**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 55229

**Manuscript Type:** ORIGINAL ARTICLE

***Observational Study***

**Detection of reflux-symptom association in children with esophageal atresia by video-pH-impedance study**

Settachote M *et al.* Detection of reflux in children with EA by video-pH-impedance

Settachote Maholarnkij, Anapat Sanpavat, Katawaetee Decharun, Termpong Dumrisilp, Chomchanat Tubjareon, Benjawan Kanghom, Tanisa Patcharatrakul, Nataruks Chaijitraruch, Voranush Chongsrisawat, Palittiya Sintusek

**Settachote Maholarnkij**, Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

**Anapat Sanpavat**, Division of Pathology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

**Katawaetee** **Decharun**, Division of Pediatric Surgery, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

**Katawaetee Decharun, Benjawan Kanghom**, **Nataruks Chaijitraruch, Palittiya Sintusek,** Division of Gastroenterology, and Pediatric Gastroenterology and Hepatology STAR (Special Task Force for Activating Research), Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

**Termpong Dumrisilp, Chomchanat Tubjareon, Benjawan Kanghom, Nataruks Chaijitraruch, Voranush Chongsrisawat**, **Palittiya Sintusek,** Division of Gastroenterology, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

**Tanisa Patcharatrakul**, Center of Excellence in Neurogastroenterology and Motility, Department of Gastroenterology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

**Tanisa Patcharatrakul**, Division of Gastroenterology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand

**Author contributions:** Maholarnkij S participated in design of the study, drafted the manuscript, collected the data, assisted with data analysis; Sunpavat A interpreted the histopathological data; Decharun K was involved with data collection and approved the final manuscript; Dumrisilp T, Tubjareon C and Kanghom B was involved with data collection; Chaijitraruch N, Patcharatrakul T and Chongsrisawat V approved the final manuscript; Sintusek P designed and oversight of the study, involved with data collection, interpretation and analysis, draft and approved the final manuscript.

**Corresponding authors:** **Palittiya Sintusek, MD, Assistant Professor,** Department of Gastroenterology and Pediatric Gastroenterology and Hepatology STAR (Special Task Force for Activating Research), Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University, No. 1873, Rama 4 Road, Pathumwan, Bangkok 10330, Thailand. palittiya.s@chula.ac.th

**Received:** March 12, 2020

**Revised:** April 30, 2020

**Accepted:** July 14, 2020

**Published online:**

**Abstract**

BACKGROUND

Children with esophageal atresia (EA) have risk of gastroesophageal reflux disease (GERD), suggesting reflux monitoring for prompt management.

AIM

To evaluate GERD in children with EA and specific symptom association from combined video with multichannel intraluminal impedance and pH (MII-pH) study.

METHODS

Children diagnosed with EA with suspected GERD and followed up at King Chulalongkorn Memorial Hospital between January 2000 and December 2018 were prospectively studied. All underwent esophagogastroduodenoscopy with esophageal biopsy and video MII-pH study on the same day. Symptoms of GERD which included both esophageal and extra-esophageal symptom were recorded from video monitoring and abnormal reflux from MII-pH study based on the statement from the European Paediatric Impedance Group. Prevalence of GERD was also reported by using histopathology as a gold standard. Endoscopic appearance was recorded using Los Angeles Classification and esophagitis severity was graded using Esohisto criteria.

RESULTS

Fifteen children were recruited with age of 3.1 (2.2, 9.8) years (40%, male) and the common type was C (93.3%). The symptoms recorded were cough (75.2%), vomiting (15.2%), irritability or unexplained crying (7.6%) and dysphagia (1.9%) with the symptom-reflux association of 45.7%, 89%, 71% and 0%, respectively. There were abnormal endoscopic appearance in 52.9%, esophagitis in 64.7% and high reflux score in 47.1%. Video MII-pH study has high diagnostic value with the sensitivity, specificity and accuracy of 72.7%, 100% and 82.4%, respectively.

CONCLUSION

Prevalence of GERD in children with EA was high. Video MII-pH study to detect GERD in children with EA had high diagnostic value with the trend of specific symptom association.

**Key words:** Gastroesophageal reflux disease; Esophageal atresia; Children; Impedance pH study; Video; Symptom association

Maholarnkij S, Sanpavat A, Decharun K, Dumrisilp T, Tubjareon C, Kanghom B, Patcharatrakul T, Chaijitraruch N, Chongsrisawat V, Sintusek P. Detection of reflux-symptom association in children with esophageal atresia by video-pH-impedance study. *World J Gastroenterol* 2020; In press

**Core tip:** This was a cross sectional study with 15 patients diagnosed with esophageal atresia (EA) and suspected gastroesophageal reflux disease (GERD). Combined Video Multichannel Intraluminal Impedance and pH study has a good diagnostic accuracy to diagnose GERD in these children and there was a trend of specific symptom-reflux association in children diagnosed with EA.

**INTRODUCTION**

Esophageal atresia (EA) is a common digestive malformation occurring in 1:2400-4500 births. Improvements in operative and medical care enable them to have longer life expectancy but suffering from comorbidities including pathological gastroesophageal reflux (GER). Although GER disease (GERD) is defined as the reflux of gastric contents lead to troublesome symptoms[1], unlike other children, EA children with GERD could be asymptomatic or present with extraesophageal symptoms[2]. Therefore, the recent European Society of Paediatric Gastroenterology Hpatology and Nutrition and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN) guideline for EA children recommended to routinely prescribe proton pump inhibitors (PPIs) up to the first year of life and monitor reflux episodes using combined esophageal multichannel intraluminal impedance and pH (MII-pH) monitoring and/or endoscopy at time of discontinuation and during long-term follow up[2].

The prevalence of GERD in EA patients varied from 22%-45%, depending on the diagnostic criteria[3-7]. Esophageal histopathology is the gold standard test to diagnose pathological reflux but it has low sensitivity compared to others[8]. MII-pH monitoring is one of the best diagnostic tools for GERD as its ability to detect the frequency, height and type of reflux event. However, the normal value of reflux event in children is scarce hence the data should be interpreted with caution. The international guideline[9] recommended using MII-pH study to correlate persistent troublesome symptoms with reflux episodes instead. Using video monitoring, symptoms should be recorded more precisely with time of reflux than by caregivers in EA children. We aim to study the prevalence of GERD and the symptom correlation in EA children using video MII-pH.

**MATERIALS AND METHODS**

***Patients***

Children diagnosed with EA who received esophageal anastomosis and regularly followed up at King Chulalongkorn Memorial Hospital between 1 January 2000 and 31 December 2018 were recruited. This cross sectional study has been approved by the Institutional Review Board of Chulalongkorn University (IRB number 243/61). Written informed consent was obtained from all parents and informed assent from patients over 7 years old before any procedure was performed.

***Data collection and outcome measurements***

All patients were admitted. Detailed demographic data, comorbidities, signs and symptoms followed the international guidelines[9] (Table 1), and previous investigations were collected by investigator’s interview and medical records.

***Esophagogastroduodenoscopy***

On the following day, all patients were nil by mouth for at least 6 h before esophagogastroduodenoscopy (EGD) under general anesthesia. Esophageal biopsy was performed at 3-5 cm above z-line for at least 2 pieces.

***Combined video MII-pH monitoring***

The age appropriate catheter (Pediatric ZandorpH catheter with 1 Antimony and 6 impedance rings with 2 cm interval, LABORIE, The Netherlands) was inserted after EGD and under general anesthesia. When the patient woke up, the catheter position was adjusted to place pH sensor at 2 vertebraes above the diaphragm from a plain chest x-ray in upright and full inspired position, followed the statement from British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) motility working group[10]. All chest x-ray was reviewed by a pediatric gastroenterologist (PS) to confirm the proper position. Then combined MII-pH machine (Ohmega, Laborie, The Netherland) was started and monitored for at least 24 h. Video monitoring was done and the MII-pH study was synchronized with the video. All signs and symptoms of GERD according to ESPGHAN and NASPGHAN guidelines[9] were recorded by instructed caregivers while the main investigator (Maholarnkij S) independently recorded them from the video record. Carbonated drink, juices and acidic foods were prohibited from the patient during the monitoring.

***Combined video MII-pH analysis***

Tracing from MII-pH study results were initially analyzed using Laborie automated analysis software (MMS Database software, The Netherland) and revised visually and manually analyzed by the pediatric gastroenterologist (Sintusek P). The criteria for all parameters followed the position statement by BSPGHAN Motility Working Group[10] and the normal values of reflux followed the European Paediatric Impedance Group (EURO-PIG)[11]: (1) Reflux is classified as acid (pH < 4), weakly acid (pH 4-7), and weakly alkaline (pH > 7); (2) Reflux index (RI) is defined as percentage of time with esophageal pH though the pH sensor above lower esophageal sphincter < 4. We considered pathological acid reflux if RI > 3% in children aged > 1 year; (3) Number of refluxes is defined as the number of retrograde bolus movements that ≥ 100 episodes in infant and ≥ 70 episodes in children aged > 1 year considered to be pathologic; (4) Symptom index is defined as the following formula: [Reflux-related symptom events/the total symptoms events] × 100. It was considered positive if the value ≥ 50%; (5) Symptom sensitivity index is defined as the following formula: [Number of symptom-associated reflux/total number of reflux episodes] × 100. It is positive if the value ≥ 10% for each symptom; (6) Symptom association probability (SAP) is from complex statistical calculation by the machine in for the symptom correlation in each 2-min window of the study. SAP values are considered positive if the value ≥ 95%; (7) Esophageal acid clearance is defined as the time from drop in esophageal pH at pH channel < 4 to restoration of pH above ≥ 4; (8) Mean bolus clearing time is defined as the mean time in seconds required for the impedance, distal channel, to go back to the initial value after an episode of reflux; and (9) Longest reflux period (min) is defined as the total time that esophageal pH above pH channel < 4.

***Esophageal gross finding***

Endoscopic appearance was recorded by the pediatric gastroenterologist using Los Angeles Classification[12]. Grade A indicated ≥ 1 mucosal breaks confined to the mucosal folds < 5 mm length. Grade B indicated ≥ 1 mucosal breaks > 5 mm, but not continuous between the 2 mucosal folds. Grade C indicated continuous mucosal breaks < 75% of the esophageal circumference. Grade D indicated mucosal breaks which involves ≥ 75% of the esophageal circumference.

***Esophageal histopathology finding***

 Histopathological severity were reported by a pathologist using modified Esohisto criteria[13]. The criteria included the first 4 in these 6 parameters: (1) Basal cell layer hyperplasia: measure thickness of basal cell layer in micrometers and express as a proportion (%) of total epithelial thickness (× 10). The severity score defined as 0 (< 15%), 1 (15%-30%), and 2 (> 30%); (2) Papillary elongation: measure papillary length in micrometers and express as a proportion (%) of total epithelial thickness (×10). The severity score defined as 0 (< 50%), 1 (50%-75%), and 2 (> 75%); (3) Dilatation of intercellular spaces: identified as irregular round dilatations or diffuse widening of intercellular space (×40). The severity score defined as 0 (absent), 1 (small; diameter < 1 lymphocyte), and 2 (large; diameter ≥ 1 lymphocyte); (4) Intraepithelial eosinophils: counted in the most affected high-power field (×40). The severity score defined as 0 (absent), 1 (1-2 cells), and 2 (> 2 cells); (5) Intraepithelial neutrophils: counted in the most affected high-power field (×40). The severity score defined as 0 (absent), 1 (1-2 cells), and 2 (> 2 cells); and (6) Intraepithelial mononuclear cells: counted in the most affected high-power field (×40). The severity score defined as 0 (0-9 cells), 1 (10-30 cells), and 2 (> 30 cells).

The sum of severity scores divided by the number of lesion types assessed can be stratified into degree of esophagitis. Score 0-0.25 were indicated normal, score 0.5-0.75 were regarded as mild esophagitis, and score 1 or higher qualified for severe esophagitis.

***Statistical analysis***

Data were analysed with IBM SPSS statistics 22.0. Demographic data were reported as median (IQR) for numerical variables while percentage or proportion for categorical variables. Diagnostic test was calculated and presented as sensitivity, specificity, accuracy, positive predictive value, and negative predictive value by using histopathology of esophageal histopathology as the gold standard. Statistical significance between paired continuous variables were calculated by Wilcoxon signed ranks test. *χ*2 or Fisher’s exact test for categorical variables. Clinically significance were defined as *P*-value < 0.05. The statistical review of the study was performed by a biomedical statistician at Department of Statistics Science, Kasetsart University, Thailand, Bangkok, Thailand.

The primary outcome is to study the prevalence of GERD in children with EA using combined Video MII-pH study. The secondary outcome is to evaluate the specific symptom association of GERD in children with EA.

**RESULTS**

***Patient characteristics***

There were 15 patients diagnosed with EA recruited into the present study. The median age was 3.08 (range from 1.4 to 12.9) years (40%, male) and the most common type was C (93.3%). Ten (33.3%) patients had at least one comorbidity [cardiac malformations (*n* = 9), renal malformation (*n* = 3), anorectal malformations (*n* = 2), musculoskeletal malformations (*n* = 2), lung hypoplasia (*n* = 1), vertebral anomalies (*n* = 1), others (skin tags, growth hormone deficiency) (*n* = 3)]. Eleven (73.3%) patients underwent esophageal anastomosis since neonate and 4 (26.7%) underwent delayed esophageal anastomosis within the first year of life.Ten patients underwent EGD with esophageal biopsy before and seven of them had reflux esophagitis.Five patients were using proton pump inhibitors (33%) (omeprazole 1-2 mg/kg per day; *n* = 2, lanzoprazole 2-3 mg/kg per day; *n* = 3) and two of these were using prokinetic drugs (13.3%) (domperidone 0.3-0.5 mg/kg/dose every 6-8 h) at the time of recruitment. The medication was continued before MII-pH monitoring due to esophagitis finding from previous endoscopy and histopathology. Fundoplication was performed in two patients because of the pharmacological failure. The most common previously symptom reported were recurrent regurgitation with or without vomiting (60%) and cough (60%). Dental screening was performed in six patients and founded dental erosion in three patients (50%). The most common previously signs documented were esophagitis (53%) and recurrent respiratory tract infection (53%) (Table 2). In these 15 children diagnosed with EA, we got 17 records from video MII-pH study due to two patients were performed for two times for reassessment during pharmacological therapy.

***GERD diagnosed by gross and histopathology***

Gross appearance on endoscopic view showed abnormality in 52.9% while esophageal histopatholgy demonstrated esophagitis in 64.7% of them. Three (37.5%) patients with normal gross appearance had histopathology of reflux esophagitis (Table 3).

***GERD diagnosed by combined video MII-pH study and the symptom association***

The median of monitoring period excluding fed periods (hours) was 21.2 (19.3-22.1). The median RI (%), and esophageal clearance (minutes) were 2.7 (0.5-9.5) and 1.4 (0.6-2.5), respectively. There was no statistical significance of the symptom recorded by caregivers and video monitoring that was recorded by primary investigators [2.5 (1-4.5) *vs* 3 (1-5), *P* = 0.282]. Using the cut-off value from EURO-PIC for the RI and/ or total reflux time, 47.1% of them considered acid/weakly acid related GERD diagnosis. Other MII-pH study parameters are shown in Table 4. In subgroup analysis, there was no significantly different result of combined video MII-pH monitoring between using and non-using acid suppression therapy during the monitoring (Table 5).

The total symptoms recorded from video of all 17 combined video MII-pH monitoring were cough (67.3%), vomiting (17.3%), irritability or unexplained crying (13.4%) and dysphagia (1.9%). In aspect of symptom association, vomiting was the symptom that mostly associated with reflux followed by irritability or unexplained crying and cough (Table 6).

***Diagnostic value of combined video MII-pH study compared to esophageal histopathology***

Using esophageal histopathology as the gold standard for GERD, combined video MII-pH has high diagnostic value with the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 72.7%, 100%, 100%, 67% and 82.4%, respectively.

**DISCUSSION**

The present study demonstrated the high prevalence of GERD in children with EA based on the gold standard tools, esophageal histopathology and/or combined MII-pH study. Most of them had the previous symptoms suspected GERD in aspect of general, gastrointestinal and respiratory system (Table 1). In this study, combined video MII-pH study could depict a trend of symptom-reflux association of vomiting, irritability or unexplained crying and cough.

Previous studies supported the high incidence of GERD in children with EA though the different diagnostic tools[3,4,9,14,15]. Esophageal histopathology is considered the gold standard to detect the early reflux esophagitis while MII-pH study, previous gold-standard test for GERD[16], had the main limitation in aspect of normal value for age. The strength of MII-pH study is its high accuracy if there is the specific symptom correlation during monitoring. The present study found most children with EA had histopathology result compatible with reflux esophagitis and MII-pH study had high specificity to this reflux esophagitis. Moreover, there is a trend of symptom-reflux correlation of vomiting, irritability or unexplained crying and cough. However, symptom recorded during video MII-pH study per person was too small to extrapolate that GERD was the cause of these symptoms. Reevaluation of these clinical symptoms with video MII-pH study after adequate treatment might strongly confirm that the symptom-reflux association for further study. As the prevalence of GERD and it’s complications tended to increase very early, the ESPGHAN-NASPGHAN guidelines for children with EA recommended using PPIs in all EA patients in the neonatal period and should be longer, depending on persistence of GERD. As a result all EA patients should undergo MII-pH study, at least, at the time of discontinuation of PPIs and during long-term follow-up. Furthermore, significant esophageal morbidity in adult with EA is evidenced. The prevalence of Barrett esophagus is at lease 4-fold higher among adult population with EA[17] and the cumulative incidence of esophageal squamous cell carcinoma at fourth decade was 50 times[18] when compared with general population. Consequently, regular surveillance and follow-up patients with EA and GERD should be included not only MII-pH study but also EGD and esophageal biopsy to optimize therapy so that Barrett esophagus and esophageal carcinoma, hopefully, could be avoided.

In theory, combined video MII-pH study should provide the accurate symptoms that could be confidently correlated with the reflux from the tracer. We could confirm the more numbers and specificity of the symptom recorded by video monitoring compared to the record from caregivers even though it did not reach statistical significance that might because of low number of subjects. Moreover, the precise time of symptom recorded could increase the symptom association as the machine will count the 2-min window period before a reflux event. However, this precise recording consumes time (more than 3-h recording by a pediatrician per patient) that makes it impossible in routine clinical practice. In the future, real-time video MII-pH monitoring machine should be developed for children suspected GERD so that clinician will manually correlate the reflux with the real-time symptoms from video monitoring. For the overall symptoms during the MII-pH study, we could use the symptom record from caregivers and manually analyze the suspected symptom correlation by checking the video in case that caregiver might delay recording more than the 2-min window period.

Pathological mechanism of GERD in EA was postulated in many studies. Disruption of vagal denervation, vascular interruption, or traction on the lower esophagus occurred after esophageal corrective procedure could be the risk factors of GERD in children with EA[19] However, children with isolated tracheoesophageal fistula could have severely esophageal motility before surgical repair that might imply the congenital esophageal dysmotility rather than acquired from surgical correction[20] Esophagus per se might be the main risk factor of GERD in children with EA. Although the MII-pH study could not evaluate the esophageal motility, the long duration of esophageal clearance and mean bolus clearance time from the present study might reflect the esophageal dysmotility of children with EA. Apart from esophageal dysmotility, the present study demonstrated that mainly GERD in these children was acid reflux in etiology that 3 and 2 of them has no response with PPIs therapy and fundoplication, respectively. More aggressive management could be considered and esophageal motility should be evaluated before surgical fundoplication as this surgery could impair esophageal clearance and worsening the reflux esophagitis.

The strength of the present study is the evaluation of both esophageal histopathology and combined MII-pH study in the meantime. To the best of our knowledge, this is the first study that integrate video recording into the MII-pH study and a pediatrician was the person recording the symptom that might associate with reflux event. These methods lead to the most reliable symptom recorded albeit consuming time. However, the small number and in homogenous characteristic of the subjects are the main limitation of this pilot study. Further large study that highlights the accurate symptom association using real-time video or developed artificial intelligence MII-pH machine for children suspected of GERD should be more meritorious.

**ARTICLE HIGHLIGHTS**

***Research background***

Esophageal atresia (EA) is a common digestive malformation with increasing risk of esophageal complications even after successful surgical correction. Gastroesophageal reflux disease (GERD) is the frequent gastrointestinal co-morbidity causing serious long-term consequences namely esophageal stricture and esophageal carcinoma. Hence, early detection and prompt treatment are crucial.

***Research motivation***

This research aimed to study the prevalence of GERD using esophageal histopathology and the novel tool, combined video multichannel intraluminal impedance and pH (MII-pH) study, in children diagnosed with EA. We believe that symptoms from video monitoring should be recorded more precisely with time reflux than by caregivers and make the interpretation of reflux-symptom association more meaningful.

***Research objectives***

To investigate the prevalence of GERD and the symptom association in children diagnosed EA by combined video MII-pH study.

***Research methods***

Seventeen investigations that included esophagogastroduodenoscopy with biopsy and combined video MII-pH study were performed in 15 children diagnosed EA. All signs and symptoms of GERD from video were recorded during MII-pH monitoring. MII-pH study was manually analysis including the symptom-reflux association using the symptoms from video record. Diagnostic value of combined video MII-pH study was calculated using the result of esophageal histopathology as the gold standard to diagnose GERD.

***Research results***

The total symptoms recorded from video of all 17 combined video MII-pH monitoring were cough (67.3%), vomiting (17.3%), irritability or unexplained crying (13.4%) and dysphagia (1.9%). In aspect of symptom association, vomiting was the symptom that mostly associated with reflux followed by irritability or unexplained crying and cough. Using esophageal histopathology as the gold standard for GERD, combined video MII-pH has high diagnostic value with the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 72.7%, 100%, 100%, 67% and 82.4%, respectively.

***Research conclusions***

Prevalence of GERD in children with EA was high. Combined video MII-pH study to detect GERD in children with EA had high diagnostic value with the trend of specific symptom association.

***Research perspectives***

MII-pH study has limitation to be the gold-standard test for GERD as the data of the reflux value in each age group are scarce. To improve the utility and diagnostic value of this machine, we synchronized the video recording during the study. The precise time of symptom recorded from video could increase symptom-reflux association albeit its time consuming. In the future, real-time video MII-pH monitoring machine should be developed to improve the accuracy and clinical utility of MII-pH study.

**ACKOWLEDGEMENTS**

The author would like to thank Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University (Grant No RA62/001), the Pediatric Gastroenterology and Hepatology STAR (Special Task Force for Activating Research), Department of Pediatrics, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University for research funding.

**REFERENCES**

1 **Onyeador N**, Paul SP, Sandhu BK. Paediatric gastroesophageal reflux clinical practice guidelines. *Arch Dis Child Educ Pract Ed* 2014; **99**: 190-193 [PMID: 24722652 DOI: 10.1136/archdischild-2013-305253]

2 **Krishnan U**, Mousa H, Dall'Oglio L, Homaira N, Rosen R, Faure C, Gottrand F. ESPGHAN-NASPGHAN Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Esophageal Atresia-Tracheoesophageal Fistula. *J Pediatr Gastroenterol Nutr* 2016; **63**: 550-570 [PMID: 27579697 DOI: 10.1097/MPG.0000000000001401]

3 **Somppi E**, Tammela O, Ruuska T, Rahnasto J, Laitinen J, Turjanmaa V, Järnberg J. Outcome of patients operated on for esophageal atresia: 30 years' experience. *J Pediatr Surg* 1998; **33**: 1341-1346 [PMID: 9766349 DOI: 10.1016/s0022-3468(98)90003-3]

4 **Deurloo JA**, Ekkelkamp S, Schoorl M, Heij HA, Aronson DC. Esophageal atresia: historical evolution of management and results in 371 patients. *Ann Thorac Surg* 2002; **73**: 267-272 [PMID: 11834021 DOI: 10.1016/s0003-4975(01)03263-5]

5 **Koivusalo A**, Pakarinen M, Rintala RJ, Lindahl H. Does postoperative pH monitoring predict complicated gastroesophageal reflux in patients with esophageal atresia? *Pediatr Surg Int* 2004; **20**: 670-674 [PMID: 15372290 DOI: 10.1007/s00383-004-1270-z]

6 **Koivusalo A**, Pakarinen MP, Rintala RJ. The cumulative incidence of significant gastrooesophageal reflux in patients with oesophageal atresia with a distal fistula--a systematic clinical, pH-metric, and endoscopic follow-up study. *J Pediatr Surg* 2007; **42**: 370-374 [PMID: 17270551 DOI: 10.1016/j.jpedsurg.2006.10.010]

7 **Legrand C**, Michaud L, Salleron J, Neut D, Sfeir R, Thumerelle C, Bonnevalle M, Turck D, Gottrand F. Long-term outcome of children with oesophageal atresia type III. *Arch Dis Child* 2012; **97**: 808-811 [PMID: 22753768 DOI: 10.1136/archdischild-2012-301730]

8 **Saito T**, Uesato M, Terui K, Nakata M, Komatsu S, Yoshida H. Acid and bolus exposure in pediatric reflux disease according to the presence and severity of esophageal mucosal lesions. *Pediatr Surg Int* 2019; **35**: 887-893 [PMID: 31144005 DOI: 10.1007/s00383-019-04490-5]

9 **Rosen R**, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **66**: 516-554 [PMID: 29470322 DOI: 10.1097/MPG.0000000000001889]

10 **Mutalib M**, Rawat D, Lindley K, Borrelli O, Perring S, Auth MKH, Thapar N. BSPGHAN Motility Working Group position statement: paediatric multichannel intraluminal pH impedance monitoring-indications, methods and interpretation. *Frontline Gastroenterol* 2017; **8**: 156-162 [PMID: 28839903 DOI: 10.1136/flgastro-2016-100796]

11 **Wenzl TG**, Benninga MA, Loots CM, Salvatore S, Vandenplas Y; ESPGHAN EURO-PIG Working Group. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. *J Pediatr Gastroenterol Nutr* 2012; **55**: 230-234 [PMID: 22711055 DOI: 10.1097/MPG.0b013e3182592b65]

12 **Lundell LR**, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172-180 [PMID: 10403727 DOI: 10.1136/gut.45.2.172]

13 **Schneider NI**, Plieschnegger W, Geppert M, Wigginghaus B, Hoess GM, Eherer A, Wolf EM, Rehak P, Vieth M, Langner C. Validation study of the Esohisto consensus guidelines for the recognition of microscopic esophagitis (histoGERD Trial). *Hum Pathol* 2014; **45**: 994-1002 [PMID: 24746203 DOI: 10.1016/j.humpath.2013.12.013]

14 **Montgomery M**, Frenckner B. Esophageal atresia: mortality and complications related to gastroesophageal reflux. *Eur J Pediatr Surg* 1993; **3**: 335-338 [PMID: 8110713 DOI: 10.1055/s-2008-1066039]

15 **Pedersen RN**, Markøw S, Kruse-Andersen S, Qvist N, Hansen TP, Gerke O, Nielsen RG, Rasmussen L, Husby S. Esophageal atresia: gastroesophageal functional follow-up in 5-15 year old children. *J Pediatr Surg* 2013; **48**: 2487-2495 [PMID: 24314192 DOI: 10.1016/j.jpedsurg.2013.07.019]

16 **Vandenplas Y**, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG, North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009; **49**: 498-547 [PMID: 19745761 DOI: 10.1097/MPG.0b013e3181b7f563]

17 **Sistonen SJ**, Koivusalo A, Nieminen U, Lindahl H, Lohi J, Kero M, Kärkkäinen PA, Färkkilä MA, Sarna S, Rintala RJ, Pakarinen MP. Esophageal morbidity and function in adults with repaired esophageal atresia with tracheoesophageal fistula: a population-based long-term follow-up. *Ann Surg* 2010; **251**: 1167-1173 [PMID: 20485152 DOI: 10.1097/SLA.0b013e3181c9b613]

18 **Jayasekera CS**, Desmond PV, Holmes JA, Kitson M, Taylor AC. Cluster of 4 cases of esophageal squamous cell cancer developing in adults with surgically corrected esophageal atresia--time for screening to start. *J Pediatr Surg* 2012; **47**: 646-651 [PMID: 22498376 DOI: 10.1016/j.jpedsurg.2011.09.065]

19 **Di Pace MR**, Caruso AM, Catalano P, Casuccio A, Cimador M, De Grazia E. Evaluation of esophageal motility and reflux in children treated for esophageal atresia with the use of combined multichannel intraluminal impedance and pH monitoring. *J Pediatr Surg* 2011; **46**: 443-451 [PMID: 21376190 DOI: 10.1016/j.jpedsurg.2010.08.012]

20 **Lemoine C**, Aspirot A, Morris M, Faure C. Esophageal dysmotility is present before surgery in isolated tracheoesophageal fistula. *J Pediatr Gastroenterol Nutr* 2015; **60**: 642-644 [PMID: 25493344 DOI: 10.1097/MPG.0000000000000667]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the Institional Review Board of Chulalongkorn University, Thailand (IRB number 243/61).

**Informed consent statement:** All study participants, or their legal guardian, provided written consent prior to study enrolment.

**Conflict-of-interest statement:** The authors of this manuscript having no conflict of interest to disclose.

**Data sharing statement:** There is no additional data available.

**STROBE statement:** The authors have read the STROBE statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited Manuscript

**Corresponding Author’s Membership in Professional Societies:** American Association for the Study of Liver Diseases.

**Peer-review started:** March 12, 2020

**First decision:** April 25, 2020

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Thailand

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Gallo G, Polat F, Yellanthoor RB **S-Editor:** Wang JL **L-Editor:** **E-Editor:**

**Table 1 Symptoms and signs that may be associated with gastroesophageal reflux in infants and children[9]**

|  |  |
| --- | --- |
| **Symptoms** | **Signs** |
| **General** | **General** |
|  Discomfort/irritability1 |  Dental erosion |
|  Failure to thrive |  Anemia |
|  Feeding refusal |  |
|  Dystonic neck posturing (Sandifer syndrome) |  |
| **Gastrointestinal** | **Gastrointestinal** |
|  Recurrent regurgitation with/without |  Esophagitis |
|  vomiting in the older children |  Esophageal stricture |
|  Heartburn/chest pain2 |  Barrett esophagus |
|  Epigastric pain2 |  |
|  Hematemesis |  |
|  Dysphagia/odynophagia |  |
| **Airway** | **Airway** |
|  Wheezing |  Apnea spells |
|  Stridor |  Asthma |
|  Cough |  Recurrent pneumonia associated with aspiration |
|  Hoarseness | Recurrent otitis media |

1If excessive irritability and pain is the single manifestation, it is unlikely to be related to gastroesophageal reflux disease. 2Typical symptoms of gastroesophageal reflux disease in older children.

**Table 2 Patient demographic data and characteristics (*n* = 15)**

|  |  |
| --- | --- |
| **Characteristics** | **Median (IQR) or *n* (%)** |
| Male sex | 6 (40) |
| Age (yr) | 3.1 (2.2-9.8) |
| Weight for height (%) | 100 (89.4-104.6) |
| **Previous symptoms** | 　 |
|  **General** | 　 |
| Discomfort/ Irritability in infants | 3 |
| Failure to thrive or weight loss | 8 |
| Feeding refusal | 3 |
|  Total  | 10 (66.7) |
|  **Gastrointestinal**  | 　 |
| Recurrent regurgitation with or without vomiting | 9 |
| Heartburn or chest pain | 1 |
| Epigastric pain | 1 |
| Hematemesis | 1 |
| Dysphagia, odynophagia | 6 |
|  Total | 11 (73.3) |
|  **Airway** |  |
| Wheezing**,** stridor | 4 |
| Cough | 9 |
| Hoarseness | 2 |
|  Total | 10 (66.7) |
| **Previous signs** | 　 |
|  **General** | 　 |
|  Dental erosion | 4 |
|  Anemia | 2 |
|  Total | 4 (26.7) |
| **Gastrointestinal**  |  |
|  Esophagitis | 8 |
|  Esophageal stricture | 7 |
|  Barret’s esophagus | 2 |
|  Total | 12 (80) |
|  **Airway** |  |
|  Asthma | 1 |
|  Recurrent respiratory tract infection | 8 |
|  Recurrent otitis media | 2 |
| Total | 8 (53.3) |

EA: Esophageal atresia; GER: Gastroesophageal reflux; IQR: Interquartile range.

**Table 3 Esophagogastroduodenoscopy findings and biopsy results of children with esophageal atresia after esophageal anastomosis (*n* = 17)**

|  |  |
| --- | --- |
| **Classification** | ***n* (%)** |
| Los Angeles Classification |
| Normal1 | 8 (47.1) |
|  A2 | 2 (11.8) |
|  B3 | 4 (23.5) |
|  C4 | 3 (17.6) |
| Pathology |
|  Normal | 6 (35.3) |
|  Mild esophagitis | 2 (11.8) |
|  Severe esophagitis | 9 (52.9) |

1One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length. 2One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds. 3Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference. 4Mucosal breaks which involve at least 75% of the esophageal circumference.

**Table 4 Parameters used and the analysis result of combined multichannel intraluminal impedance and pH study in children diagnosed esophageal atresia after esophageal anastomosis (*n* = 17)**

|  |  |
| --- | --- |
| **Parameters** | **Median ( IQR)** |
| Monitoring period excluding fed periods (h)  | 21.2 (19.3-22.1) |
| RI (%) | 2.7 (0.5-9.5) |
| Longest reflux period (min) | 20 (5-29) |
| Esophageal clearance (min) | 1.4 (0.6-2.5) |
| Total reflux (times) | 19 (11-36) |
| Acid | 9 (4-14) |
| Weakly acid | 10 (6-15) |
| Weakly alkaline | 0 (0-0) |
| mean bolus clearance time (s) | 14.9 (10.4-19.2) |

RI: Reflux index.

**Table 5 Parameters used and results from the analysis of combined video multichannel intraluminal impedance and pH study in children diagnosed esophageal atresia after esophageal anastomosis between using and non-using acid suppression therapy (*n* = 17)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Acid suppression therapy (*n* = 7)** | **No acid suppression therapy (*n* = 10)** | ***P* value** |
| Monitoring period (h) | 21.2 (18.1-24.5) | 21.3 (19.5-22.1) | 0.696 |
| RI (%) | 7.1 (1.4-10) | 1.45 (0.3-4.2) | 0.24 |
| Longest reflux period (min) | 29 (5-96) | 16 (4-24) | 0.143 |
| Esophageal clearance (min) | 2.0 (1.0-3.6) | 1.0 (0.5-1.7) | 0.261 |
| Total reflux (times)  | 19.0 (11-46) | 19.0 (11-29) | 0.66 |
| Acid | 10.0 (4-16) | 6.5 (3-11) | 0.558 |
| Weakly acid | 13.0 (4-32) | 9.0 (6-14) | 0.733 |
| Weakly alkaline | 0.0 (0-0) | 0.0 (0-1) | 0.123 |
| Mean bolus clearance time (s) | 11.9 (9.3-16.5) | 17.3 (10.4-21.7) | 0.242 |
| Number of symptoms (times) | 3.0 (1.0-5.0) | 4.0 (1.0-7.0) | 0.452 |
| SI (%) | 25 (0.0-50) | 10.5 (0-66.7) | 0.84 |
| SSI (%) | 1.4 (0-5.3) | 3.7 (0.0-17.6) | 0.419 |
| SAP (%) | 73.9 (0-90.9) | 83.9 (0-99.1) | 0.649 |

Present as median (IQR). RI: Reflux index; SAP: Symptom association probability; SI: Symptom index; SSI: Symptom sensitivity index.

**Table 6 Symptoms and symptom correlation from video recording in children with esophageal atresia (*n* = 17)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Symptom** | **Symptoms** | **Symptom-reflux****correlation** | **Acid** | **Weakly acid** | **Non acid** | **SI** | **SSI** | **SAP** |
| Cough | 35 | 16 (45.7) | 9 | 7 | 0 | 58.5 (6.2-100) | 2.9 (0.3-7.1) | 95 (18.9-99.2) |
| Vomit | 9 | 8 (89) | 5 | 3 | 0 | 75 (50-100) | 3.9 (2.3-60.7) | 99.6 (87.8-99.9) |
| Irritability or unexplained crying | 7 | 5 (71) | 4 | 1 | 0 | 50 (25-50) | 3.8 (2.5-3.8) | 92.8 (72.9-92.8) |
| Dysphagia | 1 | 0 (0) | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 52 | 29 (55.7) | 18 | 11 | 0 | 58.4 (27-100) | 3.9 (1.3-7.1) | 92.3 (77.4-99.6) |

Present as *n* (%) or median (IQR). SI: Symptom index; SSI: Symptom sensitivity index; SAP: Symptom association probability.