

Esophageal Inlet Patch: An Under-Recognized Cause of Symptoms in Children

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Objectives To determine the incidence of inlet patch (IP) and to assess the clinical and pathological features, role of the diagnostic workup in treatment decision making, efficacy of medical and endoscopic therapy, and natural history in a pediatric population.

Study design Consecutive patients aged <18 years (n = 1000) undergoing esophagogastroduodenoscopy were enrolled prospectively. Biopsy specimens were obtained from IPs and the proximal and distal esophagus, stomach, and duodenum. Multichannel intraluminal impedance and pH monitoring (MII-pH) was performed in all symptomatic patients. Symptomatic patients were treated with proton pump inhibitors for 8 weeks, and IP ablation by argon plasma coagulation (APC) was performed in unresponsive patients.

Results The endoscopic incidence of IP was 6.3%, with a cumulative missing rate of 5.8%. Thirty-five of the 63 patients (56%) were asymptomatic, 11 (17%) had symptoms clearly related to the underlying digestive disorder, and 17 (27%) had chronic IP-related symptoms. MII-pH was positive in 10 of the 28 symptomatic patients. All 17 patients with IP-related symptoms were unresponsive to proton pump inhibitors and were treated with APC, and all had achieved complete remission by the 3-year follow-up. Patients with underlying disorders were successfully treated with medical therapy, and asymptomatic patients remained symptom-free, with no endoscopic or histological changes seen at the 3-year follow-up.

Conclusion IP is an under-recognized cause of symptoms in children with unexplained esophageal and respiratory symptoms. MII-pH and bioptic sampling are needed to exclude entities mimicking IP symptoms and to direct therapy. APC is safe and effective for treating IP-related symptoms. (*J Pediatr* 2016; ■: ■ - ■).

An inlet patch (IP) is a salmon-colored, velvet-appearing, distinct area of heterotopic gastric mucosa typically located in the proximal esophagus just distal to the upper esophageal sphincter. It is usually a single lesion but can be multiple, ranging in size from a few millimeters to >5 cm.¹⁻³

The endoscopic-detected incidence of IP ranges from 0.1% and 10% in published studies.^{1,4-6} The true incidence may be underestimated; in daily practice, IP is often missed during routine endoscopy. This might be related to the fact that the lower part of the esophagus is more often in the focus of the endoscopist, owing to the frequent pathological findings in this area.^{5,7,8}

Although generally asymptomatic, the presence of IP has been associated with laryngopharyngeal symptoms (ie dysphagia, laryngospasms, hoarseness, globus throat discomfort, and chronic cough), likely related to acid production.^{4,9-13} IPs also have been linked to complications including esophageal strictures, tracheoesophageal fistula, ulcerations, bleeding, and perforation.¹⁴⁻¹⁸ Furthermore, in an autopsy study of a pediatric population, the presence of an IP was associated with unexplained death; the authors speculated that pulmonary aspiration of esophageal contents may cause death in some of these children.¹⁹

IPs are also potential sites for *Helicobacter pylori* infection.^{18,20} In addition, Barrett esophagus and adenocarcinoma within IPs have been reported in adults, proving its potential, albeit rare, malignant progression.²¹⁻³²

To date, only a few studies on IP in the pediatric population have been published, most of which are in case report form and limited by their small sample size and retrospective design.^{10,11,33-38} The aims of the present prospective study were to assess: (1) IP in a pediatric population in which the endoscopist is sensitized to search for this entity; (2) the associated clinicopathological

APC	Argon plasma coagulation
AR	Acid reflux
EGD	Esophagogastroduodenoscopy
EoE	Eosinophilic esophagitis
GERD	Gastroesophageal reflux disease
IP	Inlet patch
MII-pH	Multichannel intraluminal impedance and pH monitoring
PPI	Proton pump inhibitor
RSI	Reflux symptom index
SAP	Symptom association probability
SI	Symptom index

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features of IP; (3) the role of the diagnostic workup in treatment decision making; (4) the efficacy of medical and endoscopic therapy; and (5) the natural history of IP.

Methods

Consecutive patients aged <18 years (n = 1000; 621 females) undergoing esophagogastroduodenoscopy (EGD) for various indications were prospectively assessed for the presence of IP between January 2011 and December 2012 at the Pediatric Gastroenterology Units of the University of Rome and University of Bologna. Patients who underwent endoscopy for such indications as urgent, interventional, capsule placement, enteroscopy, and systemic disorders (eg, Sjögren syndrome, scleroderma) were excluded. The appropriate Institutional Ethical Committees approved the study design. Written informed consent was obtained from all parents, and children when applicable, after they received a thorough explanation of the research protocol.

Before EGD, all patients were carefully questioned about symptoms experienced within the previous month using a self-administered 9-item reflux symptom index (RSI).³⁹ Patients graded the severity of each item from 0 (none) to 5 (severe problem). Clinical response was defined as a reduction in clinical score of at least 3 points for each symptom.

Endoscopic Procedures

All EGD procedures were performed under general anesthesia by an experienced endoscopist using a video gastroscope (GIF-180; Olympus, Hamburg, Germany). During the procedure, the esophagus was carefully surveyed, with particular attention to the area of the upper esophageal sphincter. This area was best examined by slowly withdrawing the endoscope, with repeated short inflations while rotating the instrument.

IPs were identified as patches covered with salmon-red mucosa distinguishable from surrounding grayish-pearl-colored esophageal mucosa by well-defined margins (Figure 1, A). Each IP was measured by comparing it with the length of the metallic tip of the biopsy forceps (5 mm).

In patients with multiple patches, the sizes of all patches were summed. Reflux esophagitis and Barrett esophagus were surveyed and classified according to the Los Angeles classification system⁴⁰ and the Prague C & M criteria,⁴¹ respectively. Hiatal hernia was considered when the maximum length of the gastric mucosal folds above the gastroesophageal junction exceeded 20 mm.

Histopathological Assessment

At least 2 biopsy specimens were obtained from each IP using disposable endoscopy biopsy forceps (EndoJaw FB 230V; Olympus). Biopsy specimens were also obtained from the proximal and distal esophagus, fundus, antrum, corpus, and duodenum of the patients with an IP. All biopsy specimens were blindly reviewed by a single pathologist. The squamous mucosa was examined for changes of reflux esophagitis,⁴² and the columnar mucosa was examined for the presence and degree of inflammation and/or intestinal metaplasia according to the modified Sydney classification system.⁴³ IP mucosal type was classified based on the presence of parietal and chief cells as antral type, fundic type, or transitional type. The presence of *H pylori* was evaluated using hematoxylin and eosin and Giemsa staining in the IP and the gastric mucosa.

Multichannel Intraluminal Impedance and pH Monitoring

The presence of gastroesophageal reflux or IP-related acid production was assessed using multichannel intraluminal impedance and pH monitoring (MII-pH). For ethical reasons, MII-pH was performed only in symptomatic patients with IP.

The procedure was performed with a combined MII-pH flexible catheter (Covidien-Medtronic, Minneapolis, Minnesota) with 8 impedance rings (representing 6 impedance channels) and 2 antimony pH sensors. The distal pH sensor was located at 4.5 cm from the catheter tip, and the proximal pH sensor was located 15 cm from the distal sensor. The 6 impedance channels were located in the MII-pH probe at -2, 0, 2, 4, 13, and 15 cm from the distal pH sensor. The probe was then

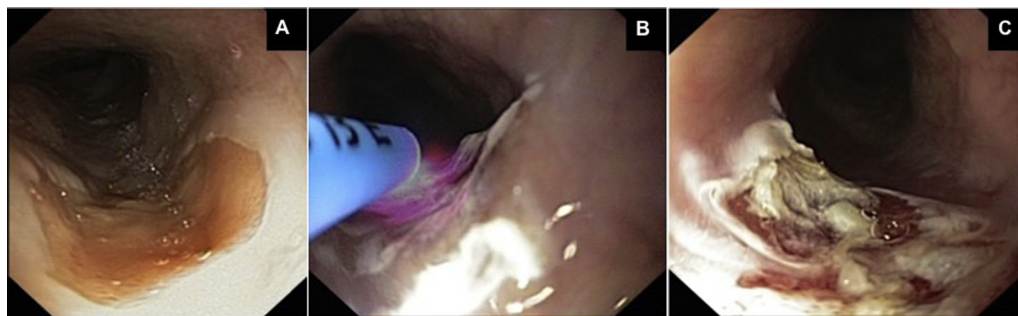


Figure 1. A, Typical endoscopic appearance of IP. B, IP treatment with APC. C, Endoscopic findings at the end of the APC treatment.

inserted transnasally in the esophagus, and the distal pH sensor was placed at 87% of the nares–lower esophageal sphincter distance (Strobel formula)⁴⁴ and verified with fluoroscopy to be at 2 vertebral bodies above the diaphragm. The catheter was connected to a data recorder (Digitrapper pH-Z; Covidien-Medtronic), and data were analyzed with dedicated software (AccuView 5.2; Covidien-Medtronic). Tracings (meal included) were also reviewed manually.

The following MII-pH variables were analyzed: total number of reflux episodes, number of acid reflux (AR) episodes, number of weakly AR and weakly alkaline reflux episodes, percentage of recording time with a pH <4 (RSI), number of proximal reflux episodes, number of episodes of long duration (>5 minutes), number of proximal acid-independent episodes, symptom index (SI), and symptom association probability (SAP).^{45,46}

Acid secretion from IP was defined as any recording of pH <4 by the proximal sensor that was not preceded by a recording of pH <4 by the distal sensor. Such episodes are termed “acid-independent” episodes. SI and SAP were calculated for AR, weakly AR, and alkaline reflux and were considered positive at scores of $\geq 50\%$ and $>95\%$, respectively.^{45,46}

The MII-pH analysis was considered abnormal at an RSI of $>5\%$ or an SI of $\geq 50\%$ or SAP of $>95\%$ for each symptom.

Medical, Endoscopic Therapy, and Follow-up

Regardless of the MII-pH results, all symptomatic patients were treated with a proton pump inhibitor (PPI) for 8 weeks (omeprazole 2 mg/kg twice daily, not to exceed 60 mg/day). Ablation of the lesions by argon plasma coagulation (APC) was proposed to patients unresponsive to PPI.

Each APC procedure was performed by 1 of 3 experienced endoscopists using a gastrointestinal argon plasma system (APC 300; ERBE Elektromedizin, Tübingen, Germany) at a power setting of 60 W and an argon flow of 2 L/min. A mucosectomy cap was fitted at the distal tip of the endoscope to improve the view and decrease the risk of damage to surrounding squamous epithelium.^{35,47,48} The procedure aimed to completely ablate all IPs in a single session (Figure 1, B and C).

Symptoms were reevaluated at 3 months after APC treatment, with a follow-up endoscopy performed to check for potential side effects (eg, stricture formation) and completeness of ablation. All patients were followed with telephone interviews at 6, 12, 24, and 36 months after enrollment. An endoscopic control was proposed to all patients with IP at 3 years after the first endoscopy.

Statistical Analyses

Demographic characteristics are reported as descriptive statistics: quantitative parameters are expressed as mean \pm SD, and qualitative parameters as absolute and relative frequencies. Symptom incidence was compared between the 2 groups using the Fisher exact test. Comparisons of continuously scaled variables were performed using the parametric independent-samples *t* test. If assumptions for proper application of the parametric *t* test (ie, normality and/or

homogeneity of variance) were violated, then the nonparametric Mann-Whitney *U* test was performed. The statistical significance was set at a *P* value < .05 (2-tailed test). All statistical analyses were conducted using SPSS version 19.0 (IBM, Armonk, New York).

Results

IPs were endoscopically found and biopsy-confirmed in 63 of the 1000 consecutive enrolled children, for an incidence of 6.3%. The study cohort comprised 37 females and 26 males, with a median age of 12 ± 3.5 years (range, 4–17 years). Interestingly, 19 of the IPs were detected in a group of 323 children who underwent previous EGD (performed by another endoscopist than the endoscopist involved in the present study), with a cumulative missing rate of 5.8%. There was no significant difference in the missing rate between the symptomatic patients and the asymptomatic patients (*P* = .36).

At endoscopy, a single IP was identified in 58 patients, and multiple IPs were detected in 5 patients. The IPs were located just distal to the upper esophageal sphincter and had a median size of 13.3 ± 6 mm (range, 5–25 mm). There was no correlation between IP size and presence/absence of symptoms.

Two cases were associated with *H pylori* erosive gastritis without synchronous colonization of the IP. Three patients had endoscopic findings suggestive of eosinophilic esophagitis (EoE), which was confirmed on histological examination. No patient had erosive esophagitis, Barrett esophagus, or hiatal hernia.

Histology revealed that 26 of the 63 patients had fundic type mucosa in the IP, 17 had antral type mucosa, and 13 had both antral and fundic type mucosa. Five patients had intestinal metaplasia in the IP; 3 of these patients had IP-related symptoms and the other 2 were asymptomatic. Mild to moderate chronic inflammation was seen in 7 patients. There was no correlation between the degree of inflammation and the presence or absence of symptoms. No patients exhibited *H pylori* infection or any dysplastic changes. EoE was diagnosed in 4 patients, 1 of whom had a normal endoscopic mucosal appearance.

Thirty-five of the 63 patients (56%) were asymptomatic, and IP was an incidental finding. The clinical indications were celiac disease in 11 patients, ulcerative colitis in 9, Crohn's disease in 13, and Peutz-Jeghers syndrome in 2.

Eleven of the 63 patients (17%) had symptoms clearly related to the underlying digestive disorder: EoE in 3 patients, *H pylori* infection in 2, and gastroesophageal reflux disease (GERD) in 6 (in 2 as a consequence of esophageal atresia repair). This was confirmed by complete clinical remission with specific disease-directed therapy.

Seventeen of the 63 patients (27%) had chronic unexplained symptoms unresponsive to specific therapy, including dysphagia and odynophagia in 2 patients, dysphagia and pyrosis in 3, dysphagia in 2, globus sensation and sore throat in 3, globus sensation and hoarseness in 1, chronic cough in 4, and laryngospasm in 2.

MII-pH was positive in 10 of the 28 symptomatic children. No acid-independent episodes of secretion from the IP were detected.

Clinical Outcomes and Management of Symptomatic Patients

Among the 17 patients with persistent symptoms, 1 patient with EoE (typical endoscopic and histological finding), dysphagia, and pyrosis had persistent symptoms despite a complete histological remission with oral topical steroid plus PPI therapy negative MII-pH results. Four patients with a MII-pH-based diagnosis of GERD (1 patient with globus sensation and hoarseness, 2 patients with chronic cough, and 1 patient with laryngospasms) had persistent symptoms despite therapy with omeprazole 2 mg/kg and a second MII-pH performed during the course of PPI therapy showing good acid control with no correlation between symptoms and AR/weakly AR/nonacid reflux events. Twelve symptomatic patients with isolated IP had persistent symptoms despite therapy with omeprazole 2 mg/kg for 8 weeks.

All 17 patients with persistent symptoms were treated with APC. Endoscopic follow-up performed 3 months after APC showed complete IP eradication in all patients in the absence of complications.

Natural History

Twelve of the 17 patients treated with APC were asymptomatic at the 3-year clinical follow-up. The patient with EoE required a cycle of standard therapy with satisfactory clinical response and 4 patients with GERD (detected by MII-pH) required PPIs on demand. Endoscopic follow-up after 3 years revealed no residual or recurrent IP lesions in any patients.

The 11 patients with an underlying disorder were treated with standard therapy, and all exhibited a satisfactory clinical response. Endoscopic follow-up performed in all but 2 of the patients at 3 years did not reveal any endoscopic or histological changes. The 2 patients lost to follow-up had *H pylori* infection and refused repeat endoscopy, and were available only for clinical follow-up (Figure 2; available at www.jpeds.com).

Thirty-five asymptomatic patients continued to be symptom-free at the 3-year follow-up. Endoscopic follow-up was available for only 25 of these patients. Ten patients with celiac disease refused repeat endoscopy and were available only for clinical follow-up. No endoscopic or histological changes were evident in any of these patients.

Discussion

Traditionally considered a nonpathological incidental finding, IP has now been identified as the possible cause of unexplained digestive and respiratory symptoms, such as chronic cough, laryngospasm, sore throat, globus pharyngeus, dysphagia, hoarseness, and vocal cord dysfunction,^{2-7,9-12} at least in a subgroup of patients. Moreover, case reports have shown that IP can play a role in the development of severe complications, such as webs, strictures, ulcers, perforation, fistulas, and adenocarcinoma.¹⁴⁻³²

The endoscopic incidence of IP in pediatric patients ranges from 0.03% to 1.4% in retrospective studies.^{33,34} The sole prospective pediatric study, performed in 407 children, showed an incidence of 5.9%,¹¹ similar to that found in our study population. We found a missing rate of 5.8% in a selected group of children who had undergone previous EGD. These data confirm results reported by Azar et al⁸ in adults showing a higher incidence of IP when the operator is aware of the entity. Taken together, these data suggest that IP is a frequently unrecognized entity that has received little attention in the pediatric literature. This may be due to technical difficulties related to endoscopic evaluation of the proximal esophagus. Data from adult studies show that narrow-band imaging increases the detection of IP by approximately 3-fold compared with standard white light endoscopy.^{49,50}

In our series, we did not find associations between IP and erosive esophagitis, Barrett esophagus, or hiatal hernia, but did find an association between IP and EoE. This intriguing finding, although related to the high incidence of EoE in the subjects followed in our center (18 new EoE diagnoses in the study period, and a total of 44 patients with EoE under follow-up), confirms the importance of careful examination and appropriate biopsy sampling of the entire esophagus in children undergoing upper endoscopy for dysphagia.

In our cohort, we found a predominant fundic type mucosa, with no correlation between inflammation degree and symptoms. In contrast to previous reports,^{18,20,33,34} we found no evidence of *H pylori* colonization. We identified intestinal metaplasia in the IP in 5 patients, 2 of whom were asymptomatic. Given the preneoplastic nature of this abnormality in adults,^{21,25-32} our data support the relevance of IP biopsy sampling to identify patients requiring endoscopic and histological surveillance. Furthermore, future studies based on MII-pH, immunohistochemical, and molecular analyses in all patients (ie, symptomatic and asymptomatic) might explain the development of metaplasia in IP.

An important challenge for clinicians is to determine whether IP is associated with symptoms. Compared with healthy controls, both children and adults with IP have a higher incidence of digestive and respiratory symptoms.^{1,3-7,9-12} This led us to hypothesize that acid secretion plays a role in symptom generation and such complications as stricture, ulceration, and fistulas.^{13,51,52} Acid secretion from the IP was documented in only a small proportion of symptomatic patients, however.^{13,53} In this study, we did not find any acid-independent episodes related to IP, suggesting that mechanisms other than acid-induced injury are involved in symptom generation.

Approximately 56% of our subjects were asymptomatic (ie, IP considered an incidental finding), 17% had symptoms related to another underlying disorder, and 27% had IP-related symptoms. Among the subjects with non-IP-related symptoms, histological analysis and MII-pH monitoring identified 3 cases of EoE, 2 cases of *H pylori* infection, and 6 cases of GERD, and IP was an incidental finding in all of these subjects. Among the subjects with IP-related symptoms, we identified overlap with EoE in 1 and overlap with GERD in

4; in these patients, complete remission of symptoms was obtained only after IP ablation with APC, suggesting IP as the main cause of the symptoms. In all of the symptomatic cases, an extensive diagnostic workup was essential to correctly identify the role of IP in symptom generation, thereby avoiding unnecessary treatments (eg, surgical treatment for GERD, APC ablation for IP).

There are no standardized treatment strategies for IP. Treatment should be recommended to symptomatic patients and may include pharmacologic therapy with PPIs or H2 receptor antagonists, complete endoscopic mucosal resection, APC, and dilatation of strictures.^{1,15-18} Only a few previous case reports have suggested the use of PPIs in patients with history of laryngopharyngeal symptoms and IP in this region. Unfortunately, no MII-pH studies were performed in these patients, and for this reason we cannot exclude the possibility of GERD overlap. In our study, 6 of 10 children with IP and pathological MII-pH monitoring suggestive of GERD were successfully treated with PPIs, and in the other 4 children, MII-pH was useful in directing therapy toward IP ablation. A positive effect of APC endoscopic ablation has been demonstrated in adults with IP-related symptoms.⁴⁸ This approach was described in 3 pediatric cases as well, confirming the safety and efficacy of this technique,³⁵ although large and long-term follow-up studies are lacking. Here we report the safety and efficacy of APC in 17 patients with IP-related symptoms, who remained asymptomatic at 3-year follow-up in the absence of endoscopic recurrence.

In conclusion, IP is an under-recognized cause of symptoms and should be suspected during endoscopic examination of children with unexplained esophageal and respiratory symptoms. MII-pH and bioptic sampling of both IP and esophageal mucosa aid in the exclusion of other entities potentially responsible for symptoms and in the choice of appropriate therapeutic management strategies. ■

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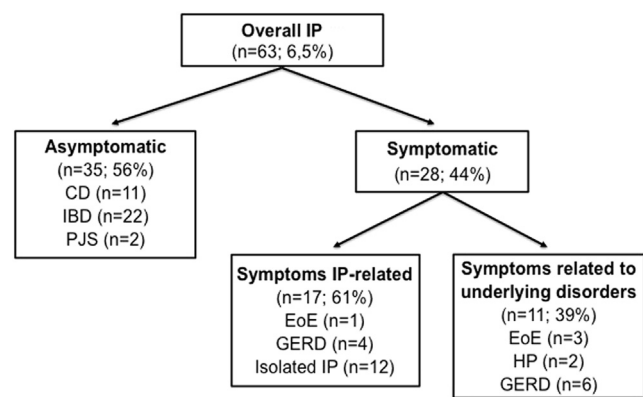


Figure 2. Study flow. *IP*, inlet patch; *CD*, celiac disease; *IBD*, inflammatory bowel disease; *PJS*, Peutz-Jeghers syndrome; *EoE*, eosinophilic esophagitis; *GERD*, gastroesophageal reflux disease; *HP*, *Helicobacter pylori*.