Pediatric Surgery International (2019) 35:887–893
https://doi.org/10.1007/s00383-019-04490-5

ORIGINAL ARTICLE

Acid and bolus exposure in pediatric reflux disease according to the presence and severity of esophageal mucosal lesions

Takeshi Saito[1] · Masaya Uesato[2] · Keita Terui[1] · Mitsuyuki Nakata[1] · Shugo Komatsu[1] · Hideo Yoshida[1]

Accepted: 17 May 2019 / Published online: 29 May 2019

Abstract

Purpose The relationship between reflux index (RI) and bolus exposure parameters in multichannel intraluminal impedance (MII) has not been examined sufficiently among children. The significance of acid and bolus exposure in evaluating pediatric reflux disease (RD) was explored by focusing on mucosal lesions.

Methods We conducted MII-pH on 28 patients (median age 8 years) with suspected RD. We assessed relationships between RI and bolus exposure indices, and also compared acid and bolus exposures across patients grouped by endoscopic esophageal mucosal lesions.

Results RI correlated significantly with distal acid reflux events ($r = 0.60$), acid bolus exposure time (BET) (0.55), and bolus clearance time (BCT) (0.48). Significant differences were observed among the control, non-erosive RD (NERD), and erosive RD (ERD) groups in all acid and several bolus exposure indices (distal and proximal frequencies, and BCT), while no significant difference was apparent between NERD and ERD. Acid exposure tended to be more severe in high-grade than in low-grade ERD, while no similar tendency was found in any bolus parameters other than BCT.

Conclusions MII-pH showed great potential for investigating the pathophysiology of pediatric RD, with RI revealing different correlations with variable bolus exposure indices. However, no specific parameters allowing precise discrimination between RDs or mucosal severities were identified.

Keywords Impedance · Gastroesophageal reflux · GERD · Reflux esophagitis

Abbreviations

BCT	Bolus clearance time
BET	Bolus exposure time
ERD	Erosive reflux disease
GERD	Gastroesophageal reflux disease
MII	Multichannel intramural impedance
NERD	Non-erosive reflux disease
RD	Reflux disease
RI	Reflux index

✉ Takeshi Saito
takk@faculty.chiba-u.jp

[1] Department of Pediatric Surgery (E6), Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan

[2] Department of Frontier Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan

Introduction

Multichannel intraluminal impedance-pH (MII-pH) monitoring has been introduced to evaluate the composition, direction, and destination of the refluxate among patients with suspected gastroesophageal reflux disease (GERD), irrespective of the acidity of the contents, using the electrical resistance of the esophagus. Even though some time has passed since the application of this method to the pediatric population, the relationships between reflux index (RI) as commonly used in the pH test and a wide range of bolus exposure parameters in MII have not been thoroughly investigated.

Frequent symptoms of gastroesophageal reflux affect 10–30% of the adult population [1]. GERD can occur in the conditions either with normal lower esophageal sphincter pressure (LESP) through frequent transient lower esophageal sphincter relaxation or with lower LESP through hiatus hernia, and also under conditions with impaired esophageal clearance, causing some patients to develop erosive reflux disease (ERD). Even though acid exposure is the key element for developing ERD, previous studies have failed to identify the determinant factor among pH-metry variables for elucidating the severity of ERD [1].

Non-erosive reflux disease (NERD) has caught attention, particularly in the adult field, as a distinct disease presenting with esophageal and extra-esophageal symptoms without evident endoscopic mucosal damage. Several papers have investigated the significance of MII-pH parameters among adult GERD subgroups to distinguish ERD from NERD [2–6] and to predict the severity of mucosal damage [7, 8]. Comparative data about comprehensive acid and bolus exposure indices of MII-pH among pediatric patients with various degrees of reflux diseases remain limited [9].

This study examined correlations between RI and a wide range of bolus exposure indices from MII-pH testing among pediatric patients with suspected GERD. We also attempted to clarify the potential of MII-pH in discriminating each pathophysiology of pediatric GERD and evaluating the presence and severity of esophageal macroscopic mucosal lesions.

Patients and methods

Patients

From 2013 to 2017, a total of 28 patients (14 males and 14 females) without distinct esophageal dysmotility but with suspected GERD (presenting with respiratory problems and/or gastrointestinal symptoms) were enrolled. All patients were more than 1 year old (median age 8 years; range 1–33 years). The 2 patients over 20 years old included in this study were neurologically impaired and weighed 14 kg and 19 kg. Eighteen patients showed underlying disease, comprising neurological impairment in 16 patients and postoperative congenital diaphragmatic hernia in 2 patients.

Methods

Medications for suspected GERD (acid suppression, prokinetics, and herbal medicine) were discontinued for at least 5 days before MII-pH testing. All MII-pH was performed using catheters that included 6 electrodes and 2 pH sensors (Sandhill Scientific, Denver, CO). The catheter was placed trans-nasally, and its location was confirmed on radiography so that the proximal pH sensor was 2 vertebrae up from the gastric cardia. During the study, patients ate regular meals or had their diet injected into the stomach or jejunum using a nasogastric or nasojejunal tube when oral intake was not feasible. Postures, meals, and symptoms were recorded chiefly by their guardians. The location of the catheter was reconfirmed on X-ray before removal. For the data to be included in this study, the recording period needed to be more than 20 h. Data were automatically analyzed using BioView analysis software (Sandhill Scientific Inc., Highlands Ranch, CO), followed by manual correction by an investigator (T.S.) with ample experience.

The parameters analyzed in this study included acid and bolus exposures. The former included number of episodes of acid reflux, reflux index (RI; percentage time with esophageal pH < 4.0), acid clearance time, and longest acid reflux time. The latter included bolus exposure time (BET; percentage time of bolus reflux) (total, acid, non-acid), bolus clearance time (BCT), longest reflux time, number of episodes of distal reflux (total, acid, non-acid), and number of episodes of proximal reflux (total, acid, non-acid). Proximal reflux was defined as refluxate reaching up to Z2 (or Z3 in cases among small children where Z2 was positioned outside the esophagus). In this study, reflux symptom indices were not considered, because the majority of patients showed neurological impairment and were not always able to make their guardians aware of the presence of symptoms.

GERD was defined as both having symptoms suspected to be due to gastroesophageal reflux and showing the following MII-pH results, based on previous reports [10, 11]:

Age < 1 year: RI $> 10\%$ and/or number of distal total reflux episodes > 100.

Age ≥ 1 year: RI $> 5\%$ and/or number of distal total reflux episodes > 70.

Gastroendoscopy was performed within several days after MII-pH testing. Endoscopically proven ERD was evaluated and graded in accordance with the Los Angeles classification. Furthermore, cases with LA grade A/B and grade C/D were designated as mild and severe ERD, respectively. Patients showing endoscopically normal esophageal mucosa but meeting the MII-pH criteria for GERD mentioned above were diagnosed with NERD, while those with normal mucosa who did not meet the criteria were classified as controls. Eventually, 11 patients were classified to the control group, including 7 with neurological impairment and 1 with postoperative congenital diaphragmatic hernia.

The institutional review board at our hospital approved this retrospective study. First, the relationship between RI and a wide range of MII bolus parameters was examined. The particularities of acid and bolus exposure parameters of reflux disease were then explored with comparison to normal subjects. Finally, a variety of MII-pH parameters were compared between mild ERD and severe ERD.

Statistical analysis

JMP® Pro version 13 software (SAS Institute Inc., Cary, NC) was used for all statistical analyses. Normally distributed continuous variables are expressed as the

Table 1 Correlations between RI and bolus exposure parameters

	r	p value
Bolus exposure time		
Total	0.44	0.007
Acid	0.55	0.0005
Non-acid	−0.03	0.86
Bolus clearance time	0.48	0.003
Longest reflux time	0.30	0.07
Number of distal reflux episodes		
Total	0.42	0.01
Acid	0.60	< 0.0001
Non-acid	−0.13	0.45
Number of proximal reflux episodes		
Total	0.28	0.09
Acid	0.36	0.03
Non-acid	0.04	0.81

mean ± standard deviation. Analysis of variance and Fisher's exact test were used to compare laboratory and clinical data. Data were defined as significant at the level of $p < 0.05$.

Results

Relationships between RI and bolus exposure parameters

The relationships between RI and a variety of bolus exposure parameters are shown in Table 1. Significant linear correlations were shown for distal acid reflux episodes ($p < 0.0001$), acid BET ($p = 0.0005$), BCT ($p = 0.003$), total BET ($p = 0.007$), distal total reflux episodes ($p = 0.01$), and proximal acid episodes ($p = 0.03$). RI correlated moderately with distal acid reflux events ($r = 0.60$) (Fig. 1a), and weakly with acid BET ($r = 0.55$) (Fig. 1b) and BCT ($r = 0.48$) (Fig. 1c). However, RI did not show significant correlations with non-acid BET ($p = 0.86$), or distal or proximal non-acid reflux episodes ($p = 0.45$ and 0.81, respectively).

MII-pH particularities in reflux disease

The demographic data of each group are shown in Table 2. Table 3 shows the particularities of MII parameters among ERD, NERD, and controls. In terms of acid exposure, all 4 parameters including number of episodes of acid reflux, RI, acid clearance time, and longest reflux time showed

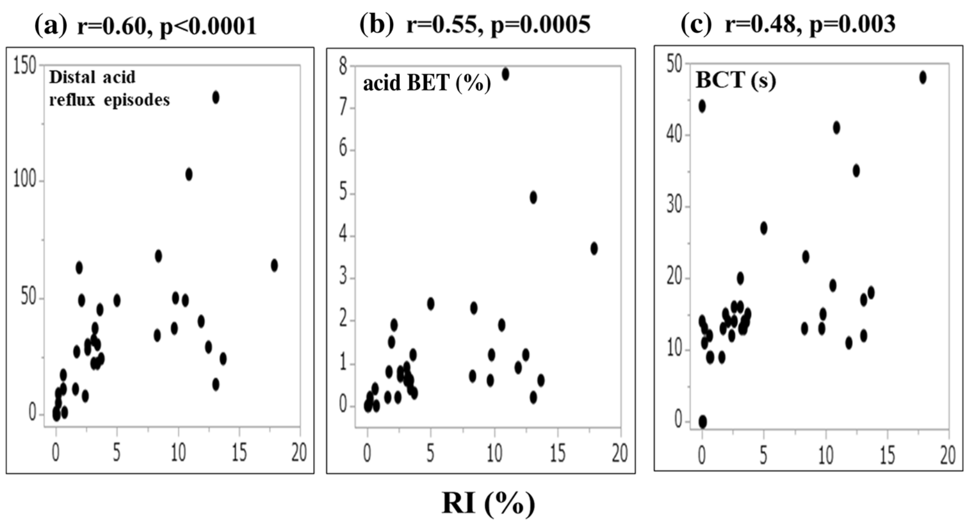

Fig. 1 Relationship between reflux index (RI) and MII bolus exposure parameters. RI demonstrated moderate and weak correlations with the number of episodes of distal acid reflux (**a**), and acid bolus exposure time (BET) (**b**) and bolus clearance time (BCT) (**c**), respectively

Table 2 Demographic data among ERD, NERD, and control patients

	ERD ($n = 12$)	NERD ($n = 5$)	control ($n = 11$)	p value
Disease				
Neurologically impaired	7	2	7	
Postoperative CDH	1	0	1	
Age (years)	11.6 (1.3–24.6)	5.0 (3.4–12.6)	3.8 (1.1–20.0)	0.02
Body (kg)	21.1 (7.7–46.5)	14.4 (9.6–22.7)	13.1 (8.4–48.4)	0.40

Values are given as number or median (range)

CDH congenital diaphragmatic hernia, *ERD* erosive reflux disease, *NERD* non-erosive reflux disease

Table 3 Comparison of MII-pH parameters among ERD, NERD, and control patients

	ERD ($n=12$)	NERD ($n=5$)	Control ($n=11$)	p value
Acid exposure				
Number of reflux	94.5 ± 47.5	78.4 ± 53.6	18.9 ± 21.0	0.0005
Reflux index (%)	9.8 ± 7.0	6.2 ± 3.6	0.97 ± 1.11	0.0010
Acid clearance time (s)	89.1 ± 39.8	76.4 ± 43.7	30.9 ± 21.2	0.0014
Longest reflux time (min)	14.8 ± 9.1	15.1 ± 9.4	2.3 ± 2.3	0.0007
Bolus exposure				
Bolus exposure time (%)				
Total	2.38 ± 2.80	1.60 ± 0.91	0.43 ± 0.40	0.07
Acid	1.83 ± 2.28	1.24 ± 0.80	0.31 ± 0.36	0.085
Non-acid	0.57 ± 0.68	0.34 ± 0.34	0.11 ± 0.10	0.091
Bolus clearance time (s)	19.8 ± 9.6	15.4 ± 4.3	11.9 ± 5.0	0.0497
Longest reflux time (min)	2.3 ± 1.6	2.3 ± 1.8	0.9 ± 0.9	0.06
Number of distal reflux episodes				
Total	67.6 ± 46.1	63.8 ± 23.2	19.0 ± 15.4	0.0045
Acid	46.8 ± 37.0	43.6 ± 15.4	11.9 ± 12.2	0.011
Non-acid	20.8 ± 19.5	20.0 ± 20.3	7.1 ± 7.2	0.11
Number of proximal reflux episodes				
Total	34.5 ± 32.7	40.6 ± 23.1	6.6 ± 6.5	0.01
Acid	23.8 ± 25.9	17.6 ± 11.8	5.1 ± 5.6	0.06
Non-acid	10.8 ± 14.1	23.4 ± 24.1	1.6 ± 2.8	0.02

ERD erosive reflux disease, *NERD* non-erosive reflux disease

significant differences among groups ($p=0.0005$, 0.0010, 0.0014, and 0.0007, respectively). Significant differences were also found in bolus exposure parameters including BCT ($p=0.0497$), number of distal total and acid reflux episodes ($p=0.005$ and 0.01, respectively), and number of proximal total and non-acid reflux episodes ($p=0.01$ and 0.02, respectively). Considering which combinations created the difference, ERD and controls showed differences in BCT ($p=0.04$), distal total and acid reflux episodes ($p=0.005$ and 0.01, respectively), and proximal total reflux episodes ($p=0.03$). Between NERD and controls, significant differences were observed in proximal total and non-acid reflux episodes ($p=0.04$ and 0.02, respectively). On the other hand, we did not find any significant differences between the ERD and NERD groups in any of these MII parameters.

Comparison of parameters between mild ERD and severe ERD

Demographic data of each group are shown in Table 4. The 12 patients with ERD on endoscopy consisted of 3, 3, 5, and 1 with grades A, B, C, and D according to the Los Angeles classification, respectively. MII-pH parameters were compared between patients with mild (A/B, 6 cases) and severe (C/D, 6 cases) ERD (Table 5). Regarding acid exposure, patients with severe ERD tended to be affected more severely, although the difference was not significant.

Table 4 Demographic data among patients with mild and severe ERD

	Mild ERD ($n=6$)	Severe ERD ($n=6$)	p value
Age (years)	9.9 (7.0–22.5)	15.4 (1.3–24.6)	0.93
Body (kg)	21.1 (14.3–27.7)	20.9 (7.7–46.5)	0.73

Values are given as median (range)

ERD erosive reflux disease

However, similar tendencies were not found in bolus exposure parameters other than BCT.

Discussion

We investigated the relationship between RI and a wide range of bolus exposure parameters among pediatric patients with suspected GERD. In addition, we examined the particularities of representative MII-pH indices according to the pathophysiology of GERD and esophageal mucosal lesions. The results showed distal acid reflux frequency had the most significant correlations with RI, followed by acid BET, and BCT. MII-pH indices were also found to be unable to distinctly differentiate between ERD, NERD, and normal controls, or severe and mild ERD. This was because acid and bolus exposure parameters overlapped, even though pediatric patients with the presence of or greater severity of

Table 5 Comparison of MII-pH parameters between mild ERD and severe ERD

	Mild ERD ($n=6$)	Severe ERD ($n=6$)	p value
Acid exposure			
Number of reflux	82.0 ± 19.5	107.0 ± 19.5	0.39
Reflux index (%)	7.2 ± 4.6	12.4 ± 8.4	0.22
Acid clearance time (s)	71.0 ± 23.9	107.2 ± 46.2	0.12
Longest reflux time (min)	12.2 ± 7.8	17.5 ± 10.3	0.34
Bolus exposure			
Bolus exposure time (%)			
Total	3.52 ± 2.70	2.80 ± 0.71	0.17
Acid	2.67 ± 2.02	2.04 ± 0.76	0.22
Non-acid	0.85 ± 0.53	0.76 ± 0.38	0.16
Bolus clearance time (s)	18.7 ± 11.1	21.0 ± 8.7	0.69
Longest reflux time (min)	2.92 ± 2.09	2.05 ± 0.83	0.22
Number of distal reflux episodes			
Total	92.5 ± 52.8	72.7 ± 20.1	0.06
Acid	63.2 ± 47.2	51.3 ± 12.1	0.13
Non-acid	29.3 ± 16.3	21.4 ± 19.9	0.14
Number of proximal reflux episodes			
Total	46.5 ± 28.4	32.5 ± 22.9	0.22
Acid	34.3 ± 23.7	23.2 ± 8.6	0.17
Non-acid	12.2 ± 9.8	9.3 ± 15.3	0.75

Values are given as mean ± standard deviation

ERD erosive reflux disease

mucosal lesions showed more effects on acid exposure than on bolus exposure.

Comprehensive studies focusing on the associations between RI and various MII parameters remain limited, particularly for pediatric populations. Even though Mattioli et al. [12] reported on their preliminary experience with 50 children and found fair concordance between RI and MII results, the latter dealt with only BET. The present study revealed correlations between RI and other bolus exposure indices on MII and also found that each bolus exposure parameter associated with acid reflux exhibited variations in correlations with RI. That is, the number of episodes of distal acid reflux showed the strongest correlation, followed by acid BET and the number of episodes of proximal acid reflux. In addition, BCT showed weak correlations with RI. These results undoubtedly demonstrated that RI reflects only part, and not the entire pathophysiology of GERD, indicating the additional value of MII-pH and possible roles of non-acid reflux and static refluxate in investigating some entities of GERD.

In terms of bolus transport, the present study demonstrated a significant difference between the ERD and control groups in BCT, number of distal total and acid bolus episodes, and number of proximal total bolus episodes, even though previous studies of children have suggested inconsistent results for MII-pH parameters in distinguishing normal esophagus from reflux esophagitis [5, 8, 9]. This discrepancy may be partly due to differences in the definitions of reflux esophagitis. That is, several studies have relied on histological evidence for the diagnosis [5, 6], meaning that some cases might have been defined as control or NERD in our study, since discordance between endoscopic and histological diagnoses of reflux esophagitis has been suggested [6]. The difference may also be partly attributable to the selection of different conventional bolus exposure indices in each study. Although distal reflux bolus frequency has generally been included in investigations, only a few studies have even considered bolus exposure and clearance times, longest impedance episodes, or number of proximal reflux episodes [5]. The strong point of the present study was considered to be the method for dealing with pediatric patients with macroscopic reflux esophagitis using a wide range of MII-pH parameters.

Several previous studies with children have selected different criteria for MII-pH indices defining NERD, such as BET at 1.4% [13], the upper limit of the normal reference in adults, the combination of RI and symptom association probability [4, 6], or the combination of RI, BET, or number of distal reflux bolus events [9]. We introduced the provisional diagnostic criteria of MII-pH based on previous studies [10, 11], comprising the number of distal reflux episodes and RI with the boundary of 1 year of age. The exclusion of symptom-related indices such as symptom index and symptom association probability was due to the low reliability of those parameters [12], because quite a number of our subjects were neurologically impaired with difficulties in verbal expression, and small children often cannot verbalize their complaints accurately.

Savarino et al. [2] demonstrated significantly higher numbers of total and acid reflux episodes in the distal esophagus and a higher percentage of reflux reaching the proximal esophagus in adult ERD compared to NERD patients, whereas Conchillo found no significant difference between comparable groups in the numbers of distal total and acid bolus events [3]. Meanwhile, investigations into MII-pH particularities between pediatric ERD and NERD have been limited and inconclusive [4–9]. Reasons for the small number of publications include the difficulties in evaluating symptom-related complaints, fewer opportunities to perform gastroendoscopy (which often requires general anesthesia), and a lack of normal reference data for each MII-pH parameter.

Our study demonstrated that pediatric NERD involved a higher number of proximal total and non-acid reflux episodes, shorter BCT, and lower BET than ERD, while the number of episodes of distal bolus reflux was comparable between groups. This finding is probably indicative of the importance of the static duration, the ability to clear contents, or the proximal reaching point of the refluxate in developing NERD. The extent of esophageal secretion [14] and the presence of bile acids and pepsin in the refluxate [15] may also contribute to the presence and degree of esophageal mucosal lesions. Of note, the characteristics of adult NERD are unlikely to completely coincide with those of pediatric NERD, partly because again our study included a fairly large proportion of cases with neurological impairment.

The comparison of MII-pH parameters between adult patients with mild and severe ERD showed a large degree of overlap in acid exposure time, bolus clearance time, and number of total and acid reflux episodes [7]. Inconclusive results in the pediatric field may be due to the inclusion of fewer MII-pH indices [8] or only several cases with severe ERD [9]. One strength of the present study was the coverage of a considerable number of acid and bolus exposure parameters and inclusion of a large number of patients with severe ERD (4 with LA grade C and 2 with grade D), revealing no distinct indices reflecting the severity of mucosal lesions. Interestingly, even though high-grade ERD demonstrated more severe acid exposure than low-grade ERD, no similar tendency was observed in terms of bolus exposure. This may indicate the predominance of acid exposure over bolus exposure in determining the severity of esophageal mucosal breaks in the pediatric population. In addition, the result may also suggest greater difficulties in identifying reflux events in tracings of severe ERD due to the lower impedance baselines associated with a more affected mucosa, causing possible underestimation of bolus exposures.

The key limitations of this study were as follows: First, the sample size was relatively small. In this context, inclusion of a high proportion of pediatric ERD patients is rare, particularly high-grade cases. Second, the effect of neurological impairment in 16 children cannot be ignored. Even though we confirmed the normal bolus pattern of impedance in traces during swallowing, not all aspects of esophageal function in those cases were examined. Third, there was quite an age distribution of subjects and patient ages differed significantly among groups (Table 2). That is, patients in the ERD group were older than control subjects, even though body weight did not show a significant difference. Fourth, the directions of cause-and-effect relationships between abnormal MII-pH values and esophageal mucosal damage remain to be determined. Mucosal damage itself thus can affect esophageal bolus transport (Table 5) [16]. Last, this study has not sufficiently investigated a possible role of MII-pH in evaluating RD without esophagitis chiefly caused by non-acid reflux.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Avidan B, Sonnenberg A, Schnell TG et al (2002) Acid reflux is a poor predictor for severity of erosive reflux esophagitis. Dig Dis Sci 47:2565–2573
2. Savarino E, Tutuian R, Zentilin P et al (2010) Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. Am J Gastroenterol 105:1053–1061
3. Conchillo JM, Schwartz MP, Selimah M et al (2008) Acid and non-acid reflux patterns in patients with erosive esophagitis and non-erosive reflux disease (NERD): a study using intraluminal impedance monitoring. Dig Dis Sci 53:1506–1512
4. Borrelli O, Salvatore S, Mancini V et al (2012) Relationship between baseline impedance levels and esophageal mucosal integrity in children with erosive and non-erosive reflux disease. Neurogastroenterol Motil 24:828-e394
5. Salvatore S, Hauser B, Devreker T et al (2009) Esophageal impedance and esophagitis in children: any correlation? J Pediatr Gastroenterol Nutr 49:566–570

6. van der Pol RJ, Loots CM, Peeters L et al (2013) Outcomes of endoscopy and novel pH-impedance parameters in children: is there a correlation? J Pediatr Gastroenterol Nutr 56:196–200
7. Bredenoord AJ, Hemmink GJ, Smout AJ (2009) Relationship between gastro-oesophageal reflux pattern and severity of mucosal damage. Neurogastroenterol Motil 21:807–812
8. Liu YW, Wu JF, Chen HL et al (2016) The correlation between endoscopic reflux esophagitis and combined multichannel intraluminal impedance-pH monitoring in children. Pediatr Neonatol 57:385–389
9. Pilic D, Hankel S, Koerner-Rettberg C et al (2013) The role of baseline impedance as a marker of mucosal integrity in children with gastro esophageal reflux disease. Scand J Gastroenterol 48:785–793
10. Wenzl TG, Benninga MA, Loots CM, ESPGHAN EURO-PIG Working Group et al (2012) Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. J Pediatr Gastroenterol Nutr 55:230–234
11. Pilic D, Fröhlich T, Nöh F et al (2011) Detection of gastroesophageal reflux in children using combined multichannel intraluminal impedance and pH measurement: data from the German Pediatric Impedance Group. J Pediatr 158:650.e1–654.e1
12. Mattioli G, Pini-Prato A, Gentilino V et al (2006) Esophageal impedance/pH monitoring in pediatric patients: preliminary experience with 50 cases. Dig Dis Sci 51:2341–2347
13. Fukahori S, Yagi M, Ishii S et al (2017) A baseline impedance analysis in neurologically impaired children: a potent parameter for estimating the condition of the esophageal mucosa. Neurogastroenterol Motil. https://doi.org/10.1111/nmo.13012
14. Marcinkiewicz M, Han K, Zbroch T et al (2000) The potential role of the esophageal pre-epithelial barrier components in the maintenance of integrity of the esophageal mucosa in patients with endoscopically negative gastroesophageal reflux disease. Am J Gastroenterol 95:1652–1660
15. Koek GH, Sifrim D, Lerut T et al (2008) Multivariate analysis of the association of acid and duodeno-gastro-oesophageal reflux exposure with the presence of oesophagitis, the severity of oesophagitis and Barrett's oesophagus. Gut 57:1056–1064
16. Chen CL, Yi CH (2008) Utility of esophageal impedance in identifying dysmotility in patients with erosive esophagitis. Dis Esophagus 21:539–543