

Intestinal lymphoid nodular hyperplasia in children: The relationship to food allergy

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Abstract

Background: Lymphoid nodular hyperplasia (LNH) of the lower gastrointestinal tract is a common finding during paediatric colonoscopies, and its clinical significance has not yet been clearly established.

Objective: The purpose of this prospective, parallel multi-arm, randomized clinical trial was to study relationship between food allergy and LNH.

Methods: We recruited 268 children who had undergone a diagnostic colonoscopy between 1 January 2009 and 30 September 2011. The inclusion criteria were the following: (i) demonstration of LNH; (ii) no concomitant inflammatory or immune disease; (iii) no treatment since the clinical onset. The patients were assigned 1:1:1 to elimination diet (Group A), mesalamine (Group B) or symptomatic treatment with antispasmodics or antidiarrhoeal drugs (Group C) for an 8-wk period. Patients were followed for 24 months.

Results: We enrolled 72 of 97 children with intestinal LNH who were referred for haematochezia (76%), recurrent abdominal pain (68%) and/or chronic diarrhoea (32%). Clinical improvement was observed in 75%, 83% and 79% of the patients in Groups A, B and C, respectively. The difference in the response to treatment among the groups and the association to the clinical, endoscopic and allergic features of the patients were not statistically significant.

Conclusions: Intestinal LNH should be considered a benign finding in children without red flags, because the symptoms are largely self-limiting. The use of mesalamine or elimination diet does not modify the clinical outcome compared to symptomatic therapy. The presence of food allergy was not predicted by allergy skin testing and was found in a minority of patients.

The lumen of the gastrointestinal (GI) tract is continuously exposed to many immunogenic stimuli, such as food antigens and colonizing or pathogenic microorganisms. Besides all of its other functions, the gut is a crucial site for the immunologic response. The highly specialized lymphoid tissues within the gut, such as Peyer's patches and small lymphoid aggregations, are collectively referred to as gut-associated lymphoid

tissue (GALT) (1–3). A particular abundance of human GALT is observed in a condition known as lymphoid nodular hyperplasia (LNH), which is frequently observed in childhood. LNH is characterized by multiple nodules consisting of lymphoid aggregates, typically located in the terminal ileum and/or colon and macroscopically appears as closely spaced, thin areas separated by 1–2 mm. LNH of the lower GI tract is a common finding during paediatric colonoscopies and has been initially regarded as a pathological or age-related variant with unknown clinical significance (3–5). Lymphoid follicles are normally present in the human large bowel, and in an autopsy series, their number seems to be distinctly higher in children than adults (6). This observation supports the benign nature of this finding in children, even though children with

Abbreviations

APT, atopy patch test; DBPCFC, double-blind placebo-controlled food challenge; FA, food allergy; GALT, gut-associated lymphoid tissue; GI, gastrointestinal; LNH, lymphoid nodular hyperplasia; RAP, recurrent abdominal pain; SGARC, subject's global assessment of relief for children; SPTS, skin prick tests; TI, terminal ileum.

endoscopic evidence of LNH can show an increased number and size of lymphoid follicles than controls. The enlarged follicles can result in thinning of the overlying mucosa, which explains their visibility at the time of endoscopic examination (6). Why these nodules are more frequently observed in infants and children than in adults is open to speculation. Krauss et al. (3) suggested that this difference could be most likely related to the development of the intestinal immune system, immature oral tolerance and frequent infections occurring in childhood. The observed association with different immune-mediated disorders, such as inflammatory bowel disease (7, 8), immunodeficiency (9–12) and rheumatic disease (4, 5, 12, 13), have led to the hypothesis that local immune up-regulation is involved in its pathogenesis. Recently, a relationship between upper and lower GI tract LNH and food allergy (FA) (7, 14–18) has been reported, with some authors suggesting that this finding is a marker of immune reactivity to many foods that are potentially responsible for intestinal complaints.

The primary aim was to define whether the clinical outcomes of children with LNH isolated to the lower GI tract are significantly affected by dietary or anti-inflammatory treatment. Second, we evaluated whether symptom severity, site of LNH, the presence of food sensitization and predisposition to atopy can predict the clinical response. Finally, our objective was to define the clinical significance of intestinal LNH, the usefulness of allergy skin testing, and potential indications for specific treatments, with the aim to identify an appropriate management approach.

Methods

This prospective, randomized (allocation ratio 1:1:1), multi-arm, clinical trial was conducted in the Paediatric Department of Umberto I Hospital (Rome, Italy). While the patients were aware of the allocation arm, both outcome assessors and data analysts were blinded to the allocation. The trial was approved by the 'Sapienza' University Ethical Committee of Research (Rome, Italy).

Participants

Children who were referred for GI symptoms with an indication for diagnostic colonoscopy were consecutively recruited between 1 January 2009 and 30 September 2011. The inclusion criteria were the following: (i) isolated finding of LNH, defined as a significant cluster of lymphoid nodules (>10/visible field) by endoscopy and lymphoid follicle hyperplasia by histology; (ii) negative results from a preliminary evaluation. The exclusion criteria were the following: (i) diagnosis of a concomitant inflammatory, rheumatic or infectious process; (ii) starting any dietary or therapeutic intervention after clinical onset.

Sample size

We assessed the size of each of three arms in order to be able to estimate equivalence among the groups with a power of 80%

(alpha value = 0.05). We defined the minimum difference of practical interest equal to 0.35.

Preliminary evaluation

A detailed family and personal history was taken to assess the duration and severity of symptoms and to exclude irritable bowel syndrome or chronic constipation as the cause for the GI complaints. A complete physical exam was performed, with an evaluation of anthropometric parameters, palpable abdominal masses, the presence of anal lesions (fissures and skin tags) and signs of systemic diseases. Microbiologic testing of stool for parasitic, viral and bacterial enteropathogens was performed. Laboratory blood tests included routine biochemistries, C-reactive protein, erythrocyte sedimentation rate, T- and B-cell count, total serum IgA, antitransglutaminase IgA antibody, antisaccharomyces cerevisiae antibody and p-antineutrophil cytoplasmic antibody. Children with hematochezia were also evaluated for Meckel's diverticulum using scintigraphy.

Endoscopy and histology

Under general anaesthesia or conscious sedation with i.v. midazolam (0.1 mg/kg), based on the patient's age, endoscopy was performed by blinded paediatric gastroenterologists using a paediatric instrument (diameter, 11.3 mm; Olympus PCF-Q180, Tokyo, Japan). After filling the area of interest with air in the colon and approximately 10–15 cm of the terminal ileum (TI), the severity/prominence of lymphoid nodular hyperplasia of the mucosa was graded according to Guandalini et al. (19) (Table 1; Fig. 1). Biopsies were routinely taken from macroscopically normal mucosa in the TI and each colonic segment and from areas in which LNH or other lesions were found. A histological examination was performed by an experienced pathologist blinded to the patients' clinical data.

Allergological evaluation

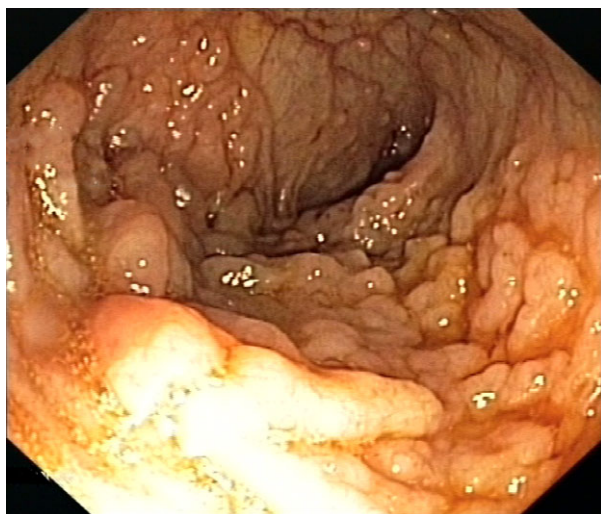
Personal history for atopic disease (eczema, asthma or allergic rhinitis) and allergy skin tests were performed by paediatric allergists blinded to patients' allocation. Both IgE and non-IgE mediated sensitization to allergens in common foods (cow's milk, egg, soya, wheat, rice, barley, fish, tomato, peanuts, hazelnut and cocoa) were assessed. To confirm the presence of a concomitant non-gastrointestinal allergy, a standard panel of chronic and seasonal aeroallergens and contact delayed-reactions to nickel were tested. Family history of allergy in parents and siblings was recorded.

Skin prick tests (SPTs)

Using a 1-mm, one-peak lancet (Biofarma Laboratories, Torino, Italy) with a shoulder to prevent deeper penetration, a panel of commercially available allergens, histamine dihydrochloride (10 mg/ml) (positive control) and diluent negative controls (Lofarma, Milano, Italy) were tested on the volar aspect of the forearm. The largest diameter of the wheal (in millimetres) was recorded at 15 min; a wheal of 3 mm greater

Table 1 Scoring system for prominence of intestinal lymphoid nodular hyperplasia (19)

Grade	Endoscopy
0	None/sparsely dispersed lymphoid follicles
1	Mild, lymphoid follicles dispersed all through the walls
2	Severe, terminal ileum massed with lymphoid tissue, the valve protruding towards the caecum

**Figure 1** Endoscopic appearance of ileal LNH: clusters of small nodular lesions.

than the negative control was considered to be positive reaction (20).

Atopy patch test (APT)

According to the European Task Force on Atopic Dermatitis (ETFAD) protocol (21), on the test day, 2 ml of each allergen was placed in large Finn chambers on Scanpor tape (Haye's Service, The Netherlands). Fresh native foods, or lyophilized particles in a petrolatum vehicle, and commercially available nickel preparation (Lofarma, Milano, Italy) plus a negative control (petrolatum) were tested. The patch was attached for 48 h to a non-lesion area of the upper back, and the results were read at 48 and 72 h and classified based on the standardized reading key for the APT (20).

Interventions

A computer-generated sequence was used to allocate patients to Groups A, B and C using simple randomization (1:1:1 ratio; Fig. 1). No additional therapy was used during the study. Written informed consent was obtained from the parents of all of the patients. Group A: dietary avoidance of cow's milk, eggs and foods with allergic reactions detected by skin tests was recommended by a paediatric allergist. The elimination diet was provided to parents with the list of allowed foods and

supplementation of macro and micronutrients as prescribed by a nutritionist. Group B: a standard 50-mg/kg daily dose of oral mesalamine was prescribed by a paediatric gastroenterologist, who informed the parents of the potential side effects. If the drug was not well tolerated, the patient dropped out. Treatment was later discontinued after 8 wk to look for symptom recurrence. Group C: close clinical observation with antispasmodics or antidiarrhoeal drugs was used for the control patients, for whom the parents were instructed to contact their doctor immediately if symptoms persisted or worsened.

Follow-up

The clinical severity at times 0 and 1 (after 8 wk) was assessed by paediatric gastroenterologists blinded to the intervention group. Based on a standardized child behaviour checklist completed by the parents, the symptoms were graded using a modified version of Subject's Global Assessment of Relief for children (SGARC) (18) (Table 2). Clinical response was defined as an improvement of ≥ 1 point in a symptom score from time 0 to 1 (19).

Diagnosis of FA

For the patients from Group A whose symptoms improved after dietary treatment, double-blind, placebo-controlled food challenges (DBPCFC) were performed by paediatric allergists. The challenge was considered to be positive, thus confirming the diagnosis of FA, if previous symptoms relapsed within a 2-wk period after food re-exposure. With a minimum interval of 3 wk, each previously avoided food was challenged, and delayed-onset reactions were observed and recorded by parents.

Statistical analysis

The data were analysed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA; <http://www.graphpad.com>). For the primary outcome, the chi-squared test was used to assess the statistical significance (p value < 0.05) of differences in the clinical response among the groups. For the secondary outcome, frequency analysis, performed using the Student's t -test or Bonferroni test (where appropriate), was used for mean comparisons. We assessed the association between clinical (age and symptom severity and duration), endoscopic (site of LNH) and allergological features (personal or first-degree family history of atopy, skin tests results) with the clinical outcomes. For means, always SD is provided.

Long-term follow-up

The patients were clinically observed by paediatric gastroenterologists every 3 months during a 2 yr period, to look for the clinical course after treatment was discontinued. The patients whose symptoms worsened or persisted were further monitored, and additional laboratory or instrumental evaluation were performed if necessary.

Table 2 Symptom severity score

SCORE	Frequency	Social activity	School absence
0	Absent	–	–
1	1 episode/2 wk	Scarce/no interference	None
2	1–2 episodes/wk	Occasional interference	≤1 day/2 wk
3	>2 episodes per wk	Frequent interference	1–2 days/2 wk
4	Daily episodes	Major limitation	>2 days/2 wk

Results

Patients

Of the 268 children (mean age, 11.7 ± 3.2 yr; range, 2–15 yr; 162 females) recruited, LNH was found during 97 (36%) colonoscopies. Associated signs of inflammatory bowel disease were present in 24 patients; of them, 14 had Crohn's disease, and 10 had ulcerative colitis. LNH was the only finding in the remaining 73 patients, of whom one had juvenile rheumatoid arthritis. We finally enrolled 72 patients (41 M: 31 F), with a mean age at baseline observation of 8.3 ± 3.3 yr (range 3–15 yr) (Fig. 2). The clinical, endoscopic and allergological features for each group are shown in Table 3. No significant difference in the baseline patient characteristics was found among the groups. The main indications for colonoscopy were hematochezia (76%), recurrent abdominal pain (RAP) (68%) and/or chronic diarrhoea (32%), associated with minor symptoms, such as mucus in the stools. The median duration of symptoms during our study was 8.5 months (range 1–28 months). Systemic symptoms and signs were absent in all, except for the patients who were excluded for concomitant disease. In these 25 patients, accompanying symptoms were

chronic asthenia ($n = 12$), malnutrition ($n = 10$), anaemia ($n = 9$), increased CRP and or ESR ($n = 8$), nocturnal symptoms ($n = 5$), arthralgia ($n = 3$).

Endoscopy and histology

Grade 2 LNH in the TI was found in all of the patients, in association with colonic LNH in 33%, and was confirmed by histological demonstration of lymphoid aggregates in both sites. Additional non-specific features of oedema and a mild lymphoplasmatic infiltrate were found in 68 of 72 colonic biopsies, even in absence of macroscopic lesions and with no significant difference among the groups.

Allergy

A family or personal history of atopy was present in 24 (33%) and 14 (19%) patients, respectively. A positive response to the allergy skin tests was found in 25 (35%) patients: SPT for 15 (61%), APT for 9 (35%), both for 1 (4%). IgE and non-IgE mediated sensitization to foods was present for 13 (18%) and 6 (8%) patients, respectively. Sensitization to aeroallergens in 15 (20%) and nickel in 11 (15%) patients was detected by SPT and APT, respectively.

Clinical outcome

Clinical improvement was observed in 57 (79%) patients, with no statistically significant difference among the groups (Table 3). No mesalamine side effects were observed in group B. The DBPCFC was performed in 18 patients from Group A, with positive result in two patients (11%). Both patients had delayed-onset reactions (mean 3.2 days, range 1–7 days) to cow's milk proteins. No significant association between the examined patient characteristics and the response to treatment was found.

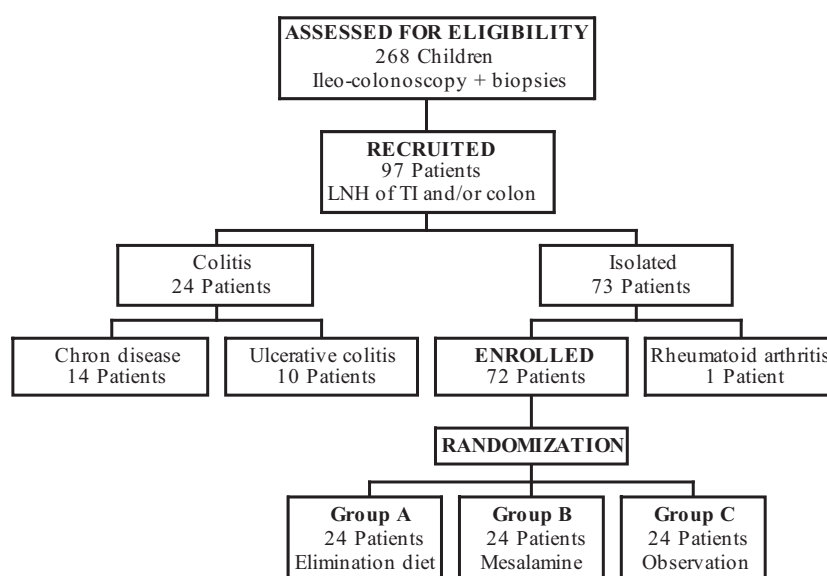
**Figure 2** Study flow diagram.

Table 3 Major clinical features of 72 patients with intestinal lymphoid nodular hyperplasia (LNH), clinical response after 8 wk of treatment with hypoallergenic diet (Group A) or mesalamine (Group B) or symptomatic drugs (Group C) and confidence interval (CI) 95% for the frequency of presentation in the three Groups

Baseline features	Group A n = 24 (%) CI 95%	Group B n = 24 (%) CI 95%	Group C n = 24 (%) CI 95%
Patients	8.2 ± 3.2 16.8	8.3 ± 2.9 15.9	8.3 ± 2.9 15.9
Age (yr) Mean ± SD			
Gender M:F			
Symptoms*	19 (79) 0.6270–0.9530 15 (67) 0.4819–0.8581	18 (75) 0.5768–0.9232 17 (71) 0.5285–0.8915	18 (75) 0.5768–0.9232 17 (71) 0.5285–0.8915
	RAP 5 (21) 0.0470–0.3730	9 (37) 0.1768–0.5632	9 (37) 0.1768–0.5632
Site of LNH**	Chronic diarrhoea 8 (33) 0.1419–0.5181	7 (29) 0.1085–0.4715	7 (29) 0.1085–0.4715
History of atopy	TI + Colon 10 (42) 0.2225–0.6175	10 (42) 0.2225–0.6175	10 (42) 0.2225–0.6175
	Familial*** 6 (25) 0.0768–0.4232	4 (17) 0.0197–0.3203	4 (17) 0.0197–0.3203
	Personal 8 (33) 0.1419–0.5181	6 (25) 0.0768–0.4232	6 (25) 0.0768–0.4232
Sensitization to foods	SPTs 4 (17) 0.0197–0.3203	5 (21) 0.0470–0.3730	2 (8) 0.0000–0.1885
	APT 18 (75) 0.5768–0.9232	20 (83) 0.6797–0.9803	19 (79) 0.6270–0.9530
Clinical outcome (Improvement ≥ 1 point)			

SD, standard deviation; LNH, lymphoid nodular hyperplasia; TI, terminal ileum; SPTs, skin prick tests; APT, atopy patch test; RAP, recurrent abdominal pain.

*More than 1 presenting symptoms was present in each patient.

**The remaining patients had an isolated LNH of terminal ileum. No patient had an isolated colon LNH.

***Atopic disease in siblings and/or parents.

Further assessment

After a therapy-free, observational period of 8 wk (time 2), a clinical improvement was observed in 10 of the 15 pts whose symptoms persisted at time 1, and only symptomatic treatment was administered in five with diarrhoea and two with abdominal pain. The remaining 5/15 patients, because of persistent haematochezia (2/15) or symptoms worsening (3/15) at time 2, underwent routine biochemistry and sideropenic anaemia was found in two of them. Capsule endoscopy of small bowel was additionally performed in the two patients with haematochezia and in one with chronic diarrhoea and failure to thrive, and intestinal LNH was the sole finding. The two patients with anaemia were supplemented with oral iron therapy, and control laboratory tests were performed after 8 wk. A cow's milk elimination diet for 4 wk was undergone in one of them because of persistent anaemia, and delayed-onset CM allergy was demonstrated by the DBPCFC.

Long-term observation

Of the 15/72 children with LNH whose symptoms persisted at time 1 (2 months), the clinical improvement was obtained with no specific therapy at time 2 (4 months) and at time 4 (8 months) in 10 and four patients, respectively. In 3/72 children, the dietetic treatment for CM allergy was required for a mean time of 12 months (8–15 months). In all patients, the symptoms completely recovered within a mean period of 6 ± 1.2 months (range 2–8 months). After 2 yr of clinical observation, none of these patients developed IBD or immune disease.

Discussion

Main findings

The clinical management of the GI symptoms in children with only LNH has not yet been clearly established. To determine the correct approach to these patients, we compared the clinical outcomes of 72 children randomized to different treatment strategies. Independent of the clinical or allergological features, dietary changes, mesalamine or symptomatic treatment was observed after 8 wk, and all of the three arms showed a high rate of clinical improvement regardless of the therapy. Interestingly, the symptom score was reduced ≥ 1 point in most of the patients assigned to antispasmodic or antidiarrhoeal drugs (79%) (Group C), with no significant difference compared to specific treatment with an elimination diet (75%) (Group A), or anti-inflammatory drugs (83%) (Group B). In the 2-yr follow-up period, none of them developed inflammatory bowel or systemic disease. The type, duration and severity of clinical presentation, endoscopic or histologic characteristics of the lymphoid nodules, were not predictive for differences in the clinical outcomes after 8 wk. The results of the allergy skin tests, familial or personal history of atopy and ileo-colonic site of LNH, were not associated with the clinical response to dietetic therapy.

Interpretation of findings

The clinical improvement frequently found in our case series might indicate the spontaneous resolution of symptoms and consequently the benign nature of LNH as isolated finding in childhood. As previously reported (8, 22–26), the majority of children with LNH had rectal bleeding and abdominal pain, with or without a change in bowel movements, which are the most common indications for colonoscopy. A hypothetical explanation for rectal bleeding in patients with LNH is that ulcerations may occur over the follicles (27, 28), but LNH can be found also in asymptomatic children.

Comparison with the relevant findings from other studies

Our data demonstrate a 36% incidence of LNH in the lower gastrointestinal tracts from 268 paediatric colonoscopies performed in a 2-yr period in our tertiary paediatric gastroenterology unit, thus confirming that this condition is very common in children. The association of upper and lower intestinal LNH with FA has been reported by many studies (3, 7, 14–18). Kokkonen et al. (7) suggested the LNH of the TI is associated with a variety of immune-activity states, while LNH of the colon seemed to be more specifically related to FA. In our case series, LNH was observed in 32% of 72 patients in the colon, always with concomitant nodularity of the TI, and was not associated with differences in the clinical response regardless to the dietary treatment. Furthermore, to assess whether the improvement achieved for 18 of our 24 patients treated with an elimination diet was due to a FA, we performed a DBPCFC with two positive reactions (11%). Of 15 patients whose symptoms did not improve at first follow-up, the diagnosis of CM allergy was confirmed in one by recurrence of haematochezia after DBPCFC. This observation suggests only a minority of children with LNH requires a specific treatment for FA, and the indication should be only confirmed by the DBPCFC. Troncone et al. (29) reported similar results in 10 patients with lower intestinal LNH, who all experienced clinical healing on a hypoallergenic diet, but only 2 (20%) relapsed after food challenge. We agree with their assumption that FA is most likely responsible for intestinal symptoms only in a minority of patients with LNH.

The skin test in patients with LNH was never extensively evaluated in previous studies. Kokkonen et al. (13) reported 4 of 9 positive skin prick tests in patients with LNH and FA and none in those with LNH but no FA. The presence of both IgE and non-IgE mediated sensitization to foods was detected in 18% and 8% by SPT and APT, respectively. However, in our patients, the results of the allergy skin tests were not able to

predict differences in the clinical response in the presence or absence of dietary treatment, suggesting the DBPCFC should be performed independently on their results.

Study limitations

Whether the symptoms observed were related to LNH is unknown because for ethical reasons, we could not perform a control colonoscopy after clinical improvement. The atopy details and the clinical outcomes of our patients were not compared to those of the 203 children without LNH who underwent ileocolonoscopy for the same symptoms. The classification of LNH is largely non-quantitative and the intraobserver as well as interobserver variation is likely high.

Conclusion

Children with isolated LNH of the lower GI tract should frequently have a self-limiting clinical course, which is unlikely to be affected by food exclusion or mesalamine treatment. Once inflammatory bowel diseases and infections have been excluded, LNH can be considered to be benign and most likely coincidental finding with no clinical significance. Skin testing for foods is not recommended for those patients because the only indication for dietary treatment is a positive DBPCFC. Consequently, we propose first performing non-invasive tests to assess for an infectious, inflammatory or immune aetiology. In patients with no pathological findings except for LNH, clinical observation with only symptomatic approach is most likely the most appropriate management. The long-term clinical outcome is benign, and these children may appear able to wean off medications over the succeeding months.

Conflict of interests

The authors declare that they have no competing interests. Patient consent: Approval for the study was obtained from the Ethics Committee, Policlinico Umberto I Hospital, Rome, Italy.

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SL¹: protocol design, gastroenterology evaluation, editing manuscript; GDN¹: gastroenterology and endoscopy evaluation; GL¹: protocol design, gastroenterology evaluation; YDA¹: protocol design, gastroenterology evaluation; MA¹: protocol design, editing manuscript; SO¹: gastroenterology and endoscopy evaluation; SF²: gastroenterology and endoscopy evaluation, editing manuscript; DS¹: protocol design, gastroenterology evaluation; TF³: protocol design, allergology evaluation, editing manuscript.

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