Gastric juice acidity in upper gastrointestinal diseases

Pei-Jung Lu, Ping-I Hsu, Chung-Hsuan Chen, Michael Hsiao, Wei-Chao Chang, Hui-Hwa Tseng, Kung-Hung Lin, Seng-Kee Chuah, Hui-Chun Chen

Pei-Jung Lu, Institute of Clinical Medicine, National Cheng Kung University, Tainan 701, Taiwan, China
Ping-I Hsu, Kung-Hung Lin, Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, National Yang-Ming University, Kaohsiung 813, Taiwan, China
Chung-Hsuan Chen, Michael Hsiao, Wei-Chao Chang, Genomics Research Center, Academia Sinica, Taipei 115, Taiwan, China
Hui-Hwa Tseng, Department of Pathology, Kaohsiung Veterans General Hospital and National Yang-Ming University, Kaohsiung 813, Taiwan, China
Seng-Kee Chuah, Division of Gastroenterology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, College of Medicine, Chang Gung University, Kaohsiung 833, Taiwan, China
Hui-Chun Chen, Department of Radiation Oncology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, College of Medicine, Chang Gung University, Kaohsiung 833, Taiwan, China

Author contributions: Chen HC designed the study; Lu PJ conducted the tests and analyzed the data; Hsu PI, Lin KH and Chuah SK enrolled patients and collected the specimens; Chen CH, Hsiao M, Chang WC and Tseng HH controlled the quality of tests.

Supported by Research grant NSC-96-2314-B-075B-009 from the National Science Council, Taiwan.

RESULTS: Multivariate analysis revealed that bile stain of gastric juice, high acute inflammatory score of the corpus, and atrophy of the corpus were independent risk factors for the development of gastric hypoacidity with odds ratios of 3.1 (95% CI: 1.3-7.3), 3.1 (95% CI: 1.2-7.9) and 3.5 (95% CI: 1.3-9.2). Esophageal ulcer and duodenal ulcer patients had a lower pH level (1.9 and 2.1 vs 2.9, both P < 0.05) of gastric juices than healthy subjects. In contrast, gastric ulcer and gastric cancer patients had a higher pH level (3.4 and 6.6 vs 2.9, both P < 0.001) than healthy controls. Hypoacidity existed in 22%, 5%, 29%, 5% and 88% of healthy subjects, esophageal ulcer, gastric ulcer, duodenal ulcer and gastric cancer patients, respectively.

CONCLUSION: Bile reflux, atrophy and dense neutrophil infiltrate of the corpus are three independent factors determining the acidity of gastric juice.

© 2010 Baishideng. All rights reserved.

Key words: Acidity; Gastric juice; Gastric cancer; Peptic ulcer; Esophageal ulcer

Peer reviewer: Tomasz Brzozowski, Professor, Department of Physiology, Jagiellonian University Medical College, 16 Grzegezeka St, Cracow 31-531, Poland

Lu PJ, Hsu PI, Chen CH, Hsiao M, Chang WC, Tseng HH, Lin KH, Chuah SK, Chen HC. Gastric juice acidity in upper gastrointestinal diseases. World J Gastroenterol 2010; 16(43): 5496-5501. Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i43/5496.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i43.5496

Abstract

AIM: To search the independent factors determining gastric juice acidity and to investigate the acidity of gastric juices in various benign and malignant upper gastrointestinal diseases.

METHODS: Fasting gastric juice acidity of 165 healthy subjects and 346 patients with esophageal ulcer (n = 21), gastric ulcer (n = 136), duodenal ulcer (n = 100) or gastric cancer (n = 89) were measured and compared. Additionally, gastric specimens were taken from the antrum and body for rapid urease test and histological examination.

RESULTS: Multivariate analysis revealed that bile stain of gastric juice, high acute inflammatory score of the corpus, and atrophy of the corpus were independent risk factors for the development of gastric hypoacidity with odds ratios of 3.1 (95% CI: 1.3-7.3), 3.1 (95% CI: 1.2-7.9) and 3.5 (95% CI: 1.3-9.2). Esophageal ulcer and duodenal ulcer patients had a lower pH level (1.9 and 2.1 vs 2.9, both P < 0.05) of gastric juices than healthy subjects. In contrast, gastric ulcer and gastric cancer patients had a higher pH level (3.4 and 6.6 vs 2.9, both P < 0.001) than healthy controls. Hypoacidity existed in 22%, 5%, 29%, 5% and 88% of healthy subjects, esophageal ulcer, gastric ulcer, duodenal ulcer and gastric cancer patients, respectively.

CONCLUSION: Bile reflux, atrophy and dense neutrophil infiltrate of the corpus are three independent factors determining the acidity of gastric juice.

© 2010 Baishideng. All rights reserved.

Key words: Acidity; Gastric juice; Gastric cancer; Peptic ulcer; Esophageal ulcer
INTRODUCTION

Gastric juices are liquids found in the stomach. They contain numerous compounds, including hydrochloric acid (HCl), pepsin, lipase, mucin, intrinsic factor, peptides, nucleic acids and electrolytes[8]. Additionally, they may also contain salivary constituents due to swallowing, bile due to gastroduodenal reflux and inflammatory mediators or blood from damaged gastric walls[9]. In their normal state, gastric juices are usually clear in color.

HCl is an important component in gastric juice. It is a strong acid produced by the parietal cells in the corpus generating a gastric pH of 2-3[1]. Activation of pepsin and absorption of nutrients relies on an acidic pH in the stomach. HCl is also important in protecting the stomach and intestines from pathogens. Increased gastric pH induced by disease process, reflux of bile or pharmaceuticals allows for bacterial overgrowth in the stomach[10]. These pathogenic bacteria in the hypochlorhydria stomach can produce nitrite and nitroso-compounds, which act as one of the triggers in the atrophy-metaplasia-dysplasia-carcinoma pathway[11].

Helicobacter pylori (H. pylori) infection is an important biological factor which can induce marked alterations in gastric acid secretion of hosts[12]. In subjects with an antrum-predominant gastritis following H. pylori infection there is increased release of gastrin and consequently increased acid secretion. Such subjects have an increased risk of developing duodenal ulcers (DU)[13]. In contrast, the infection induces a corpus-predominant gastritis with hyposecretion of acid in some subjects. These infected subjects have an increased risk of developing gastric cancer (GC)[14]. Gastric juices can lead to mucosal damage when they enter the esophagus. Patients with gastroesophageal reflux disease (GERD) may develop esophageal breaks, along with damage to the enamel of the teeth caused by the high acidity of the stomach contents[15].

Since the acidity of gastric juice is one of the crucial factors in the development of most upper gastrointestinal diseases, we designed this study to search the independent factors determining gastric juice acidity and to investigate the acidity of gastric juices in various upper gastrointestinal diseases.

MATERIALS AND METHODS

Subjects
One hundred and sixty-five consecutive healthy subjects (HSs), 21 patients with esophageal ulcer (EU), 136 patients with gastric ulcer (GU), 100 patients with DU and 89 patients with GC participated in the study. The HSs recruited from our health examination clinics had no clinical history of gastrointestinal diseases, and their endoscopic findings were normal or showed mild gastritis only. The diagnoses of EU, GU, DU and GC were confirmed by endoscopic examination. An EU was defined as a well-defined mucosal break present in the lower esophagus[16]. A gastric or duodenal ulcer was defined as a circumscribed mucosal break 5 mm or more in diameter, with a well-defined ulcer crater in the stomach or duodenum, respectively[17].

The size of ulceration was measured by opening a pair of biopsy forceps of known span in front of the ulcer. The diagnosis of GC was confirmed by histology. Additionally, GC was classified as intestinal ($n = 50$), diffuse ($n = 31$) and mixed ($n = 8$) according to the Lauren’s classification[18]. The patient exclusion criteria included (1) the use of proton pump inhibitors or H2-receptor antagonists within 4 wk prior to the study; (2) coexistence of two kinds of gastroduodenal lesions; (3) presentation with upper gastroduodenal bleeding; and (4) coexistence of severe systemic diseases. The study was approved by the Medical Research Committee of the Kaohsiung Veterans General Hospital. All patients and controls gave informed consent.

Clinical methods
Endoscopies were performed with the Olympus GIF XV10 and GIF XQ200 (Olympus Co., Tokyo, Japan) after patients had fasted overnight. Immediately after insertion of the scope into the stomach, 5 mL of gastric fluid was aspirated through the suction channel of the endoscope and collected in a sterile trap placed in the suction line for acidity assay and color assessment. Routine inspection of the upper gastrointestinal tract was then performed. Additionally, gastric specimens were taken for rapid urease test (one specimen from the antrum) and histological examination (two specimens from the antrum and another two from the body)[12].

To adjust for clinical characteristics, the following data were recorded for each subject: age, sex, family history of gastric cancer, smoking, alcohol drinking, coffee consumption, tea consumption.

Acidity and color of gastric juice
The pH of gastric juice was measured just after collection with a glass-electrode pH meter. Hypoacidity was defined as pH level of gastric juice greater than 3.5[19]. The color of gastric juice was carefully assessed, and bile stain of gastric juice was defined as yellowish or greenish discoloration of the gastric juices.

Rapid urease test
The rapid urease test was performed according to our previous studies[20]. Each biopsy specimen was placed immediately in 1 mL of a 10% solution of urea in deionized water (pH 6.8) to which two drops of 1% phenol red solution had been added and incubated at 37 °C for up to 24 h. If the yellowish color around the area of inserted specimen changed to bright pink within the 24-h limit, the urease test was considered positive. In our laboratory, the sensitivity and specificity of the rapid urease test were 96% and 91%, respectively.

Histological assessment
A histological examination of the stomach was carried out for the subjects who provided informed consent for topographical histopathological study. The biopsy specimens were fixed in 10% buffered formalin, embedded in
paraffin, and sectioned. The sections were stained with a haematoxylin and eosin stain and a modified Giemsa stain as previously described[13]. Sections were examined blind to the patient’s clinical diagnosis. The scores of acute inflammation (neutrophil infiltrate), chronic inflammation (mononuclear cell infiltrate), glandular atrophy, intestinal metaplasia and H. pylori density were graded from 0 to 3 as described by the updated Sydney system[13,14].

Statistical analysis
Statistical evaluations were performed using the SPSS program (version 10.1, Chicago, Illinois, USA). The differences in gastric juice acidity between HSs and patients with EU, GU, DU or GC were assessed by Student’s t-test. The chi-square test with or without Yate’s correction for continuity and Fisher’s exact test, when appropriate, were applied to analyze the categorized variables. Differences were considered to be significant at P < 0.05. A multivariate analysis with logistic regression method was carried out to assess the independent factors influencing gastric acidity of gastric juices. The studied variables included the following: age (< 60 years or ≥ 60 years), gender, family history of gastric cancer (presence or absence), history of smoking (< 1 pack/wk or ≥ 1 pack/wk), history of alcohol consumption (< 80 g/d or ≥ 80 g/d), history of tea consumption (< 1 cup/d or ≥ 1 cup/d), coffee consumption (< 1 cup/d or ≥ 1 cup/d), bile stain of gastric juice, H. pylori status (presence or absence) and parameters of histological gastritis.

RESULTS
Table 1 shows the demographic characteristics of HSs and patients with EU, GU, DU and GC. Patients with GU and GC were significantly older than HSs (63 ± 15, 67 ± 12 years vs 54 ± 12 years, both P < 0.001). Additionally, the EU, DU and GC patient groups had higher male-to-female ratios than the HS group (all P < 0.05). No significant differences in history of alcohol consumption were identified between groups. However, the rates of cigarette smoking in EU, GU and DU patients were significantly higher than that of HSs (P < 0.05, 0.05 and 0.01, respectively). Furthermore, the rates of H. pylori infection in GU, DU and GC patients were also significantly higher than that of HSs (P < 0.05, < 0.001 and < 0.05, respectively).

Table 1 Baseline characteristics of healthy subjects and patients with gastric esophageal ulcer, gastric ulcer, duodenal ulcer and gastric cancer n (%)

|                | HS (n = 165) | EU (n = 21) | GU (n = 136) | DU (n = 100) | GC (n = 89) |
|----------------|--------------|-------------|--------------|--------------|-------------|
| Age (yr)       | 51 ± 14      | 54 ± 12     | 63 ± 15      | 54 ± 15      | 67 ± 14     |
| Sex (M/F)      | 85/82        | 17/4*       | 75/61        | 67/33*       | 63/26*      |
| Smoking        | 20 (12)      | 6 (29)*     | 39 (29)*     | 37 (27)*     | 12 (13)     |
| Alcohol drinking | 12 (8)      | 2 (10)      | 4 (3)        | 9 (9)        | 6 (7)       |
| Helicobacter pylori infection | 68 (41) | 6 (28) | 76 (56)* | 75 (75) | 45 (51)* |

*p < 0.05, *P < 0.01, **P < 0.001 vs healthy subjects. HS: Healthy subjects; EU: Esophageal ulcer; GU: Gastric ulcer; DU: Duodenal ulcer; GC: Gastric cancer.

Independent factors determining the acidity of gastric juice
Univariate analysis of 15 clinical and histological factors demonstrated that the following nine factors were significantly associated with hypoacidity: old age (P < 0.001), family history of GC (P < 0.005), bile reflux (P < 0.001), H. pylori infection (P < 0.05), intestinal metaplasia of the antrum (P < 0.01), and acute inflammatory score, chronic inflammatory score, atrophy and intestinal metaplasia of the corpus (all P values < 0.001, Table 2). Smokers had a lower frequency of gastric hypoacidity than non-smokers, and alcohol drinkers also had less hypoacidity than drinkers. However, the differences concerning smoking and drinking did not reach statistical significances (P = 0.258 and 0.100, respectively). Multivariate analysis with a stepwise forward logistic regression method disclosed only bile reflux, high acute inflammatory score of the corpus, and atrophy of the corpus were independent risk factors for the development of gastric hypoacidity with odds ratios of 3.1 (95% CI: 1.3-7.3), 3.1 (95% CI: 1.2-7.9) and 3.5 (95% CI: 1.3-9.2, Table 3).

The subjects with H. pylori infection had higher frequencies of high acute inflammatory score (76% vs 37%, P < 0.001) and high chronic inflammatory score (96% vs 74%, P < 0.001) in the antrum than those without H. pylori infection. Additionally, they also had higher frequencies of high acute inflammatory score (50% vs 31%, P = 0.018), high chronic inflammatory score (80% vs 60%, P = 0.006) and gland atrophy (38% vs 21%, P = 0.028) in the corpus than unaffected subjects.

Acidity of gastric juices in HSs and upper gastrointestinal diseases
Table 4 showed the pH levels of gastric juices in benign and malignant gastrointestinal diseases. EU and DU patients had a higher gastric acidity than HSs (1.91 ± 0.28 and 2.09 ± 0.09 vs 2.90 ± 0.16, both P < 0.05). In contrast, GU and GC patients had a lower gastric acidity than HSs (3.42 ± 0.20 and 6.62 ± 0.22 vs 2.90 ± 0.16, both P < 0.001). Overall, hypoacidity existed in 22%, 5%, 29%, 5% and 88% of HSs, EU, GU, DU and GC patients, respectively.

DISCUSSION
This work demonstrated the differences in acidity of
Table 2 Univariate analysis for clinical and histological factors related to the hypoacidity of gastric juice

| Principal parameters                        | n  | Rate of hypoacidity (%) | P value |
|--------------------------------------------|----|-------------------------|---------|
| **Clinical factors**                       |    |                         |         |
| Age (yr)                                   |    |                         | < 0.001 |
| < 60                                       | 282| 24.8                    |         |
| ≥ 60                                       | 229| 25.3                    |         |
| Sex                                        |    |                         | 0.496   |
| Female                                     | 206| 29.6                    |         |
| Male                                       | 305| 32.9                    |         |
| Family history of gastric cancer           |    |                         | 0.048   |
| -                                          | 497| 31.0                    |         |
| +                                          | 14 | 50.0                    |         |
| Smoking                                    |    |                         | 0.259   |
| -                                          | 396| 33.3                    |         |
| +                                          | 15 | 52.2                    |         |
| Alcohol consumption                        |    |                         | 0.100   |
| -                                          | 478| 32.6                    |         |
| +                                          | 33 | 51.5                    |         |
| Bile stain of gastric juice                |    |                         | < 0.001 |
| -                                          | 301| 20.9                    |         |
| +                                          | 210| 46.7                    |         |
| *Helicobacter pylori infection*            |    |                         | 0.013   |
| -                                          | 241| 25.7                    |         |
| +                                          | 270| 37.6                    |         |
| **Histological factors**                   |    |                         |         |
| Antrum                                     |    |                         |         |
| Acute inflammatory score                   |    |                         | 0.476   |
| Low (grade 0, 1)                           | 61 | 44.3                    |         |
| High (grade 2, 3)                          | 91 | 38.5                    |         |
| Chronic inflammatory score                 |    |                         | 0.292   |
| Low (grade 0, 1)                           | 20 | 30.0                    |         |
| High (grade 2, 3)                          | 132| 42.4                    |         |
| Atrophy                                    |    |                         | 0.195   |
| -                                          | 43 | 32.6                    |         |
| +                                          | 109| 44.0                    |         |
| Intestinal metaplasia                      |    |                         | 0.006   |
| -                                          | 91 | 31.9                    |         |
| +                                          | 61 | 54.1                    |         |
| Corpus                                     |    |                         | < 0.001 |
| Acute inflammatory score                   |    |                         |         |
| Low (grade 0, 1)                           | 88 | 28.4                    |         |
| High (grade 2, 3)                          | 64 | 57.8                    |         |
| Chronic inflammatory score                 |    |                         | < 0.001 |
| Low (grade 0, 1)                           | 43 | 18.6                    |         |
| High (grade 2, 3)                          | 109| 49.5                    |         |
| Atrophy                                    |    |                         | < 0.001 |
| -                                          | 106| 28.3                    |         |
| +                                          | 46 | 69.6                    |         |
| Intestinal metaplasia                      |    |                         | < 0.001 |
| -                                          | 126| 34.9                    |         |
| +                                          | 26 | 69.2                    |         |

Table 3 Multivariate analysis for independent factors determining hypoacidity of gastric juice

| Risk factors                        | Coefficient | SE  | OR (95% CI) | P value |
|-------------------------------------|-------------|-----|-------------|---------|
| Bile reflux                         | 1.116       | 0.446| 3.1 (1.3-7.3) | 0.012   |
| Acute inflammatory score of the corpus | 1.115       | 0.488| 3.1 (1.2-7.9) | 0.022   |
| Atrophy of the corpus               | 1.245       | 0.497| 3.5 (1.3-9.2) | 0.012   |

Several histological studies also showed chronic atrophic gastritis present in 80%-90% of GC patients. In this study, gastric hypoacidity existed in 88% of the patients with GC. This finding indicates atrophic gastritis with gastric hypoacidity is a crucial step for the development of gastric adenocarcinoma. *H. pylori* infection, old age and cagA and vacA m1 positivity have been identified as independent risk factors for the development of atrophic gastritis. We propose that the high prevalence of *H. pylori* infection, advanced age, some bacterial virulent factors and susceptible host factors may contribute to the development of gastric atrophy and hypoacidity of the GC patients in this study.

The current work also showed that DU patients had a higher gastric acidity than HSs. This result supported previous observations demonstrating increased basal and stimulated acid secretion by the body of the stomach and increased acid load in the duodenum in patients with DU. On the contrary, GU patients in this study had a lower gastric acidity than HSs, suggesting that mucosal defensive impairments are more important than increased acid load in the pathogenesis of GU. The findings were consistent with previous reports revealing that the majority of gastric ulcers do not have increased gastric acid secretion.

Multivariate analysis in this study revealed that bile stain of gastric juice, high acute inflammatory score and atrophy of the corpus were independent factors for the development of gastric hypoacidity. The atrophy of the corpus was the most important factor for gastric hypoacidity with an odds ratio of 3.5. Since gastric acid is secreted by the parietal cells in the corpus, gland atrophy of the corpus leading to hyposecretion of acid and gastric hypoacidity is logical.

In 1988, Correa et al. proposed a human model of gastric carcinogenesis that gastric cancers develop through a complex sequence of events from normal mucosa to superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and finally to intestinal-type adenocarcinoma. Gland atrophy resulting in hypochlorhydria is a key step in this theory and accounts for gastric bacterial colonization, reduction of dietary nitrates to nitrites and the formation of potentially carcinogenic N-nitroso compounds. In this study, *H. pylori*-infected patients had higher frequencies of gland atrophy in the corpus (38% vs 21%) and gastric hypoacidity (37% vs 26%) than uninfected subjects. Additionally, they also had stronger acute and chronic inflammation in the corpus than uninfected subjects.
subject. These findings suggest that *H. pylori* infection is an important factor contributing to the development of atrophic gastritis in the corpus and hypo-secretory status of the stomach.

Primary duodenogastric reflux may occur due to antroduodenal motility disorder or incompetent pyloric sphincter.[28] The retrograded bile and duodenal contents can induce damage of the gastric mucosa.[29] It has been observed that duodenogastric reflux plays a crucial role in the pathogenesis of alkaline gastritis and GU.[29] Since the presence of bile in the gastric juice implies retrograde passage of alkaline duodenal contents into the stomach, it is reasonable to expect increased pH levels of gastric juice in the subjects with bile in gastric juice.

A higher degree of acute inflammation was the other histological factor predicting gastric hypoacidity in this study. Currently, we have no definite rationale to explain the association between dense neutrophil infiltrate and increased pH level in gastric juices, but dense neutrophil infiltrates may reflect the high density of *H. pylori* in the stomach,[30] and have also been reported as one of the important factors related to the progression of atrophic gastritis.[20]

In this study, smokers had a trend of less hypoacidity than non-smokers. The finding was supported by previous studies showing that nicotine increases acid secretion and decreases prostaglandin synthesis.[31] It is interesting to note that alcohol drinkers also had a trend of less hypoacidity than nondrinkers. The reasons for this finding remain unclear, but some studies demonstrated that fermented and nondistilled alcoholic beverages increase gastrin levels and acid secretion.[32] Additionally, succinic and maleic acid contained in certain alcoholic drinks also stimulate acid secretion.[33]

In conclusion, bile reflux, atrophy and neutrophil infiltration of the corpus are three independent factors determining the acidity of gastric juices. Gastric acidities in patients with various upper gastrointestinal diseases are quite different. EU and DU patients have a higher gastric acidity whereas GU and GC patients have a lower gastric acidity compared with HSs.

**ACKNOWLEDGMENTS**

The authors express their deep appreciation to Dr. Feng-Woei Tsay and Miss Yu-Shan Chen for their generous support.

| **Table 4 pH levels of gastric juices in upper gastrointestinal diseases (%)** |
| pH of gastric juice | HS (n = 165) | EU (n = 21) | GU (n = 136) | DU (n = 100) | GC (n = 89) |
|---------------------|-------------|-------------|-------------|-------------|-------------|
| Level               |             |             |             |             |             |
| pH < 2              | 82 (50)     | 19 (91)     | 33 (24)     | 55 (55)     | 5 (5)       |
| 2 ≤ pH < 3.5        | 46 (28)     | 1 (5)       | 63 (46)     | 40 (40)     | 6 (7)       |
| 3.5 ≤ pH < 4.0      | 6 (4)       | 0 (0)       | 5 (4)       | 2 (2)       | 5 (6)       |
| 4.0 ≤ pH < 5.0      | 5 (3)       | 0 (0)       | 7 (5)       | 0 (0)       | 5 (6)       |
| 5.0 ≤ pH < 6.0      | 5 (3)       | 0 (0)       | 3 (2)       | 1 (1)       | 2 (2)       |
| 6.0 ≤ pH < 7.0      | 2 (1)       | 0 (0)       | 2 (2)       | 1 (1)       | 9 (10)      |
| 7 ≤ pH < 7.5        | 19 (12)     | 7 (42)      | 23 (17)     | 1 (1)       | 57 (65)     |
| mean ± SE           | 2.90 ± 0.16 | 1.91 ± 0.28 | 3.42 ± 0.20 | 2.09 ± 0.09 | 6.62 ± 0.22 |

*p < 0.05, *p < 0.001 vs healthy subjects. HS: Healthy subjects; EU: Esophageal ulcer; GU: Gastric ulcer; DU: Duodenal ulcer; GC: Gastric cancer.

**REFERENCES**

1. Freeman HJ, Kim YS. Digestion and absorption of protein. *Annu Rev Med* 1978; 29: 99-116
2. Kasirga E, Coker I, Aydogdu S, Yağcı RV, Taneli B, Gousseinov A. Increased gastric juice leukotriene B4, C4 and E4 concentrations in children with Helicobacter pylori colonization. *Turk J Pediatr* 1999; 41: 335-339
3. Husebye E. The pathogenesis of gastrointestinal bacterial overgrowth. *Chemotherapy* 2005; 51 Suppl 1: 1-22
4. Naylor G, Axon A. Role of bacterial overgrowth in the stomach as an additional risk factor for gastritis. *Can J Gastroenterol* 2003; 17 Suppl B: 13B-17B
5. Hsu PI, Graham DY. Helicobacter pylori infection. In: Schlessert D, editor. Clinical infectious disease. New York: Cambridge University Press, 2008: 969-976
6. Schubert ML, Peura DA. Control of gastric acid secretion in health and disease. *Gastroenterology* 2008; 134: 1842-1860
7. Gillen D, el-Omar EM, Wirz AA, Ardill JE, McColl KE. The
acid response to gastrin distinguishes duodenal ulcer patients from Helicobacter pylori-infected healthy subjects. Gastroenterology 1998; 114: 50-57
8 Moss SF, Legon S, Bishop AE, Polak JM, Calam J. Effect of Helicobacter pylori on gastric somatostatin in duodenal ulcer disease. Lancet 1992; 340: 930-932
9 Graham DY. Helicobacter pylori infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. Gastroenterology 1997; 113: 1983-1991
10 Sipponen P, Kosunen TU, Valle J, Riihela M, Seppälä K. Helicobacter pylori infection and chronic gastritis in gastric cancer. J Clin Pathol 1992; 45: 319-323
11 Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. N Engl J Med 2008; 359: 1700-1707
12 Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galimiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45: 172-180
13 Hsu PI, Lai KH, Lo GH, Tseng HH, Lo CC, Chen HC, Tsai WL, Jou HS, Peng NJ, Chien CH, Chen JL, Hsu PN. Risk factors for ulcer development in patients with non-ulcer dyspepsia: a prospective two year follow up study of 209 patients. Gut 2002; 51: 15-20
14 Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965; 64: 31-49
15 Chen A, Li CN, Hsu PI, Lai KH, Tseng HH, Hsu PN, Lo GH, Lo CC, Lin CK, Huang IR, Yamaoka Y, Chen HC. Risks of interleukin-1 genetic polymorphisms and Helicobacter pylori infection in the development of gastric cancer. Aliment Pharmacol Ther 2004; 20: 203-211
16 Hsu PI, Chen CH, Hsieh CS, Chang WC, Lai KH, Lo GH, Hsu PN, Tsay FW, Chen YS, Hsiao M, Chen HC, Lu PJ. Alpha1-antitrypsin precursor in gastric juice is a novel biomarker for gastric cancer and ulcer. Clin Cancer Res 2007; 13: 876-883
17 Hsu PI, Lai KH, Tseng HH, Liu YC, Yen MY, Lin CK, Lo GH, Huang RL, Huang JS, Cheng JS, Huang WK, Ger LP, Chen W, Hsu PN. Correlation of serum immunoglobulin G Helicobacter pylori antibody titers with histologic and endoscopic findings in patients with dyspepsia. J Clin Gastroenterol 1997; 25: 587-591
18 Hsu PI, Lai KH, Tseng HH, Lin CK, Lo GH, Cheng JS, Chan HH, Chen GC, Jou HS, Peng NJ, Ger LP, Chen W, Hsu PN. Risk factors for presentation with bleeding in patients with Helicobacter pylori-related peptic ulcer diseases. J Clin Gastroenterol 2000; 30: 386-391
19 Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996; 20: 1161-1181
20 de Vries DR, van Herwaarden MA, Smout AJ, Samsom M. Gastroesophageal pressure gradients in gastroesophageal reflux disease: relations with hiatal hernia, body mass index, and esophageal acid exposure. Am J Gastroenterol 2008; 103: 1349-1354
21 Kuipers EJ, Klinkenberg-Knol EC, Vandenbroucke-Grauls CM, Appelmelk BJ, Schenk BE, Meeuwsen SG. Role of Helicobacter pylori in the pathogenesis of atrophic gastritis. Scand J Gastroenterol Suppl 1997; 223: 28-34
22 Kim N, Park YS, Cho SI, Lee HS, Choe G, Kim IW, Won YD, Park JH, Kim JS, Jung HC, Song IS. Prevalence and risk factors of atrophic gastritis and intestinal metaplasia in a Korean population without significant gastroduodenal disease. Helicobacter 2008; 13: 245-255
23 McColl KE. Pathophysiology of duodenal ulcer disease. Eur J Gastroenterol Hepatol 1997; 9 Suppl L: S9-S12
24 Mertz HR, Walsh JH. Peptic ulcer pathophysiology. Med Clin North Am 1991; 75: 799-814
25 Correa P. A human model of gastric carcinogenesis. Cancer Res 1988; 48: 3554-3560
26 Sakaki N, Kozawa H, Egawa N, Tu Y, Sanaka M. Ten-year prospective follow-up study on the relationship between Helicobacter pylori infection and progression of atrophic gastritis, particularly assessed by endoscopic findings. Aliment Pharmacol Ther 2002; 16 Suppl 2: 198-203
27 Naito Y, Yoshikawa T. Molecular and cellular mechanisms involved in Helicobacter pylori-induced inflammation and oxidative stress. Free Radic Biol Med 2002; 33: 323-336
28 Mabrut JY, Collard JM, Baulieux J. [Duodenogastric and gastroesophageal bile reflux]. J Chir (Paris) 2006; 143: 355-365
29 Niemela S. Duodenogastric reflux in patients with upper abdominal complaints or gastric ulcer with particular reference to reflux-associated gastritis. Scand J Gastroenterol Suppl 1985; 115: 1-56
30 Fareed R, Abbas Z, Shah MA. Effect of Helicobacter pylori density on inflammatory activity in stomach. J Pak Med Assoc 2000; 50: 148-151
31 Endoh K, Leung FW. Effects of smoking and nicotine on the gastric mucosa: a review of clinical and experimental evidence. Gastroenterology 1994; 107: 864-878
32 Bujanda L. The effects of alcohol consumption upon the gastrointestinal tract. Am J Gastroenterol 2000; 95: 3374-3382

S- Editor Tian L. L- Editor O’Neill M E- Editor Zheng XM