻咽喉，口腔領域からの *H. pylori* 感染に関する報告が近年多く出されており，感染経路として，また病態に関与するものとして興味深い．わが国の検討[16]であるが，くり返す扁桃炎または IgA 腎症で扁桃摘出した 55 名について扁桃からの *H. pylori* 検出を試みた．55 名中 43 名（78.2%）で扁桃に *H. pylori* が存在した．15 名（27.3%）は胃にも *H. pylori* が存在し，全員扁桃でも検出された．CagA は 43扁桃中 38（88.4%）で陽性であった．扁桃からは *H. pylori* の培養は成功しなかった．IgA 腎症のあるすべての患者に扁桃で *H. pylori* が検出され，*H. pylori* が IgA 腎症の原因になっていることが示唆された．扁桃に *H. pylori* が存在することから口-口感染を支持する結果であるともいえる．口腔内に *H. pylori* が存在するかどうか，消化器症状がある患者とないもので検討した報告[17]であるが，対象は 98 名でこのうち有症状者は 43 名であった．43 名は内視鏡をおこない胃生検し，98 名全員が歯垢と唾液を採取した．胃生検組織は鏡検染色法で *H. pylori* を，歯垢と唾液は PCR 法で *H. pylori* を検出した．98 名のうち歯垢または唾液で *H. pylori* が検出されたのは 18 名（18.4%），有症状者 43 名のうち 38 名（88.4%）は胃組織で *H. pylori* 陽性であった．口腔内で *H. pylori* が検出されたのは有症状者が 15 名（34.9%）であり，有症状の口腔内では消化器症状のないものと比較して有意に *H. pylori* が多く検出され，口-口感染を支持する結果である．耳鼻咽喉科領域では中耳の浸出液中から PCR 法などで *H. pylori* を検出したという報告もある[18][19]．

2）感染性胃腸炎（嘔吐・下痢）との関連

新たな *H. pylori* 感染は胃腸炎の流行後に多く生じるという報告[20]であるが，カリフォルニアの 1,752 名の非感染者を 1 年間追跡し，30 名が *H. pylori* 感染であった．全体の新規感染率は 7%/年であったが，新たに感染した多くは 2 歳未満の乳幼児で感染率は 21%/年であった．感染している家族が嘔吐を伴う胃腸炎であるとオッズ比は 6.3 で，下痢だけの症状では 3.0 であった．バングラデシュ，ダッカで 28 名の急性胃腸炎患者の嘔吐物，下痢便から real-time PCR 法と便中 *H. pylori* 抗原測定法を用いて *H. pylori* の分離を試みた[21]．嘔吐物では 26 名のうち 23 名（88%）で *H. pylori* が PCR 法で陽性となり，便では 23 名のうち 17 名（74%）で陽性であり，嘔吐物や下痢便は感染源になる可能性が示唆された．いずれの検体でも培養は成功しなかった．

よく引用される報告であるが，Parsonnet ら[22]は 16 名の無症状の *H. pylori* 感染者を対象とし，下剤，催吐剤投与前後の便，唾液，嘔吐物の *H. pylori* 培養をおこなった．感染者の前の唾液からは 18.8%（3/16）で少量の *H. pylori* が培養されたが，催吐剤で嘔吐後の唾液からは 56.3%と高率に培養でき，下痢便からも培養が可能であった．*H. pylori* 感染者が嘔吐・下痢を伴う病態では感染源となりうることが示唆される．嘔吐物から培養が成功した報告はほかにもあり，感染源として重要であると考える．