

# EVALUATING THE VALIDITY OF THE SEROLOGIC TEST FOR DETECTING *HELICOBACTER PYLORI* INFECTION IN MONGOLIAN GERBILS

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A strong correlation between *Helicobacter pylori* infection and gastric cancer has been reported. Mongolian gerbils are regarded as the most suitable animal model in which to study carcinogenesis associated with *H. pylori*. The aim of our study was to evaluate the accuracy of the serologic test for detecting *H. pylori* infection in Mongolian gerbils. The model was developed as follows: the *H. pylori* colony (vacuolating cytotoxin A (+)/cytotoxin-associated gene A (+)) was cultured from the mucosae of previously *H. pylori*-fed gerbils. These colonies were cultured in broth. Then, we fed the gerbils with 0.5–1 mL of broth (about 10<sup>9</sup> CFU/mL) (intra-gastric administration) twice within a 3-day period. After inoculation for 6 or 26 weeks, the gerbils were sacrificed and their gastric mucosae were sampled for a series of examinations. Blood samples for serologic testing (STAT-PAK) were collected. *H. pylori* infection was confirmed. Statistical analysis was performed using the  $\chi^2$  test. Differences were regarded as significant when the *p* value was less than 0.05. A total of 50 gerbils were inoculated with *H. pylori* and the success rate reached 88%. All 10 gerbils in the control group showed a negative result. Damage to the mucosae was more obvious following increasing periods of inoculation. The rates of sensitivity and specificity, as determined by the STAT-PAK test, were 90.9% and 100%, respectively. The positive and negative predictive values were 100% and 60%, respectively. The STAT-PAK test seemed to be more sensitive and accurate (*p* < 0.05) in high *H. pylori* densities. In conclusion, the STAT-PAK test (blood-sampling) showed acceptable results and was suitable for long-term observation of *H. pylori* infection.

**Key Words:** *Helicobacter pylori*, Mongolian gerbil, serologic test  
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Since *Helicobacter pylori* was first detected on human gastric mucosa in 1983 [1], the role of *H. pylori* in gastric

disorders has been well demonstrated. Previous studies [2–4] have shown higher anti-*H. pylori* titers in patients with gastric cancer than in controls. The World Health Organization International Agency for Research on Cancer concluded in 1994 that *H. pylori* is a group I carcinogen in humans.

Gastric cancer is a multifactorial disease [5]. Thus, it is logical to use animals to understand the basis of gastric disorders. Animals used to study experimental

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*H. pylori* infection [6] include monkeys, dogs, piglets, domestic cats and rodents [7–15]. None of these models are optimal due to a variety of reasons.

Naturally acquired gastritis is rare among gerbils [16]. Furthermore, natural infection of gerbils with *Helicobacter* spp. does not appear to occur [17,18]. Several experiments in Japan have demonstrated that chronic *H. pylori* infection in Mongolian gerbils leads to the development of gastric carcinomas [19–21].

The previous *H. pylori* animal models are generally used in small-scale experiments because they are expensive, time-consuming and require special facilities. Furthermore, most previous studies used invasive tests to determine whether inoculation was successful or not, and as the gerbils must regrettably be sacrificed, many gerbils have been used for research. Therefore, it is important to find a valid noninvasive method for detecting *H. pylori* infection in gerbils.

Previous studies have cited many kinds of noninvasive tests developed for detecting *H. pylori* infection in humans. These include <sup>13</sup>C-UBT (urea breathing test) [22], HpSA (stool-sampling) [23], RapidRun (urine-sampling) [24] and the serologic test [22]. However, there has been little discussion on appropriate noninvasive tests in gerbils.

The aim of our study was to evaluate the accuracy of the serologic test for detecting *H. pylori* infection in Mongolian gerbils.

## MATERIALS AND METHODS

### *Animals and housing*

Eight-week-old gerbils weighing 30–50 g were purchased from the Kaohsiung Medical University Experimental Animals Center, Kaohsiung, Taiwan. Four to five gerbils per cage were housed and maintained under standard laboratory conditions (room temperature, 23–26°C; relative humidity, 55–65%; 12/12-hour light/dark cycle) with free access to a commercial rodent diet and tap water.

### *H. pylori* inoculation

The *H. pylori* colony used in this study had been isolated from a patient with a gastric ulcer. The strain produced vacuolating cytotoxin (VacA) and contained the cytotoxin-associated gene (cagA). It was cultured on blood agar at 37°C under microaerobic conditions for 4 days, harvested, and then incubated in *Brucella*

broth (DIFCO Laboratories, Detroit, MI, USA) containing 10% horse serum for 24 hours. Inoculum size was adjusted with sterile saline to produce an optical density of McFarland 4 at 540 nm. Five gerbils were first inoculated with the above strain. These were sacrificed 4 weeks later, and their gastric mucosas were collected for culture as described above. This harvested colony was used for the inoculation of other gerbils.

Fifty Mongolian gerbils were challenged with 10<sup>9</sup> CFU (colony forming units) of *H. pylori* in 1.0 mL of *Brucella* broth by intragastric gavages after fasting for 24 hours. They were then fed with chow (Oriental Yeast, Tokyo, Japan) and water, beginning 12 hours after *H. pylori* inoculation. On the day of infection, 10 gerbils were only fed with 1.0 mL of *Brucella* broth, as uninfected controls.

### *Diagnostic test of H. pylori infection*

Gerbils were sacrificed at 6 weeks (group A) and 26 weeks (group B) after inoculation. The gastric mucosas were examined using the following tests: culture, histology, rapid urease test (ProntoDry test) [25] and polymerase chain reaction (PCR). Gerbil blood samples were collected before sacrifice and sent for STAT-PAK tests.

Culture of *H. pylori* was performed on the second set of specimens by rubbing on the surface of a Campy-BAP agar plate [*Brucella* agar (Difco) + IsoVitalax (Gibco) + 10% whole sheep blood], and then incubating at 35°C under microaerobic conditions (5% O<sub>2</sub>, 10% CO<sub>2</sub>, 85% N<sub>2</sub>) for 4–5 days. A culture of *H. pylori* was considered positive if one or more colonies of Gram-negative, oxidase (+), catalase (+), and urease (+) spiral or curved rods were present.

A biopsy base ProntoDry test (Medical Instruments Corp., Solothurn, Switzerland) was performed on the third set of specimens. The results of the ProntoDry test were interpreted as positive if the color of the gel changed from yellow to pink or red within 24 hours at room temperature—the reaction time was recorded in minutes.

Histologic examination was performed using one set of biopsy specimens that were fixed with formalin, embedded in paraffin and stained with hematoxylin and eosin. An experienced pathologist (who was blinded to the experiment) examined the results of the assessed biopsy specimens. The density of *H. pylori* in the tissue was graded as normal (0), mild (1), moderate (2), or severe (3) based on the Sydney system

[26,27]. Gastritis was graded as normal, mild, moderate or severe also based on the Sydney system. Histopathologic lesions of the glandular stomach were categorized as follows: (1) active chronic gastritis (characterized by severe inflammatory cell infiltration and multiple lymphoid follicle formation throughout the pyloric region and part of the fundic region); (2) ulcer; (3) regenerative hyperplasia; (4) invagination of glands into the submucosa; (5) hyperplastic polyp; (6) intestinal metaplasia (diagnosed by the presence of goblet cells that were positive for AB-HID staining); and (7) adenocarcinoma.

The *cagA* PCR fragment was obtained using the following primers: 5'-GATATAGCCACTACCACCACCG-3' and 5'-GGAAATCTTAAATCTCAGTTCGG-3'. The *vacA* PCR fragment was obtained using the primers 5'-AGTAACAGACTCATAT-3' (nt 1708 to 1725) and 5'-AAGCTTGATTGATCACTCC-3' (nt 4134 to 4116) for 35 amplification cycles of 94°C for 1 minute, 41°C for 2 minutes, and 72°C for 2 minutes.

Gerbils were tail-bled 6 and 26 weeks after intra-gastric challenge. Serum samples were stored at -20°C before being used for antibody determinations. The sera were tested with the STAT-PAK test (Abbott Laboratories), with strict adherence to the manufacturer's instructions. The appearance of two distinct lines was regarded as positive, a single control line represented a negative result, and the absence of any line indicated an invalid test. The presence of a faint line in the expected positive position was also regarded as a positive result. To avoid interobserver variation, a single observer, who was unaware of the sample identification, read all of the rapid whole-blood test results.

### Confirmation of *H. pylori* infection

*H. pylori* infection was confirmed when the culture was positive, or two of the following three tests were positive: histology, PCR and ProntoDry test.

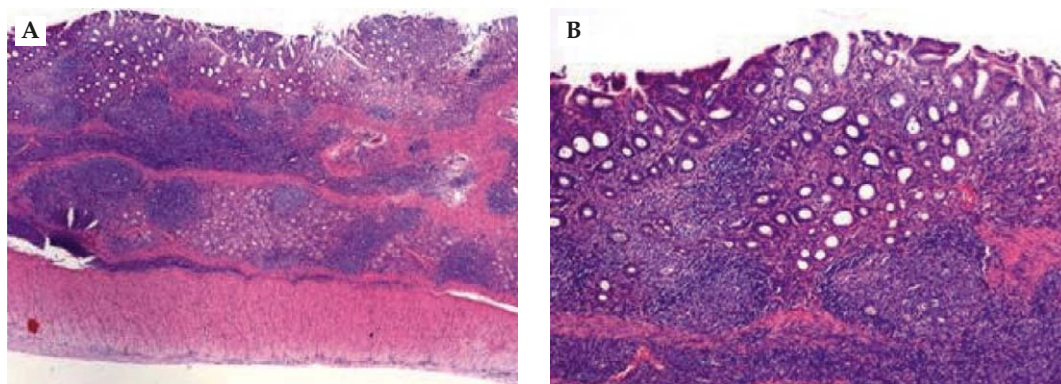
### Statistical analysis

The sensitivity, specificity and positive and negative predictive values were measured. The  $\chi^2$  test was used to compare these results. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

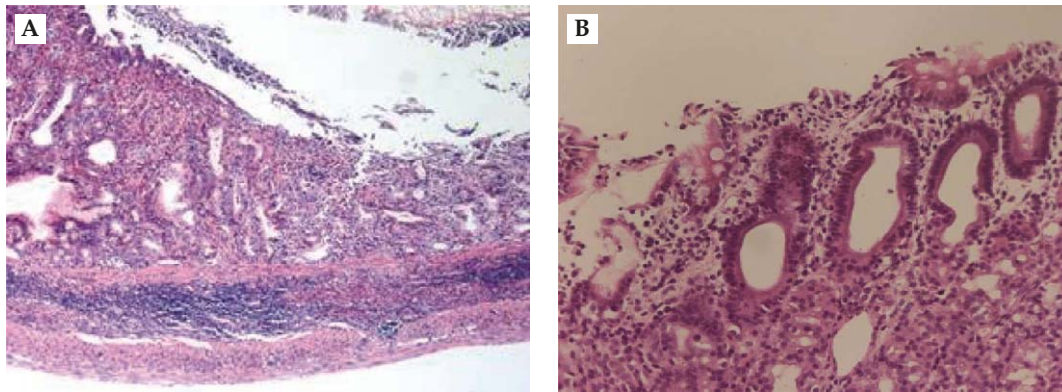
Fifty gerbils were inoculated with *H. pylori*. The success rate of inoculation reached around 88%. All gerbils in the control group showed a negative result.

Histologic findings in gerbil gastric mucosas are shown in Figures 1 and 2 and listed in Table 1. By the 6<sup>th</sup> week after infection, neutrophil and mononuclear cell infiltration could be observed in both the mucosas and submucosas of 10% of infected gerbils, demonstrating the presence of active gastritis. In our study, development of gastric ulcer, atrophic gastritis and focal intestinal metaplasia began to emerge approximately 5-6 months after *H. pylori* inoculation. Epithelial hyperplasia occurred, and intestinal metaplasia was observed in the mucosa of the pyloric region, especially in the area close to the ulcer. The severity of active gastritis, ulcer and intestinal metaplasia became more and more obvious with increasing periods of inoculation. The density of *H. pylori* seemed higher in group B. No evidence of cancer was found at either of the two time points investigated.



**Figure 1.** Active chronic gastritis observed in Mongolian gerbils 6 weeks after *H. pylori* inoculation. The gastritis is characterized by severe neutrophil and mononuclear cell infiltration in both the mucosa and submucosa (hematoxylin & eosin): (A) 65 $\times$ ; (B) 130 $\times$ .





**Figure 2.** More severe mucosal changes were observed in Mongolian gerbils 26 weeks after *H. pylori* inoculation (hematoxylin & eosin). The normal mucosal architecture was almost completely lost. (A) An ulcer (65×) and (B) intestinal metaplasia (130×) were observed.

**Table 1.** Histologic findings in gerbils at 6 and 26 weeks after inoculation

	Active chronic gastritis (%)	Ulcer (%)	Density of <i>H. pylori</i>				Intestinal metaplasia (%)
			0	1	2	3	
6 weeks (Group A)							
Control (n=5)	0	0	5	0	0	0	0
Infected (n=25)	10 (2/25)*	0*	2	12	6	5	0 <sup>†</sup>
26 weeks (Group B)							
Control (n=5)	0	0	5	0	0	0	0
Infected (n=25)	100 (25/25)*	80 (20/25)*	4	6	5	10	60 (15/25) <sup>†</sup>

\* $p < 0.05$ , gastric mucosal damage in gerbils was more obvious in group B than in group A; <sup>†</sup> $p < 0.05$ , intestinal metaplasia was only observed in group B. *H. pylori* density on the mucosa seemed higher in group B.

**Table 2.** Results of the STAT-PAK test\*

	<i>H. pylori</i>	
	Positive	Negative
STAT-PAK		
Positive	40	0
Negative	4	6

\*The results of the STAT-PAK test revealed positive results in 40 gerbils and negative results in 10. The rates of sensitivity and specificity were 90.9% and 100%, respectively.

**Table 3.** Accuracy of the STAT-PAK test in different densities of *H. pylori*

	Low <i>H. pylori</i> density	High <i>H. pylori</i> density
Positive	14	26
Negative	2	2
Accuracy (%)	87.5*	92.8*

\* $p > 0.05$ . The accuracy rates of the STAT-PAK test in low- and high-*H. pylori* density gerbils were 87.5% and 92.8%, respectively. There was no significant difference between groups ( $p > 0.05$ ).

The results of the STAT-PAK test showed positive results in 40 gerbils and negative results in 10. The rates of sensitivity and specificity were 90.9% and 100%, respectively. The positive and negative predictive values were 100% and 60%, respectively. The accuracy of the STAT-PAK test was 92%. The results in the 26<sup>th</sup> week were the same as the above data. In addition, the results in the 6<sup>th</sup> week were as follows: sensitivity, specificity, positive and negative predictive

values were 86.4%, 100%, 100% and 50%, respectively. There was no significant difference between these two time points ( $p > 0.05$ ) (Table 2).

We also analyzed the accuracy of the STAT-PAK test in different *H. pylori* densities. The accuracy rates of the STAT-PAK test in gerbils with low- and high-*H. pylori* infections were 87.5% (14/16) and 92.8% (26/28), respectively. There was no significant difference between these groups ( $p > 0.05$ ) (Table 3).

## DISCUSSION

The Mongolian gerbil model has provided important clues to the mechanism underlying gastric carcinogenesis as a result of *H. pylori* infection. In our opinion, the requirements of Koch's postulates regarding *H. pylori* and gastric carcinoma have now been fulfilled.

In our study, the severity of active gastritis, ulcer and intestinal metaplasia became more obvious with increasing periods of inoculation. This demonstrated that *H. pylori* infection was chronic in our gerbil model, and the success rate was high (88%).

The detection methods currently used in *Helicobacter* animal models rely on a combination of culture, histologic examination, detection of specific antibodies, and rapid urease-based assays [28–31]. All of these techniques have some disadvantages. Culturing of these fastidious, slow-growing organisms, which require a rich medium and special culture conditions, is often difficult. The urease assay has a detection limit of  $10^6$  cells per assay [31], but is also nonspecific, because other non-*H. felis* bacteria (such as *Proteus* spp.) in the stomachs of CV mice are urease producers that also give positive urease reactions. When examined by histology, similarities in the morphology of *Helicobacter* spp. and other spiral-shaped bacteria could also be misinterpreted, and the pathologic inflammation responses observed could be a consequence of other bacteria or conditions [31,32]. Although PCR is a very powerful technique in terms of sensitivity and specificity, it is limited in terms of its ability to perform accurate quantification, and it requires special facilities [33,34]. Virtually all of these techniques also have the same disadvantage: gerbils must be sacrificed.

The more frequently used noninvasive tests are  $^{13}\text{C}$ -UBT and stool antigen tests because they are convenient, safe and able to detect current infection. Nevertheless, these two tests also have their limitations in a gerbil model. We compared the STAT-PAK test and  $^{13}\text{C}$ -UBT (unpublished data) and showed that the STAT-PAK test had higher sensitivity than  $^{13}\text{C}$ -UBT, in contrast to reports on human populations. This may be due to the fact that we did not have an accurate cut-off value of  $^{13}\text{C}$ -UBT in gerbils and the difficulty in collecting samples in gerbils. Thus, we chose the STAT-PAK test as the noninvasive test for gerbils.

There are also limitations of stool antigen tests in terms of collecting samples. One is that we are unable

to exactly determine the timing of gerbil defecation. Sensitivity and accuracy also decreased if a stool sample is stored for more than 4–6 hours after defecation [22]. Another is that mouse chowder might interfere with the results of stool antigen tests [22].

The value of a serologic test is in its initial detection of *H. pylori* antibodies. A common drawback of serologic analysis is that it measures antibodies to *H. pylori* that persist long after the bacterium is eradicated by antibiotics. This disadvantage may not arise if we do not give any antibiotics to gerbils, as the possibility that gerbils have spontaneous infection or eradication of *H. pylori* is very low [30].

In summary, we have established stable and reliable *H. pylori* infection in a Mongolian gerbil model by re-cultured *H. pylori* colonies obtained from infected gerbils. The STAT-PAK test was found to be a sensitive and accurate test. In addition, sacrificing too many gerbils during long-term studies can be avoided. Accordingly, the serologic test may be the most reliable and economic method for confirming *H. pylori* infection in gerbils.

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# 評估血清學檢測法在蒙古沙鼠感染幽門螺旋桿菌模式之正確性

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幽門螺旋桿菌 (*Helicobacter pylori*) 和胃癌之相關性已被許多研究證實。近來，蒙古沙鼠已被認為是研究幽門螺旋桿菌導致胃癌的最佳動物模式。本研究之目的在於評估血清學檢測方式用在蒙古沙鼠模式之正確性及效益。我們使用 50 隻 8 週大之雄性沙鼠，並以之前沙鼠黏膜培養出的 (VacA (+)/CagA (+)) 之幽門螺旋桿菌菌株餵食，幽門桿菌之餵食濃度為  $10^9$ /CFU，以胃管餵食 (IG) 之方式餵食上述溶液 0.5—1.0 mL，餵食之頻率為 2 次，間隔 3 天。餵食幽門桿菌後，分別在第 6 週及第 26 週分別各犧牲 25 隻沙鼠。在犧牲前由沙鼠尾部取得血液進行 STAT-PAK 測驗，犧牲後，取得沙鼠胃前壁黏膜進行下列測試：培養、組織學、快速尿素酶法 (RUT) 及 PCR，以確認沙鼠感染幽門桿菌與否。再以此結果評估 STAT-PAK 方法之正確性。在 50 隻之餵食幽門桿菌的沙鼠中，成功感染率為 44/50 (88%)，而對照組之 10 隻沙鼠均呈陰性反應。我們發現沙鼠胃壁之黏膜受損隨著餵食期間的增加更明顯。STAT-PAK 方法的敏感度：85.6%，特異度 100%，陽性預測值 100%，陰性預測值 50%，正確率為 88%，且幽門桿菌感染密度較高時，STAT-PAK 之正確率較高。我們成功地建立一個穩定且長期之蒙古沙鼠感染幽門桿菌之模型，研究顯示 STAT-PAK 法 (血清學法) 呈現可接受之結果，且非常適合於蒙古沙鼠模式之長期觀察上。

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