Future of GERD Research in Asia

13

Srinivas Gaddam and Prateek Sharma

Abstract

Until recently, GERD was thought to be a rare disease in Asia, and research on this topic was sparse. Now several publications have evaluated the prevalence of reflux symptoms in the Asian population. These large studies have predominantly been from China, Korea, Japan, Turkey, Iran, and Israel and show the incidence of GERD is rising throughout Asia.

Keywords

Gastroesophageal reflux disease • Barrett's esophagus • Low-grade dysplasia • High-grade dysplasia • Endoscopy • Endoscopic ablation • Endoscopic mucosal resection • Advanced imaging

Introduction

Until recently, gastroesophageal reflux disease (GERD) was thought to be a rare disease in Asia [1–3]. Several diseases of the gastrointestinal tract have been shown to have increasing incidences in India. Crohn's disease was thought to be nonexistent in the latter part of the twentieth century in India. However, there is accumulating data now that the incidence is steeply higher than previously thought [4]. A recent study by Mathew et al. found that the incidence of Barrett's esophagus is not uncommon in India [5]. Similarly, recent studies have shown a rising incidence of

S. Gaddam
Department of Gastroenterology and Hepatology, Veterans Affairs Medical Center, 4801 E. Linwood Blvd, Kansas City, MO 64128-2295, USA

P. Sharma (✉)
University of Kansas School of Medicine, VA Medical Center, Kansas City, MO, USA
e-mail: psharma@kumc.edu

P. Sharma et al. (eds.), *The Rise of Acid Reflux in Asia*,
DOI 10.1007/978-81-322-0846-4_13

GERD in India [3, 6–9]. Whether these increases are due to improved recognition and access to better diagnostic tools or a true increase in the prevalence is unclear [10].

GERD is a well-studied disease in the western world. Based on population-based data, at least 20% of the general population experiences heartburn and/or regurgitation weekly [11]. It is the most common gastrointestinal disease and is associated with a significant decrease in quality of life and is a huge economic burden [2, 12–16]. In the USA, GERD accounts for $10 billion in direct costs and up to $75 billion in indirect costs per year [13, 14]. Moreover, uncontrolled GERD can result in complications such as strictures, Barrett's esophagus, and esophageal adenocarcinoma (EAC) [17–19].

Status of Research on GERD in Asia

Contrary to the western world, research on this topic in Asia was sparse until recently, and GERD was considered to be uncommon in this part of the world [1]. However, now several publications have evaluated the prevalence of reflux symptoms in the Asian population [1]. These large studies have predominantly been from China, Korea, Japan, Turkey, Iran, and Israel. Three large studies from China, based on a symptom questionnaire and each with more than 2500 patients, estimated the prevalence of GERD (defined as at least once-a-week symptoms of heartburn and/or regurgitation) to be 2.5–4.8% [16, 20–22]. Large studies out of Korea (n = 1902) and Japan (n = 6035) have reported similar prevalence rates of 3.5% and 6.6%, respectively [23, 24]. Western and southern Asia have reported much higher prevalence of GERD [25, 26]. Bor et al. from Turkey report a prevalence of 20% using face-to-face interviews utilizing the Gastroesophageal Reflux Questionnaire (GERQ) [25]. Similar studies from Iran and Israel report a GERD prevalence of 21.2% and 9.3%, respectively [26, 27]. Whether these geographic differences in prevalence of GERD are due to variations in study design or due to other cultural and ethnic differences is unclear. An interesting study by Ho et al. based on a multiracial population in Singapore suggests that this variation is likely due to racial differences [28]. They report GERD prevalence of 7.5% among Indians compared to a low prevalence of 0.8% among Chinese. Nonetheless, there is emerging data that the incidence and prevalence of GERD continue to rise [29].

Research on GERD has been scarce in India. Therefore, in 2011, the Indian Society of Gastroenterology formed a task force to study the prevalence and risk factors for GERD. Bhatia et al. studied 3224 urban and rural adult populations and found that the prevalence of GERD was 7.6% and that consumption of nonvegetarian food was an independent risk factor for GERD [6]. Another study by Sharma et al. found that the GERD was present in 16.2% of 4039 employees of a tertiary care center [8]. They found that high BMI, smoking, asthma, and hypertension were independent risk factors for the development of GERD. Finally, a study by Kumar et al. reported a prevalence of 18.7% while studying 905 adult patients [7]. They found that younger age, sedentary lifestyle, serum LDL of more than 150 mg/dL, high consumption of meat, and low consumption of tea and fresh fruits were

independent risk factors for GERD. These studies had varying definitions and methodology. Nonetheless, they are the first large-scale evaluations of burden of disease of GERD in India and draw our attention to a high prevalence that is comparable to the western world.

The complications of chronic GERD have received much less attention in Asia. This is likely due to the initial data showing a much lower prevalence of reflux esophagitis and Barrett's esophagus in Asia when compared to the western world [29]. Low prevalence of erosive esophagitis was reported (5.6–16.8%) in patients undergoing an endoscopy [30–37]. Similarly, most studies have suggested a low prevalence of Barrett's esophagus (0.06–0.22% in general population and 0.5–2% in symptomatic patients) in Asia [38–42]. However, newer studies show that the prevalence of BE in symptomatic GERD patients (7.4–9%) is likely higher than previously reported [5, 37]. The data on incidence and time trends in esophageal adenocarcinoma from Asia are also unclear. There appear to be an increasing trend in Japan and Singapore, no change in Hong Kong, but a decreasing trend in Taiwan and Korea [43–47]. Data is almost nonexistent on this topic from other parts of Asia. These studies on complications of GERD show contrasting results, but even so, they draw attention to the paucity of data regarding Barrett's esophagus and esophageal adenocarcinoma from Asia.

Challenges and Future Directions to GERD Research in Asia

Healthcare Disparities

There are several challenges to conducting research in Asia due to its multilingual, multiethnic, and multicultural variations. There are several plausible explanations for these differences in epidemiology. Most studies are performed on patients seeking medical care. Due to variations in the structure of healthcare finance and delivery across different countries, there are wide disparities in equity and access to gastroenterologists and endoscopy suites. In addition, there are also variations to physician recognition, diagnostic practices, and referral patterns. These issues can result in the study of a biased patient group, resulting in confounded results. Therefore, large population-based studies are needed to understand the true epidemiology of GERD. Future research should also focus on understanding health behaviors such as healthcare-seeking behaviors, adherence to medical advice, and compliance to medications.

Language Barriers

GERD is a symptom-based diagnosis and does not have a gold standard test. GERD is evaluated in most studies by using patient-response symptom questionnaires that were validated in the western world. Most times, the translations of these questionnaires have not been validated. In some languages such as Chinese, Malay, and

Korean, there is no direct representative term for heartburn. This can severely impair the validity of the study results. Therefore, culturally acceptable and validated GERD questionnaires in a local language should be used as an instrument for diagnosis.

Economic Inequalities

Asia has experienced economic inequalities and very disparate growth rates. On one hand, there are countries that have showed rapid growth and attained the status of developed countries over three or four decades (four Asian tigers—Singapore, Hong Kong, South Korea, and Taiwan), while on the other hand, there are several countries below the poverty line. This results in wide dissimilarities in education and access to healthcare. Even within each country, there are significant dissimilarities between the urban and rural populations. This limits the generalizability of any study and more so studies on GERD. It is suggested that the increase in GERD may be related to urbanization, improvement in socioeconomic status, and adaptation of a western lifestyle [29]. Therefore, the prevalence outcomes may be profoundly affected by the geographic location of its participants. Future studies should attempt to include diverse populations while studying GERD. A stratified analysis by geographic location, level of education, and socioeconomic status may be warranted to better understand the influence of each of these factors on GERD.

Extraesophageal GERD Symptoms and Complications

There are limited data on extraesophageal GERD symptoms. Future studies must utilize other diagnostic studies, such as pH-impedance studies, to better evaluate extraesophageal symptoms where applicable. In addition, complications of GERD such as stricture rates, Barrett's esophagus, and esophageal adenocarcinoma need to be evaluated. These potentially preventable complications can have profound impact on costs, health-related quality of life, and morbidity. Research on true prevalence and data on outcomes on therapy of extraesophageal symptoms and complications of GERD can guide policy-makers on suitable allocations of healthcare resources.

Efficacy of Therapy for GERD

GERD is chronic disorder that requires long-term acid suppression therapy [48]. Proton pump inhibitors (PPI) are considered the gold standard treatment for GERD. Previous studies have shown high healing rates of erosive esophagitis in the Asian population [49]. While it has been shown that GERD phenotypes of nonerosive reflux esophagitis and erosive esophagitis are not categorical diseases in the western population, this has never been evaluated in the Asian population. Furthermore, the role of *H. pylori* and its influence on PPI therapy are unclear. It has

been suggested that PPI therapy in patients who harbor *H. pylori* is likely to progress to atrophic gastritis [50]. Future studies should evaluate for the role of these potential risk factors and confounders in the management of GERD.

Conclusion

GERD is an extremely common GI disease and is associated with poor health-related quality of life and is a huge financial burden. The current status of research on GERD, its complications, and management are not well studied in the Asian population. The diverse nature of Asian countries with regard to cultural beliefs, socioeconomic status, health equity, access, and delivery makes for a challenging environment for research studies. Well-designed studies on all aspects of GERD, listed below, are needed to help with effective management of GERD patients and, in addition, to provide policy-makers with data to help with allocation of healthcare resources.

Directions for Future Research on GERD in Asia

1. Consensus on a common definition of GERD
2. Determination of incidence and prevalence of GERD and extraesophageal symptoms of GERD
3. Determination of incidence and prevalence of complications of GERD (strictures, Barrett's esophagus, and esophageal adenocarcinoma)
4. Separation of true GERD from functional heartburn, peptic ulcer disease, and functional dyspepsia
5. Evaluation of effects of GERD on health-related quality of life
6. Culturally apt translations of existing questionnaires and validation of these instruments
7. Population-based studies to account for inequity and lack of access to healthcare resources
8. Endoscopy, pH-impedance, and manometry-based studies to help with accurate diagnosis
9. Interaction between *H. pylori* infection and GERD symptoms
10. Delineation of risk factors for GERD and its complications
11. Evaluation of efficacy and role of medical and surgical therapy for GERD
12. Comparative efficacy of therapeutic agents for GERD
13. Role and efficacy of non-pharmacologic therapy for GERD
14. Qualitative research on health behaviors such as healthcare-seeking behaviors, adherence to medical advice, and compliance to medications
15. Assessment of physician knowledge and training with regard to GERD and its complications
16. Identification of health education techniques and evaluation of efficacy of education program

17. Long-term outcomes of GERD and its complications
18. Identification of potential causes and confounders that predispose patients to GERD in the Asian population
19. Evaluation for pathophysiologic differences and pharmacokinetic variations based on ethnicity and geographic location
20. Assessment of influence of changes in socioeconomic status, changes in diet, and urbanization on the prevalence of GERD

References

1. Sharma P, Wani S, Romero Y, Johnson D, Hamilton F. Racial and geographic issues in gastroesophageal reflux disease. Am J Gastroenterol. 2008;103(11):2669–80. doi:10.1111/j.1572-0241.2008.02089.x. Epub 2008 Nov 27. PMID: 19032462
2. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005;54(5):710–7. doi:10.1136/gut.2004.051821. Epub 2005 Apr 16. PMID: 15831922; PMCID: PMC1774487
3. Ho KY. From GERD to Barrett's esophagus: is the pattern in Asia mirroring that in the west? J Gastroenterol Hepatol. 2011;26(5):816–24. doi:10.1111/j.1440-1746.2011.06669.x. Epub 2011 Jan 27. PMID: 21265879
4. Desai HG, Gupte PA. Increasing incidence of Crohn's disease in India: is it related to improved sanitation? Indian J Gastroenterol. 2005;24(1):23–4. Epub 2005 Mar 22. PMID: 15778522.
5. Mathew P, Joshi AS, Shukla A, Bhatia SJ. Risk factors for Barrett's esophagus in Indian patients with gastroesophageal reflux disease. J Gastroenterol Hepatol. 2011;26(7):1151–6. doi:10.1111/j.1440-1746.2011.06714.x. Epub 2011 Mar 8. PMID: 21375585
6. Bhatia SJ, Reddy DN, Ghoshal UC, Jayanthi V, Abraham P, Choudhuri G, et al. Epidemiology and symptom profile of gastroesophageal reflux in the Indian population: report of the Indian Society of Gastroenterology Task Force. Indian J Gastroenterol. 2011;30(3):118–27.
7. Kumar S, Sharma S, Norboo T, Dolma D, Norboo A, Stobdan T, et al. Population based study to assess prevalence and risk factors of gastroesophageal reflux disease in a high altitude area. Indian J Gastroenterol. 2011;30(3):135–43. doi:10.1007/s12664-010-0066-4. Epub 2010 Dec 25. PMID: 21181325
8. Sharma PK, Ahuja V, Madan K, Gupta S, Raizada A, Sharma MP. Prevalence, severity, and risk factors of symptomatic gastroesophageal reflux disease among employees of a large hospital in northern India. Indian J Gastroenterol. 2011;30(3):128–34. doi:10.1007/s12664-010-0065-5. Epub 2010 Nov 10. PMID: 21061110
9. Ramu B. Mohan P. Jayanthi V. Prevalence and risk factors for gastroesophageal reflux in pregnancy. Indian J Gastroenterol: Rajasekaran MS; 2010. doi:10.1007/s12664-010-0067-3. Epub 2010 Jan 3. PMID: 21125366
10. Gaddam S, Sharma P. Shedding light on the epidemiology of gastroesophageal reflux disease in India--a big step forward. Indian J Gastroenterol. 2011;30(3):105–7. doi:10.1007/s12664-011-0108-6. Epub 2011 Jul 26. PMID: 21785993
11. Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology. 1997;112(5):1448–56. PMID: 9136821
12. Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. N Engl J Med. 2008;359(16):1700–7. doi:10.1056/NEJMcp0804684. Epub 2008 Oct 17. PMID: 18923172
13. Shaheen NJ, Hansen RA, Morgan DR, Gangarosa LM, Ringel Y, Thiny MT, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol. 2006;101(9):2128–38. doi:10.1111/j.1572-0241.2006.00723.x. Epub 2006 Jul 20. PMID: 16848807

14. Wahlqvist P, Reilly MC, Barkun A. Systematic review: the impact of gastro-oesophageal reflux disease on work productivity. Aliment Pharmacol Ther. 2006;24(2):259–72. doi:10.1111/j.1365-2036.2006.02996.x. Epub 2006 Jul 18. PMID: 16842452
15. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol. 2007;5(1):17–26. doi: S1542-3565(06)00944-X10.1016/j.cgh.2006.09.016. Epub 2006 Jan 5. PMID: 17142109
16. Wong BC, Kinoshita Y. Systematic review on epidemiology of gastroesophageal reflux disease in Asia. Clin Gastroenterol Hepatol. 2006;4(4):398–407. doi:10.1016/j.cgh.2005.10.011. Epub 2006 Apr 18. PMID: 16616342
17. Sharma P. Clinical practice. Barrett's esophagus. N Engl J Med. 2009;361(26):2548–56. doi: 361/26/254810.1056/NEJMcp0902173. Epub 2009 Dec 25. PMID: 20032324
18. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825–31. doi:10.1056/NEJM199903183401101. Epub 1999 Mar 18. PMID: 10080844
19. Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med. 2014;371(9):836–45. doi:10.1056/NEJMra1314704. Epub 2014 Aug 28. PMID: 25162890
20. Wong WM, Lai KC, Lam KF, Hui WM, Hu WH, Lam CL, et al. Prevalence, clinical spectrum and health care utilization of gastro-oesophageal reflux disease in a Chinese population: a population-based study. Aliment Pharmacol Ther. 2003;18(6):595–604. Epub 2003 Sep 13. PMID: 12969086
21. Hu WH, Wong WM, Lam CL, Lam KF, Hui WM, Lai KC, et al. Anxiety but not depression determines health care-seeking behaviour in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study. Aliment Pharmacol Ther. 2002;16(12):2081–8. Epub 2002 Nov 28. PMID: 12452941
22. Guozong P, Guoming X, Meiyun K, Shaomei H, Huiping G, Zhaoshen L, et al. Epidemiological study of symptomatic gastroesophageal reflux disease in China: Beijing and shanghai. Chinese J Dig Dis. 2000;1(1):2–8. doi:10.1046/j.1443-9573.2000.00001.x.
23. Cho YS, Choi MG, Jeong JJ, Chung WC, Lee IS, Kim SW, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Asan-si. Korea Am J Gastroenterol. 2005;100(4):747–53. doi:10.1111/j.1572–0241.2005.41245.x. Epub 2005 Mar 24. PMID: 15784014
24. Fujiwara Y, Higuchi K, Watanabe Y, Shiba M, Watanabe T, Tominaga K, et al. Prevalence of gastroesophageal reflux disease and gastroesophageal reflux disease symptoms in Japan. J Gastroenterol Hepatol. 2005;20(1):26–9. doi:10.1111/j.1440–1746.2004.03521.x. Epub 2004 Dec 22. PMID: 15610442
25. Bor S, Mandiracioglu A, Kitapcioglu G, Caymaz-Bor C, Gilbert RJ. Gastroesophageal reflux disease in a low-income region in Turkey. Am J Gastroenterol. 2005;100(4):759–65. doi:10.1111/j.1572–0241.2005.41065.x. Epub 2005 Mar 24. PMID: 15784016
26. Nouraie M, Radmard AR, Zaer-Rezaii H, Razjouyan H, Nasseri-Moghaddam S, Malekzadeh R. Hygiene could affect GERD prevalence independently: a population-based study in Tehran. Am J Gastroenterol. 2007;102(7):1353–60. doi:10.1111/j.1572–0241.2007.01208.x. Epub 2007 Apr 18. PMID: 17437507
27. Sperber AD, Halpern Z, Shvartzman P, Friger M, Freud T, Neville A, et al. Prevalence of GERD symptoms in a representative Israeli adult population. J Clin Gastroenterol. 2007;41(5):457–61. doi:10.1097/01.mcg.0000225664.68920.96. Epub 2007 Apr 24. PMID: 17450026
28. Ho KY, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. American J Gastroenterol. 1998;93(10):1816–22. doi:10.1111/j.1572-0241.1998.00526.x. Epub 1998 Oct 15. PMID: 9772037
29. Wu JC. Gastroesophageal reflux disease: an Asian perspective. J Gastroenterol Hepatol. 2008;23(12):1785–93. doi:10.1111/j.1440-1746.2008.05684.x. Epub 2009 Jan 6. PMID: 19120871

30. Khuroo MS, Mahajan R, Zargar SA, Javid G, Munshi S. Prevalence of peptic ulcer in India: an endoscopic and epidemiological study in urban Kashmir. Gut. 1989;30(7):930–4. Epub 1989 Jul 1. PMID: 2788113; PMCID: PMC1434311
31. Kang JY, Tay HH, Yap I, Guan R, Lim KP, Math MV. Low frequency of endoscopic esophagitis in Asian patients. J Clin Gastroenterol. 1993;16(1):70–3. Epub 1993 Jan 01. PMID: 8421153
32. Rosaida MS, Goh KL. Gastro-oesophageal reflux disease, reflux oesophagitis and non-erosive reflux disease in a multiracial Asian population: a prospective, endoscopy based study. Eur J Gastroenterol Hepatol. 2004;16(5):495–501. Epub 2004 Apr 21. PMID: 15097043
33. Yeh C, Hsu CT, Ho AS, Sampliner RE, Fass R. Erosive esophagitis and Barrett's esophagus in Taiwan: a higher frequency than expected. Dig Dis Sci. 1997;42(4):702–6. Epub 1997 Apr 1. PubMed PMID: 9125635
34. Yeom JS, Park HJ, Cho JS, Lee SI, Park IS. Reflux esophagitis and its relationship to hiatal hernia. J Korean Med Sci. 1999;14(3):253–6. Epub 1999 Jul 13. PMID: 10402166; PMCID: PMC3054374
35. Furukawa N, Iwakiri R, Koyama T, Okamoto K, Yoshida T, Kashiwagi Y, et al. Proportion of reflux esophagitis in 6010 Japanese adults: prospective evaluation by endoscopy. J Gastroenterol. 1999;34(4):441–4. Epub 1999 Aug 19. PMID: 10452674
36. Inamori M, Togawa J, Nagase H, Abe Y, Umezawa T, Nakajima A, et al. Clinical characteristics of Japanese reflux esophagitis patients as determined by Los Angeles classification. J Gastroenterol Hepatol. 2003;18(2):172–6. Epub 2003 Jan 25 PMID: 12542602
37. Toruner M, Soykan I, Ensari A, Kuzu I, Yurdaydin C, Ozden A. Barrett's esophagus: prevalence and its relationship with dyspeptic symptoms. J Gastroenterol Hepatol. 2004;19(5):535–40. doi:10.1111/j.1440-1746.2003.03342.x. Epub 2004 Apr 17. PMID: 15086597
38. Park JJ, Kim JW, Kim HJ, Chung MG, Park SM, Baik GH, et al. The prevalence of and risk factors for Barrett's esophagus in a Korean population: a nationwide multicenter prospective study. J Clin Gastroenterol. 2009;43(10):907–14. doi:10.1097/MCG.0b013e318196bd11. Epub 2009 May 7. PMID: 19417682
39. Lee IS, Choi SC, Shim KN, Jee SR, Huh KC, Lee JH, et al. Prevalence of Barrett's esophagus remains low in the Korean population: nationwide cross-sectional prospective multicenter study. Dig Dis Sci. 2010;55(7):1932–9. doi:10.1007/s10620-009-0984-0. Epub 2009 Oct 3. PMID: 19798574.
40. Lee HS, Jeon SW. Barrett esophagus in Asia: same disease with different pattern. Clin Endosc. 2014;47(1):15–22. doi:10.5946/ce.2014.47.1.15. Epub 2014 Feb 27.PMID: 24570879; PMCID: PMC3928486
41. Tseng PH, Lee YC, Chiu HM, Huang SP, Liao WC, Chen CC, et al. Prevalence and clinical characteristics of Barrett's esophagus in a Chinese general population. J Clin Gastroenterol. 2008;42(10):1074–9. doi:10.1097/MCG.0b013e31809e7126. Epub 2008 Mar 25.PMID: 18360296
42. Wong WM, Lam SK, Hui WM, Lai KC, Chan CK, Hu WH, et al. Long-term prospective follow-up of endoscopic oesophagitis in southern Chinese--prevalence and spectrum of the disease. Aliment Pharmacol Ther. 2002;16(12):2037–42. Epub 2002 Nov 28.PMID: 12452935
43. Hongo M. Review article: Barrett's oesophagus and carcinoma in Japan. Aliment Pharmacol Ther. 2004;20(Suppl 8):50–4. doi:10.1111/j.1365-2036.2004.02230.x. Epub 2004 Dec 4. PMID: 15575874
44. Fernandes ML, Seow A, Chan YH, Ho KY. Opposing trends in incidence of esophageal squamous cell carcinoma and adenocarcinoma in a multi-ethnic Asian country. Am J Gastroenterol. 2006;101(7):1430–6. doi:10.1111/j.1572-0241.2006.00570.x. Epub 2006 Jul 26. PMID: 16863543
45. Yee YK, Cheung TK, Chan AO, Yuen MF, Wong BC. Decreasing trend of esophageal adenocarcinoma in Hong Kong. Cancer Epidemiol Biomark Prev. 2007;16(12):2637–40. doi:10.1158/1055-9965.EPI-07-0421. Epub 2007 Dec 19. PMID: 18086768
46. Chung JW, Lee GH, Choi KS, Kim DH, Jung KW, Song HJ, et al. Unchanging trend of esophagogastric junction adenocarcinoma in Korea: experience at a single institution

based on Siewert's classification. Dis Esophagus. 2009;22(8):676–81. doi:10.1111/j.1442-2050.2009.00946.x. Epub 2009 Feb 13. PMID: 19222529

47. Lu CL, Lang HC, Luo JC, Liu CC, Lin HC, Chang FY, et al. Increasing trend of the incidence of esophageal squamous cell carcinoma, but not adenocarcinoma, in Taiwan. Cancer Causes Control. 2010;21(2):269–74. doi:10.1007/s10552-009-9458-0. Epub 2009 Oct 29. PMID: 19866363
48. Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, Stolte M, Lind T, et al. Long-term treatment of patients with gastro-oesophageal reflux disease in routine care - results from the ProGERD study. Aliment Pharmacol Ther. 2007;25(6):715–22. doi:10.1111/j.1365-2036.2007.03249.x. PMID: ISI:000245173000009
49. Wong WM, Lai KC, Hui WM, Lam KF, Huang JQ, Hu WH, et al. Double-blind, randomized controlled study to assess the effects of lansoprazole 30 mg and lansoprazole 15 mg on 24-h oesophageal and intragastric pH in Chinese subjects with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2004;19(4):455–62. Epub 2004 Feb 12. PubMed PMID: 14871286
50. Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, Snel P, Goldfain D, Kolkman JJ, et al. Cure of Helicobacter pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. Gut. 2004;53(1):12–20. Epub 2003 Dec 20. PMID: 14684569; PMCID: PMC1773939