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Original Article

Reflux esophagitis in children with feeding problems: A preliminary study

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Abstract

Background Untreated gastroesophageal reflux can cause reflux esophagitis, a condition characterized by damage to the esophageal mucous layer due to exposure to caustic gastric contents. Manifestation of esophagitis in young children include feeding problems, irritability, and back-arching. Persistent esophagitis may cause growth failure, gastric bleeding, and anemia. Reflux esophagitis should be considered an etiology of feeding problems, especially in children with a history of gastroesophageal reflux during infancy.

Objective The purpose of this study is to determine the prevalence of reflux esophagitis in children with feeding problems.

Methods A cross-sectional study was done in November 2007 to April 2008. Children under 5 years of age with feeding problems and a history of regurgitation or vomiting started from age 6 months or more underwent endoscopy and biopsy examinations. Reflux esophagitis was diagnosed based on the Los Angeles classification of endoscopic examination.

Results Reflux esophagitis was diagnosed in 18 of 21 children with feeding problems and a history of regurgitation or vomiting. Most subjects were boys aged 12 to 36 months. Feeding problems has lasted for more than 6 months, regurgitation or vomiting for more than 12 months, and suffered from mild malnutrition. Vomiting was observed to be a common symptom in children with reflux esophagitis.

Conclusion The prevalence of reflux esophagitis in children with feeding problems and a history of regurgitation or vomiting started from age $\geq$ 6 months is high, therefore it will influence treatment. **[Paediatr Indones. 2010;50:284-90]**.

Keywords: *feeding problems, reflux esophagitis, regurgitation, vomitus*

Gastroesophageal reflux is defined as the involuntary passage of gastric contents into the esophagus.[1-5] Untreated gastroesophageal reflux can cause reflux esophagitis, a condition in which the esophageal mucous layer is damaged by exposure to caustic gastric contents.[6-11] Reflux esophagitis has been reported in approximately 2-5% of the population.[5] Regurgitation is a specific and common symptom of gastroesophageal reflux. Other symptoms of esophagitis in infants include feeding problems, irritability, and back-arching. Persistent esophagitis can cause growth failure, hematemesis, melena, and anemia.[4,5,10,13] Among children who are clinically suspected to suffer from reflux esophagitis, 15-80% are confirmed to have this disorder, while 0.1-3% have Barrett's esophagus, and 6-13% have refractory gastroesophageal reflux requiring surgery.[5,12,14] Reflux esophagitis is diagnosed based on clinical symptoms, endoscopy, and biopsy.[13,15,16]

A feeding problem is defined as the failure to consume an adequate amount of food. It is a serious issue in children because of its impact on growth and development. Twenty-five to forty percent of children

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under 5 years of age experience feeding problems.[20-22] There are multiple etiologies associated with feeding problems, and reflux esophagitis should be considered one of them, especially in children with a history of gastroesophageal reflux during infancy. Unfortunately, there is still little data available about reflux esophagitis in children with feeding problems. One study reported 17% (121 of 700) of children with feeding problems had reflux esophagitis in the absence of other problems.[23]

Until now there has been no study to determine the prevalence of reflux esophagitis in children with feeding problems in Indonnesia. Therefore, we proceeded to study the prevalence of reflux esophagitis in children under 5 years old with feeding problems and who had regurgitation or vomiting at age $\geq$ 6 months.

Methods

A cross-sectional study was conducted at the Pediatric Gastrohepatology and General Pediatric Outpatient Clinics, Cipto Mangunkusumo Hospital, Jakarta from November 2007 to April 2008. We included children aged one to five years with feeding problems (refusal to eat or irritable during mealtimes) lasting at least one month and with a history of regurgitation or vomiting at the age of $\geq$ 6 months. Informed consent was obtained from parents. We excluded children with severe malnutrition and diseases requiring special treatment. Also excluded were patients using certain medications (cisapride, domperidone, metoclopramide, histamine-2 antagonist, proton pump inhibitors, and theophylinne) in the 2 weeks prior to the study, due to concerns about their effects gastroesophageal reflux. Other exclusion criteria were congenital abnormalities, cerebral palsy and other diseases impacting the feeding process, history of esophageal surgery, and conditions contraindicated to endoscopy. This study was approved by the Research Ethics Committee, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital.

A consecutive sampling was done with sample size calculation based on the formula for single proportion, using the following parameters: estimated prevalence of reflux esophagitis in children with feeding problem (17%),[23] a variation of this prevalence around 10%, standard deviation (σ) = 1.96, and a 95% confidence interval. The minimal sample size was calculated to include 54 children, however, only 21 children were available for our study.

Children that met the inclusion criteria were asked for data including identity, duration of feeding problem, duration of regurgitation, other symptoms of reflux esophagitis, body weight and height. All subjects underwent endoscopy and biopsy by a Pediatric Gastroenterology consultant. Endoscopy was performed at Cipto Mangukusumo Hospital using a forward viewing Olympus® video endoscope, CLV-10 model. The endoscopic findings of the esophagus were classified according to Los Angeles classification for reflux esophagitis. REF (**Figure 1**). Biopsies were taken from the distal esophagus, at least 2 cm above the lower esophageal sphincter using biopsy forceps. Biopsy specimens were immersed in 10% formalin and submitted to routine histological processing, stained with hematoxylin & eosin (HE) at the Pathology Anatomy Department of Cipto Mangunkusumo Hospital. Specimens were examined by a pathology consultant. The histology findings were graded according to Knuff & Leape classification as recommended by the European Society for Pediatric Gastroenterology Hepatology and Nutrition REF (**Table 1**).

Reflux esophagitis was graded based on the Los Angeles classification in endoscopic assessment.[17] Duration of regurgitation or vomitus was defined as the length of time between the first regurgitation or vomitus and the last regurgitation or vomitus or the time of the study. All data were analyzed using a *Statistical Program for Social Science* (SPSS).

Table 1. Histology classification for reflux esophagitis (base on Knuff & Leape)[2]

Grade	Histology criteria
0	Normal
IA	Basal zone hyperplasia
IB	Elongated stromal papillae
IC	Vascular ingrowth
II	Polymorphonuclear cell in the epithelium, lamina propria or both
III	Polymorphs with ephitelial defect
IV	Ulceration
V	Abnormal columnar epithelium

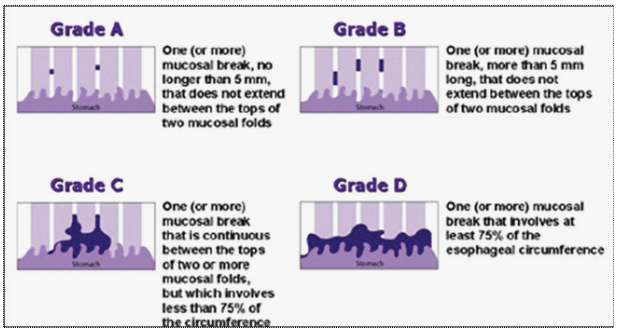

Figure 1. Los Angeles classification on endoscopy assessment for reflux esophagitis.[17]

Results

Subject characteristics

This study involved 21 children with mean age of 28 months, ranging from 12 months to 54 months. All children had experienced regurgitation or vomiting within a few days after birth until ≥ 6 months. Ten of 21 children still had these symptoms when the study was performed. Characteristics of the subjects' are shown in **Table 2**.

Table 2. Subject characteristics (n=21)

Variable		Total
Age	12 - <36 months	15
	36 - 60 months	6
Sex	Boy	13
	Girl	8
Feeding problem	Refusal to eat	21
	Irritable during mealtimes	21
Duration of feeding problem	1 - < 3 months	5
	3 - 6 months	4
	> 6 months	12
Nutritional status	Under nutrition	13
	Good nutrition	8
Other symptoms	Vomitus	14
	Back arching	6
	Hematemesis	2
	Melena	2
	Pallor	1
Duration of regurgitation or vomiting	6 -12 months	9
	>12 - 36 months	9
	>36 - 60 months	3

Reflux esophagitis in children with feeding problems

Based on endoscopic examination, varying degrees of esophageal mucosal damage were observed in 18 of 21 children. The remaining 3 children had no esophageal mucosal damage. Therefore, the prevalence of reflux esophagitis in children with feeding problems who had regurgitation or vomitus at ≥ 6 months old was 18 of 21 children (95% CI 70 to 100). According to Los Angeles classification, most of the children had reflux esophagitis grade C (6/18) and grade D (6/18). The remaining children had reflux esophagitis grade A (2/18) and grade B (4/18). No other esophageal abnormalities were observed by endoscopy in all subjects. Subjects' reflux esophagitis grades were analysed according to duration of feeding problems and are shown in **Table 3**. Interestingly, all children with grade D reflux esophagitis had feeding problems for more than 6 months and regurgitation or vomitus for more than 12 months. Children with feeding problems for less than 6 months had reflux esophagitis of grades A, B, and C but not grade D.

Distribution of reflux esophagitis grades according to duration of regurgitation or vomiting is shown in **Table 4**. Subjects having regurgitation or vomitus from 6-60 months, had varying grades (A-D), but in children with regurgitation or vomiting lasting less than 12 months, we observed no grade D reflux esophagitis.

Pathology examination results

Only 14 children could be assessed pathologically due to non-representative esophageal biopsy specimens.

Table 3. Distribution of reflux esophagitis according to duration of feeding problem

Duration of	Reflux esophagitis (Los Angeles classification)					
feeding problem	No esophagitis	Grade A	Grade B	Grade C	Grade D	Total
1- <3 months	3	0	1	1	0	5
3-6 months	0	1	2	1	0	4
> 6 months	0	1	1	4	6	12
Total	3	2	4	6	6	21

Table 4. Distribution of reflux esophagitis according to duration of regurgitation or vomitus

Duration of regurgitation	Reflux esophagitis (Los Angeles classification)					
or vomitus	No esophagitis	Grade A	Grade B	Grade C	Grade D	Total
6-12 months	2	1	2	4	0	9
>12-36 months	1	1	2	1	4	9
>36-60 months	0	0	0	1	2	3
Total	3	2	4	6	6	21

Table 5. Distribution of reflux esophagitis degrees based on endoscopy and pathology anatomy examination

Reflux esophagitis (Endoscopic examination)	Reflux esophagitis (Pathology examination)				
	Grade 1C	Grade 2	Grade 3	Grade 5	Total
No esophagitis (normal)	0	0	0	0	0
Grade A	0	0	0	0	0
Grade B	1	1	1	1	4
Grade C	0	3	2	1	6
Grade D	0	0	2	2	4
Total	1	4	5	4	14

We observed varying degrees of reflux esophagitis based on Knuff & Leape classification in those 14 children. Reflux content was found in 2 of the biopsy specimens. No other abnormalities were found in the esophageal specimens. We found that the level of esophageal damage observed by endoscopy did not always correlate with the level of the esophageal damage that found by pathology examination. The distribution of reflux esophagitis grades based on endoscopy vs pathology examination in those 14 children is shown in **Table 5**.

Discussion

A study on preschool children (4-6 years old) with feeding problems in Jakarta showed most children (79.2%) had feeding problems lasting longer than 3 months, with 45.5% of the subjects having mild to moderate malnutition.[22] The characteristics of those subjects were similar to those in our study. Previous studies on gastroesophageal reflux have shown a wide range of prevalence of reflux esophagitis in children with feeding problems clinically suspected of having reflux esophagitis (15-80%). In those studies, 0.1-3% had Barrett's esophagus and 6-13% needed surgical intervention.[5,12,14] A study of 33 children with suspected gastroesophageal reflux disease in India showed reflux esophagitis in 26 children (78.8%).[51] In our study, there were no children with Barrett's esophagus and none requiring surgical intervention. Prevalence of reflux esophagitis in our study is higher than in the studies mentioned above due to the unspecific and wide variety of subjects with feeding problems included in those studies.

We diagnosed reflux esophagitis by endoscopic examination using the Los Angeles classification for grading severity. Our study showed reflux esophagitis in 18 of 21 children with feeding problems who had regurgitation or vomiting at aged 6 months or more, with 95% confidence interval of 70-100%. These statistics indicate that with 95% confidence, 70-100% of children with feeding problems and a history of regurgitation or vomiting at aged $\geq$ 6 months have reflux esophagitis.

In a study of 700 children under 10 years of age with severe feeding problems, Rommel et al[23] found that 33% suffered from reflux esophagitis, but only 17% (121/700) had this condition in the absence of other diseases. That study focused on finding the etiology of feeding problems. Reflux esophagitis was one of the etiologies found, but it was not the main focus of diagnosis. All subjects in that study were referred to them because of severe feeding problems. Endoscopy and biopsy were performed only in cases where strongly indicated. By contrast, our study focused on finding the prevalence of reflux esophagitis in children with feeding problems. Our criteria for

inclusion were more specific than Rommel et al. We included children with feeding problems who had history of regurgitation or vomiting at ≥ 6 months of age. These subjects have greater tendency to develop reflux esophagitis due to persistent gastroesophageal reflux. In addition, we performed endoscopy and biopsies on all subjects in order to diagnose reflux esophagitis. These differences may explain the contrasting results in the two studies.

Our results showed that children with grade D reflux esophagitis had feeding problems for more than 6 months (**Table 3**) and regurgitation or vomiting for more than 12 months (**Table 4**). This result indicates that the duration of feeding problems and duration of regurgitation or vomiting may influence the degree of reflux esophagitis (based on endoscopy findings), although these results were not statistically analyzed. It is important to determine the risk factors that influence the degree of reflux esophagitis because they will help determine the type and duration of therapy given. [4]

The data in **Table 4** also indicate that regurgitation or vomiting during infancy may be a risk factor for reflux esophagitis. This observation is consistent with a study by Gold BD,[35] who suggests that in children with symptomatic gastroesophageal reflux at 1 year of age, the condition tends to continue and lead to reflux esophagitis even until adulthood. Optimal management should be given to every baby with gastroesophageal reflux so that this problem will not be lifelong.

Nelson et al[26] performed a 1-year, cohort study in babies aged 6-12 months experiencing regurgitation. They found feeding problems in more babies with regurgitation compared to the control group. Feeding problems included refusal to eat, meal times of greater than 1 hour, and parental reports of upset children during meal time. Our study subjects were also experiencing these feeding problems, as well as regurgitation or vomiting at ≥ 6 month of age.

Reflux esophagitis can cause pain upon swallowing food, which makes the child refuse to eat. Hyman[32] found that the neurological development in infants with esophageal exposure to gastric acid can be affected, causing them to experience motility disorders and hypersensitivity to pain, even without tissue damage. Therefore, a child with gastroesophageal reflux may feel that food consumption is associated with discomfort, thus avoiding eating. This explanation may account for the 3 children in our study who had feeding problems in the absence of esophageal mucosal damage observed by endoscopy.

Another study evaluating feeding problems in infants with reflux esophagitis found that these children experience oral motor dysfunction, episodes of dysphagia, feeding refusal, and unpleasant feeding experiences for either mother or infant.[33] These findings were supported by another study in which children with reflux esophagitis more often experienced feeding problems and oral sensory and motor disorders.[52]

We observed that endoscopic findings did not always correlate with pathologic examinations, possibly because specimens from some subjects could not be examined microscopically, thus affecting the sample size of the study. However, Vandenplas[53] found that the degree of reflux esophagitis found by microscopic examination was influenced by patchy esophageal lesions. On the other hand, some studies point out the importance of biopsy and microscopic examination in order to support the diagnosis of reflux esophagitis and rule out other abnormalities of the esophagus.[13,15,16]

We were unable to increase the sample size, even after extending the study duration from 6 months to 1 year. Also, some children who fulfilled the inclusion criteria were not enrolled in the study because their parents refused to consent to endoscopic and biopsy procedures. In addition, biopsy specimens from 7 subjects could not be microscopically assessed for technical reasons, further reducing our sample size. Since we included subjects with both feeding problems and regurgitation or vomiting at ≥ 6 months of age, there was a selection bias because these children have a greater probability of having reflux esophagitis than those with feeding problems alone.

We conclude that the prevalence of reflux esophagitis in children with feeding problems and regurgitation or vomiting ≥ 6 months of age is 18 of 21 children. Our findings suggest that we should consider reflux esophagitis to be an etiology of feeding problems, especially in children experiencing regurgitation or vomiting at ≥ 6 months of age. Further studies are needed to understand the influence of other gastrointestinal organs in reflux esophagitis.

References

1. Hegar B, Vandenplas Y. Gastro-oesophageal reflux in infancy. J Gastroenterol Hepatol. 1999;14:13-9.
2. Vandenplas Y. Reflux esophagitis in infants and children: a report from the working group on gastroesophageal reflux disease of the European Society of Paediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 1994;18:413-22.
3. Hegar B. Refluks gastro-esofagus pada anak. Presented at 12th National Congress of Child Health and 11th Asean Pediatric Federation Conference; 2002 June 30- July 4; Bali, Indonesia.
4. Vandenplas Y, Hegar B. Diagnosis and treatment of gastro-oesophageal reflux disease in infants and children. J Gastroenterol Hepatol. 2000;15:593-603.
5. Salvatore S, Vandenplas Y. Gastro-oesophageal reflux disease and motility disorders. Best Pract Res Clin Gastroenterol. 2003;17:163-79.
6. Vandenplas Y, Hegar B. Esophagitis ini children. In: Trihono PP, Pudjiarto PS, Syarif DR, Hegar B, Gunardi H, Oswari H, et al, editors. Hot topics in pediatrics II. Jakarta: Balai Penerbit FKUI; 2002. p. 74-83.
7. Orlando RC. Reflux esophagitis. In: Yamada T, editor. Textbook of gastroenterology. 2nd ed. Philadelphia: Lippincott Company; 1995. p. 1214-41.
8. Hamilton SR. Reflux esophagitis and Barrett esophagus. In: Goldman H, Appelman HD, Kaufman N, editors. Gastrointestinal pathology. Baltimore: Williams & Wilkins; 1990. p. 11-29.
9. Hogan WJ, Dodds WJ. Gastroesophageal reflux disease (reflux esophagitis). In: Wickland E, editor. Gastrointestinal disease. 4th edition. Philadelphia: WB Saunders; 1989. p. 594-616.
10. Chu AS. Esophagitis. [cited 2004 Sep 9]. Available from: http://www.emedicine.com.
11. Spechler SJ. Gastroesophageal reflux disease and its complications. In: Grendell JH, McQuaid KR, Friedman SL, editors. Current diagnosis and treatment in gastroenterology. USA: Appleton and Lange; 1996. p. 245-60.
12. El-Serag HB, Bailey NR, Gilger M, Rabeneck L. Endoscopic manifestations of gastroesophageal reflux disease in patients between 18 months and 25 years without neurological deficits. Am J Gastroenterol. 2002;97:1635-9.
13. Hegar B, Firmansyah A. Diagnosis refluks gastroesofagus pada anak. Maj Kedokt Indones. 1999;49:70-4.
14. Salvatore S, Hauser B, Vandenplas Y. The natural course of gastro-oesophageal reflux. Acta Paediatr. 2004;93:1063-9.
15. Aw M. Pediatric gastro-oesophageal reflux disease (GERD) - a relook at a common problem. Singapore: National University hospital; 2003.
16. Vieira MC, Pisani JC, Mulinari RA. Diagnosis of reflux esophagitis in infants: histology of the distal esophagus must complement upper gastrointestinal endoscopy. J Pediatr. 2004;80:197-202.
17. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45:172-80.
18. Samsudin. Penyebab dan tata laksana kesulitan makan. Presented at 2nd Periodic Scientific Meeting Indonesian Pediatric Society; 1992; Yogyakarta, Indonesia.
19. Palmer S, Horn S. Feeding problem in children. In: Palmer S, Ekvall S, editors. Pediatric nutrition in developmental disorders. Springfield: Charles C. Thomas publisher; 1978. p. 107-29.
20. Bonnin AC. Feeding problem of infant and toddlers. Can Fam Physic. 2006;52:1247-51.
21. Nasar SS. Masalah makan pada anak. In: Pulungan AB, Hendarto A, Hegar B, Oswari H, editors. Nutrition growth development. Jakarta: Indonesian Pediatric Society; 2006. p. 53-68.
22. Amirani DF. Kesulitan makan pada anak prasekolah usia 4-6 tahun: prevalens, karakteristik, antropometris dan keluarga [thesis]. Jakarta: University of Indonesia; 1998.
23. Rommel N, Meyer AM, Feenstra L, Wauters GV. The complexity of feeding problems in 700 infants and young children presenting to a tertiary care institution. J Pediatr Gastroenterol Nutr. 2003;37:75-84.
24. Hegar B, Boediarso A, Firmansyah A, Vandenplas Y. Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants. World J Gastroenterol. 2004;10:1795-7.
25. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. Arc Pediatr Adolesc Med. 1997;151:569-72.
26. Nelson SP, Chen EH, Syniar GM, Christoffel KK. One-year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatrics. 1998;102:1-4.
27. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during childhood. Arc Pediatr Adolesc Med. 2000;154:150-4.
28. Mittal RK. Pathophysiology of gastroesophageal reflux: motility factors. J Gastroenterol. 2003;38:7-12.
29. Davidson GP, Omari TI. Pathophysiological mechanisms of gastroesophageal reflux disease in children. Gastroenterology. 2001;3:257-62.

30. Yoshida N, Yoshikawa T. Defense mechanism of the esophageal mucosa and esophageal inflammation. J Gastroenterol. 2003;38:31-34.
31. Orel R, Marcovic S. Bile in the esophagus: a factor in the pathogenesis of reflux esophagitis in children. J Ped Gastroenterol Nutr. 2003;36:172-74.
32. Hyman PE. Gastroesophageal reflux: one reason why baby won't eat. J Pediatr. 1994;125:S103-9.
33. Mathisen B, Worrall L, Masel J, Wall C, Shepherd RW. Feeding problems in infants with gastro-oesophageal reflux disease: A controlled study. J Paediatr Child Health. 1999;35:163-9.
34. Martin JA, Pratt N, Kennedy JD, Ryan P, Ruffin R, Miles H, et al. Natural history and familial relationships of infant spilling to 9 years of age. Pediatrics. 2002;109:1061-7.
35. Gold BD. Gastroesophageal reflux disease: could intervention in childhood reduce the risk of later complications? Am J Med. 2004;117:S23-7.
36. Gold BD. Review article: epidemiology and management of gastro-oesophageal reflux in children. Aliment Pharmacol Ther. 2004:19;22-7.
37. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations for the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroentrol Nutr. 2001;32(Suppl 1):S1-31.
38. Bronner MP. Inflammatory disorders of the esophagus. Available from: http:// www.google.com. Cited 2004 Dec 9.
39. Esposito S, Valente G, Zavallone A, Guidali P, Rapa A, Oderda G. Histological score for cells with irregular nuclear contour for the diagnosis of reflux esophagitis in children. Hum Path. 2004;35:96-100.
40. Cohen RC, O'Loughlin EV, Davidson GP, Moore DJ, Lawrence DM. Cisapride in the control of symptoms in infants with gastroesophageal reflux: a randomized, double-blind, placebo-controlled trial. J Pediatr. 1999;134:287-92.
41. DeVault KR, Castell DO. Update guidelines for diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 1999;94:1434-42.
42. Zimmermann AE, Walters JK, Katona BG, Souney PF, Levine D. A review of omeprazole use in the treatment of acid-related disorders in children. Clin Ther. 2001;23:660-79.
43. Israel DM, Hassall E. Omeprazol and other proton inhibitors: pharmacology, efficacy and safety, with special reference to use in children. J Pediatr Gastroenterol Nutr. 1998;27:568-79.
44. Karjoo M, Kane R. Omeprazol treatment of children with peptic esophagitis refractory to ranitidine therapy. Arch Pediatr Adolesc Med. 1995;149:267-71.
45. Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, et al. A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med. 1995;333:1106-10.
46. Madrazo-de la Garza A, Dibildox M, Vargas A, Delgado J, Gonzalez J, Yanez P. Efficacy and safety of oral pantoprazol 20 mg given once daily for reflux esophagitis in children. J Pediatr Gastroenterol Nutr. 2003;36:261-5.
47. Christensen ML, Gold BD. Clinical management of infant and children with gastroesophageal reflux disease: disease recognition and therapeutic options. Proceedings of American Society of Health-system Pharmacist Midyear Clinical Meeting; 2002 Dec 9; Atlanta, Georgia. p.1-11.
48. Gibson RS. Principles of nutritional assessment. New York: Oxford university press; 1990. p. 163-86.
49. Samsudin, Soedibjo S. Penilaian keadaan gizi dan pertumbuhan: cara, kegunaan, dan keterbatasan. In: Samsudin, Nasar SS, Sjarif DR, editor. Masalah gizi ganda dan tumbuh kembang anak. Proceedings of 35th Pediatric Continuing Professional Development. Jakarta: Indonesian Pediatric Society; 1995. p. 149-58.
50. Wikipedia: the free encyclopedia. [cited 2005 Sep 9]. Available from: http://www.wikipedia.org.
51. Dadhich SK, Yachha SK, Srivastava A, Sikora SS, Pandey R. Endoscopic and histologic evaluation of reflux esophagitis. Indian Pediatr. 2000;37:1111-4.
52. Drent LV, Pinto EALC. Feeding disorders in children with gastro-esophageal reflux disease. Pro Fono. 2007;19:59-66.
53. Vandenplas Y. Reflux esophagitis: biopsy or not? J Pediatr Gastroenterol Nutr. 1996;22:326-7.