Specific Subjective Symptoms for Gastroesophageal Reflux Disease in Ulcer Like Dyspepsia

Poerniati Koes Andrijani, Chudahman Manan**, Marcellus Simadibrata**, Parlindungan Siregar****

*Department of Internal Medicine, Faculty of Medicine,
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital
** Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine,
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital
*** Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine,
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital

ABSTRACT

Background: The Aim of study is to identify specific subjective symptoms for gastroesophageal reflux disease (GERD), GERD proportion in ulcer like dyspepsia and the correlation between specific subjective symptoms for GERD and endoscopic examination result in ulcer like dyspepsia

Materials and Methods: A cross-sectional study was conducted in 67 patients with ulcer like dyspepsia. The patient's history of illness was taken, and physical and endoscopic examinations were performed. A questionnaire on dyspepsia symptoms was completed. Data analysis was performed to identify the correlation between subjective symptoms and endoscopic examination results using chi-square test. T test was performed to determine the correlation between dyspepsia scores and endoscopic results.

Result: Subjective symptoms that correlated with endoscopic results were severe epigastric pain (p=0.080) and the absence of bloating (p=0.055). Dyspepsia scores did not correlate with endoscopic examination results (p=0.725).

Conclution: Specific subjective symptoms for GERD in clinical dyspepsia-like ulcer were severe epigastric pain and absence of bloating. The proportion of such symptoms in ulcer like dyspepsia could assist clinical diagnosis of GERD.

***Keywords**: GERD, symptom, dyspepsia*

INTRODUCTION

Aside from epigastric pain or discomfort, symptoms that often accompany dyspepsia include early satiation, nausea, vomiting, heartburn, gassines and belching.[1-7] Dyspepsia is a common complaint for people to suffer once in a while, and is often encountered in daily practice.[5] A study on the general population found that 15-30% of adults have suffered from uninvestigated dyspepsia within few days.[5] Dyspepsia is an important problem, thus the creation of the term uninvestigated dyspepsia, which refers to dyspepsia as a dominant symptom, which has not undergone further investigation, particularly endocopy, while investigated dyspepsia refers to dyspepsia with a known diagnosis of functional or organic etiology, such as gastric or duodenal ulcer, gastroesophageal reflux disease or gastric cancer.[2,3]

The prevalence of dyspepsia according to Doll et al is 25-30%, specifically 26% in the United States and 7-41% in the United Kingdom and Scandinavia.[4,5] According to Jones and Lydeard, the prevalence in Hampshire is 38%, and 23-41% in Western Society.[4,5,8] According to Melleney and Willoughby from the United Kingdom, Department of Health, out of 84 patients that underwent gastroscopy, 10 patients (11.9%) were normal, 30 patients (35.7%) suffered from esophagitis,

24 patients (28.6%) had mild hyperemia of the gastric or duodenal mucosa, 4 patients (4.8%) were found with peptic ulcer, only 6 cases (7.1%) were detected with esophageal or gastric ulcer, and 10 cases (11.9%) were found with various mild abnormalities such as hiatus hernia, gastric polyp and gastric erosion.[8] Data on dyspepsia from Indonesia, mostly from hospitals with endoscopic facilities, found functional dyspepsia in 60-70% of cases, 10-20% with reflux esophagitis, 10-15% with peptic ulcer, and gastric malignancy in 2- 5%.[6]

More than half of patients with dyspepsia are found with overlapping symptoms (42.7%), heartburn (24.7%), or epigastric pain (32.6%), which often makes it difficult to differentiate dyspepsia from gastroesophageal reflux disease (GERD).[4,5,7,9] Among patients who were diagnosed with peptic ulcer, 28% come with a complaint of heartburn, while among patients with complaints of epigatric pain, 9% were found with peptic ulcer and 14% were found with esophagitis.[10,11] AGA reported a prevalence of GERD of 0-29% among dyspepsia patients.[9] Gastroesophageal reflux disease has a high prevalence in the West, reaching 18-42% in the United States. GERD is a condition where gastric contents enter the esophagus, creating symptoms that make up the dyspepsia syndrome. GERD has unique symptoms of heartburn and regurgitation. These clinical symptoms are often accompanied by dyspeptic symptoms.[12-15]

In Indonesia, there are no data on specific subjective symptoms due to GERD in ulcer like dyspepsia, particularly from Dr. Cipto Mangunkusumo General National Hospital. Thus, careful history taking to quickly identify clinical symptoms of GERD could hopefully facilitate early detection of GERD. It is also important to establish the correlation of specific subjective symptoms of GERD in ulcer like dyspepsia and endoscopic findings. For the purpose of this study, we will evaluate subjective symptoms of dyspepsia using the scoring system according to the criteria made by Talley et al, in order to obtain the degree of dyspeptic syndrome.[16]

METHOD

This study was performed as a cross-sectional study at the outpatient clinic of the Department of Internal Medicine and the outpatient clinic of the Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital, Jakarta, from February 2003 to July 2003. The population of this study consisted of all patients with ulcer like dyspeptic symptoms who have received empirical treatment with antacids and/or H2 receptor antagonists who came to seek medical attention at the outpatient clinic of the Department of Internal Medicine and the outpatient clinic of the Division of Gastroenterology of the Department of Internal Medicine of Dr. Cipto Mangunkusumo General National Hospital, Jakarta. The samples were selected in a consecutive non-random manner.

The number of sample for the study was determine by using the largest sample size from the minimal sample size for various questions the study attempts to answer using the appropriate statistical methods. Bearing in mind that there are several variables, five variables were established to determine the sample size, which were: epigastric pain, heartburn, nausea, vomiting, and gassiness. The calculation was based on a confidence interval of 90%. The sample size was 67 patients.

The inclusion criteria for this study was ulcer like dyspepsia patients who have received empirical treatment with antacids and/or H2 receptor antagonists who came to seek medical attention at the outpatient clinic of the Department of Internal Medicine and the outpatient clinic of the Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital, Jakarta and was voluntarily willing to participate in the study, while the exclusion criteria was as follows:

a. Patients already receiving treatment for dyspepsia with prokinetic agents or proton pump inhibitors for 2 weeks prior to the commencement of the study
b. Contraindication for H2 antagonist receptor
c. Gastrointestinal malignancy
d. Absolute or relative contraindication for endoscopy and upper gastrointestinal tract biopsy: patient uncooperative, shock, coma, congestive heart disease, acute stroke, massive gastrointestinal bleeding, post abdominal surgery, and pregnancy
e. Liver cirrhosis
f. Gall stone, cholecystitis, pancreatitis
g. Acute myocardial infarct
h. Diabetes mellitus
i. Chronic renal failure

Data sorting and analysis was performed using the

SPSS version 10 statistical software for the computer.

Table 1. Distribution of Study Subjects According to Age and Sex

Age (years)		
Mean	37.5	
Minimum	15.0	
Maximum	60.0	
Sex	**n**	**%**
Male	35	52.2
Female	32	47.8

RESULTS

Out of the 67 study subjects, the youngest was 15 years old and the oldest 60 years old, with a mean age of 37.5 years, while the male to female proportion was almost equal, with 52.2% males and 47.8% females.

Table 2. Distribution of Study Subjects According to Endoscopic Findings

Endoscopic Findings	n	%
Esophagitis (-)	27	40.3
Esophagitis (+)	40	59.7
Gastritis	24	35.8
Gastritis+ulcer	3	4.5
Esophagitis 1 + gastritis with/without ulcer	30	44.8
Esophagitis 2 + gastritis with/without ulcer	9	13.4
Esophagitis 4 + gastritis with/without ulcer	1	1.5

A large number of the study subjects turned out to be positive for esophagitis (59.7%) and most had esophagitis grade 1 with gastritis accompanied with ulcer or without ulcer (44.8%) and only 1.5% suffer from esophagitis grade 4 with gastritis accompanied with ulcer or without ulcer.

Table 3. Distribution of Study Subjects According to Subjective Symptom

Subjective Symptom	n	%
Epigastric pain		
Moderate	30	44.8
Severe	37	55.2
Heartburn		
Normal/no complaint	20	29.8
Mild	31	46.3
Moderate	15	22.4
Severe	1	1.5
Nausea		
Normal/no complaint	13	19.4
Mild	54	80.6
Vomiting		
Normal/no complaint	57	85.1
Mild	10	14.9
Bloating		
Normal/no complaint	17	25.4
Mild	50	74.6
Dyspepsia score		
Mean	5.2	
Standard Error of Mean	0.1	
Median	5.0	
Standard Deviation	1.1	
Minimum	3.0	
Maximum	8.0	
Degree of Dyspepsia		
Mild	46	68.7
Moderate	21	31.3

Most of the study subjects suffered from severe epigastric pain (55.2%) but only 1.5% suffered from severe heartburn, and the most mentioned mild heartburn (46.3%). Almost all study subjects suffer from mild nausea (80.6%) and mild gassiness (74.6%). The calculated total score for dyspepsia was: mean score 5.2 with a standard deviation of 1.1, minimum score of 3.0 and maximum of 8. When the score was classified according to the degree of dyspepsia, most study subjects had mild dyspepsia (68.7%) and the rest moderate dyspepsia (31.3%).

Table 4. Distribution of Study Subjects According to Subjective Symptom and Endoscopic Findings

Subjective Symptom	Endoscopic Findings				Total	*p*
	Esophagitis (-)		Esophagitis (+)			
	n	%	n	%		
Epigastric pain						
Moderate	16	53.3	14	46.7	30	0.080
Severe	11	29.7	26	70.3	37	
Heartburn						
Normal/no complaint	8	40.0	12	60.0	20	0.871
Mild	13	41.9	18	58.1	31	
Moderate	6	40.0	9	60.0	15	
Severe	0	0.0	1	100.0	1	
Nausea						
Normal/no complaint	7	53.8	6	46.2	13	0.427
Mild	20	37.0	34	63.0	54	
Vomiting						
Normal/no complaint	22	38.6	35	61.4	57	0.508
Mild	5	50.0	5	50.0	10	
Bloating						
Normal/no complaint	3	17.6	14	82.4	17	0.055
Mild	24	48.0	26	52.0	50	
Degree of dyspepsia						
Mild	18	39.1	28	60.9	46	0.984
Moderate	9	42.9	12	57.1	21	

The results of the analysis demonstrated that out of 67 study subjects suffering from severe epigastric pain, 70.3% were positive for esophagitis, while in those with heartburn, the percentage without complaint and moderate complaint demonstrated equal percentage of subjects who were positive for esophagitis (60%). Among the study subjects suffering from mild nausea, 63% turned out positive for esophagitis, while among those with no complaint, only 46.2% were positive for esophagitis. Nevertheless, the condition was reversed among study subjects with vomiting and gassiness, where normal study subjects/those with no complaint had a greater percentage of positive esophagitis, of 61.4 % and 82.4% respectively.

According to the degree of dyspepsia, there was almost the same percentage of positive esophagitis among those with mild and moderate dyspepsia of 60.9% and 57.1% respectively. There was a statistically significant correlation between endoscopic findings and a subjective symptom of severe epigastric pain ($p < 0.1$) and the absence of bloating ($p < 0.1$), while other symptoms did not demonstrate a statistically significant correlation ($p > 0.1$).

Table 5. Distribution of Study Subjects According to Dyspepsia Score and Endoscopic findings

	Endoscopic Findings		*p*
	Esophagitis (-)	Esophagitis (+)	
Dyspepsia Score	27	40	0.555
Mean	5.15	5.25	
Standard Deviation	1.17	1.15	
Mean Standard - Error	0.22	0.18	

T test, 90 % CI

The result of the analysis demostrated that the mean dyspepsia score among those with negative esophagitis were lower (5.15) compared to the positive for esophagitis (5.25). After statistical analysis, no significant correlation was found between dyspepsia score and endoscopic findings (table 5).

DISCUSSION

In this study, the male to female proportion was almost equal, with 52.2% males and 47.8% females. This

finding is in line with the study by Jones and Lydeard in Hampshire, who found dyspepsia an almost equivalent prevalence of males as females, of 45% and 55% respectively, while in the United Kingdom, the study by Melleney and Willoughby found 48 males (48%) and 52 females (52%). The study by Lelosutan in Jakarta in 1998 found 56.7% males and 43.3% females. The study by Bommel et al found 45% males and 55% females.[4,7,8,12] In the study by Juwanto in 2000, there were 46.87% males and 53.13% females.[17]

Several studies in Indonesia as well as abroad found an almost equivalent proportion of males and females, which is in line with the results of this study.

The mean age of the patients in this study was 37.5 years, with the youngest 15 years of age and the oldest 60 years of age. The study by Melleney and Willoughby found a mean age of 59 years, with the youngest being 15 years and the oldest 84 years. The study by Bommel et al found 68% of patients to be over 45 years of age. The study by Juwanto found a mean age of 35.5 years, with the youngest being 18 years of age and the oldest 60 years.

Esophagogastroduodenoscopy (EGD) revealed a large number of the study subjects to be positive for esophagitis (59.7%), while the remaining 40.3% did not suffer from esophagitis. Such results are in line with the study by Tobey et al in Europe, who found 59% esophagitis.[12] The study by Melleney and Willoughby at the Department of Health of the United Kingdom found that out of 84 patients who underwent gastroscopy, 35.7% were found with esophagitis. The American Gastroenterology Association (AGA) as well as Robinson found a prevalence of esophagitis of 5-15% based on endoscopic findings.[8,18,19] In the study at Dr. Cipto Mangunkusumo General National Hospital, Jakarta, in 1994, out of 591 cases with dyspepsia, 5.91% were found to be positive for esophagitis (35 cases) based on EGD. McQuaid found 25% with esophagitis.[5,20] In 1996, Goh reported a study in Malaysia with a prevalence of 0.8%, and 4.5% in Singapore, while in Indonesia, the study by Aziz Rani in Jakarta found a prevalence of 22.2%, an Djayapranata found esophagitis in 11.5% in Surabaya. In 1998, Lelosutan found esophagitis in 22.8% of patients with clinical dyspepsia at Dr. Cipto Mangunkusumo General National Hospital, while in the year 2000, Juwanto found esophagitis in 78.13% of patients with clinical reflux dyspepsia.[12,17] In 5 years in Jakarta, Syam et al found a prevalence of reflux esophagitis of 13.13% out of 1,718 patients, and reported an increased prevalence of reflux esophagitis from 5.7% in 1997 to 25.18% in the year 2002. Such results were almost congruent to the one obtained by Lelosutan.[12,21] In the study by Syam et al, most patients with reflux esophagitis presented with dyspeptic symptoms (75.11%), and only 9.71% with symptoms of gastroesophageal reflux (heartburn and regurgitation).[14] According to Goh, the low prevalence of esophagitis and dyspepsia in general in Asia could be due to:[12]

1. Underdiagnosis
2. Low number of reported cases of esophagitis
3. Lack of attention to diagnostic instruments
4. Gastric disturbance that causes atrophic gastritis with reduced acid production.

In this study, first and second degree esophagitis was found in 56.7% of cases, and fourth degree in 1.5%. In the study by Marshall et al, first and second degree esophagitis was found in 54% of cases, while third and fourth degree esophagitis was found in 4% of cases.[22] Robinson found a prevalence of erosive GERD (second degree esophagitis) of 5-15%.[18] Juwanto found 72% with first degree esophagitis out of 25 study subjects with a clinical presentation of reflux dyspepsia.[17] Lelosutan found 86.7% cases with first degree esophagitis, and 3.3% with second degree esophagitis.[12] Differences in the results of EGD examination may be due to differences in sampling and lack of attention to the initial diagnostic process of obtaining a unique history of heartburn. In daily practice, patients do not spontaneously report their complaint with this term.

In this study, 100% of subjects suffered from epigastric pain, classified into 55.2% with severe epigastric pain and 44.8% with moderate epigastric pain. In the study by Hu et al (The Hongkong Index of dyspepsia), 58.5% were found with epigastric pain.[23] In the study by Lelosutan at Dr. Cipto Mangunkusumo General National Hospital, Jakarta, epigastric pain was found in 36.6% of cases.[12] This study was performed among patients with ulcer like dyspepsia, where the dominant symptom is epigastric pain. Thus, all of the patients (100%) were found with epigastric pain.

Heartburn was found in 70.2% of the patients, while 29.8% were found without it. The study by Hu et al found 18.5% with heartburn.[23] The study by Juwanto at Dr. Cipto Mangunkusumo General National Hospital found heartburn/pyrosis among 65.64%.[17] Lelosutan found heartburn in 80%.[12] Marshall et al found this symptom in 78%.[22] The difference in findings is due to different inclusive criteria. This subjective symptom is

a unique symptom of gastroesophageal reflux disease (GERD), where there are unique symptoms of retrosternal pain or burning sensation in the chest surging towards the neck and regurgitation, which often occur following meals and often occur simultaneously or together with epigastric pain, causing this condition to be commonly thought to be dyspeptic syndrome.[4,7,9,10,18,24,25]

The subjective symptom of nausea is found in 80.6% in this study. The study by Hu et al found nausea in 46.2%.[23] Lelosutan found nausea in 33.3% at Dr. Cipto Mangunkusumo General National Hospital, Jakarta.[12] Marshall found nausea in 46%.[22] We could hereby see that in this study there is a greater prevalence of nausea compared to that in other studies. This is in line with the finding that EGD discovered not only poor esophagitis, but in line with reference, that GERD is sometimes accompanied by dyspeptic syndrome.[12-15]

In this study, vomiting was found in 14.9%, while the remaining 85.1% did not. The study by Hu et al found 20% vomiting. Marshall found vomiting in 36% of cases.[22]

Bloating is found in 74.6% cases in this study, while the remaining 25.4% were not found with bloating. Such finding is similar to that obtained by Hu et al, who found bloating in 76.9% of cases.[23] Lelosutan, in a study at Dr. Cipto Mangunkusumo General National Hospital, Jakarta, found bloating in 46.6%.[12] Such findings are in line with references that state that esophagitis is often accompanied by symptoms of dyspepsia.[12-15] This is also in line with the findings from EGD that did not find poor esophagitis.

Thus, the clinical approach of dyspeptic patients need to be carefully performed, with history taken to determine the most dominant dyspeptic symptom, as well as its intensity and duration. Physical examination should be performed to find "danger signs" such as severe vomiting, fever, hematemesis, anemia, jaundice, or loss of weight as well as organomegaly.[7,9,10,18,24,25] Organic diseases that often cause dyspepsia are gastroduodenal ulcer, gastroesophageal reflux disease and gastric cancer.[9,10,16,18,20,24,25]

In gastroesophageal reflux disease, there are unique symptoms of retrosternal pain or burning sensation in the chest surging towards the neck and regurgitation, which often occur following meals and often occur simultaneously or together with epigastric pain, causing this condition to be commonly thought to be dyspeptic syndrome.[4,7,9,10.18,24,25] Over half of patients with complaints of dyspepsia are found with overlapping symptoms (42.7%), heartburn (24.7%), or epigastric pain (32.6%), which often makes it difficult to differentiate dyspepsia from gastroesophageal reflux disease (GERD).[4,5,7,9] Among patients who were diagnosed with peptic ulcer, 28% come with a complaint of heartburn, while among patients with complaints of epigatric pain, 9% were found with peptic ulcer and 14% were found with esophagitis.[10,11] After calculating the dyspepsia score, 68.7% were found with mild dyspepsia and 31.3% with moderate dyspepsia.

From chi-square bivariant analysis to determine the correlation between subjective symptoms of dyspepsia and endoscopic findings of GERD, there was a statis-tically significant correlation between the subjective symptom of severe epigastric pain ($p = 0.080 < 0.1$) and absence of bloating ($p = 0.055 < 0.1$) with endoscopic findings of GERD, while other symptoms such as heartburn, nausea, and vomiting did not demonstrate a statistically significant correlation ($p < 0.1$). This means that subjective symptoms specific for an endoscopic diagnosis of GERD are severe epigastric pain and absence of bloating. In this study, the presence of severe epigastric pain and absence of ulcer like dyspepsia could serve as a clinical means to diagnose esophagitis.

In gastroesophageal reflux disease, there are unique symptoms of retrosternal pain or burning sensation in the chest surging towards the neck, and regurgitation, which often occur following meals and often occur simultaneously or together with epigastric pain, causing this condition to be commonly thought to be dyspeptic syndrome.[4,7,9,10.18,24,25] Over half of patients with complaints of dyspepsia are found with overlapping symptoms (42.7%), heartburn (24.7%) or epigastric pain (32.6%), which often makes it difficult to differentiate dyspepsia from gastroesophageal reflux disease (GERD).[4,5,7,9]

The clinical approach of dyspeptic patients need to be carefully performed, with history taken to determine the most dominant dyspeptic symptom, as well as its intensity and duration. Physical examination should be performed to find "alarm symtoms" such as severe vomiting, fever, hematemesis, anemia, jaundice or loss of weight as well as organomegaly.[7,9,10,18,24,25] In addition, the development of dyspeptic symptoms in patients less than 45 years of age poses a higher risk of organic disease. If the factors mentioned above are not found, dyspepsia treatment may be administered based on the most dominant symptom for 2 to 4 weeks. If there is no response, conduct further evaluation to eliminate

organic abnormalities.[9-11,18,19,24-28]

Thus, we should be more alert of subjective symptoms of severe epigastric pain in ulcer like dyspepsia, since such symptom is not only a symptom of dyspepsia, but should also consider the possibility of GERD.

Based on this study, it was found that from the two statistical tests performed (tests to determine the diffe-rence of 2 means/t-test), no significant correlation was found between dyspepsia score and endoscopic findings of GERD, with $p = 0.725$ ($p > 0.1$). Thus, we could conclude from this study that dyspepsia score is not correlated with endoscopic findings.

CONCLUSION

1. The proportion of gastroesophageal reflux disease (GERD) among patients with ulcer like dyspepsia post empirical treatment who came to seek medical attention at the outpatient clinic of the Department of Internal Medicine and the outpatient clinic of the Division of Gastroenterology of Dr. Cipto Mangunkusumo General National Hospital, Jakarta, was 59.7%.
2. Specific subjective symptoms for GERD among ulcer like dyspepsia are severe epigastric pain with the absence of bloating.
3. Most cases of ulcer like dyspepsia were found with esophagitis using endoscopy.
4. The degree of dyspepsia is not correlated with the results of esophagogastroduodenoscopy (EGD).

SUGGESTION

1. Good and careful history taking directed to patients with symptoms of ulcer like dyspepsia could be used as the basis of clinical diagnosis of GERD (esophagitis).
2. We should be alert for the presence of GERD (esophagitis) among patients with ulcer like dyspepsia with severe epigastric pain with absence of bloating.

REFERENCES

1. Fisher RS, Parkman HP. Management of non ulcer dyspepsia. N Engl J Med 1998; 339:1376–81.
2. Talley NJ., Review article: Dyspepsia: how to manage and how to treat? aliment pharmacol ther 2002; 16:95-104.
3. Talley NJ. Functional dyspepsia. In: Drossman D, Corazziari E, Talley NJ, Eds. The functional gastrointestinal disorders, 2nd. Degnon Associates 2000:299-327.
4. Jones R, Lydeard S. Prevalence of symptoms of dyspepsia in the community. Br Med J 1989; 289:30-2.
5. Djojoningrat D. Dispepsia fungsional. Dalam: Rani AA, Manan C, Djojoningrat D, Simadibrata M, Makmun D, Abdullah M, Syam AF (editor). Dispepsia, sains dan aplikasi klinik. Pusat Informasi dan Penerbitan Bagian Ilmu Penyakit Dalam FKUI. Jakarta 2002.p.51-9.
6. Rani AA. Sindrom dispepsia. Dalam: Rani AA, Sumodiharjo S, Setiati S, Simadibrata M, Mansjoer A (editor). Sindrom dispepsia, diagnosis dan penatalaksanaan dalam praktek sehari-hari. Pusat Informasi dan Penerbitan Bagian Ilmu Penyakit Dalam FKUI/RSUPN-CM 1999.p.1-5.
7. Bommel VM, Numans ME, Wit NJ, Stalman WAB. Consultations and referrals for dyspepsia in General Practice a One Year Database Survey. Postgrad Med J 2001; 77:514-8.
8. Melleney EM, Willoughby. Audit of a nurse endoscopist based one stop dyspepsia clinic. Postgrad med J 2002; 78:161-4.
9. Spiegel B, Vakil NB. Dyspepsia management in primary care: A decision analysis of competing strategies. Gastroenterology 2002; 122:1270-85.
10. Chiba N, Sinclair P, Ferguson R A. Treating *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment–*Helicobacter pylori* positive (CADET–*Hp*) Randomized controlled trial. Br Med J 2002; 324:1012–6.
11. Talley NJ, Bytzer P, Holtmann G. Management of uninvestigated and functional dyspepsia: A working party report for the world congresses of gastroenterology 1998. Aliment Pharmacol Ther 1999; 13:1135-48.
12. Lelosutan S. Peranan derajat keasaman lambung dan tonus sfinkter esofagus bawah terhadap esofagitis pada dispepsia. Laporan akhir penelitian. Skripsi di bagian Ilmu Penyakit Dalam FKUI. Jakarta 1998:1-38.
13. Manan C, Penyakit refluks gastroesofageal-esofagitis. Subbagian gastroenterologi, Bagian Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia/RSUPN Cipto Mangunkusumo. Jakarta 2002.p.1-7.
14. Spechler ST. Gastroesofageal reflux disease and its complication. In: Grendell JH, McQuaid KR, eds. Diagnosis and treatment in gastroenterology. Stamford, Connecticut. Prentice-Hall International Inc 1996; 11.p.245-59.
15. Richter JE. Motility disorders of the esophagus In: Yamada T, Alpers DH, Powell DW, Owyang C, Silverstein FE, eds. Textbook of gastroenterology vol. 1. 2nd Ed, Philadelphia. J.B. Lippincott Company 1995.p.1174–1239.
16. Simadibrata M. Helicobacter pylori pada gastropati hipertensi portal. Laporan akhir penelitian. Skripsi di bagian Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia. Jakarta 1991.p.7–9.
17. Juwanto. Nilai diagnostik pemeriksaan esofagogram barium dan tes bernstein pada esogfagitis. Laporan akhir penelitian Skripsi di bagian Ilmu Penyakit Dalam FKUI. Jakarta 2000.p.1-28.
18. Robinson M. Dyspepsia: Challenges in diagnosis and selection of treatment. Clinical therapeutics. 2001; 23:1130–44.
19. American gastroenterological association medical position statement. Evaluation of dyspepsia. gastroenterology 1998; 114:579-95.
20. McQuaid KR. Dyspepsia and non ulcer dyspepsia. In: grendell JH, McQuaid KR, eds. Diagnosis and treatment in gastroenterology. Stamford, Connecticut. Prentice-Hall International Inc 1996.p.308-18.
21. Syam AF, Rani AA, Abdullah M. Prevalence of reflux esoph-

agitis, Barrett's esophagus and esophageal cancer: evaluation by endoscopy. Dalam: Achmad H, Rudijanto A, Arsana PM (editor). Konas XI PGI, PEGI dan PIN XII PPHI. Batu, Malang 3–7 Juli 2003.p.II–11.
22. Koek GH, Tack J, Sifrim D, Herut T, Janssens J. The Role of acid and duodenal gastroesophageal reflux in symptomatic GERD. Am J Gastroenterol 2001; 96:2033-9.
23. Hu WHC, Lam KF, Wong YH, Lam CL, Hu WM, Lai KC, Wong BCY et al. The Hongkong index of dyspepsia: A validated symptom symptom severity questionnaire for patients with dyspepsia. J Gastroenterol Hepatol 2002; 17:545- 51.
24. Bytzer P, Talley NJ. Dyspepsia. Ann Intern Med 2001; 134: 815-22.
25. Talley N J. Dyspepsia management in the millennium: The death of test and treat? Gastroenterology 2002; 122:1521-25.
26. Simadibrata M. Patofisiologi peran hipersekresi asam dan pepsin pada sindrom dispepsia. Dalam: Rani AA, Manan C, Djojoningrat D (editor). Dispepsia, sains dan aplikasi klinik. Pusat Informasi dan Penerbitan Bagian Ilmu Penyakit Dalam FKUI. Jakarta. 2002.p.41-50.
27. Peghini PL, Katz PO, Bracy NA, Castell DO. Nocturnal Recovery of gastric acid secretion with twice-daily dosing of proton pump inhibitors. Am J Gastroenterol. 1998; 5:763–7.
28. Ofman JJ. What have we learned from recent dyspepsia trials? Current gastroenterology report 2000; 2:471-7.