Indications to Upper Gastrointestinal Endoscopy in Children With Dyspepsia

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ABSTRACT

Objectives: The objective of the study was to ascertain the appropriateness of indications for upper gastrointestinal (UGI) endoscopy in children with dyspepsia.

Methods: We used the RAND/University of California at Los Angeles method to investigate the appropriateness of the opinions of a panel of experts. The panel judged 2304 theoretical patient scenarios defined by a combination of demographic and clinical variables. Descriptive and multivariate logistic regression analyses were performed.

Results: The panel rated UGI endoscopy as appropriate in 27.2% of cases, inappropriate in 14.3%, and dubious in 58.5%. Disagreement emerged for 21% of cases. UGI endoscopy was considered increasingly appropriate in cases with a positive family history of peptic ulcer and/or *Helicobacter pylori* infection (odds ratio [OR] 8.518, $P < 0.0001$), when dyspepsia interfered with activities of daily living (''sleep'' OR 7.540, $P < 0.0001$; ''normal activities'' OR 5.725, $P < 0.0001$), and when patients were older than 10 years (''≤10 years'' OR 0.310, $P < 0.0001$) the longer the duration (''0–2 months'' OR 0.002, $P < 0.0001$; ''3–5 months'' OR 0.059, $P < 0.0001$; ''6–11 months'' OR 0.516, $P = 0.0005$) and the greater the severity (''mild'' OR 0.002, $P < 0.0001$; ''moderate'' OR 0.013, $P < 0.0001$) of their dyspeptic symptoms.

Conclusions: UGI endoscopy is not appropriate for all children with dyspeptic symptoms, but only for cases with a family history of peptic ulcer and/or *Helicobacter pylori* infection, older than 10 years of age, with symptoms persisting for more than 6 months and severe enough to affect activities of daily living.

Key Words: dyspepsia, pediatric endoscopy, pediatric gastrointestinal disease, upper gastrointestinal endoscopy

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The term *dyspepsia* has yet to be given a standard definition although it is commonly used by clinicians. Dyspeptic symptoms may include epigastric pain, epigastric fullness and regurgitation, upper abdominal discomfort, early satiety, bloating, nausea, and vomiting (1–8).

The Rome III Committee recently defined the diagnostic criteria for functional dyspepsia in children. These criteria are essentially clinical and include the presence of recurrent pain or discomfort centered in the upper abdomen, above the umbilicus, at least once per week for 2 months before the diagnosis, not relieved by defecation and unassociated with any change in stool frequency or form, with no evidence of any inflammatory, anatomical, metabolic, or neoplastic process to explain the symptoms (4,6).

Given this definition of functional dyspepsia, it seems really difficult to apply it in certain clinical situations because several diseases (eg, peptic or eosinophilic esophagitis, gastritis, peptic ulcer, inflammatory bowel disease) may present with dyspeptic symptoms (7) and because there are no evidence-based guidelines for its evaluation, despite the high prevalence of abdominal pain or discomfort (5,7).

Gastrointestinal (GI) endoscopy is an accurate and informative method for assessing upper GI (UGI) lesions that should ideally be performed only in clinical situations in which the procedure has a demonstrated favorable impact on patient management and outcome. There is still considerable uncertainty, however, as to the effectiveness of endoscopy in many situations (9).

In the past few years, experts in committees and scientific societies (4,6,8–12) have been working to establish criteria for selecting the patients most likely to benefit from UGI endoscopy. Because UGI endoscopy has become easier to perform, pediatricians often prescribe it in children with various nonspecific symptoms, leading to its often inflated use. Moreover, few studies in the international medical literature have focused on the appropriateness of using UGI endoscopy in pediatric patients (13). For this reason, it is difficult to conduct an assessment of appropriateness based on high-quality evidence and that represents a primary evaluation principle.

The RAND/University of California at Los Angeles (UCLA) method is a multidisciplinary expert panel system that has been in use for some time to assess the appropriateness of procedures in many medical and surgical situations (14), in which there is little published evidence and some uncertainty as to the best diagnostic and therapeutic approach to use. It has already been applied to UGI endoscopy in adult patients (8–10, 15,16).

The aim of the present study was to apply the RAND/UCLA method to ascertain the appropriate indications for UGI endoscopy in children with dyspeptic symptoms.

METHODS

RAND/UCLA Method

The RAND/UCLA appropriateness method was used to investigate the opinions of a panel of experts on the appropriateness of UGI endoscopy for dyspepsia in children.

A procedure is defined as *appropriate* when the expected health benefit (in terms of increased life expectancy, relief of pain and symptoms, reduction of anxiety, and improved quality of health status — not necessarily in this order of importance) exceeds the expected negative consequences (eg, mortality, morbidity, anxiety of anticipating the procedure, pain produced by the procedure, time off work) by a wide enough margin to make the procedure worth performing (13,16). The RAND appropriateness method entails several steps:

1. A detailed review of the medical literature
2. A list of specific clinical scenarios or indications
3. The selection of a panel of experts on a given matter
4. The collection of each expert's opinion on theoretical clinical cases
5. Statistical analysis of the results

The study began in October 2006. The first 3 months were spent on reviewing the literature, selecting the panel, and conducting several training sessions for the panelists to explain the aims of the study, the definitions and classifications adopted, and the method for evaluating the clinical cases. Then each expert was given up to 3 months to express an independent and anonymous opinion on the theoretical clinical cases.

Literature Review

A detailed review of the published literature (4–7,17–61) was conducted to identify studies on dyspepsia in children (evaluating the efficacy, safety, side effects, and possible complications of UGI endoscopy) to provide the background for the panel process. The literature review considered a hierarchy of evidence-based efficacy of medical procedures (9,57). The literature was drawn from the MEDLINE database in PubMed, but the Cochrane Database was also consulted. A first set of studies on esophagogastroduodenoscopy was identified using the terms *esophagogastroduodenoscopy*, and *UGI*. A second set of studies on dyspepsia was identified using the terms *dyspepsia*, *functional GI disorders*, *recurrent abdominal pain*, *abdominal pain*, *irritable bowel syndrome*, *Helicobacter pylori* (Hp), *peptic ulcer disease*, and *lactose intolerance*. The terms were used both as free text terms and in combinations of the 2 sets. A search was also conducted combining all of these terms with the words *appropriateness* and *pediatrics*. A procedure was then used to eliminate articles that were incorrectly selected or unsuitable, based on the related titles and abstracts.

List of Indications

A list of all of the possible indications (theoretical clinical scenarios) for which endoscopy may be used in patients with dyspepsia was formulated, without referring to their appropriateness. The purpose of the list of indications was to classify children in terms of the clinical variables that physicians consider when deciding whether to recommend a particular procedure (58). The indications classify patients in terms of their personal characteristics, such as family history, age, dyspeptic symptoms (duration, entity), relation of symptoms with meals and activities of daily living, and associated symptoms. The categories of each variable (Table 1) were chosen bearing in mind the previously described literature review and the recommendations of the Rome III Committee in particular (4). In addition, *family history* refers to first-degree relatives (parents and siblings) with a diagnosis of peptic ulcer and/or Hp infection (documented by endoscopy, biopsy, and/or noninvasive tests for the diagnosis of Hp infection) (37), ''lactose intolerance'' (defined as clear symptoms such as abdominal pain, bloating, flatus, diarrhea, borborygmi after ingesting foods containing lactose, and/or hydrogen breath test positivity) (62), and ''irritable bowel syndrome'' (defined as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months, associated with 2 or more of the following: symptom improvement with defecation, onset associated with a change in frequency of stools, onset associated with a change in form, or appearance of stools) (63). The dyspeptic symptoms were then classified according to their severity as ''mild'' (infrequent symptoms causing no major impairment in function or psychological disturbance), ''moderate'' (symptoms causing intermittent disruptions in activity with a close relation between symptoms and inciting events), or ''severe'' (refractory symptoms causing a major impairment in function or psychological disturbance) (6). Finally, patients were divided into 2 age brackets, ''younger than or equal to 10 years'' and ''older than 10 years,'' relating to the child's growth and development.

The combination of the categories of the 7 variables considered produced 2304 theoretical patient scenarios that the panel of experts was asked to judge.

TABLE 1. Clinical variables used in the 2304 theoretical clinical scenarios

Variables	Categories, no.	Categories
Family history	4	No related conditions Peptic ulcer/Hp infection Lactose intolerance Irritable bowel
Duration of dyspeptic symptoms	4	<3 mo 3–5 mo 6–11 mo >12 mo
Age	2	≤10 y >10 y
Entity of dyspeptic symptoms	3	Mild Moderate Severe
Relation of symptoms with meals	2	Improvement Worsening
Effects on activities of daily living	3	None On normal activity On sleep
Associated symptoms	4	None Headache Altered bowel pattern Others (eg, lipothymia, tachycardia, flushing, sweating)

Hp = *Helicobacter pylori*.

The Panel

As recommended in the RAND method (64), 9 experts were selected for the panel. The experts belong to the endoscopy section of the Società Italiana di Gastroenterologia Epatologia e Nutrizione Pediatrica. To enable a pondered judgment for each clinical scenario considered, professionals with different roles were chosen (2 pediatric gastroenterologists and GI endoscopists, 2 pediatric gastroenterologists, 2 hospital pediatricians, 2 family pediatricians, and 1 pediatric surgeon) to take part in the decision whether to perform a UGI endoscopy in each child with dyspepsia.

Panel's Judgment

The experts were asked to independently and anonymously rate the appropriateness of UGI endoscopy for each of the 2304 cases considered on a 9-point scale (1 = extremely inappropriate, 5 = dubious, 9 = extremely appropriate).

The panelists judged these cases after analyzing the literature and taking part in training sessions, during which they were given instructions on how to assess the various cases (using their own best clinical judgment and disregarding cost) and supplied with definitions of the clinical terms used in describing the scenarios. The 9-point scale thus identified 3 different bands: inappropriate: 1 to 3, dubious: 4 to 6, and appropriate: 7 to 9.

A score of 1 meant that the procedure was absolutely unwarranted (ie, the test could have a negative effect on the patient), whereas a score of 9 suggested that the procedure was entirely appropriate (ie, a positive effect on the patient's health could be expected). A score of 5 was consistent with a dubious situation, in which it was hard to say whether endoscopy was appropriate. Intermediate scores of 2, 3 to 4, 6 to 7, and 8 were indicative of a tendency towards inappropriateness, uncertainty, and appropriateness, respectively.

Statistical Analysis

The median of the scores attributed by the panelists and the degree of agreement were calculated for each clinical case. Disagreement was considered as a situation when at least 3 panelists attributed scores of 1 to 3, whereas 3 others scored the same case as 7 to 9 (58).

Although the experts may have had some recollection of how they had judged previously evaluated scenarios, for the purposes of statistical analysis, it was assumed that all of the observations were statistically independent data points.

Each case was classified on 3 levels of appropriateness, using the following definitions: appropriate: panel median scores of 7 to 9 with no disagreement, dubious: panel median of 4 to 6 or any median with disagreement, and inappropriate: panel median of 1 to 3 with no disagreement. Each variable was assessed using a descriptive analysis, rating the panel's overall judgment of appropriateness for each category, in figures with percentages and crude odds ratios (OR).

Logistic regression analysis was used to identify the variables that most affected the panel's judgment of appropriateness, estimating model parameters (natural logarithms of OR), and their standard errors, P values, and OR with 95% confidence intervals and goodness of fit.

A P value of <0.05 was considered statistically significant. The P values for the univariate statistical tests, related to the crude OR, were not corrected for multiple testing because these statistics were considered descriptive and the hypotheses tested as exploratory. The subsequent multivariate logistic regression analysis was considered the main final outcome because it identified the factors independently associated with the panel's judgment of appropriateness, after adjusting for the contributions of the other variables.

The statistical analysis was performed using the SAS package, rel. 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

General Panel Results

The panel rated UGI endoscopy as appropriate in 628 cases (27.2%), inappropriate in 329 cases (14.3%), and dubious in 1347 cases (58.5%). Disagreement emerged for 21% of the cases.

Descriptive Analysis

When each clinical variable was considered separately (Fig. 1), the percentage appropriateness of UGI endoscopy was higher than for the sample as a whole (27.2%) in cases with severe symptoms (58.5%), dyspeptic symptoms lasting more than 12 months (44.8%) or from 6 to 11 months (38.4%), a family history of peptic ulcer (43.9%) or irritable bowel syndrome (30.4%), in patients whose symptoms disturbed their sleep (32.7%) or their normal activities of daily living (30.5%), in patients older than 10 years of age (31.5%), and in those whose dyspepsia was associated with ''other'' symptoms (31.3%) or with symptoms worsening after meals (29.9%).

UGI endoscopy was judged to be inappropriate particularly in cases with dyspeptic symptoms lasting <3 months (42.5% vs 14.3% calculated for the sample as a whole), in cases whose symptoms were mild (29.8%) or had no influence on activities of daily living (21.1%), in children younger than 10 years of age (19.6%), in those with a family history of lactose intolerance (18.2%) or irritable bowel syndrome (15.8%) or with no related conditions (15.1%), and in patients whose symptoms improved after meals (16.5%) or were unassociated with other symptoms (16.3%).

Finally, the panel considered UGI endoscopy of dubious value especially in cases with a family history of lactose intolerance (72.7% vs 58.5% calculated for the sample as a whole) or no related conditions (59.2%), in cases with moderate (70.6%) or mild symptoms (63.8%) or with dyspeptic symptoms lasting 3 to 5 months (69.6%), in patients whose symptoms had no influence on their activities of daily living (60.3%) or whose symptoms were associated with headache (62.5%) or altered bowel patterns (59.4%), in children older than 10 years of age (59.6%), and in those whose symptoms improved after meals (58.9%).

Multivariate Logistic Regression Analysis

Table 2 shows the results of the logistic regression analysis on the appropriateness of UGI endoscopy. The variables that most influenced the panel's conviction that UGI endoscopy was appropriate were a family history of peptic ulcer and/or Hp infection (OR 8.518, $P < 0.0001$) or irritable bowel syndrome (OR 1.872, $P = 0.0040$), effects on sleep (OR 7.540, $P < 0.0001$) or normal activities of daily living (OR 5.725, $P < 00001$), symptoms worsening after meals (OR 2.099, $P < 0.0001$), and in association with other symptoms (OR 1.780, $P = 0.0077$).

Variables that made the experts consider UGI endoscopy less appropriate were a shorter history of dyspeptic symptoms (''0–2 months'' OR 0.002, $P < 0.0001$; ''3–5 months'' OR 0.059, $P < 0.0001$; ''6–11 months'' OR 0.516, $P = 0.0005$), less severe dyspeptic symptoms (''mild'' OR 0.002, $P < 0.0001$; ''moderate'' OR 0.013, $P < 0.0001$), a family history of lactose intolerance (OR 0.049, $P < 0.0001$), and a younger age of the patient (''younger

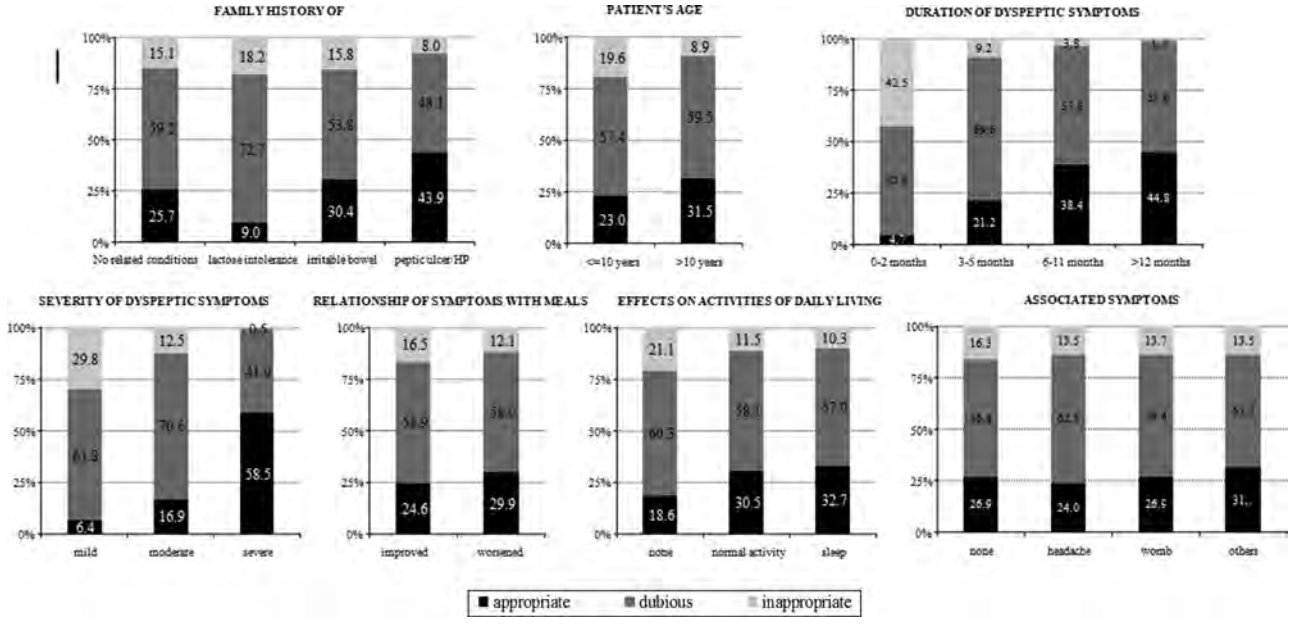

FIGURE 1. Appropriateness of upper gastrointestinal endoscopy (percentage distribution) for each clinical variable (family history of related conditions, patient's age, duration of dyspeptic symptoms, severity of dyspeptic symptoms, relation of symptoms with meals, effects on activities of daily living, associated symptoms) in children with dyspepsia.

than or equal to 10 years'' OR 0.310, $P < 0.0001$). Any influence of associated symptoms, such as headache ($P = 0.0589$) and altered bowel patterns ($P = 1.0000$), was not statistically significant.

DISCUSSION

Dyspepsia is a common, nonspecific symptom in children and adolescents that may be the expression of numerous disorders of the proximal part of the digestive tract. Its exact prevalence is not known and varies with sex and country of origin. The international medical literature reports figures that dyspepsia roughly ranges from 5% to 20% (43,52).

Although UGI endoscopy is often useful in children, as it is in adults, there is only limited direct evidence of the impact of endoscopy on the outcome of pediatric patients with dyspepsia (4,13).

The European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE and EPAGE II) used the RAND method to conduct a study on how appropriate and necessary GI endoscopy (upper and lower) (9,10) can be in adult patients in different clinical settings. Concerning dyspepsia in particular, a panel of experts considered 192 theoretical clinical scenarios representing combinations of 6 different variables (age, nonsteroidal anti-inflammatory drug intake, Hp status, previous investigations of similar symptoms, empirical acid-lowering treatment in Hp-negative patients, or Hp eradication in Hp-positive ones, and response to empirical acid-lowering or Hp eradication treatments) and ultimately concluded that UGI endoscopy was appropriate in only 48 of 192 cases (25%), inappropriate in 113 of 192 (59%), and of doubtful utility in 31 of 192 (16%), with a high level of agreement in the experts' opinions (72%) (8).

The American Society for Gastrointestinal Endoscopy also established guidelines, providing precise recommendations on the appropriateness of using UGI endoscopy in adult patients (12). Based on these guidelines, a recent prospective study (65) assessed the appropriateness of UGI endoscopy in a large sample of patients, confirming the validity of the guidelines applied to adult patients. During the same period, the American Society for Gastrointestinal Endoscopy clarified the role of endoscopy in cases of adult dyspepsia, concluding that, given the large numbers of patients with dyspepsia, it is not practical to perform endoscopy in all of them, but only in those older than 50 years of age and with alarming features (66).

There is only 1 retrospective study focusing on the appropriateness of UGI endoscopy in the pediatric population, which considered 293 UGI endoscopies performed in 251 patients for various indications (eg, failure to thrive, excessive crying, spitting up after feeding, dysphagia, recurrent abdominal pain, vomiting, bleeding, diarrhea), and assessed what impact the procedure had on the patient's treatment in accordance with the recommendations of the Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatriques (13). The results of the present study emphasize the need for the endoscopist to have guidelines on the appropriateness of UGI endoscopy in pediatric age to avoid an excessive use of this procedure and the related unnecessary exposure of patients to the related potential adverse effects.

Some years ago, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition specified the clinical situations in which UGI endoscopy was indicated (11). More recently, the Rome III Committee established that endoscopy was not ''mandatory'' for dyspepsia in children, justifying its use in the presence of dysphagia, in patients with persistent symptoms despite acid-reducing medication, in those with recurrent symptoms after suspending any such medication, and to confirm a diagnosis of Hp-associated disease (4,55).

The RAND method was developed primarily as an instrument to enable the measurement of the overuse and underuse of medical and surgical procedures. The rationale behind the method is that randomized clinical trials (the gold standards for evidence-based medicine) are often either unavailable or they cannot provide evidence with a sufficient level of detail to enable their application to the wide variety of patients seen in everyday clinical practice

TABLE 2. Crude odds ratios and results of multivariate logistic regression analysis for appropriateness

			Logistic regression analysis				
	Crude OR	95% CI	*P*	Parameter	OR	95% CI	*P*
Family history of							
No related conditions (ref)	1				1		
Lactose intolerance	0.287	0.204–0.404	<0.0001	−3.0115	0.049	0.028–0.087	<0.0001
Irritable bowel	1.262	0.975–1.633	0.0007	0.6269	1.872	1.222–2.868	0.0040
Peptic ulcer/HP infection	2.265	1.766–2.906	<0.0001	2.1422	8.518	5.498–13.198	<0.0001
Patient's age							
≤10 y	0.649	0.540–0.781	<0.0001	−1.1696	0.310	0.226–0.427	<0.0001
>10 y (ref)	1				1		
Duration of dyspeptic symptoms							
0–2 mo	0.061	0.040–0.092	<0.0001	−6.1539	0.002	0.001–0.004	<0.0001
3–5 mo	0.331	0.256–0.429	0.5187	−2.8370	0.059	0.036–0.095	<0.0001
6–11 mo	0.767	0.607–0.970	<0.0001	−0.6616	0.516	0.355–0.751	0.0005
≥12 mo (ref)	1				1		
Severity of dyspeptic symptoms							
Mild	0.048	0.035–0.067	<0.0001	−6.0543	0.002	0.001–0.004	<0.0001
Moderate	0.145	0.114–0.183	0.0009	−4.3329	0.013	0.008–0.021	<0.0001
Severe (ref)	1				1		
Relation of symptoms with meals							
Improvement (ref)	1				1		
Worsening	1.313	1.092–1.578	0.0038	0.7415	2.099	1.541–2.860	<0.0001
Effects on activities of daily living							
None (ref)	1				1		
On normal activity	1.915	1.510–2.430	0.0056	1.7448	5.725	3.782–8.665	<0.0001
On sleep	2.122	1.676–2.687	<0.0001	2.0202	7.540	4.958–11.467	<0.0001
Associated symptoms							
None (ref)	1				1		
Headache	0.856	0.656–1.116	0.0423	−0.4230	0.655	0.422–1.016	0.0589
Altered bowel pattern	1.000	0.771–1.297	0.8657	<0.0000	1.000	0.651–1.537	1.0000
Others	1.235	0.957–1.593	0.0127	0.5764	1.780	1.165–2.719	0.0077

CI = confidence interval; Hp = *Helicobacter pylori*; OR = odds ratio; ref = reference category; goodness of fit: $\chi^2 = 7.09$, $P = 0.52$; concordance = 95.4%.

(14). Although robust scientific evidence of the benefits of many procedures is lacking, physicians must nonetheless make decisions every day about when to use them (13). The RAND method was designed to deal with this need to combine the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of performing a given procedure in light of a patient's specific symptoms, medical history, and test results (14).

Our study is the first to apply the RAND method to theoretical pediatric cases with a view to assessing the appropriateness of UGI endoscopy for dyspepsia, considering 7 different variables (family history, age, duration of dyspeptic symptoms, entity of dyspeptic symptoms, their relationship with meals, their effects on activities of daily living, and associated symptoms). Age (taking the children's stage of development and degree of understanding of their symptoms into account) is the variable that most distinguishes pediatric patients from their adult counterparts.

In our study, the panel concluded that UGI endoscopy was appropriate in 27.2% of cases and inappropriate in 14.3%, with a high level of agreement among the panel members (79% of cases). In particular, UGI endoscopy seemed all the more appropriate the longer the duration and the greater the severity of the dyspeptic symptoms, in patients with a family history of peptic ulcer and/or Hp infection, when activities of daily living were affected, and in older children. It was judged less appropriate in patients whose symptoms became worse at mealtimes or in those with a family history of irritable bowel syndrome, or in cases associated with other symptoms such as lipothymia, tachycardia, flushing, and sweating. It was least appropriate for patients with a family history of lactose intolerance (Table 2).

The panel attributed a dubious role to UGI endoscopy in a considerable proportion (58.5%) of pediatric patients with dyspepsia, just as the EPAGE study found UGI endoscopy unsuitable for the majority of adult cases (59%) (8). These results are partially attributable to the fact that children's dyspeptic symptoms are more vague (51) than in adults. Moreover, dyspeptic symptoms in adult patients may express severe organic diseases, such as carcinoma or Barrett esophagus (8,67), especially in the presence of warning signs such as dysphagia and weight loss. This may influence how a panel of experts perceives the problem and the level of agreement in the experts' choice of approach to dealing with it.

Genetic factors may predispose some individuals to functional GI disorders (6), such as irritable bowel syndrome (68) and lactose intolerance (62), but finding these conditions in several members of certain families is not only a matter of genetics (69). Social learning (ie, what children learn from parents) may contribute to the risk of onset of these GI disorders (70,71).

In addition to UGI endoscopy, various sensitive and specific noninvasive tests are recommended for the diagnosis of Hp infection in children (72–74). All of the children with Hp infection have chronic gastritis, and GI endoscopy is warranted to confirm a diagnosis of Hp-associated disease (4,55); it can also rule out any other diseases, such as eosinophilic gastroduodenitis, esophagitis, or enteropathies (55,56).

Although symptoms may be vague in children with irritable bowel disease (IBD) and a positive family history of IBD may reinforce the clinical suspicion of this condition (75), we did not consider the ''family history of IBD'' variable in our study because a growing body of evidence supports the diagnostic sensitivity of noninvasive serological tests (76–79) that can be used before referring children for endoscopy (be it upper or lower); this remains the last step in the diagnostic staging procedure (74,80).

Our study found UGI endoscopy appropriate not for all children with dyspeptic symptoms, but only for those with selected features (a family history of peptic ulcer and/or Hp infection, age older than 10 years, symptoms lasting more than 6 months and severe enough to affect activities of daily living) confirming that it does not always have a role in the diagnosis of dyspepsia in children (4,6,11,81). It would be advisable to avoid overusing UGI endoscopy: Although the technique is easy to use, it still demands particular attention when applied to pediatric patients; it should be reserved for those patients who are most likely to benefit (82).

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