

# *Helicobacter pylori* seroprevalence in patients with obstructive sleep apnea syndrome among a Chinese population

Xian-Wei Ye, MD, PhD, Jun Xiao, MD, PhD, Ting Qiu, MS, MD, Yong-Jiang Tang, MS, MD, Yu-Lin Feng, MD, PhD, Ke Wang, MD, PhD, Xue-Mei Ou, MD, PhD.

## ABSTRACT

**الأهداف:** فحص الانتشار المصلي لبكتريا هيليكوباكيتور بايلوري (*H. pylori*) لدى المرضى المصابين بمتلازمة انقطاع النفس الإنسدادي أثناء النوم (OSAS) ومن أجل تحديد ما إذا كان هنالك اتحاد بين عدوى (*H. pylori*) ووحدة (OSAS).

**الطريقة:** تم توظيف 243 فرداً في هذه الدراسة العرضية بقسم الطب التنفسي بمستشفى غرب الصين - سيتشوان - الصين، خلال الفترة ما بين أكتوبر 2006 وحتى أبريل 2008م. تم استعمال مقياس النشاطات الجسمانية (PSG) لتحديد مدخلات انقطاع التنفس - ضعف التنفس (AHI) وطريقة الأنزيم المتصل المناعي لاختبار (*H. pylori* IgG). وفقاً لـ (AHI)، تم تقسيم أفراد التجربة إلى أربعة مجموعات: مجموعة التحكم (AHI <5/ساعة)، مجموعة المرضى الذين يعانون من (OSAS) بشكل خفيف (AHI 5-14/ساعة)، ومجموعة المرضى الذين يعانون من (OSAS) بشكل متوسط (AHI 15-29/ساعة)، والمجموعة التي تعاني من (OSAS) بشكل شديد (AHI ≥30/ساعة).

**النتائج:** بلغت نسبة انتشار عدوى بكتريا (*H. pylori*) بين المرضى المصابين بمتلازمة (OSAS) 75.5%، وفي مجموعة التحكم 53.4% ( $p=0.000$ ). بلغت نسبة الإصابة بين المرضى الذين يعانون من متلازمة (OSAS) بشكل بسيط ومتوسط وشديد 57.1%، 76.5% و 90.9% على التوالي. كانت هذه الاختلافات الملحوظة بين المرضى المصابين بمتلازمة (OSAS) بشكل متوسط وشديد وبين مجموعة التحكم، كذلك بين المجموعة المصابة بمتلازمة (OSAS) بشكل بسيط ومتوسط وشديد.

**خاتمة:** قد تتحد عدوى (*H. pylori*) مع متلازمة (OSAS)، بالإضافة إلى زيادة في شدة متلازمة (OSAS) وقد تتصاحب مع الانتشار الأعلى لمصل (*H. pylori*).

**Objectives:** To investigate the seroprevalence of *Helicobacter pylori* (*H. pylori*) in patients with obstructive sleep apnea syndrome (OSAS), and to determine any association between *H. pylori* infection and severity of OSAS.

**Methods:** Two hundred and forty-three subjects were recruited in this cross-sectional study at the Department of Respiratory Medicine in the West China Hospital, Sichuan, P. R. China, from October 2006 to April 2008. Polysomnography (PSG) was used to determine the apnea-hypopnea index (AHI), and enzyme-linked immunosorbent assay was used to test *H. pylori* IgG. According to the AHI, subjects were divided into 4 groups: the control group (AHI <5/hours), patients with mild OSAS group (AHI: 5-14/hours), moderate OSAS group (AHI: 15-29/hours), and severe OSAS group (AHI: ≥30/hours).

**Results:** The prevalence of *H. pylori* infection in patients with OSAS was 75.5%, and in the controls it was 53.4% ( $p=0.000$ ). The prevalence of *H. pylori* infection in patients with mild OSAS was 57.1%, with moderate OSAS was 76.5%, and with severe OSAS was 90.9%. There were significant differences between patients with moderate and severe OSAS and the controls, as well as among the mild, moderate, and severe OSAS groups.

**Conclusions:** *Helicobacter pylori* infection may be associated with OSAS. In addition, increased severity of OSAS might be associated with higher seroprevalence of *H. pylori*.

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From the Division of Pulmonary Diseases (Ye, Xiao, Qiu, Tang, Feng, Wang, Ou), State Key Laboratory of Biotherapy of China, the Department of Respiratory Medicine (Ye, Xiao, Qiu, Tang, Feng, Wang, Ou), West China Hospital of Sichuan University, Chengdu, and the Department of Respiratory Medicine (Ye), The People's Hospital of Guizhou Province, Guiyang, China.

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Address correspondence and reprint request to: Dr. Yu-Lin Feng, Department of Respiratory Medicine, West China Hospital of Sichuan University, Chengdu 610041, P. R. China. Tel. +86 (28) 85422350. Fax. +86 (28) 85423402. E-mail: respir2008@163.com

*Helicobacter pylori* (*H. pylori*) is a slow-growing, microaerophilic gram-negative spiral flagellate bacterium, its potential role in gastroduodenal disease was first described by Marshall and Warren in 1984.<sup>1</sup> Now *H. pylori* infection is one of the most common bacterial diseases worldwide. Approximately 50% of the world's population is believed to be infected with *H. pylori*.<sup>2</sup> Epidemiologic and clinical studies have provided evidence that *H. pylori* infection is related to chronic active gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue-lymphoma, gastric cancer, and dyspepsia.<sup>3-7</sup> In recent years, a variety of extra-digestive disorders, such as cardiovascular, skin, rheumatic, iron deficiency anemia, and liver diseases, has also been associated with *H. pylori* infection.<sup>8,9</sup> An increased *H. pylori* seroprevalence has been found in chronic nonspecific pharyngitis, active bronchiectasis, chronic bronchitis, active pulmonary tuberculosis, asthma, lung cancer, and chronic obstructive pulmonary disease.<sup>10-16</sup> These studies concluded that *H. pylori* is linked to the respiratory system diseases. Obstructive sleep apnea syndrome (OSAS) is characterized by repetition of partial or complete obstruction of the upper airway during sleep, resulting in oxygen desaturation, sleep fragmentation, and arousals from sleep.<sup>17</sup> The gold standard of OSAS diagnosis is overnight polysomnography (PSG) in a sleep laboratory. Obstructive sleep apnea syndrome is a very common disease; the prevalence of sleep apnea syndrome was 2% of middle-aged working women, and 4% of middle-aged working men, and 1-2% among young children.<sup>18,19</sup> Unal et al<sup>20</sup> found that there was a high association between *H. pylori* infection and OSA among a Turkish population, and there were only 19 patients in their study.<sup>20</sup> To date, there has been no data on the association between *H. pylori* infection and OSAS among a Chinese population. In this study, our purpose is to investigate the relationship between *H. pylori* infection and the severity of OSAS among a Chinese population.

**Methods.** This is a cross-sectional study in a cohort of suspected OSAS patients and control subjects at the Respiratory Medicine outpatient clinic, West China Hospital, Sichuan, P. R. China, from October 2006 to April 2008. The hospital ethics committee approved the study protocol, and written informed consent was obtained from all participants. The OSAS patients were diagnosed using conventional PSG (SW-SM2000C, Curative Medical Inc, Palo Alto, CA). The diagnostic criterion for OSAS was an apnea-hypopnea index (AHI) of at least 5 events/hour. Exclusion criteria were: 1. Prior *Helicobacter* eradication therapy. 2. Consumption of acid suppressive drugs or antibiotics in the preceding

6 months. 3. Coexistent/pre-existing systemic illness. 4. A history of vagotomy or operations of the upper gastrointestinal tract. The confirmed OSAS patients were classified into the following 3 categories according to AHI: mild OSAS was defined as AHI 5-<15/h, moderate OSAS was 15-<30/h, and severe OSAS was  $\geq 30$ /h.<sup>21</sup> As the seroprevalence of *H. pylori* infection varies between ages,<sup>22</sup> the controls who were age-frequency matched with the OSAS group, were selected from the sleep medicine education program during the period of this study. These subjects were excluded from having OSAS by conventional PSG. Any subjects with a known history of OSAS, or a known history of gastrointestinal tract pathology were not enrolled in the control group. Patients with suspected OSAS were those who met 2 of the following 3 criteria: snoring, persistent daytime sleepiness, or drowsiness while driving, and obesity or hypertension. The suspected OSAS patients and all the control subjects were asked to undergo conventional PSG. In detail, suspected OSAS patients and the controls underwent full overnight PSG to confirm whether OSAS was present or not, PSG was performed from 10:00 pm to 7:00 am, recordings included central and occipital electroencephalogram, submental electromyogram, electrooculogram, electrocardiogram, left and right leg movements and respiratory parameters, such as oro-nasal flow, thoracic, and abdominal movements.<sup>23</sup> All PSGs were manually scored both for sleep and respiratory parameters by an experienced sleep technologist. Apnea was defined as a complete cessation of airflow lasting  $\geq 10$  seconds, and hypopnea was defined as a  $\geq 50\%$  reduction in respiratory airflow for longer than 10 seconds associated with an arousal or oxygen desaturation by  $\geq 4\%$ . The AHI was calculated as the average number of apneas and hypopneas per hour of total sleep time. The blood samples of the 243 subjects enrolled (155 patients and 88 controls) were collected at 7:00-8:00 am after finished the PSG. Serum samples were stored at  $-70^{\circ}$  prior to analysis. An enzyme-linked immunosorbent assay IgG serologic test (Genesis Diagnostics Ltd, Cambridgeshire, UK) was used for *H. pylori* diagnosis in accordance with the manufacturer's guidelines. All results were analyzed simultaneously by technicians who were unaware of whether the sample belonged to cases or controls. It was assigned as a positive result when the value of the concentration of IgG antibody against *H. pylori* was greater than 20 U/mL. The specificity of the serology test, validated in our local population, was 95%, and the sensitivity was 85%.<sup>24</sup>

The statistical analysis was performed by the SPSS 15.0 (Chicago Illinois, USA). Quantitative data are expressed as mean  $\pm$  SD. The significance of differences between groups was assessed by unpaired Student's t-

test for continuous variables, multiple variables were compared with one-way analysis of variance (ANOVA), and the category data were expressed as numbers (percentages) and compared with the Chi-square test. A two-tailed *p*-value less than 0.05 was considered statistically significant.

**Results.** A total of 164 patients were enrolled in the OSAS group and 94 volunteers as controls. Nine patients in the OSAS group, and 6 volunteers were excluded for not fulfilling the inclusion criteria. Therefore, there were 155 subjects in the OSAS group, and 88 subjects in the control group. There was no significant difference concerning age, gender, or body mass index among the groups (Tables 1 & 2). There was a significant difference in *H. pylori* IgG seropositivity between the controls and OSAS groups (53.4% versus 75.5%, *p*=0.000). The incidences of seropositivity were 53.4% (47/88) in the controls, 57.1% (28/49) in the mild OSAS group, 76.5% (39/51) in the moderate OSAS group, and 90.9% (50/55) in the severe OSAS group. There was a statistical difference in *H. pylori* IgG seropositivity among the 3 patient groups. However, there was no significant difference in *H. pylori* IgG

seropositivity between the controls and patients with mild OSAS group (53.4% versus 57.1%, *p*=0.674).

**Discussion.** Data in the literature on the relationship between *H. pylori* infection and OSAS are poor. The results of our study showed that *H. pylori* infection might be associated with OSAS. In addition, increased severity of OSAS might be associated with higher seroprevalence of *H. pylori*. This was in accordance with Unal et al,<sup>20</sup> who carried out a pilot study consisting of 19 patients with OSA and found 17 patients (89.5%) to be *H. pylori* seropositive. The result showed that there was a high association between *H. pylori* infection and obstructive sleep apnea.<sup>20</sup> However, due to the small number of patients and lack of information on the relationship of AHI and *H. pylori* infection in Unal's study, it could not tell us whether an association existed between *H. pylori* infection and severity of OSA.

The main finding of our study shows that an association exists between *H. pylori* infection and severity of OSAS. The risk of seroprevalence of *H. pylori* infection in patients with moderate-to-severe OSAS is higher than patients with mild OSAS. Also, the risk of seroprevalence of *H. pylori* infection in patients with severe OSAS is higher than those with moderate OSAS. In other words, increased severity of OSAS is associated with higher seroprevalence of *H. pylori* infection. The observation of an association between *H. pylori* infection and the severity of OSAS may be important for the progression of OSAS. In previous studies on *H. pylori* infection, no attention was paid to the subgroups in the respiratory system diseases. Tsang et al<sup>11</sup> investigated the seroprevalence of *H. pylori* infection and active bronchiectasis, and found that the patients with active bronchiectasis were divided into 2 subgroups (produced >5 ml sputum/24h and 0-5 ml sputum/24h), the results revealed that the seroprevalence of *H. pylori* was statistically different between the 2 subgroups. Nevertheless, the same subgroups divided have not been found in studies of chronic obstructive pulmonary disease, lung cancer, and so forth.

In this study, *H. pylori* seropositivity of the controls was 53.4%, which shows that *H. pylori* infection exists at a high prevalence rate in China, as well as other areas. Meanwhile, there was also significantly higher seropositivity in OSAS patients than in controls; the risk of seroprevalence of *H. pylori* infection in patients with OSAS was higher than patients without OSAS. Moreover, increased OSAS severity was associated with higher seroprevalence of *H. pylori*. Regarding the potential etiopathogenetic role of *H. pylori* infection in OSAS, above all, *H. pylori* strains can stimulate the host immune response and the release of a variety of inflammatory cytokines, including interleukin-1 (IL-

**Table 1** - Demographic and *H. pylori* serologic parameters in the controls and OSAS patients.

Parameter	Controls (n=88)	OSAS (n=155)	<i>P</i> -value
Age (years, mean ± SD)	47.8±6.4	49.3±6.5	0.07
Males (n, %)	59 (67.1)	107 (69.0)	0.749
BMI (kg/m <sup>2</sup> , mean ± SD)	23.9±2.0	24.4±2.0	0.097
<i>H. pylori</i> IgG seropositivity (n, %)	47 (53.4)	117 (75.5)	0.000

BMI - body mass index, *H. pylori* - *Helicobacter pylori*, OSAS - obstructive sleep apnea syndrome

**Table 2** - Demographic and *H. pylori* serologic parameters in the controls and different severity in patients with OSAS.

Parameter	Controls (n=88)	Mild OSAS (n=49)	Moderate OSAS (n=51)	Severe OSAS (n=55)	<i>P</i> -value
Age (years, mean ± SD)	47.8±6.4	49.0±6.4	49.4±6.4	49.6±6.8	0.085
Males (n, %)	59 (67.1)	33 (67.4)	35 (68.6)	36 (65.5)	0.989
BMI (kg/m <sup>2</sup> , mean ± SD)	23.9±2.0	24.1±1.9	24.4±2.0	24.5±2.2	0.268
<i>H. pylori</i> IgG seropositivity (n, %)	47 (53.4)	28 (57.1)	39 (76.5)	50 (90.9)	0.000

BMI - body mass index, *H. pylori* - *Helicobacter pylori*, OSAS - obstructive sleep apnea syndrome

1), IL-8, and tumor necrosis factor-alpha (TNF- $\alpha$ ), and eicosanoids.<sup>25-27</sup> *Helicobacter pylori* can cause systemic inflammation.<sup>28</sup> However, systemic inflammation was a constitutive component and a consequence of OSAS.<sup>29</sup> Inflammation may contribute to anatomic upper airway narrowing, abnormalities in upper airway reflexes, upper airway collapsibility, and inspiratory pharyngeal muscle dysfunction. These unfavorable processes may increase the severity of OSAS setting up a vicious cycle.<sup>30</sup> Entzian et al<sup>31</sup> revealed that TNF- $\alpha$  might play a pathophysiologic role in OSAS. Therefore, a pathogenic link may exist as both the *H. pylori* infection and diseases are characterized by activation of inflammatory mediators. The activation of inflammatory mediators induced by *H. pylori* infection might lead to the development of OSAS. In other words, it seems that the association between the severity of the OSAS and *H. pylori* might exist via inflammation.

Another potential pathogenetic mechanism could be the spilling, or inhalation of *H. pylori* or its exotoxins into the respiratory tract.<sup>16</sup> Some studies discovered that *H. pylori* had been isolated from many tissues, such as oral cavity epithelium, dental plaque, tonsillar tissues, and salivary secretions.<sup>32-34</sup> It might lead to *H. pylori* accumulation in lung tissue.<sup>25</sup> Although neither identification of the *H. pylori* species in human bronchial tissues, nor isolation of *H. pylori* from bronchoalveolar lavage fluid has been achieved yet.<sup>35</sup> We suppose that *H. pylori* infection and airway obstruction during sleep may effect each other. In this study, we did not find a relationship between the controls and mild OSAS. It is possible that the amount of *H. pylori* accumulation in the respiratory tract is insufficient, the levels of inflammatory mediators are low, and it could develop mild OSAS.

As far as we know, biopsy-based methods have been accepted as the gold standard to determine whether subjects were infected with *H. pylori*. However, it was difficult to take tissue biopsies in the present study, so we preferred serological testing for *H. pylori*. The sensitivity and specificity for the *H. pylori* antibody tests are approximately 95%,<sup>36</sup> and the serological test is non-invasive and easily performed.

In summary, this study suggests that patients with OSAS have an increasing seroprevalence of *H. pylori* infection, and the severity of OSAS increases with seroprevalence of *H. pylori* infection. Our results should be confirmed in a larger number of subjects. Further studies should be undertaken, to study not only infection, but also eradication of *H. pylori* to clarify the pathogenetic mechanisms underlying this association and to confirm our observed results.

## References

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; 1: 1311-1315.
2. Czeńnikiewicz-Guzik M, Karczewska E, Bielański W, Guzik TJ, Kapera P, Targosz A, et al. Association of the presence of *Helicobacter pylori* in the oral cavity and in the stomach. *J Physiol Pharmacol* 2004; 55 Suppl 2: 105-115.
3. Cave DR. Chronic gastritis and *Helicobacter pylori*. *Semin Gastrointest Dis* 2001; 12: 196-202.
4. Cohen H. Peptic ulcer and *Helicobacter pylori*. *Gastroenterol Clin North Am* 2000; 29: 775-789.
5. Gisbert JP, Aguado B, Luna M, Nistal S, Asenjo LM, Reina T, et al. [Gastric MALT lymphoma: clinical characteristics and prevalence of *H. pylori* infection in a series of 37 cases]. *Rev Esp Enferm Dig* 2006; 98: 655-665. Spanish
6. Trajkov D, Stardelova K, Dimitrova M, Mishevski J, Serafimovski V. *Helicobacter pylori* and gastric carcinoma. *Prilozi* 2007; 28: 39-46.
7. Ayoola AE, Ageely HM, Gadour MO, Pathak VP. Prevalence of *Helicobacter pylori* infection among patients with dyspepsia in South-Western Saudi Arabia. *Saudi Med J* 2004; 25: 1433-1438.
8. Richey F, Mégraud F. [*Helicobacter pylori* infection as a cause of extra-digestive diseases: myth or reality?] *Gastroenterol Clin Biol* 2003; 27: 459-466. French.
9. Hershko C, Ianculovich M, Souroujon M. A hematologist's view of unexplained iron deficiency anemia in males: impact of *Helicobacter pylori* eradication. *Blood Cells Mol Dis* 2007; 38: 45-53.
10. Aladag I, Bulut Y, Guven M, Eyibilen A, Yelken K. Seroprevalence of *Helicobacter pylori* infection in patients with chronic nonspecific pharyngitis: preliminary study. *J Laryngol Otol* 2008; 122: 61-64.
11. Tsang KW, Lam SK, Lam WK, Karlberg J, Wong BC, Hu WH, et al. High seroprevalence of *Helicobacter pylori* in active bronchiectasis. *Am J Respir Crit Care Med* 1998; 158: 1047-1051.
12. Roussos A, Tsimpoukas F, Anastasakou E, Alepopoulou D, Paizis I, Philippou N. *Helicobacter pylori* seroprevalence in patients with chronic bronchitis. *J Gastroenterol* 2002; 37: 332-335.
13. Filippou N, Roussos A, Tsimpoukas F, Tsimogianni A, Anastasakou E, Mavrea S. *Helicobacter pylori* seroprevalence in patients with pulmonary tuberculosis. *J Clin Gastroenterol* 2002; 34: 189-190.
14. Jun ZJ, Lei Y, Shimizu Y, Dobashi K, Mori M. *Helicobacter pylori* seroprevalence in patients with mild asthma. *Tohoku J Exp Med* 2005; 207: 287-291.
15. Najafizadeh K, Falah Tafti S, Shiehmorteza M, Saloor M, Jamali M. *H. pylori* seroprevalence in patients with lung cancer. *World J Gastroenterol* 2007; 13: 2349-2351.
16. Roussos A, Philippou N, Krietsipi V, Anastasakou E, Alepopoulou D, Koursarakos P, et al. *Helicobacter pylori* seroprevalence in patients with chronic obstructive pulmonary disease. *Resp Med* 2005; 99: 279-284.
17. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22: 667-689.
18. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230-1235.

19. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med* 1999; 159: 1527-1532.
20. Unal M, Oztürk L, Oztürk C, Kabal A. The seroprevalence of *Helicobacter pylori* infection in patients with Obstructive sleep apnoea: a preliminary study. *Clin Otolaryngol Allied Sci* 2003; 28: 100-102.
21. McGinley BM, Patil SP, Kirkness JP, Smith PL, Schwartz AR, Schneider H. A nasal cannula can be used to treat obstructive sleep apnea. *Am J Respir Crit Care Med* 2007; 176: 194-200.
22. Everhart JE, Kruszon-Moran D, Perez-Perez GI, Tralka TS, McQuillan G. Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J Infect Dis* 2000; 181: 1359-1363.
23. Unal M, Oztürk L, Kanik A. The role of oxygen saturation measurement and body mass index in distinguishing between non-apnoeic snorers and patients with obstructive sleep apnoea syndrome. *Clin Otolaryngol Allied Sci* 2002; 27: 344-346.
24. Philippou N, Koursarakos P, Anastasakou E, Krietsepi V, Mavrea S, Roussos A, et al. *Helicobacter pylori* seroprevalence in patients with lung cancer. *World J Gastroenterol* 2004; 10: 3342-3344.
25. Perri F, Clemente R, Festa V, De Ambrosio CC, Quitadamo M, Fusillo M, et al. Serum tumour necrosis factor-alpha is increased in patients with *Helicobacter pylori* infection and CagA antibodies. *Ital J Gastroenterol Hepatol* 1999; 31: 290-294.
26. Russo F, Jirillo E, Clemente C, Messa C, Chiloiro M, Riezzo G, et al. Circulating cytokines and gastrin levels in asymptomatic subjects infected by *Helicobacter pylori* (*H. pylori*). *Immunopharmacol Immunotoxicol* 2001; 23: 13-24.
27. Crabtree JE. Role of cytokines in pathogenesis of *Helicobacter pylori*-induced mucosal damage. *Dig Dis Sci* 1998; 43 (9 Suppl): 46S-55S.
28. Bunch TJ, Day JD, Anderson JL, Horne BD, Muhlestein JB, Crandall BG, et al. Frequency of *Helicobacter pylori* seropositivity and C-reactive protein increase in atrial fibrillation in patients undergoing coronary angiography. *Am J Cardiol* 2008; 101: 848-851.
29. Gozal D, Serpero LD, Sans Capdevila O, Kheirandish-Gozal L. Systemic inflammation in non-obese children with obstructive sleep apnea. *Sleep Med* 2008; 9: 254-259.
30. Hatipoğlu U, Rubinstein I. Inflammation and obstructive sleep apnea syndrome pathogenesis: a working hypothesis. *Respiration* 2003; 70: 665-671.
31. Entzian P, Linnemann K, Schlaak M, Zabel P. Obstructive sleep apnea syndrome and circadian rhythms of hormones and cytokines. *Am J Respir Crit Care Med* 1996; 153: 1080-1086.
32. Oshowo A, Gillam D, Botha A, Tunio M, Holton J, Boulos P. *Helicobacter pylori*: the mouth, stomach, and gut axis. *Ann Periodontol* 1998; 3: 276-280.
33. Song Q, Lange T, Spahr A, Adler G, Bode G. Characteristic distribution pattern of *Helicobacter pylori* in dental plaque and saliva detected with nested PCR. *J Med Microbiol* 2000; 49: 349-353.
34. Unver S, Kubilay U, Sezen OS, Coskuner T. Investigation of *Helicobacter pylori* colonization in adenotonsillectomy specimens by means of the CLO test. *Laryngoscope* 2001; 111: 2183-2186.
35. Peterson WL, Graham DY. *Helicobacter pylori*. In: Feldman M, Scharschmidt BE, Sleisenger MH, editors. *Gastrointestinal and liver Disease. Pathophysiology, diagnosis, management*. Philadelphia (PA): WB Saunders; 1998. p. 604-619.
36. Mégraud F. Epidemiology of *Helicobacter pylori* infection. *Gastroenterol Clin North Am* 1993; 22: 73-88.

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Pellicano R, Astegiano M, Rizzetto M. *Helicobacter pylori* and type 2 diabetes mellitus. Negative results and goals of future studies. *Saudi Med J* 2008; 29: 1213.

Haghi-Ashtiani MT, Monajemzadeh M. Comparison of anemia between *Helicobacter pylori* negative and positive adults. *Saudi Med J* 2008; 29: 917-918.

BaHammam AS, Alrajeh MS, Al-Jahdali HH, BinSaeed AA. Prevalence of symptoms and risk of sleep apnea in middle-aged Saudi males in primary care. *Saudi Med J* 2008; 29: 423-426. Review.