 ISSN 1007-9327 CN 14-1219/R WJG, 1998;4(4):280-284

A review of reflux esophagitis around the world

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Subject headings gastroesophageal reflux/epidemiology; gastroesophageal reflux/ pathophysiology; gastroesophageal reflux/complications;gastroesophageal reflux/diagnosis; gastroesophageal reflux/therapy

In the Western world, esophageal reflux is a common condition. In other parts of the world, the prevalence is less well defined, but appears to be swiftly approaching the levels seen in the West. As complications of this condition such as Barrett's epithelium and esophageal adenocarcinoma have seen huge increases over the past several decades in the West, there seems a likelihood that the rest of the world is at risk for a similar explosion in esophageal complications. This article will review the epidemiologic information about esophageal reflux, and pathophysiologic components of acid migration and altered peristaltic motility, and examine the advantages of treating this growing medical illness with acid suppression and prokinetic medication, as well as other nonpharmacologic therapies.

EPIDEMIOLOGY

The prevalence and incidence of esophageal reflux are difficult to establish. These values are dependent on the population under study. Reported frequencies tend to be lower if the studied population is based on the general population as opposed to a study of patients from a medical facility. Frequencies based upon endoscopic observation tend to be substantially lower than symptom surveys, which is consistent with the observation that endoscopic evidence of damage is present in only 10% of symptomatic patients.

Despite the differences in methods for collecting prevalence and incidence data, there appears to be variability in frequencies of reflux around the world (Table 1). In a 1997 U.S. report, the prevalence of weekly heartburn symptoms in the general population was 19. 8% (95% confidence interval 17.7-21.9)[1]. This appears to be higher than the often quoted weekly heartburn rate of 14% from 1976[2], suggesting an increase in reflux over the past two decades. Reflux was reported to be rare in Nigeria fifteen years ago[3], and the low frequency was postulated to be due to protective differences in the structure of the lower esophageal sphincter. The frequency of symptoms in Taiwan recently was thought to be similar to the U.S. frequency reported two decades ago[4], and the authors expressed concern that westernization of the diet, aging of the population, and increasing obesity would put the Taiwanese at higher risk of reflux and its sequelae.

Table 1 Prevalence of reflux in various geographic sites(%)

	Weekly symptoms	Monthly symptoms	Endoscopic damage
U.S.A.[1,2,10]	19.8	36	7
Europe[8,37,39,40]	12-23	21-34	2
East Asia[4,7,8,9]	14		1.5-5

In the U.S., heartburn occurring at least once per month is reported in 36%[2] of patients. This seems similar to the 40% prevalence of dyspepsia in the British population[5], and heartburn prevalence of 38% in Danish males and 30% in Danish females[6].

The prevalence of endoscopic esophagitis in the U.S. is approximately 7%. In non-Western countries, the prevalence of esophagitis seems to be lower. It is seen during endoscopic observation in 1.5% to 5% of cases in China[7,8], 2.7% in Korea[9], and 2% in Germany[10].

The pattern of higher prevalence of reflux in the Western countries, lower prevalence in Asia, and the lowest prevalence in Africa is similar to the frequencies of hiatal hernia around the world. As reviewed by Wienbeck and Barnert[10], hiatal hernia are found most frequent in the industrialized countries.

CLINICAL PRESENTATION

Reflux can present at any age, but seems most common in the 20 to 50 year age group. Symptoms occur equally often in males and females[10], and the like lihood of hospitalization is similar for the two genders[11]. However, occurrence of esophageal damage is two to three times more often in males both in the West[6-10] and in China[7]. As individual patients age, they become less likely to experience symptoms of reflux but their risk for esophageal damage remains constant[4]. Patients with Barrett's epithelium are substantially less likely to feel

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Received 1998-05-25

discomfort during acid regurgitation. Mild and moderate obesity is strongly associated with the development of reflux.

Typical symptoms of esophageal reflux are epigastric or lower retrosternal pain. The pain lasts one or two hours and occurs one hour after a meal, or sooner if aggravating food was consumed such as spicy food, tomatoes, citrus fruit, onions or alcohol. The pain usually is described as burning, and may be accompanied by nausea or regurgitation. If the reflux occurs during sleep, the patient often notices a bile taste and hyper-salivation. Regurgitation without vomiting is also frequently reported. Many patients report a history of attempted therapy with over the counter antacids which usually provide relief that is effective but of too short duration.

In addition to the typical presentation, some patients reports symptoms which should serve as a warning that the reflux may be more severe or complicated than the classical case. Such warning symptoms may include dysphagia, weight loss, and anemia. If present, dysphagia may be suggestive of a motor dysmotility if it occurs to both solids and liquids, occurs intermittently, and is not associated with the need for vomiting in order to obtain relief. The presentation is more suggestive of an esophageal stricture if it occurs regularly and in response to solid food, or of regurgitation is the only method for relief.

Atypical presentations of reflux are being recognized in a widening arena of medical conditions. Certainly, many patients with atypical chest pain derive their symptoms from gastrointestinal reflux[12]. Pulmonary symptoms such as chronic bronchiectasis or repeat aspiration pneumonia may be due to esophageal reflux. More commonly, small volumes of reflux such as micro-aspiration or acid regurgitation without aspiration are thought to produce chronic cough, hoarseness, or asthma. The asthmatic events usually occur in non-allergic young adults who have nocturnal reflux. Over 80% of adults with asthma have esophageal reflux. This is mediated by a vagal reflex and may require anti-reflux surgery for long term treatment. Recently, chronic nasal sinusitis is being investigated for possible association with GERD.

Regardless which form of presentation occurs, reflux is most often seen in patients with mild to moderate obesity. Interestingly, 50 massively obese patients with a mean BMI of 42 had a prevalence of symptoms that was similar to that of normal controls, and they were not found to have macroscopic evidence of reflux[13]. It is unclear why this occurs. Aside from mild obesity, reflux occurs more often in cigarette smokers. Patients with *H. Pylori* infections are less likely to have reflux [14]. The mechanism of this phenomenon may be related to decreased acid production in patients with chronic *H. Pylori* infections.

PATHOPHYSIOLOGY

Esophageal reflux occurs when gastric contents move in a retrograde direction into the esophagus. This regularly occurs in everyone on a daily basis. Problems develop when the gastric contents have prolonged exposure time to esophageal mucosa. This happens when the lower esophageal sphincter fails to provide an adequate mechanical barrier, when the esophageal peristaltic contractions fail to provide adequate clearing of the gastric contents, or when gastric contents are available for a prolonged time due to gastroparesis. The various physiologic events which contribute to the development of reflux are listed in Table 2.

Table 2 Pathophysiologic factors contributing to the development of reflux

Incompetent lower esophageal sphincter
Low pressure sphincter
Short sphincter length
Poor esophageal peristalsis
Decreased amplitude of contractions
Absence of propagated peristalsis
Delayed gastric emptying
Inadequate gastric contractions
Partial gastric outlet obstruction
Mucosal susceptablity to refluxate
Acid
Pepsin
Bile
Duodenal fluid

The lower esophageal sphincter pressure is low in one third of reflux patients, and normal in the remainder. Reflux may occur in the setting of normal sphincter pressure if the functional length of the sphincter is short, as shown by DeMeester *et al*[15]. As there is some inherited predisposition towards development of reflux,[16] it seems possible that worldwide variations in reflux prevalence may in part be due to genetically determined differences in sphincter length.

The normal action of peristaltic clearing of esophageal contents may fail in reflux disease. The magnitude of the failure of esophageal clearance is directly proportional to the severity of esophageal mucosal injury[17]. The most common peristaltic malfunction is a decreased amplitude of contractions in the distal esophagus, and occasionally a total failure of peristaltic propagation through this region. With these failures, gastric contents which have gained access to the esophageal mucosa will have extended exposure to this tissue. While it is unclear whether the peristaltic failure or the mucosal damage occurs first, it is commonly seen in clinical practice that pharmacologic resolution of the tissue injury is followed by return of the contractile activity.

A delay in gastric emptying can contribute to esophageal reflux, because it provides a substantial pool of acidic gastric contents for an extended period of time. Approximately half of patients with esophageal reflux have abnormal gastric emptying [18] which can be measured by radio nucleotide scintiscan or by electrogastrogram. Patients who fail to improve on acid suppression therapy should be evaluated for this comorbid condition.

A large sliding hiatal hernia traps gastric contents in its pouch above the diaphragm. This leads to free retrograde flow of acid into the esophagus[19] and is associated with poor esophageal emptying. Large hernias typically are at least four or five centimeters in length. More common smaller hernias are associated with comparatively normal esophageal emptying, and usually do not contribute to symptoms of reflux.

The injurious agent in reflux disease principally is gastric acid, however pepsin and perhaps other compounds also contribute. Because pepsin requires acid for activation, it is felt to be a less important caustic agent. In some surgical conditions such as partial gastrectomy, symptoms of reflux and the presence of esophageal damage may be due to regurgitation of duodenal fluid including bile into the esophagus. This may be directly measured and assessed with specialized research equipment[20].

COMPLICATIONS

Chronic reflux can lead to esophageal stricture formation, hemorrhage, and development of Barrett's mucosa. Strictures usually occur in patients with chronic esophageal ulceration. Hemorrhage is an uncommon complication, and most often is an acute problem seen in patients confined to an intensive care unit.

Barrett's mucosal transformation is found in Caucasians more often than in Africans or Orientals[4]. This may be a reflection of the lower prevalence of reflux in those populations. However, reflux is becoming more common in Asia, and there is concern that the risk of Barrett's and adenocarcinoma may rise in the coming decades[4]. Barrett's mucosa is eventually found in 15% of patients with reflux disease, however the condition is probably under diagnosed. In a study of Minnesota residents, the clinically diagnosed prevalence of Barrett's was 18 per 100 000 adults but the autopsy diagnosed prevalence was 376 per 100 000 cases[21]. This under diagnosis may occur because Barrett's patients are less likely to feel symptoms of reflux, and thus are less likely to present for medical evaluation. In addition, the extent of Barrett's mucosal changes may be very limited. These cases of short segment Barrett's are detected by extensive biopsy, or more recently by biopsy directed through the endoscopic use of stains such as methylene blue or an iodine solution. According to a study which was age and gender matched, Barrett's patients develop reflux symptoms at an earlier age (onset at the age of 35 *vs* 44 for non Barrett's GERD patients), have a longer duration of symptoms (16 years *vs*12 years), and were more likely to have smoking histories[22]. Efforts to reverse Barrett's changes with long term, high dose acid suppression by proton pump inhibitors have been unsuccessful. Recent reports suggest preliminary success with mucosal ablation by laser, cautery, and photo therapy[23].

DIAGNOSTIC APPROACH

The American College of Gastroenterology suggests that empirical therapy is appropriate in patients with typical symptoms of uncomplicated reflux disease[24]. All others should be considered for a diagnostic evaluation to confirm the diagnosis and define the extent of disease. The evaluation options include endoscopy, barium esophagram, 24 hour pH is monitoring, and esophageal motility testing.

Endoscopy is a very valuable tool in the evaluation of esophageal reflux. It permits assessment of the mucosa, both visually and by biopsy. Over 85% of reflux patients have a normal visual findings at endoscopy, which can leave the origin of their symptoms in doubt. The use of biopsy in the distal esophagus is invaluable for confirming the presence of reflux which fortunately is too mild to produce visible damage.

Barium esophagram seems to have lost popularity after the advent of endoscopy. Currently, the best use of radiography is to establish the presence of minor strictures which can produce dysphagia. This uncommon condition may be hard to detect by endoscopy. One study reported that patients primarily evaluated by radiography rather than gastrointestinal consultation or endoscopy had higher total costs for their care[25].

The 24 hour pH is monitored to confirm and quantify the existence of esophageal reflux, and to correlate the occurrence of symptoms with the presence of acid in the esophagus. This tool is most often used in patients with atypical presentations. It is also useful in patients with typical symptoms who do not improve on maximal medical therapy. In these patients, the 24 hour test should be done while the patient consumes the full pharmacologic regimen prescribed.

Esophageal motility testing is most useful prior to the decision for surgery. Patients found to have poor esophageal peristalsis are at risk for dysphagia after an antireflux procedure.

TREATMENT

Lifestyle changes

The prevalence of smoking is higher in reflux patients than in healthy controls. This suggests that smoking may promote the development of esophageal reflux damage, perhaps due to its

relaxation of the lower esophageal sphincter. Symptoms in patients who smoke are more difficult to control than those in non smokers. Thus it is beneficial in the treatment of reflux for the patient to stop the use of tobacco products.

With the observation that moderate obesity aggravates or initiates reflux symptoms, patients are advised to achieve a modest weight loss. Symptoms are improved once there is a weight loss of 5% to 10%.

Elevation of the head of the bed aids the gravitational drainage of the esophagus. Since a substantial portion of reflux patients have impaired esophageal emptying, the lifting of the head of the bed by six inches should be beneficial. This has been demonstrated in a study which noted equivalent rates of healing of esophageal ulcers when bed elevation was compared to standard dose of a histamine receptor antagonist[26].

Pharmacologic options

As listed in Table 3, the currently available options for reflux treatment include acid suppression drugs such as histamine receptor antagonists (H2RA) or proton pump inhibitors (PPI), and promotility agents. While some studies have reported a beneficial effect of isolated promotility drugs in cases of mild esophagitis, most others suggest a lesser role. Several authors recommend that mild to moderate reflux patients be treated initially with H2RA, and that severe cases use PPI drugs[27,28]. This practice suggestion is consistent with observations of actual practice patterns by primary care physicians and gastroenterologists[29]. Prokinetic agents may be added to acid suppression therapy for additional symptomatic and healing effects.

Several review papers have reported that all four H2RA agents are similar in efficacy[24]. However, there are very few direct studies which attempt to compare two or more of these agents using equivalent doses in appropriate clinical populations. Thus it is unclear whether all branded H2RA agents, or their generic equivalents now beginning to appear on the markets, are truly similar.

Table 3 Pharmacologic agents used in the treatment of reflux

	Dosage*	Possible mechanism
H2 receptor antagonist		
Cimetidine	800mg bid or 400mg qid	Reduce acid
Famotidine	20mg bid or 40mg bid	Reduce acid
Nizatidine	150mg bid	Reduce acid, prokinetic
Ranitidine	150mg qid	Reduce acid
Proton pump inhibitor		
Lansoprazole	30mg qd	Reduce acid
Omeprazole	20mg qd	Reduce acid
Prokinetic		
Cisapride	10mg qid or 20mg qid	Prokinetic
Metoclopramide	15mg qid	Prokinetic

*Dosages for erosive esophagitis, except for cisapride which is suggested for symptomatic treatment only[41].

A review of the medical literature suggests several potential differences among the H2RA drugs. In order to clinically measure whether these differences are important in clinical practice, carefully designed studies will be needed which compare H2RA drugs in the mild and moderate severity groups of reflux esophagitis. A potential point of differentiation among the H2RA drugs in the observation that one agent, nizatidine, has prokinetic acitivity. In a dog model, the intensity of this activity may exceed that of cisapride[30]. Prokinetic activity was not significantly present in the other H2RA. Nizatidine has been shown in human, dog and rat models to improve gastric emptying[30-32]. The mechanism of the prokinetic activity may be due to nizatidine's antiacetylcholinesterase activity[30]. Another point of differentiation is that two agents, famotidine and nizatidine, have no interaction with the hepatic P-450 enzyme system. As this system is capable of metabolizing many medications, interference with its function by one of the other H2RA drugs has the potential to alter the clearance of other medications taken by a patient. Whether such a hypothetical interaction has clinical significance is not known.

The proton pump inhibitor drugs available in the U.S. are both capable of healing esophageal ulcers and relieving symptoms of reflux. At least one study suggests that lansoprazole (30mg per day) was better at symptom relief than omeprazole (20mg per day)[33]. The two drugs seem to differ in that lansoprazole has fewer interferences with blood levels of other medications.

Surgical therapy

While the vast majority of patients with esophageal reflux can be successfully treated with lifestyle and pharmacologic therapies, a small number need surgical help. Patients who fail to respond to maximal medical therapy are candidates for surgical correction. Another group of candidates are the patients who are unable to stop their medication and yet unwilling to take the medicine over a long time frame. Both groups of medically resistant patients are often younger than the usual reflux patient, and tend to have a near normal body weight. A third group of surgical candidates are those with atypical symptoms such as asthma. Often they do not resolve their atypical symptoms on maximal medical therapy.

Of the patients undergoing a Nissen fundoplication, over 90% can anticipate cures of their symptoms. This figure appears to hold true for both the open procedure as well as the laparoscopic approach. The rate of conversion from laparoscopic to open Nissen procedure is less than 2%[34]. The reoperation rate for this laparoscopic approach is 3.9%. Unfortunately, the laparoscopic Toupet procedure may not promote such good long term results, as one study reported the Toupet procedure

was associated with a high incidence of recurrent postoperative esophageal reflux disease[35].

Maintenance therapy

After a course of anti-reflux medication has been completed, those patients who succeeded in their lifestyle changes are the ones most likely to be symptom free. Of the patients who immediately redevelop their complaints, symptomatic relief can be reacquired by giving the former H2RA patients one half of their former dose, and by giving the former PPI patients a standard dose of H2RA. The duration of this maintenance dose is variable, but commonly exceeds six months. During this time, further efforts at long term life style changes should be made. Maintenance therapy with acid suppression alone is not as effective as the combination of acid suppression plus prokinetic activity[36].

Over extended time, the reflux symptoms resolve, as shown by a study of the natural history of reflux disease[37]. Of patients thought to have severe disease, the prevalence of erosive esophagitis fell from 60% to 10% over a two-decade study. Symptoms reduced in most patients, and the use of medications ended in 68% of the patients. This suggests that reflux, even in severe patients, will slowly resolve over time.

Summary

Approximately 85% to 90% of patients with heartburn have mild disease. This can be suspected in patients who are under the age of 50 years, have intermittent symptoms only during the waking hours, and have no warning symptoms. Other patients with mild illness may be discovered by finding normal esophageal tissue at endoscopy, or the presence of only distal esophageal erythema. These mild patients should begin therapy with H2RA[38]. The use of H2RA plus prokinetic agents is more effective than acid suppression alone[36]. The uncommon patient with more severe illness may need PPI. These medicines are continued for six to eight weeks. During this time, all necessary lifestyle changes should be attempted, particularly loss of weight and cessation of smoking. Patients who do not respond to therapy, and are not already receiving a medication with prokinetic activity, should be considered for further evaluation which may include gastric emptying time, esophageal pH probe, or manometry.

REFERENCES

1 Locke GR, Talley NJ, Zinsmeister AR, Melton LJ. Prevalence and clinical spectrum of gastroesophageal reflux: a population based study in Olmested County, Minnesota. *Gastroenterology,* 1997;112(5):1448-1456
2 Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitation factors. *Am J Dig Dis,* 1976;21(11):953-956
3 Ofoegbu RO. Incidence, pattern and African variations of common benigndisorders of the esophagus. Experience from Nigeria. *Am J Surg,* 1982; 144(2):273-276
4 Chen PH. Review: Barrett¡äs oesophagus in Taiwan. *J Gastro Hepatol,* 1997; 12(6):S19-22
5 Penston JG, Pounder RE. A survey of dyspepsia in Great Britain. *Alim Pharm Therapeutic,* 1996;10(1):83-89
6 Kay L, Jorgensen T, Jensen KH. Epidemiology of abdominal symptoms in a random population: prevalence, incidence, and natural history. *Eur J Epidemiol,* 1994;10(5):559-566
7 Zhang TC, Zhu MZ, Geng XC, Li YJ, Cao T, Zhang LP. Endoscopic study of reflux esophagitis. *JAMA Southeast Asia,* 1996;12(2Suppl):22-24
8 Chang CS, Poon SK, Lien HC, Chen GH. The incidence of reflux esophagitis among the Chinese. *Am J Gastrol,* 1997;92(4):668-671
9 Min YI, Lee SK, Kim MH, Yi SY, Jung HY. Epidemiology of reflux esophagitis in a general health screening population. *JAMA Southeast Asia,* 1996;12 (2Suppl):11-15
10 Wienbeck M, Barnert J. Epidemiology of reflux disease and reflux esophagitis. *Scand J Gastro,* 1989;156:7-13 supplement
11 Zarling EJ, Bernsen MB. The effect of gender on the rates of hospitalization for gastrointestinal illnesses. *Am J Gastrol,* 1997;92(4):621-623
12 Voskuil JH, Cramer MJ, Breumelhof R, Timmer R, Smout AJ. Prevalence of esophageal disorders in patients with chest pain newly referred to the cardiologist. *Chest,*1996;109(5):1210-1214
13 Lundell L, Ruth M, Sandberg N, Bove-Nielsen M. Does massive obesity promote abnormal gastroesophageal reflux. *Dig Dis Sci,* 1995;40(8):1632-1635
14 Xia HH, Talley NJ. Helicobacter pylori infection, reflux esophagitis, and atrophic gastritis: an unexplored triangle. *Am J Gastrol,* 1998;93(3):394-400
15 DeMeester TR, Mason RJ, Ritter MP, Gadenstatter M, Bremner CG, Peters JH. Association of lower esophageal sphincter length with postprandial gastroesophageal reflux. *Gastroenterol,* 1997;112(4):A1458
16 Trudgill N. Familial factors and gastroesophageal reflux disease. *Gastroenterol,* 1997;112(4):A315
17 Rakic S, Stein HJ, DeMeester TR, Hinder RN. Role of esophageal body function in gastroesophageal reflux disease: implications for surgical management. *J Am Col Surg,* 1997;185(4):380-387
18 Soykan I, Lin Z, Jones S, Chen J, McCallum RW. Gastric myoelectrical activity, gastric emptying and correlations with dyspepsia symptoms in patients with gastroesophageal reflux. *J Invest Med,* 1997;45(8):483-487
19 Sloan S, Kahrilas PJ. Impairment of esophageal emptying with hiatal hernia. *Gastroenterol,* 1991;100(3):596-605
20 Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. *Gastroenterology,* 1996;111(5):1192-1199
21 Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA. Prevalence of columnar lined (Barrett's) esophagus. *Gastroenterology,* 1990;99(4):918-922
22 Eisen GM, Sandler RS, Murray S, Gottfried M. The relationship between gastroesophageal reflux disease and its complications with Barrett's esophagus. *Am J Gastrol,* 1997;92(1):27-31
23 Mayrand S. Treatment of Barrett's esophagus. *Can J Gastrol,* 1997;11 Suppl B:98B-102B
24 DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Arch Intern Med,* 1995;155:2165-2173
25 Longstreth GF. Long term costs after gastroenterology consultation with endoscopy versus radiography in dyspepsia. *Gastrointest Endosc,* 1992;38(1):23-26
26 Harvey RF, Cordon PC, Hadley N, Long DE, Gill TR, MacPherson RI, Beats BC, Tottle AJ. Effects of sleeping with the bed head raised and of ranitidine in patients with severe peptic oesophagitis. *Lancet,* 1987;ii:1200-1203
27 Rex D. Gastroesophageal reflux disease in adults: pathophysiology, diagnosis, and management. *J Fam Pract,* 1992;35(6):673-681
28 Robinson M. Gastroesophageal reflux disease. *Postgrad Med,* 1994;95(2):88-102
29 Kim SL, Goldschmid S. A survey of community practice patterns for refractory gastroesophageal reflux disease. *Gastroenterology,* 1997;112(4):A175
30 Ueki S, Seiki M, Yoneta T, Aita H, Chaki K, Hori Y, Morita H, Tagashira E, Itoh Z. Gastroprokinetic activity of nizatidine, a new H-2 receptor antagonist, and its possible mechanism of action in dogs and rats. *J Pharm Exp Therap,* 1993;264(1):152-157
31 Kaneko H, Mitsuma T, Uchida K, Nagai H, Harada M, Kotera H. Nizatidine accelerates gastric emptying of a solid meal in rats. *Dig Dis Sci,* 1995;40(9);2043-2051
32 Harasawa S, Miwa T. The effect of nizatidine on gastric emptying and plasm gastrin concentrations in patients with peptic ulcer. *Jpn Pharmacol Ther,* 1993;21(3):327
33 Mee AS, Rowley JL. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. *Aliment Pharm Ther,* 1996;10(5):757-763
34 Hinder RA, Perdikis G, Klinger PJ, DeVault KR. The surgical option for gastroesophageal reflux disease. *Am J Med,* 1997;103(5A):144S-148S
35 Jobe BA, Wallace J, Hansen PD, Swanstrom LL. Evaluation of laparoscopic Toupet fundoplication as a primary repair for all patients with medically resistant gastroesophageal reflux. *Surg Endosc,*1997;11(11):1080-1083
36 Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, DiMario F, Battaglia G, Sandro G, Pilotto A, Plebani M, Davi G. A comparison of five maintenance therapies for reflux esophagitis. *New Engl J Med,* 1995;333(17):1106-1110
37 Isolauri J, Luostarinen M, Isolauri E, Reinikainen P, Vijakka M, Keyrilainen O. Natural course of gastroesophageal reflux disease: 17-22 year follow up of 60 patients. *Am J Gastrol,* 1997;92(1):37-41
38 Beck LT, Champion MC, Lemire S, Thomson ABR. The second Canadian consensus conference on the investigation and treatment of gastroesophageal reflux disease. *Gastroenterology,* 1997;112(4):A3
39 Corder AP, Jones RH, Sadler GH, Daniels P, Johnson CD. Heartburn, esophagitis and Barrett's esophagus in self medicating patients in general practice. *Br J Clin Pract,*1996;50(5):245-248
40 Isolauri J, Jaippala P. Prevalence of symptoms suggestive of gastro-esophageal reflux disease in an adult population.*Ann Med* 1995;27(1):67-70
41 Physicians' Desk Reference, 52nd edition. Montvale NJ:Medical Economics Company, 1998