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Original Article

Practice Patterns for Eosinophilic Esophagitis Patients in Busan and Gyeongnam: A Korean Multicenter Database Study

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Background/Aims
The prevalence of eosinophilic esophagitis is increasing in Korea and there are few single-center studies regarding eosinophilic esophagitis in Korea. In particular, data about management for eosinophilic esophagitis are lacking. We aim to evaluate the practice patterns, including initial treatment and response, in the Busan city and Gyeongnam province area.

Methods
We retrospectively reviewed medical records to gain data on patient characteristics, medication, endoscopic images, and esophageal biopsy results. From January 2009 to December 2019, a total of 42 patients were diagnosed with eosinophilic esophagitis.

Results
The mean age was 50.7 (from 22 to 81) years and the cohort was predominantly male (78.6%, 33/42). The proton pump inhibitor was the preferred treatment as an initial trial for 64.3% (27/42) of patients, followed by swallowed topical steroids (16.7%, 7/42). Clinical improvement after proton pump inhibitor therapy was achieved in 88.9% (24/27) of patients. Two patients who did not achieve improvement showed a clinical and endoscopic response after swallowed topical steroids treatment. No patient received diet elimination or balloon dilatation therapy.

Conclusions
The treatment response of eosinophilic esophagitis was good in Busan city and Gyeongnam province area in Korea. Proton pump inhibitor therapy was the preferred and most effective treatment for eosinophilic esophagitis as the initial therapy.
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Key Words
Eosinophilic esophagitis; Proton pump inhibitors; Steroids

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Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated, esophageal disorder that typically presents with dysphagia or food impaction related with esophageal dysfunction and is characterized by eosinophilic predominant inflammation.[1] Inflammation in EoE characteristically consists of ≥ 15 eosinophils per high power field (HPF) on an esophageal biopsy. The gastrointestinal eosinophilia is limited to the esophagus and other causes of esophageal eosinophilia should be ruled out.[2] The incidence of EoE appears to be rising with increased recognition of the disorder.[3] Recent Korean studies have also reported that the EoE incidence appears to have increased considerably during the observation period.[4,5]

As inflammation in EoE might persist without treatment, patients develop esophageal fibrostenosis caused by progressive esophageal remodeling.[6] The goal of treatment is symptomatic relief, ideally with histological remission. The initial management of EoE includes proton pump inhibitors (PPI), swallowed topical steroids (STS), and elimination diet.[1] PPI may benefit patients with EoE either by reducing acid production, or by other anti-inflammatory effects.[2] STS have shown effectiveness on the induction and maintenance of EoE.[7,8] The elimination diet enables the examination of specific food allergies that commonly cause hypersensitivity in the general population.[9] Future studies are needed to compare the effectiveness between these therapies. As the initial regimen to treat EoE remains undefined, the approach to patients is heterogeneous across providers.[2] In addition, the optimal second-line treatment modality after failure of the first-line therapy is also uncertain. To date, substantial variability in adherence to guidelines regarding practice patterns in EoE are documented.[10-12]

The management patterns of EoE have not been reported in Asian countries. Recent guidelines suggest that PPI should be considered as an initial treatment because of the low cost, good safety profile, and convenience; and the response of any therapy should be checked by a follow-up endoscopy with a biopsy.[2] In the present study, we aim to evaluate the practice patterns including treatment, efficacy of therapy, and follow-up in the Busan city and Gyeongnam province area in Korea.

Materials and Methods

The medical records of patients (age more than 18 years) who received endoscopy in 6 tertiary care hospitals (Kosin University College of Medicine, Pusan National University Hospital, Busan Paik Hospital, Dong-A University Hospital, Haeundae Paik Hospital, and Pusan National University Yangsan Hospital) in Busan and Gyeongnam, Korea, between January 2009 and December 2019 were retrospectively reviewed. Among 8 referral centers in Busan and Gyeongnam, 75.0% (6/8) of hospitals participated in this study. Busan-Gyeongnam is the second metropolitan area after the Seoul capital area, has a population of 7 million, as of 2010. It is located in the southeast of South Korea.

During the study period, EoE was confirmed by performing endoscopy with an esophageal biopsy. All esophageal biopsy reports of 6 center during 10 years were analyzed. Consequently, a total of 42 patients diagnosed with EoE at the 6 hospitals were included. The following data were collected and analyzed from medical records: patient characteristics, treatment details including medications, dietary and endoscopic interventions, endoscopic images and esophageal biopsy results, presence of allergies, and season of diagnosis. This study was approved by the Institutional Review Board of each hospital (05-2019-150).

Diagnosis of Eosinophilic Esophagitis

Esophageal biopsy specimens were obtained from the mid to proximal and distal (5 cm above the gastroesophageal junction) esophagus.[13] EoE was defined when all of the following criteria were fulfilled: (1) a peak value of 15 or more eosinophils per HPF, (2) endoscopic abnormality or symptoms related to esophageal dysfunction, and (3) exclusion of other causes that could potentially contribute to esophageal eosinophilia.[2] All of the biopsy specimen slides were reviewed by specialized pathologists of each center.

Endoscopic Evaluation

Endoscopic examinations with biopsy were performed by the endoscopy faculty or gastroenterology fellows under supervision of endoscopists who had the experience of over 10 000 endoscopic examinations. Endoscopic features suggestive of EoE were classified using the endoscopic reference score system (EREFS).[14] Edema was graded as 0 (absent) or 1 (present, loss of vascular markings). Rings were graded as 0 (absent), 1 (mild, circumferential ridges), 2 (moderate, distinct rings that did not impair passage of a standard endoscope), or 3 (severe, distinct ring that did not allow a standard endoscope to pass). Exudates were grade as 0 (absent), 1 (mild, covering < 10% of the esophageal mucosa), or 2 (severe, involving > 10%). Furrows were graded as 0 (absent) or 1 (present). Strictures were graded as 0 (absent) or 1 (present) (Fig. 1).

Definition

Clinical response was defined as the remission or improvement of symptoms related with esophageal dysfunction. Endoscopic response was defined as the improvement in EREFS or EREFS < 2.[15] Histological response was defined as an eosinophil peak count of < 15 eosinophils/HPF at all esophageal levels on the follow-up biopsy.[16] Lack of response was defined as persistence or worsening of symptoms combined with no improvement of endoscopic and histologic disease activity.

Statistical Methods

Categorical variables were analyzed using the chi-square test or Fisher's exact test and continuous variables were analyzed using the Student's *t* test. The Kruskal-Wallis test was used to determine whether there is a significant difference in the incidence of EoE with 3 years of interval. A *P*-value < 0.05 was considered statistically significant. Statistical calculations were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp, Armonk, NY, USA).

Results

During the study period, EoE was diagnosed in 42 patients at 6 tertiary care hospitals (Fig. 2). The mean age was 50.7 (from 22 to 81) years and the cohort was predominantly male (78.6%, 33/42). The proportion of patients with allergies was 28.6% (12/42). There was no seasonal variation in the first diagnosis of EoE. Dysphagia was the most common symptom related with esophageal dysfunction (38.1%, 16/42), followed by heartburn (21.4%, 9/42), epigastric or abdominal pain (14.3%, 6/42), food impaction (4.8%, 2/42), and globus (2.4%, 1/42) (Table 1). In the endoscopic findings, furrows and edema were the most common (57.1%, 24/42), followed by rings (42.9%, 18/42), exudates (14.3%, 6/42), and stricture (9.5%, 4/42). The follow-up endoscopy interval (mean ± standard deviation) was 10.6 ± 5.7 months.

Choice of First- and Second-line Therapy for Eosinophilic Esophagitis

PPIs were the preferred first-line therapy for 64.3% (27/42) of patients, followed by STS (16.7%, 7/42). The duration (mean ± standard deviation) of PPI and STS in first-line prescriptions were 172 ± 226 days and 98 ± 87 days, respectively. As a second-line therapy, 2 of 3 patients who did not achieve a clinical and endoscopic response after the PPI trial received STS treatment. Diet elimination or balloon dilatation therapy was not chosen as the first- or second-line treatment in this study. One-fifth of patients (19.0%, 8/42) did not received any treatment. Among the 8 non-treated patients, endoscopic improvement was found in 1 patient (12.5%).

Treatment Response for Eosinophilic Esophagitis

A clinical response to PPI therapy was observed in 88.9% (24/27) of patients. An endoscopic response was achieved in 78.6% (11/14) of patients who underwent the follow-up endoscopy after the PPI trial. Among 14 patients who received a follow-up endoscopy, esophageal biopsies were performed in 13. A histological response was observed in 84.6% (11/13) of patients who received follow-up biopsies. The interval of follow-up endoscopy was 10.6 ± 5.7 months.

The clinical response rate of the first-line STS therapy was 100.0% (7/7). Approximately half of patients (4/7) received a

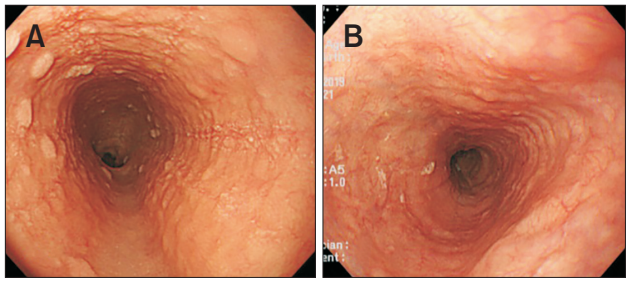

Figure 1. Endoscopic findings in eosinophilic esophagitis with application of the endoscopic reference score system. (A) E1 R0 E2 F1 S0: edema is grade as present (1); rings are graded as present (0); exudates are graded as severe (1); furrows are graded as mild (1); and stricture is graded as absent (0). (B) E1 R1 E1 F0 S0: edema is grade as present (1); rings are graded as mild (1); exudates are graded as mild (1); furrows are graded as absent (0); and stricture is graded as absent (0).

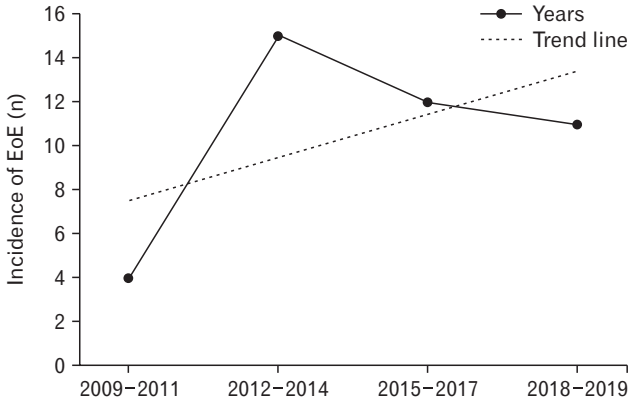

Figure 2. The changing incidence of eosinophilic esophagitis by 3 years of interval ($P = 0.392$).

follow-up endoscopy with biopsy. An endoscopic and histological response was found in all patents (4/4). STS therapy after failure of PPI treatment showed a clinical and endoscopic response in all patients (2/2). Among 2 patients who received second-line STS therapy, a follow-up biopsy was performed in only 1 patient. A histological response was achieved in this patient.

Comparison of Clinical Factors Between Therapy Choices for Eosinophilic Esophagitis

The presence of esophageal symptoms was significantly different between non-treated and treated patients (Table 2). All non-

Table 1. Baseline Characteristics of the Study Population

Characteristics	Total (N = 42)
Age (yr)	51.6 ± 15.1
Male/female	33/9 (78.6/21.4)
Alcohol	16 (38.1)
Smoking	8 (19.0)
Allergic disease	
Allergic rhinitis	4 (9.5)
Allergic dermatitis	3 (7.1)
Asthma	3 (7.1)
Food allergy	2 (4.8)
Season to diagnose EoE	
Spring/summer/autumn/winter	11 (26.2)/23 (54.8)/ 12 (28.6)/6 (14.3)
Esophageal symptom	
Dysphagia	16 (38.1)
Heartburn	9 (21.4)
Pain	6 (14.3)
Globus	1 (2.4)
Food impaction	2 (4.8)
None	15 (35.7)
EREFS	
Edema	
Grade 0 (absent)/1 (present)	24 (57.1)/18 (42.9)
Rings	24 (57.1)/15 (35.7)/ 3 (7.1)/0 (0.0)
Grade 0 (none)/1 (mild)/ 2 (moderate)/3 (severe)	(57.1/35.7/15/7.1/0)
Exudates	
Grade 0 (none)/1 (mild)/2 (severe)	36 (85.7)/1 (2.4)/5 (11.9)
Furrows	
Grade 0 (absent)/1 (present)	18/24 (42.9/57.1)
Stricture	
Grade 0 (absent)/1 (present)	38 (90.5)/4 (9.5)
Reflux esophagitis	4 (9.5)

EoE, eosinophilic esophagitis; EREFS, endoscopic reference score system.
Data are presented as mean ± SD or n (%).

Table 2. Comparison of Clinical Factors Between Non-treated and Treated Patients

Clinical factors	No treatment (n = 8)	PPI or STS (n = 34)	*P*-value
Age (yr)			> 0.999
< 40	2 (25.0)	8 (23.5)	
≥ 40	6 (75.0)	26 (76.5)	
Sex			0.168
Male	8 (100.0)	25 (73.5)	
Female	0 (0.0)	9 (26.5)	
Allergic disease			0.402
None	7 (87.5)	23 (67.6)	
Present	1 (12.5)	11 (32.4)	
Esophageal symptoms			< 0.001
None	8 (100.0)	7 (20.6)	
Present	0 (0.0)	27 (79.4)	
Endoscopic features			
Edema	2 (25.0)	16 (47.1)	0.431
Rings	5 (62.5)	13 (38.2)	0.256
Exudates	1 (12.5)	5 (14.7)	> 0.999
Furrows	5 (62.5)	19 (55.9)	> 0.999
Stricture	0 (0.0)	4 (11.8)	0.572

PPI, proton pump inhibitor; STS, swallowed topical steroid.
Data are presented as n (%).

Table 3. Comparison of Clinical Factors Between Proton Pump Inhibitor and Swallowed Topical Steroid Therapies as First Therapy

Clinical factors	PPI (n = 27)	STS (n = 7)	*P*-value
Age (yr)			> 0.999
< 40	7 (25.9)	1 (14.3)	
≥ 40	20 (74.1)	6 (85.7)	
Sex			0.644
Male	19 (70.4)	6 (85.7)	
Female	8 (29.6)	1 (14.3)	
Allergic disease			> 0.999
None	18 (66.7)	5 (71.4)	
Present	9 (33.3)	2 (28.6)	
Esophageal symptoms			
Dysphagia	12 (44.4)	4 (57.1)	0.681
Heartburn	7 (25.9)	2 (28.6)	> 0.999
Pain	4 (14.8)	2 (28.6)	0.580
Globus	1 (3.7)	0 (0.0)	> 0.999
Food impaction	2 (7.4)	0 (0.0)	> 0.999
Endoscopic features			
Edema	15 (55.6)	1 (14.3)	0.090
Rings	9 (33.3)	4 (57.1)	0.387
Exudates	3 (11.1)	2 (28.6)	0.268
Furrows	16 (59.3)	3 (42.9)	0.672
Stricture	1 (3.7)	3 (42.9)	0.021

PPI, proton pump inhibitor; STS, swallowed topical steroid.
Data are presented as n (%).

treated patients (8/8) and one-fifth of treated patients (7/34) had no esophageal symptoms ($P < 0.001$). In patients who received therapy, the proportion of esophageal stricture was higher in STS (42.9%, 3/7) than PPI (3.7%, 1/27) ($P = 0.021$) (Table 3).

Discussion

This multicenter study of 42 EoE cases from Busan city and Gyeongnam province in Korea assessed the management pattern and clinical factors affected by the choice of first-line therapy. PPI was the preferred option as an initial therapy (64.3%, 27/42). Furthermore, STS was often chosen as an initial treatment especially in patients with esophageal stricture (16.7%, 7/42). STS was regarded as the preferred option after failure of a PPI trial. Both PPI and STS showed effectiveness in EoE treatment. Half of patients without symptoms related to esophageal dysfunction (8/15) did not receive any treatment.

The role of PPI in the updated international consensus for EoE has evolved from exclusion of PPI-responsive EoE to treatment through the gastric acid inhibiting effect and anti-inflammatory effect unrelated to gastric acid.[2] PPI is recommend as a potential early or initial therapy because of its low cost, good safety profile, and convenience.[2] A recent Korean study demonstrated that PPI (77.8%, 56/72) and STS (5.6%, 4/72) were used as initial therapies in EoE.[4] Another Korean study reported that PPI (66.6%, 6/9) and STS (22.2%, 2/9) were prescribed as first-line treatments.[17] These results are consistent with the present study.

However, several previous studies have also reported that STS was the most common initial therapy.[10,11] Our results demonstrated that the choice of STS as the first-line therapy was preferred in patients with esophageal stricture. This may be the reason for the difference in preferred initial therapy between Korea and other countries.

The prevalence of esophageal stricture is lower in Korean studies compared to other studies.[4,10,11,17] First, the Korean National Gastric Cancer Screening Program using biannual endoscopy or barium study was performed in adults aged more than 40 years. It may lead to the early detection of fibrostenotic type EoE before progression to small caliber esophagus. Second, the biopsy based EoE diagnosis in this study can also contribute to the low incidence of esophageal strictures. Eosinophil counts are generally low in cases of advanced EoE with fibrosis. Third, the disease duration from diagnosis may be short compared to the Western countries as an awareness of EoE has been growing recently in Korea. This situation can also result in the low incidence of esophageal strictures. In the present study, There were no patients who received dilation therapy. Two previous Korean studies also reported only 1 case of balloon dilation for esophageal stricture.[4,17]

Previous studies reported that the clinical and histological response rates ranged from 25.0% to 96.0% and 23.0% to 83.0%, respectively.[2] In this study, the clinical response rate of 88.9% (24/27) and histological response rate of 84.6% (11/13) were similar to the maximum range of reported rates. The concept of PPI-responsive EoE may increase the possibility to exclude the patients who showed response to PPI therapy in the previous studies.[2] The exclusion of PPI-responsive EoE according to advances in the definition EoE might lead to a higher clinical and histological response to the PPI trial. All patients who received STS as first- or second-line therapy showed a 100.0% clinical (9/9) and histological (5/5) response. The requirement of esophageal dilation was reported as a predictor of poor response to STS in EoE patients.[18,19] No patient needed dilation therapy in the present study, which may explain the high response rate of STS.

Other therapeutic approaches for EoE have been reported to be as effective and safe. Novel EoE specific steroid formulations have been developed to optimize mucosal deposition. Budesonide oral suspension in United States and the budesonide effervescent tablet in Europe have been approved and show effectiveness with negligible side effects.[20,21] Biologics such as a monoclonal antibody against IL-13, dupilumab (monoclonal antibody to the alpha subunit of the IL-4 receptor), mepolizumab (monoclonal antibody against IL-5), reslizumab (IL-5 neutralizing antibody), and omalizumab (anti-IgE monoclonal antibody) are currently in phase II trials with EoE patients.[22] Further studies for these novel therapies could result in personalized therapeutic strategies for EoE.

Finally, we found a gap in real practice and adherence to guidelines in monitoring the response to treatment. Guidelines recommend that follow-up endoscopy with biopsy should be performed to confirm the effectiveness of treatment.[1,2] Half of the patients did not receive the follow-up endoscopy after first-line PPI (48.1%, 313/27) and STS (42.9%, 3/7) therapy. The decision for a follow-up endoscopy is based on the esophageal symptoms of EoE and this may contribute to the reason why the practice pattern differs from the guidelines.[23] Esophageal biopsies during a follow-up endoscopy after treatment were not performed in 2 patients (one after initial PPI therapy, the other after second-line STS therapy). Changing the guidelines about EoE can result in non-adherence to the guidelines in monitoring the response to treatment.[1,2,10]

The strength of our study is that this is the first multi-center data analysis about real-world practice pattern for EoE in Asia.

Previous Korean studies were single-center design, and Asian multi-center studies focused on the diagnosis and prevalence of EoE.[4,5,17,24-27] Recent studies to evaluate the management for EoE were published in Western countries.[10,23,28,29] The practice patterns of Busan-Gyeongnam, Korea, were different to those reported in Western countries.[12,30,31] In the United States, gastroenterologists responded that topical steroids is the preferred therapy and endoscopy with biopsy is recommend by 72.0% of academic providers and 27.0% of private practices.[31] German gastroenterologists responded that both PPI and STS were the preferred options.[12] An international study including 14 European countries reported that there were geographical differences in the choice of first-line therapy.[30] In Korea, PPI was the most commonly used first-line approach, and follow-up endoscopy with biopsy was not performed routinely.

Our study has several potential limitations. First, this was a retrospective study. Patients received different PPIs, which could have affected the response to the treatment. The meta-analysis reported that lansoprazole (70.2%) and rabeprazole (72.3%) showed higher efficacy compared with omeprazole (53.5%) and esomeprazole (46.8%), regardless of the twice daily and once-daily doses.[32] Second, the patients included in this multicenter study may not be representative of all Korean patients. There is a possibility of referral bias, because patients with severe disease may tend to visit specialized clinics in Seoul. This could have resulted in better clinical outcomes in the present study. Therefore, nationwide multicenter studies are needed to confirm this conclusion.

In conclusion, this study demonstrated that the response to PPI and STS therapies for EoE was favorable in Busan city and Gyeongnam province in Korea. PPI was the most common treatment used as the first-line therapy in this region. These results are similar to those of previous Korean studies. We found a trend in the use of STS in patients with esophageal stricture. Our findings regarding the adherence to guidelines suggest that physicians need to try to reduce the gap between guidelines and real practice in monitoring the treatment response.

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Conflicts of interest: None.

Author contributions: Moo In Park designed the model and the computational framework; Su Jin Kim analysed the data and wrote draft manuscript; Moon Won Lee, Su Jin Kim, Kyoungwon Jung, Jin Lee, Hong Sub Lee, and Jae Hwang Cha collected the data; and Sang Young Seol, Sam Ryong Jee, Moo In Park, Gwang Ha Kim, and Jin Seok Jang contributed to the final version of the manuscript and supervised the project.

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