ANNALS OF GASTROENTEROLOGY 2004, 17(2):173-180

Original article

Dyspepsia in childhood. Clinical manifestations and management

K. Spiroglou[1], G. Paroutoglou[2], N. Nikolaides[2], I. Xinias[1], Olga Giouleme[2], G. Arsos[1], Vasiliki Demertzidou[1], N. Eugenides[2]

SUMMARY

Objectives: **In recent studies there is little data regarding functional dyspepsia in childhood. This study aimed to determine the frequency, clinical manifestations and treatment of functional dyspepsia in childhood.**

Methods: **The study sample consisted of 548 children with recurrent abdominal pain (age range: 4-14 years). A standardized questionnaire was used to investigate the symptoms of functional dyspepsia as recorded in similar studies for adults. Baseline laboratory tests were carried out for each patient. Additionally, the severity of clinical manifestations and the presence of accompanying symptoms, which might trigger or exacerbate the condition, were investigated. Prokinetic or acid-reducing drugs were used according to the judgment of the attending pediatrician.**

Results: **Finally 348 children (180 male, 168 female) met the inclusion criteria. Children within severe form of dyspepsia had more frequent nausea ($p<0.0001$), vomiting ($p<0.0001$) and belching ($p<0.0001$), while children with a moderate form of dyspepsia had postprandial fullness ($p<0.002$) and bloating ($p<0.0001$). The frequency of functional dyspepsia was 70.73%. Paleness ($p<0.0001$) was the most frequent symptom in organic dyspepsia whereas epigastric pain was more prevalent in functional dyspepsia ($p<0.007$). As far as the treatment of these patients was concerned, children treated with cisapride responded marginally better than those who received ranitidine.**

Conclusions: **The frequency of functional dyspepsia in childhood reached a percentage of 70%. The majority of patients exhibited mild disease manifestations whereas the most frequent symptoms of the condition were nausea, vomiting, belching, bloating and postprandial fullness. Therapeutically, cisapride seemed to be superior to acid-reducing drugs but in a non significant manner.**

Key words: Dyspepsia, functional dyspepsia, recurrent abdominal painIntroduction

[1]Department of Pediatrics, 3rd Pediatric Clinic, Division of Digestive Diseases and [2]Department of Gastroenterology, Aristotle University of Thessaloniki, Hippocration Hospital, Thessaloniki, Greece

Author for correspondence:

Kleomenis Spiroglou, Associate Professor of Pediatrics, Aristotle University of Thessaloniki, Department of Pediatrics, 3rd Pediatric Clinic, Hippocration Hospital, Greece, Tel.: 0030310274096, Fax: 0030310992981, e-mail: klspirog@med.auth.gr

The most common complaint in children aged 4 to 14 years, is recurrent abdominal pain (RAP), which represents a heterogeneous group, encompassing both organic diseases and functional gastrointestinal disorders[1,2].

A large number of these children report an uncomfortable feeling localized in the upper abdomen and symptoms of dyspepsia, as defined in adults[3,4]. When these symptoms cannot be explained by structural, biochemical or histological abnormalities they are considered to be functional dyspepsia[5].

A review of the recent literature indicates that even though dyspepsia is common in adults, only limited data regarding dyspepsia in children is available. Spiroglou et al[6], in a recent study, found over 50% of their patients, to have functional dyspepsia with the more commonly encountered symptoms being nausea, vomiting, early satiety, awaking from sleep and increased belching. Hyams et al[7], in a prospective study, found, after esophagogastroduodenoscopy and biopsy, 35 out of 56 patients (62.5%) have functional dyspepsia.

The goals of this study were to investigate and record the incidence and clinical manifestations of dyspepsia in

childhood, to evaluate any relationship between primary (functional) and secondary dyspepsia and to clarify the management of these children.

MATERIAL AND METHODS

During a period of about 5 years (June 1996 to June 2001) 528 consecutive children 4 -14 years of age were referred to the outpatient clinic of the 3rd Department of Pediatrics, Division of Digestive Diseases (Aristotle University of Thessaloniki, Greece) with recurrent abdominal pain (RAP). All of them, (271 boys and 257 girls) were included in the study.

Children with organic diseases known to cause dyspeptic symptoms or recently receiving (the previous three months) antibiotics or anti-inflammatory drugs (NSAIDS), as well as children with swallowing difficulties, altered bowel pattern (diarrhea, fecal soiling or constipation) and viral infections in the last three months were excluded from the study.

During the initial consultation, special interest was paid to information regarding the character of abdominal pain (location, duration, nature and frequency). Other questions asked included dyspeptic symptoms for adults as referred to in different reports[3-5]. Any relationship between dyspeptic symptoms with specific events such as fever, blood in the stool or emesis, involuntary weight loss or growth deceleration, anemia, elevated ESR, relief by food, as well as possible relationships with factors (eg. meals, stress, sleep) that could alleviate or precipitate the patient's abdominal pain were sought. Information was compiled by one of the investigators (KS, VD, PG, IX) and was supplied by both the parents and the child. The consultation was completed with questions regarding family history of gastrointestinal disorders, absenteeism from school, death in the family, school problems, overprotective parents, divorce, financial problems and symptoms like headache, migraine, sweating, pallor, dizziness or any strange and unexplained feelings. As, in our experience, many children, especially those of under 6 or 7 years of age could not define which one symptom was more prominent, we used a scale to define the severity of dyspepsia. This scale (Table 1) consisted of a questionnaire, which was a modified version of the Glasgow Dyspepsia Severity Score[8], for the last six months preceding the initial consultation. It tried to evaluate the frequency of abdominal pain (predominant symptom), the number of school or preschool days of absenteeism, the duration and intensity of pain, the presence of nocturnal pain and vomiting. Scores ranged from 0 to 16, with high scores indicating grater severity. According to this scale we divided patients with dyspepsia into three groups: mild (score <6), medium (score 7 - 10) and severe (score >11) forms.

Table 1. Dyspepsia severity score

		Score
Intensity of pain:	Mild	1
	Moderate	2
	Severe	3
Duration of pain:	<15'	1
	15' – 60'	2
	>60'	3
Incidence of pain:	Once every 10 days	1
	2 – 5 times weekly	2
	Every day	3
Nocturnal awakens:	Never	0
	Rarely*	1
	Usually	2
Absenteeism:	Less than one day every week	1
	One day every week	2
	More than one day every week	3
Vomiting:	Never	0
	Rarely**	1
	Usually	2

* at least two times for the last three months

** 2 - 4 times during the last three months

The thorough physical examination was completed with a search of areas of tenderness, palpable stools in the left lower quadrant and amount of stool in the rectal ampulla. The initial evaluation included the use of routine and easily obtainable studies (full blood evaluation, erythrocyte sedimentation rate, aspartate aminotransferase, serum bilirubin, serum albumin, serum amylase, urinalysis, stool for ova and parasites, serum creatinine and electrolytes) for the determination of conditions such as parasitic infections, biliary tract or hepatic diseases, pancreatitis, irritable bowel syndrome or other organic causes of abdominal pain.

If a satisfactory diagnosis, was not obtained additional studies were performed at the discretion of the examining physician. These included breath hydrogen testing for lactose malabsorption, ultrasonography and esophageal 24-hour pH monitoring. Upper gastrointestinal endoscopy to rule out esophagitis, peptic ulcer disease, Helicobacter pylori infection or esophagitis was performed in all children with medium and severe dyspepsia.

Children under seven years of age were hospitalized and examined under general anesthesia, while children older than seven years of age were examined after conscious sedation with midazolam (0.15-0.20 mg/kg, IV) and ketamine hydrochloride (1-2 mg/kg, IV)[6]. In all patients undergoing the procedure, biopsies were taken for CLO test (Delta West Ltd) and routine histology; these comprised one duodenal biopsy, two antral and one or two from the esophagus. The presence of inflammation was judged by the quality and quantity of the cellular infiltrate in the mucosa, using generally accepted criteria[9,10]. Although the presence of Helicobacter pylori infection was also checked in the serum or by CLO test, the final diagnosis was based on histology.

All patients with gross evidence of inflammation in the upper gastrointestinal tract (esophagitis, duodenitis, gastritis, and ulcer) received acid-reducing drugs (ranitidine 5 mg/Kg daily for 4 weeks). Antibiotic therapy (amoxicillin 50 mg/Kg and clarithromycin 15 mg/Kg, daily) was used only for patients with Helicobacter pylori infection. Children with mild Helicobacter pylori negative gastritis and children with normal endoscopic and histologic findings (functional dyspepsia) were treated with promotility drugs (cisapride 0.8 mg/Kg daily in four doses for 6 weeks) or acid reducing drugs (ranitidine) at the discretion of the attending pediatrician.

Patients were observed on return visits at 1, 6 and 12 months. If no return, by telephone contact was made. At 12 months return or telephone contact, a re-evaluation was made for diagnosis and treatment. Additional symptoms, diagnostic studies or treatment changes were noted.

Definitions. *Dyspepsia* was classified as persistent or recurrent abdominal pain and/or discomfort, localized in the upper abdomen for a period of at least three months with normal biochemical tests, imaging investigations and histology findings[11]. Acid regurgitation and/or pain in the chest were considered as *gastroesophageal reflux*[12]. *Irritable bowel syndrome* was classified as any case with the presence of abdominal pain or discomfort which was relieved by defecation and usually associated with a change in stool frequency or consistency (hard – loose), in the absence of demonstrable disease. Frequently it is accompanied with a sense of incomplete evacuation, bloating, straining, urgency and the passage of mucus from the rectum[13].

Statistical analysis. Calculations and statistical analysis were made for all patient symptoms by computer support. Data are present by descriptive statistics. Comparisons between various groups were made by chi-square test. Statistical significance was accepted when $p<0.05$.

RESULTS

a. Diagnostic approach – Clinical presentation

Based on detailed history, clinical examination and basic laboratory work-up, various organic diseases were identified as the cause of RAP in sixty-five (12.31%) children. Ninety-three (17.61%) children had clinical manifestations similar to adult irritable bowel syndrome and 22 (4.16%) additional children with RAP had typical or suspected GOR disease. All the above mentioned children were excluded from the study.

The remaining 348 children (180 males and 168 females, mean age 6.94 ± 2.33 years) fulfilled the diagnostic criteria for dyspepsia and served as the study population. Abdominal pain, being the predominant symptom, was epigastric in location in 132 children and diffuse or periumbilical in 216 (Table 2). Children with epigastric pain were older than those with diffuse abdominal pain (mean age 7.5 ± 2.38 years vs 6 ± 1.98 years, $p<0.0001$). Pain was often combined with nausea, vomiting, anorexia, nocturnal awakening etc.

In relation to severity of dyspepsia (mild, moderate, severe) children with mild dyspepsia suffered more frequently from diffuse abdominal pain (73.6%), in contrast to children with moderate or severe dyspepsia, where epigastric pain was predominant (81.8%, $p<0.001$) (Table 2). Moreover, children with moderate or severe dyspepsia presented higher frequency of nausea ($p<0.0001$), vomiting ($p<0.0001$) and belching ($p<0.0001$), and lower frequency of postprandial fullness ($p=0.002$) and bloating ($p<0.0001$) compared with children with mild dyspepsia. The frequency of the rest of the symptoms did not significantly differ between the two groups (Table 3).

Because of the increased likelihood for secondary dyspepsia, children with moderate or severe dyspepsia submitted to endoscopy. Results of endoscopy along with histological findings are presented in table 4. The diagnosis of functional dyspepsia was considered in 116 children (70.73%) with normal endoscopic findings. Children with abnormal endoscopic findings were properly managed and excluded from the study. With the exception of paleness, which was more frequent in children with secondary dyspepsia ($p<0.0001$), no other difference in symptom frequency was found between

Table 2. Incidence of symptoms in the different subgroups of dyspepsia

Children investigated	**184**	**115**	**49**	**348**
Symptoms	**Mild**	**Moderate**	**Severe**	**Total**
Abdominal pain:				
Pain in the epigastrium	24 (13.04%)	62 (53.9%)	46 (93.8%)	132 (37.9%)
Periumbilical or diffuse	159 (86.4%)	49 (42.6%)	8 (16.3%)	216 (62%)
Nausea	46 (25%)	55 (47.82%)	34 (69.38)	135 (38.79)
Vomiting	33 (17.93%)	48 (41.73%)	25 (51.02%)	106 (30.45%)
Nocturnal awakens	49 (26.63%)	28 (24.34%)	14 (28.34%)	91 (26.14%)
Early satiety	37 (20.1%)	29 (25.21%)	13 (26.53%)	79 (22.7%)
Belching	33 (17.93%)	39 (33.91%)	25 (51.02%)	97 (27.87%)
Anorexia	25 (13.58)	15 (13.04%)	7 (14.28%)	47 (13.05%)
Postprandial fullness	69 (37.5%)	26 (22.6%)	12 (24.48%)	107 (30.74%)
Abdominal bloating	71 (38.58%)	25 (21.73%)	6 (12.24%)	102 (29.31%)
Other symptoms				
headache*	16 (8.69%)	18 (15.65%)	7 (14.28%)	41 (11.78%)
sweatiness	11 (5.97%)	7 (6.08%)	4 (8.16%)	22 (6.32%)
paleness	5 (2.71%)	6 (5.21%)	4 (8.16%)	15 (4.31%)
tachycardia	6 (3.26%)	8 (6.95%)	3 (6.12%)	17 (4.88%)

* Four children aged 5, 6, 8 and 10 years old, had migraine (two with familial history)

Table 3. Relationship of dyspeptic symptoms with dyspepsia severity and different forms of dyspepsia

	Dyspepsia severity			**Frequency of symptoms between functional and secondary dyspepsia**		
Symptom	**Mild 184 cases**	**Moderate or severe 164 cases**	**P**	**Functional dyspepsia 116 cases**	**Dyspepsia as a secondary symptom 48 cases**	**P**
Postprandial abdominal bloating/or distension	69	38	0.002	25	13	NS
Anorexia	25	22	NS	17	10	NS
Pain awakens	49	42	NS	27	15	NS
Headache	16	25	NS	17	8	NS
Nausea	47	89	0.0001	62	27	NS
Pallor	5	10	NS	2	8	0.0001
Early satiety	37	42	NS	43	19	NS
Belching	33	64	0.0001	47	16	NS
Sweat	11	11	NS	6	5	NS
Tachycardia	6	11	NS	6	5	NS
Fullness	71	31	0.0001	22	9	NS
Vomiting	33	73	0.0001	50	23	NS
Epigastric pain				85	24	0.007

these children and children with functional dyspepsia. However, children with functional dyspepsia suffered more often from epigastric pain ($p<0.007$), whereas in children with secondary dyspepsia periumbilical or

Table 4. Endoscopic and histologic evaluation of children with moderate to severe dyspepsia

	Helicobacter pylori	
	Positive*	**Negative**
Peptic ulcer **	5	
Esophagitis		3
Severe gastritis	15	
Mild superficial gastritis		21
Eosinophilic gastritis		1
Duodenitis		3
Functional dyspepsia		116
Total	20	144

* Helicobacter pylori infection was based on histological evaluation

** 4 children with duodenal ulcer

diffuse pain was more common (Table 3). The prevalence of *Helicobacter pylori* in children with recurrent abdominal pain was found to be 13%.

b. Management

A) Group without endoscopic examination (n=184)

Children with mild dyspepsia were initially treated empirically. Non-medical measures included repeated discussions about the nature of the problem, encouragment of acceptance and reassurance about the benign nature of the condition, and instructions for environment improvement and modification. A number of children responded to this therapy and remained symptom-free on re-evaluation, three months after treatment initiation. In particular, 47 children (25.54%) were symptom-free at 3 months, but this percentage was reduced to 16.84% (31 children) at 12 months. The remaining 153 children received two different trials: 101 were given promotility drugs (cisapride) and 52 acid-reducing drugs (ranitidine) at the discretion of the attending pediatrician. Response to therapy was classified as: a) non or partial response b) full response at the end of the 3, 6 and 12 months. By the end of 12 months (Table 5), more children given cisapride had achieved full remission compared to those given ranitidine (56.43% vs. 28.84%, p=0.002).

B) Group with endoscopic examination

B1) Children with mild, Helicobacter pylori negative gastritis (n=21)

On lack of evidence to the contrary, the diagnosis of functional dyspepsia was adopted and children were symptomatically treated as having functional dyspepsia. In particular, cisapride and ranitidine were empirically given in 14 and 7 children respectively, at the discretion of the attending pediatrician (Table 6). By the end of 12 months cisapride was more effective than ranitidine (50.0% vs. 28.6%), but this difference was not statistically significant (p=0.642), maybe due to the small number of patients in the sample.

B2) Children with functional dyspepsia (normal endoscopic and histological findings (116)

Ranitidine in 72 and cisapride in 44 children was empirically given at the discretion of the attending pediatrician (Table 7). Results concerning effectiveness of cisapride vs. ranitidine (55.55% vs. 40.90%) are similar to those of groups A and B1, thus confirming the superior beneficial effect of cisapride, although to a lesser extent than in the two previous groups. Results again show an apparently better response to cisapride by the end of the months 12 (55.55% vs. 40.90%), not however, statistically significant (p=0.185).

There were no side effects or adverse reactions with used drugs, except for diarrhea, which appeared in four children during the first days of cisapride use. The drug was discontinued for some days and restarted in smaller doses (0.4-0.6/Kg, 3-4 times daily).

Table 5. Results of treatment in the mild dyspepsia (without endoscopic evaluation) group

Response to treatment	**Cisapride group 3rd month 101 cases**	**Ranitidine group 3rd month 52 cases**	**P 3rd month**	**Cisapride group 6th month 101 cases**	**Ranitidine group 3rd month 52 cases**	**P 6th month**	**Cisapride group 12th month 101 cases**	**Ranitidine group 12th month 52 cases**	**P 12th month**
Complete remission	69 (68.31%)	18 (34.61%)	0.0001	62 (61.38%)	17 (32.69%)	0.002	57 (56.43%)	15 (28.84%)	0.002
Non or partial remission	32 (31.68%)	34 (65.39%)		39 (38.61%)	35 (67.31%)		44 (43.56%)	37 (71.16%)	

Table 6. Results of treatment in the mild (interstitial) Helicobacter pylori negative gastritis group

Response to treatment	Cisapride group 3rd month 14	Ranitidine group 3rd month 7	Cisapride group 6th month 14	Ranitidine group 3rd month 7	Cisapride group 12th month 14	Ranitidine group 12th month 7	p (12th month)
Complete remission	8 (57.14%)	4 (57.14%)	7 (50%)	3 (42.57%)	7 (50%)	2 (28.57%)	0.642 (NS)
Non or partial remission	6 (42.86%)	3 (42.86%)	7 (50%)	4 (57.43%)	7 (50%)	5 (71.43%)	

Table 7. Results of treatment in the children with functional dyspepsia group

Response to therapy	Cisapride group 3rd month 72	Ranitidine group 3rd month 44	Cisapride group 6th month 72	Ranitidine group 3rd month 44	Cisapride group 12th month 72	Ranitidine group 12th month 44	p (12th month)
Complete remission	42 (58.33%)	19 (44.18%)	41 (56.94%)	18 (40.9%)	40 (55.55%)	18 (40.9%)	0.185 (NS)
Non or partial remission	30 (41.67%)	25 (55.82%)	31 (43.06%)	26 (59.1%)	32 (44.45%)	26 (59.1%)	

DISCUSSION

Dyspepsia represents a common problem in adults, occurring at a prevalence of 20%-40% and annual incidence of 1.6%-8%[14,15]. It appears either as functional or secondary to organic disease. According to the recent literature, functional dyspepsia has been found in up to 60% of dyspeptic adults[15]. Although recent data indicates that dyspepsia is common among adults, only limited data about childhood dyspepsia is available. Recently Hyams et al[7] found an incidence of functional dyspepsia to be as high as 62.5% and Boey et al[16], up to 65.3%. In a cohort of 164 children with a moderate or severe form of dyspepsia which was assessed by detailed history, clinical examination, basic laboratory tests and endoscopy, we found functional dyspepsia at a prevalence of 70.7%, slightly higher than that reported in the previous studies.

Clinical manifestations of dyspepsia in adults have been well described and include epigastralgia or discomfort followed by nausea, vomiting, postprandial fullness, early satiety etc[4,14,15]. According to Chelimski and Czinn[17] symptoms in children are classified as major (epigastric pain, vomiting) and minor (regurgitation, anorexia, nocturnal awakening etc.). In this study we found that clinical manifestations were not substantially different from those in adults. However, the severity of dyspepsia was milder or more moderate in children. Of 348 children, dyspeptic manifestations were severe in only 49 (14.1%). Abdominal pain, mainly epigastric (81.8%), was the predominant symptom, often accompanied by belching, nausea, vomiting, postprandial fullness and bloating. Nausea, vomiting and belching were statistically more frequent in the moderate and severe cases, as opposed to mild cases in which postprandial fullness and bloating dominated.

No statistically significant differences were found in the frequency of symptoms between children with organic and functional dyspepsia, with two notable exceptions. Epigastric pain was more frequently associated with functional dyspepsia whereas paleness was more frequently associated with organic dyspepsia. Similarly to Hyams et al[7], we were also unable to distinguish the clinical subgroups of dyspepsia in the way described in adults, namely the ulcer-like or dysmotility-like dyspepsia. The reason for this could be twofold: a) the inability of children (especially those younger than 6-7 years old) to accurately perceive and verbalize dyspeptic symptoms and b) the limited experience of pediatricians to evaluate these symptoms.

The use of endoscopy as a first level investigation for the diagnosis of dyspepsia is questionable. Some

authors[18,19] consider recurrent abdominal pain to be an indication for endoscopy. However, others suggest that endoscopy should be avoided because of the discomfort caused to the pediatric patient and its limited diagnostic value[6,20]. According to Maastricht consensus[21] and the fact that in children malignancies of the gastrointestinal tract are extremely rare and peptic ulcer disease is uncommon (no more than 5%), we consider that endoscopy could not be a first-level diagnostic tool in childhood dyspepsia. In our study, endoscopy was carried out on 164 children with moderate to severe symptoms or frequent relapse of dyspepsia, since these groups are suggestive of possible underlying organic disease. It has been reported that mild, superficial, Helicobacter pylori negative gastritis is not a distinct entity[22,23] and *Helicobacter pylori* in the absence of duodenal ulcer is not a cause of symptoms[24,25]. In this study dyspeptic symptoms were attributed, after endoscopy, to a specific organic disease in only 12 cases (7,3%), namely peptic ulcer (n=5), oesophagitis (n=3), eosinophilic gastritis (n=1), duodenitis (n=3) (Table 4). This is a lower than that reported in adult studies (40%)[14,15] and therefore it does not justify the use of endoscopy as a primary diagnostic tool in the evaluation of dyspepsia during childhood. We did not notice any difference in the prevalence of Helicobacter pylori in children with recurrent abdominal pain compared to control participants (13% vs. 11.4%)[26].

To date, it is controversial whether mild epithelial or interstitial inflammation without discrete ulceration or evidence of *Helicobacter pylori* infection causes symptoms of dyspepsia[17]. According to some authors[12,17,27] a mild epithelial or interstitial inflammation is considered a normal condition. In our study, we found 21 such cases with histologic findings of interstitial inflammation without *Helicobacter pylori* infection. Until more data is available, all these cases were considered as functional dyspepsia.

In young patients with functional dyspepsia who are *Helicobacter pylori* negative, it is recommended that a trial of acid-reducing drugs (e.g. histamine H_2-receptor antagonist, antacid, proton pump inhibitor) or promotility drugs (cisapride, metoclopramide) be prescribed for one month[28,29]. If this fails to relieve symptoms, therapy may be switched between antisecretory and prokinetic classes. If, after 8 weeks of therapy, symptoms persist or rapidly recur on cessation of treatment, endoscopy is recommended. The few studies that have directly compared acid-suppressing and prokinetic agents in adults have suggested that prokinetic agents are more effective[30]. In our study, cisapride looked to be superior to ranitidine but this difference was not statistically significant (p=185).

In conclusion, we believe that functional dyspepsia is an extremely common finding among children under the broad spectrum of recurrent abdominal pain and it is probably time to reconsider this general term. We suggest that upper gastrointestinal endoscopy is not necessary as a first-level evaluation in most cases of recurrent abdominal pain, because the more severe organic reasons of dyspepsia in adults (gastroesophageal reflux disease, ulcer disease and tumor) are rather rare (ulcer, gastroesophageal reflux disease) or nonexistent (tumors) in childhood. Cases with epithelial or interstitial inflammation without *Helicobacter pylori* can also be considered as cases of functional dyspepsia until more data is available. Children with functional dyspepsia who are negative for *Helicobacter pylori,* can be treated empirically according to the prominent symptoms using either promotility or acid-reducing drugs, and be reevaluated after four weeks.

REFERENCES

1. Hyams JS, Treem WR, Justinich CJ, Davis P, Shoup M, Burke G. Characterization of symptoms in children with recurrent abdominal pain: Resemblance to irritable bowel syndrome. J Pediatr Gastroenterol Nutr 1995; 20:209-214.
2. Hyams JS, Burke G, Davis PM, Rzepski B, Andrulonis PA. Abdominal pain and irritable bowel syndrome in adolescence: A community – based study. J Pediatr 1998; 133:473-478.
3. Talley NJ, Zinsmeister AR, Schleck CD, Melton J III. Dyspepsia and dyspepsia subgoups: A population – based study. Gastroenterology 1992; 102:1259-1268.
4. Drossman DA, Thompson WG, Talley NJ, Funch-Jensen P, Janssens J, Whitehead WE. Identification of subgroups of functional gastrointestinal disorders. Gastroenterol Int 1990; 3:159-172.
5. Talley NJ, Colin-Jones D, Koch KL, Koch M, Nyren D, Stanghellini V. Functional dyspepsia: a classification with guidelines for diagnosis and management. Gastroenterol Int 1991, 4:145-160.
6. Spiroglou K, Paroutoglou G, Nikolaides N, Balaska A, Orfanou H, Raptopoulou M, *et al*. Management and treatment of children with dyspepsia. Initial endoscopy or empirical treatment with or without testing for *Helicobacter pylori*? Hell J Gastroenterol 1998; 11:36-41.
7. Hyams JS, Davis P, Sylvester FA, Zeiter DK, Justinich CJ, Lerer T. Dyspepsia in children and adolescents: A prospective study. J Pediatr Gastroenterol Nutr 2000; 30:413-418.
8. El-Omar EM, Banerjee S, Wirz A, McColl EL. The Glasgow dyspepsia severity score – a tool for the global measurment of dyspepsia. Eur J Gastroenterol Hepatol1996;

8:967-971.
9. Σπύρογλου Κ, Παρούτογλου Γ, Μπαλάσκα Α, Μόκκαλη-Βεντούρη Μ, Μπράτζου Χ, Ευγενίδης Ν, *και συν*. Ήπια καταστολή παιδιών (μέθη) για την ενδοσκόπιση του ανωτέρου πεπτικού συστήματος: εμπειρία τριών ετών. Hell J Gastroenterol 1998, 11(suppl. 264):69.
10. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996; 20:1161-1181.
11. Goldman H, Antonioli DA. Mucosal biopsy of the esophagus, stomach and proximal duodenum. Hum Pathol 1982; 13:423-448.
12. Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disease and functional abdominal pain. Gastroenterol Int 1992; 5:75-91.
13. Schindlbeck NE, Klauser AG, Voderholzer WA, Muller-Lissner SA. Empiric therapy for gastroesophageal reflux disease. Arch Intern Med 1995; 155:1808-1812.
14. Manning SP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of irritable bowel. Br Med J 1978; 2:653-654.
15. Knill-Jones RP. Geographical differences in the prevalence of dyspepsia. Scand J Gastroenterol Suppl 1991; 182:17-24.
16. Haque M, Wyeth JW, Stace NH, Talley NJ, Creen R. Prevalence, severity and associated features of gastroesophageal reflux and dyspepsia: apopulation-based study. N Z Med 2000:178-181.
17. Boey CC, Goh KL, Hassall E, Maqid M. Endoscopy in children with recurrent abdominal pain. Gastrointest Endosc 2001; 53:142-143.
18. Chelimski G, Czinn S. Peptic ulcer disease in children. Pediatr Rev 2001; 22:349-355.
19. Antonson DL. Abdominal pain. Gastrointest Endosc Clin N Am 1994; 4:1-21.
20. Boyle JT. Recurrent abdominal pain: An update. Rev Pediatr 1997; 183101-183120.
21. Galler JR, Neustein S, Walker WA. Clinical aspects of recurrent abdominal pain in children. Adv Pediatr 1980; 27:31-53.
22. Current European concepts in the management of Helicobacter pylori infection. The Maastricht consensus report. European Helicobacter Pylori Study Group. Anonymous. Gut 1997; 41:8-13.
23. Black DB,Haggitt RC, Whitington PFQ. Gastrointestinal endoscopic-histologic correlation in pediatric patients. J Pediatr Gastroenterol Nutr 1988; 7:353-358.
24. Whitehead R, Truelove SC, Gear MW. The histological diagnosis of chronic gastritis in fiberoptic gastroscope biopsy specimens. J Clin Pathol 1972; 25:1-11.
25. Morris AJ, Ali MR, Nicholson GI, Perez-Perez GI, Blaser MJ. Long term follow up of voluntary ingestion of Helicobacter pylori. Ann Intern Med 1991; 114:662-663.
26. Drumm NB, Sherman P, Cutz E, Karmali M. Association of Campylobacter pylori on the gastric mucosa with antral gastritis in children. N Engl J Med 1987; 326: 1557-1561.
27. Oster J. Recurrent abdominal pain, headache and limb pains in children and adolescents. Pediatrics 1972; 50:429-436.
28. Jones RH, Baxter G. Lansoprazole 30mg daily versus ranitidine 150mg bd in the treatment in acid-related dyspepsia in general practice. Aliment Pharmacol Ther 1997; 11:541-546.
29. Veldhuyzen van Zanten SJ, Cleary C, Talley NJ, Peterson TC, Nyren O, Bradley LA, *et al*. Drug treatment of function dyspepsia: a systematic analysis of trial methodology with recommendations for the design of future trials. (Report of an International Working Party). Am J Gastroenterol 1996; 91:660-673.
30. Halter F, Miazza B, Brignoli R. Cisapride or cimetidine in the treatment of functional dyspepsia. Results of a double–blind, randomized, Swiss multicentre study. Scand J Gastroenterol 1994; 29:618-623.