OPEN

Evaluation of Gastroesophageal Reflux in Children Born With Esophageal Atresia Using pH and Impedance Monitoring

*†Floor W.T. Vergouwe, ‡Michiel P. van Wijk, †Manon C.W. Spaander, †Marco J. Bruno, *René M.H. Wijnen, *Johannes M. Schnater, and *Hanneke IJsselstijn

ABSTRACT

Objectives: The aim of the study was to evaluate acid and nonacid gastroesophageal reflux in infants and school-aged children with esophageal atresia (EA) using pH-impedance (pH-MII) monitoring.

Methods: Between 2012 and 2017, all 24-hour pH-MII studies performed in infants (≤18 months) and 8-year olds with EA were included. Antiacid therapy was discontinued before study. Exclusion criteria were: isolated tracheoesophageal fistula; esophageal replacement therapy; tube feeding; and monitoring <18 hours. Automatically detected retrograde bolus movements (RBM) were manually reviewed and modified/deleted if necessary.

Results: We included 57 children (51% boys; 2% isolated EA; 44% thoracoscopic EA repair): 24 infants (median age 0.6 years) and 33 school-aged children (median age 8.2 years). Of the automatically detected 3313 RBM, 1292 were manually deleted from the tracings: 52% of nonacid RBM and 8% of acid RBM (mainly misinterpreted swallows or 1 event recognized as several events). In infants, median reflux index (RI; pH <4) was 2.6% (abnormal in n = 2), median RBM was 61 (62% nonacid, 58% mixed), and median of the mean BCT was 11 seconds. In older children, median RI was 0.3% (abnormal in n = 4), median RBM was 21 (64% nonacid; 75% mixed), and median of the mean BCT was 13 seconds.

Conclusions: Most children with EA off medication have a normal RI, yet experience a significant number of nonacid RBM. After manual revision of the tracings, a high percentage of RBM was deleted. Our data show that automated impedance analysis software needs refinement for use in infants and children with EA and question the need for standard antiacid therapy in these patients.

Key Words: acid reflux, nonacid reflux, pH-metry, pH-MII study, tracheoesophageal fistula

(*JPGN* 2019;69: 515–522)

What Is Known

- Many esophageal atresia patients suffer from chronic gastroesophageal reflux. Only a few experience troublesome symptoms (eg, heartburn, regurgitation, and vomiting).
- Guidelines recommend reflux monitoring in esophageal atresia patients around 1 year of age and during long-term follow-up in symptomatic children.
- Reference values for pH-impedance monitoring in children are absent.

What Is New

- We present pH-impedance data at the approximate ages at which reflux monitoring in esophageal atresia patients is recommended.
- Most children have a normal reflux index, which questions the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition-North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommendation for standard proton pump inhibitor therapy in the first year postsurgery.
- Automated software overdetects reflux events in esophageal atresia patients.

Esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) is a relatively common birth defect in which the continuity of the esophagus is interrupted (European prevalence: 2.43 per 10,000 births) (1). As a result of inborn deficient esophageal innervation and surgical nerve injury, EA patients suffer from esophageal dysmotility (2,3). Gastroesophageal reflux (GER; acid and nonacid) is a physiologic phenomenon. When GER causes troublesome symptoms interfering with daily life or complications, it is referred to as GER disease (GERD) (4). GERD is thought to be common after surgical EA repair in both children and adults (5,6). It results in respiratory and gastrointestinal problems in the short-term (eg, aspiration pneumonia, apparent life-threatening events, dysphagia, feeding problems) and long-term (eg, chronic respiratory symptoms, esophagitis, esophageal strictures, Barrett esophagus, esophageal cancer) (6–10). Given the high prevalence of GERD in children with EA (up to 54% in some studies using the definition ''fundoplication performed, pH-study positive or endoscopic esophagitis''), it is important to diagnose and manage GERD to reduce associated complications (5,6).

Although many children with EA are exposed to chronic GER, only a few experience troublesome symptoms. Results from pH-impedance (pH-MII) studies as well as endoscopic evaluations in children with EA show that asymptomatic children can have

Received March 9, 2019; accepted July 25, 2019.

From the *Department of Pediatric Surgery and Intensive Care Children, Erasmus MC University Medical Center - Sophia Children's Hospital, the †Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, and the ‡Department of Pediatric Gastroenterology, VU University Medical Center & Department of Pediatric Gastroenterology and Nutrition, Academic Medical Center - Emma Children's Hospital, Amsterdam, The Netherlands.

Address correspondence and reprint requests to Johannes M. Schnater, MD, PhD, Department of Pediatric Surgery and Intensive Care Children, Erasmus MC University Medical Center - Sophia Children's Hospital, Internal postal address: room SK 1258, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands (e-mail: j.schnater@erasmusmc.nl).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

F.W.T.V, M.C.W.S., H.I, R.M.H.W., J.M.S., M.J.B. report no conflicts of interest. M/P.v.W. is a consultant with Laborie-MMS.

DOI: 10.1097/MPG.0000000000002468

severe abnormalities (11–14). Therefore, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)-North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Guideline (2016) recommends to routinely prescribe proton pump inhibitors (PPI) for the first year of life and monitor GER using pH-MII monitoring and/or endoscopy at time of discontinuation (regardless of symptoms) and during long-term follow-up in symptomatic children with EA (6).

We hypothesized that GER occurs frequently in children with EA, not only in infancy but also thereafter. Moreover, based on clinical interpretation of several pH-MII studies before this study, we assumed that disturbed impedance patterns in EA patients leads to over-detection of reflux events in automated analysis. We aimed to evaluate and characterize acid and nonacid GER in infants and school-aged children with EA using pH-MII monitoring and to evaluate the rate of overdetection by automated software in this specific population.

METHODS

Patients

All children with EA born in our hospital are offered a 24-hour pH-MII study at the age of 0.5 and 8 years as part of a longitudinal multidisciplinary follow-up program (15). As standard of care, all children receive PPI for at least 6 months after surgical EA repair. We retrospectively reviewed all pH-MII studies conducted in children with EA between September 2012 and October 2017 and included studies performed at ages $\leq$18 months or 7 to 9 years with a duration of $\geq$18 hours. Exclusion criteria were: isolated TEF; esophageal replacement therapy (eg, gastric pull-up, jejunal/colonic interposition); and use of tube feeding. The Medical Research Involving Human Subjects Act was considered not applicable to the study protocol (protocol ID MEC-2017–185).

Data Collection

Data retrieved from patient records included baseline characteristics (eg, sex, gestational age, type of EA, type of EA repair) and clinical data at time of pH-MII monitoring (eg, symptoms, use of anti-reflux medication, *z*-scores height, and weight-for-height) (16,17). All 8-year-old children were asked to fill in an online validated questionnaire for detecting GERD by Manterola et al (18,19). A cut-off score >3 was used.

Small for gestational age was defined as a birth weight 2 standard deviations (SD) below normal. Prematurity was defined as gestational age <37 weeks. Pulmonary infections were defined as lower respiratory tract infections requiring antibiotic therapy and/or hospital admission.

pH-MII Monitoring Protocol

Children were intubated with an age-appropriate pH-MII catheter. We used 2 available types of pH-MII catheters to perform 24-hour pH-MII studies: Greenfield (Dover, USA) single use antimony pH-MII catheters (6.4 French, 6 impedance channels, 1–2 pH channels) and Laborie ion-sensitive field-effect transistor (ISFET) disposable pH-MII catheters (6 French, 6 impedance channels, 1 pH channel). A chest X-ray was performed to ensure correct pH channel position (3 vertebrae above the diaphragm) (20). All antiacid and prokinetic therapy was discontinued before the start of the pH-MII assessment (5 and 2 days, respectively). Parents were asked to fill in a diary during pH-MII monitoring to monitor symptoms, body position, and intake of food and beverages. Patients were instructed not to eat acid foods or drink carbonated beverages.

Manual Correction of Reflux Events

Initial manual review was performed to ensure correct diary records and to delete artefacts. Then MMS database software 9.5 (Medical Measurement Systems B.V., Enschede, The Netherlands) was used for automated analysis (acid/alkaline limits: pH 4.0 and 7.0; minimum reflux duration pH- and MII-results: 5 seconds; air threshold: 5000Ω). All reflux events—identified as such by the software—were manually reviewed and modified (duration; number of impedance channels involved; liquid/mixed reflux content) by 1 researcher unaware of the clinical symptoms (F.V.). A second reviewer (M.v.W.) examined inconclusive events. RBM were deleted in case both reviewers agreed the RBM was misinterpreted by the software.

Data Analysis

Parameters analyzed in this study included number of pH changes to <4; reflux index (RI; acid exposure index [%]); number of long (>5 minutes) acid exposures; longest acid exposure (minutes); number of retrograde bolus movements (RBM); number of acid/nonacid (pH $\geq$4) RBM; number of liquid/mixed RBM; mean bolus clearance time (BCT; seconds); number of proximal bolus exposures (reaching proximal impedance channel); symptom index for reflux (SI); and symptom association probability (SAP; window of 120 seconds before and after a reflux event). An RI >7% was considered to be abnormal, <3% to be normal, and 3% to 7% to be indeterminate (21). SI $\geq$50% and SAP $\geq$95% were considered positive (22).

Data are presented as frequencies, mean (SD) or median (minimum; maximum; interquartile range [IQR]). Data were analyzed with SPSS 21.0 (SPSS Inc., Chicago, IL) using descriptive statistics. Nonparametric Mann-Whitney *U* test was used to compare continuous variables and Pearson chi-square test or Fisher exact test for categorical variables. The 2-tailed level of significance was set at $P = 0.05$.

RESULTS

Demographics

Of the 69 children born between 2011 and 2017 (ages $\leq$18 months in study period), 3 children had died. Sixteen children fulfilled exclusion criteria, mainly because of tube feeding (Fig. 1). We included 24/50 (48.0%) eligible infants (median age 0.6 [range 0.2–1.5] years). Reasons for not being included are listed in Figure 1.

Of the 74 children born between 2004 and 2009 (ages 8 years in study period), 6 children had died. Nine children fulfilled exclusion criteria. We included 33/59 (55.9%) children (median age 8.2 (range 8.0–9.0) years; Fig. 1).

Demographics of the 57 included children (Table 1) and the 52 nonincluded children did not significantly differ (Supplementary Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B702*). In 43.9% of included children, thoracoscopic EA repair was performed. Twenty-four children were using antireflux medication (91.7% of infants and 6.1% of older children), which was discontinued before pH-MII monitoring. Nissen fundoplication was previously performed in 8 (24.2%) 8-year-old children (median age 0.5 years) (Table 1).

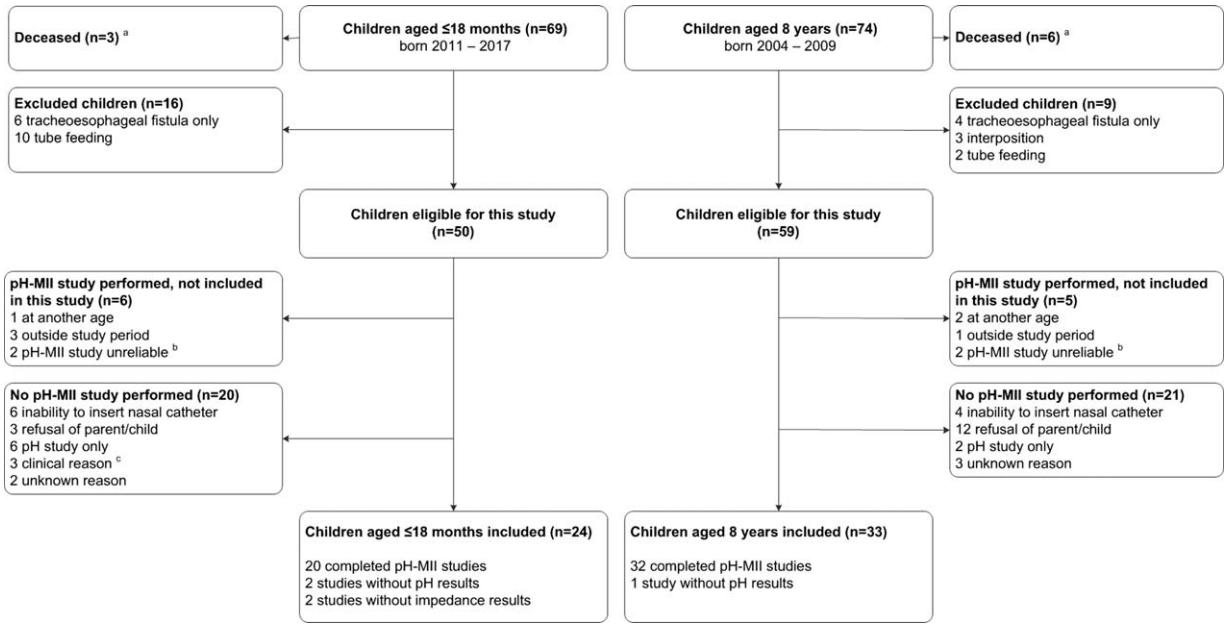

FIGURE 1. Flowchart of children included in study. [a] Deceased at a median age of 71 (range 3–704) days. Causes: multiple major anomalies (n = 5), recurrent sepsis (n = 1), reanimation complicated with sepsis and severe neurological impairment (n = 1), acute apparent life-threatening event based on intracerebral bleeding and ischemia (n = 1), sudden death with unknown cause (n = 1). [b] Inappropriate position of pH catheter (n = 2) and software/electrode failure with negative pH values and impedance artefacts (n = 2). [c] Clinical reasons for absence of pH-MII studies: absence of symptoms after a recent Nissen fundoplication (n = 1); normal esophagus observed at endoscopy in an asymptomatic child treated with antireflux medical therapy (n = 1); and expectative management in a child with a short esophagus, intrathoracic stomach, and proven gastroesophageal reflux (n = 1).

pH-MII Studies

Greenfield catheters were used in 30 (52.6%) and ISFET catheters in 27 (47.4%) of the 57 pH-MII studies. Of the 57 included pH-MII studies, we evaluated 52 complete pH-MII studies, 3 studies showed no reliable pH results because of pH-sensor malfunctioning and in 2 studies, impedance results were not analyzed (after deleting artefacts, duration of the impedance tracing was <18 hours).

Manual Correction of Reflux Events

In total, 3313 RBM were detected by MMS software of which 1287 (39%) RBM were manually deleted from the tracings: 52% of all nonacid RBM (mainly swallows misinterpreted as being a RBM) and 8% of all acid RBM (mainly swallowing or a single event being recognized as several events by the software; Supplementary Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/B702*). Median RI was 2.6% in infants and 0.6% in older children. Table 2 shows all other pH-MII parameters.

In infants, pH results were abnormal in 2/22 (10%) evaluated pH studies; one of these had apparent life-threatening events suspected to be GER-related. Indeterminate pH results were found in 6 (27%) infants, 2 of whom (33%) suffered from daily regurgitation/vomiting. Normal pH results were found in 14 (64%) infants, 1 was symptomatic (day and night cough). A median of 61 (range 0–134) RBM were observed. Four infants had >100 RBM/24 hours (22).

In older children, pH results were abnormal in 4/32 (12.5%) pH studies, 3 of them (75%) were symptomatic (regurgitation, acid reflux, and night cough). None of the older children with abnormal pH results had undergone fundoplication surgery before the pH-MII study. Indeterminate pH results were found in 2 (6%) children, both asymptomatic, and pH results were normal in 26 (81%) children, 5 (19%) reported symptoms (regurgitation, nausea, nausea/abdominal pain, foetor ex ore/abdominal pain, and night cough). A median of 21 (range 0–54) RBM were observed and none of the older children had >70 RBM/24 hours (22).

Symptoms

Before pH-MII monitoring, 12 children/parents spontaneously reported symptoms (16.7% of the infants and 24.2% of the older children; Table 1). Diaries recorded during the measurement were missing in 2 children. Twenty-seven children did experience symptoms during pH-MII monitoring, of whom 21 reported nonspecific and unlikely to be GER related (eg, sneezing, hiccup) or very few (<3 times per 24 hours) symptoms. As a result, symptom analysis was performed in only 4 infants (coughing, belching, and twice crying) and 2 older children (coughing and nausea/burping/regurgitation/vomiting). SI and SAP were positive in 1/6 (16.7%) and 3/6 (50.0%), respectively. If only acidic episodes were considered, SI and SAP were positive in 0/6 and 4/6 (66.7%), respectively. Without manual correction, only 3 of these latter 4 children had a positive SAP.

Questionnaire

Twenty-four (72.7%) 8-year old children completed the Manterola questionnaire (Supplementary Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B702*). Demographics, RI, and number of RBM of these children did not significantly differ

TABLE 1. Patient demographics (N = 57)

	Age ≤18 months (N = 24) n (%)/median (min; max; IQR)	Age 8 years (N = 33) n (%)/median (min; max; IQR)
Male sex	14 (58.3)	15 (45.5)
Age, years	0.6 (0.2; 1.5; 0.5–1.1)	8.2 (8.0; 9.0; 8.1–8.4)
Gestational age, weeks	38.1 (30.4; 41.7; 35.3–40.0)	38.6 (28.9; 42.3; 37.0–40.1)
Prematurity	7 (29.2)	7 (21.2)
Birthweight, gram	2595 (854; 3630; 1746–3078)	2850 (1080; 3810; 2235–3190)
Small for gestational age	4 (16.7)	4 (12.1)
Type of esophageal atresia		
Gross type A	0	1 (3.0)
Gross type C	24 (100.0)	31 (93.9)
Gross type D	0	1 (3.0)
Type of esophageal correction		
Primary anastomosis	23 (95.8)	30 (90.9)
Delayed anastomosis	1 (4.2)	3 (9.1)
Type of surgery		
Thoracoscopy	17 (70.8)	8 (24.2)
Thoracotomy	6 (25.0)	25 (75.8)
Converted	1 (4.2)	0
Z-score for weight-for-height; mean (SD)	−0.5 (1.1)	−0.3 (1.1)
Wasting (acute malnutrition)	2 (8.3)	2 (6.1)
Use of antireflux medication		
Proton pump inhibitor	11 (45.8)	2 (6.1)
H2 antagonist ± prokinetic drug	11 (45.8)*	0
None	2 (8.3)	31 (93.9)
Pulmonary infections†	1 (4.2)‡	8 (24.2)§
Prophylactic antibiotics (airways)	2 (8.3)	2 (6.1)
Symptoms		
Gastrointestinal	2 (8.3)‖	6 (18.2)¶
Respiratory	2 (8.3)‖	2 (6.1)¶
None	20 (83.3)	25 (75.8)
Gastroesophageal reflux questionnaire (Manterola)	–	2 (0; 9; 1–4)
Nissen fundoplication surgery	0	8 (24.2)#

IQR = interquartile range.
*Five children used Ranitidine and Domperidone.
†Defined as lower respiratory tract infections requiring antibiotics and/or hospital admission since birth (infants) or in the previous year (8-year olds).
‡One infection in the previous year.
§One (n = 4) and 2–4 (n = 4) infections in the previous year.
‖Vomiting unrelated to food intake/physical activity (n = 1), frequent vomiting (n = 1), ALTE (n = 1), cough (n = 1).
¶Regurgitation (n = 2), acidic reflux (n = 1), nausea (n = 1), nausea/abdominal pain (n = 1), foetor ex ore and abdominal pain related to food intake (n = 1), night cough (n = 2).
#Median age of 5 (range 3–87) months at time of Nissen fundoplication.

from the 9 children who did not complete the questionnaire (Supplementary Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/B702*). The score was suggestive for GERD in 7 (29.2%) children. Nocturnal cough (n = 7), regurgitation (n = 6, weekly in 4), dysphagia (n = 5) and heartburn (n = 5, weekly in 1 and daily in 1) were the most frequently reported symptoms. In only 2/7 children abnormal pH results were found: an RI of 13% in a child with complaints of heartburn at least once a month and an index of 14% in a child with occasional chest pain. pH-MII parameters (automated or manual), SI and SAP did not differ significantly between children with a high (>3) or low (≤3) score.

Change of Antireflux Treatment

The majority (22/24; 91.7%) of infants were using anti-reflux medication before the pH-MII study. In infants, medication was continued in 3 (1 abnormal and 2 indeterminate pH results), discontinued in 18 (4 indeterminate, 12 normal, and 2 unreliable pH results), and discontinued in 1 infant with abnormal pH results who underwent Nissen fundoplication (Supplementary Table 4, Supplemental Digital Content, *http://links.lww.com/MPG/B702*).

Of the older children, only 2/33 (6%) were using anti-reflux medication before the pH-MII study. Medication was discontinued in both (normal pH results). Upper endoscopy was performed in 3 children with abnormal pH results, in 2/3 PPI was started for mild esophagitis (Supplementary Table 4, Supplemental Digital Content, *http://links.lww.com/MPG/B702*). In 2 children (1 with abnormal pH results and 1 with night cough), medication was started without endoscopy.

DISCUSSION

In this study, we evaluated acid and nonacid GER using pH-MII monitoring in 57 children with EA in infancy and at school-age. Observed RBM were mainly nonacid boluses (infants: 62% of RBM, older children: 64% of RBM) and mixed boluses (infants: 58% of RBM, older children: 75% of RBM).

TABLE 2. Results from pH-impedance monitoring in children born with esophageal atresia after manual modification of reflux events

	Age ≤ 18 months (N = 24)*			[0,6-7]Age 8 years (N = 33)†		
	N	Median	Min; max; IQR	N	Median	Min; max; IQR
Monitoring duration (min)	24	1369	1123; 1478; 1334–1407	33	1352	1230; 1511; 1331–1393
pH results						
Number of acid exposures	22	35.0	4.0; 186.0; 17.5–68.5	32	7.5	0.0; 65.0; 2.0–17.8
Reflux index (%)	22	2.6	0.1; 28.5; 1.1–4.6	32	0.3	0.0; 14.4; 0.1–2.5
Number of long acid exposures	22	1.0	0.0; 11.0; 0.0–1.3	32	0.0	0.0; 8.0; 0.0–1.0
Longest acid exposure (min)	22	6.0	0.4; 67.2; 3.3–10.0	32	2.2	0.0; 111.0; 0.6–8.4
Impedance results						
Number of RBM	22	61.2	0.0; 133.7; 16.7–98.3	33	20.7	0.0; 53.7; 11.2–31.6
Number of acid RBM	20	20.9	0.0; 85.6; 6.8–38.1	32	7.0	0.0; 45.7; 0.3–11.0
Number of nonacid RBM	20	31.2	0.0; 73.1; 9.9–60.2	32	11.2	0.0; 36.3; 6.9–16.7
Number of liquid RBM	22	21.1	0.0; 58.3; 5.5–50.0	33	4.2	0.0; 21.2; 2.2–11.8
Number of mixed RBM	22	30.2	0.0; 92.0; 11.1–60.1	33	12.6	0.0; 44.6; 6.4–23.3
Mean BCT (seconds)	22	11.0	0.0; 13.0; 9.0–12.0	33	13.0	0.0; 18.0; 8.5–14.0
Number of proximal bolus exposures	22	5.0	0.0; 80.2; 1.1–11.5	33	0.0	0.0; 8.7; 0.0–1.2

BCT = bolus clearance time; IQR = inter-quartile range; RBM = retrograde bolus movements.
*Children ages ≤18 months (n = 24): results from 20 complete pH-MII studies, 2 studies without pH results and 2 studies without impedance results are shown.
†Children ages 8 years (n = 33): results from 32 complete pH-MII studies and one study without pH results are shown.

Compared with available reference values in children without EA (asymptomatic neonates or children with symptoms), we found similar results for RI, number of RBM (Fig. 2A) and BCT (22–25).

Although several groups have published their pH-MII monitoring results in children with EA, reference values are lacking (2,11,12,26–30). Differences in patient selection and study protocols makes comparing results difficult. For instance, 1 study in 35 children with EA continued PPI therapy, whereas medication was discontinued in other studies (26). Moreover, they included children of all ages (0.3–17.2 years) whereas 2 other studies focused on infants/toddlers (29) and school-aged children (11). In the latter study, children with nonacid reflux were excluded (11). Compared with studies in children with EA, number of RBM in infants in our study was high compared with a small group of Dutch children, but similar to other cohorts (2,11,30). Results in 8-year old children were comparable. We found a lower RI in both infants (2.6% vs 5.8–6.1%) and older children (0.3% vs 2.5–8.3%) (Fig. 2C). RI was similar in 35 Australian children (ages 0–17 years) (26).

In our study, abnormal GER/GERD was diagnosed in 10/57 children (17.5%: RI >7%, n = 6, positive SI/SAP, n = 4). This is much lower than the 54% of Danish children with EA and abnormal RI (28). Others reported 38% to 45%, but they used different cutoffs for RI (>4.2% or >5% in children <12 months; >10% in older children) (13,29). Tube feeding was an exclusion criterion in the present study, which could have resulted in exclusion of children with GERD. When children with fundoplication surgery were considered as having GERD, a total of 31.6% of abnormal GER/GERD was found.

Symptom recording was insufficient for symptom association analysis as in 10/12 symptomatic children (spontaneously reported before pH-MII monitoring) symptoms were absent during pH-MII monitoring. A previous study in 20 children found a recording failure in 52% of coughs and a time lag of 11 seconds between the cough and the recording in the log (31).

The Manterola questionnaire (18) was suggestive for GERD in 29% of 8-year old children, but in only 2/7, an RI >7% was found. Compared with 130 symptomatic children without EA (ages 5–10 years), they had similar number of RBM (21 vs 24), but a lower mean BCT (11 vs 17 seconds) (22). We found similar pH-MII parameters in children with low and high Manterola scores, possibly because of a larger day-to-day variability of pH-MII studies in EA patients, or perhaps disturbed impedance patterns make pH-MII studies unsuitable for GER detection in EA patients (32). Dysphagia was scored positive by 5/7 children with a positive Manterola questionnaire, which may be the result of dysmotility, eosinophilic esophagitis, or strictures rather than GER. Furthermore, regurgitation was also scored often (6/7) which—in children with EA—can also be regurgitation from the esophagus rather than the stomach. It may, therefore, be that the Manterola questionnaire is not suitable for EA patients.

After visual validation of RBM identified as such by the software, 39% was deleted from the tracings. These were mainly nonacid swallows, which the software incorrectly identified as RBM (Supplementary Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/B702*). Abnormal esophageal motility, stasis of fluids, and gas caused disturbed patterns, which were misinterpreted by the software. Stasis of fluids was mostly present in Z3-Z4, at the level of the esophageal anastomosis. The software did not recognize this stasis and measured a shorter BCT. This is in accordance with previous literature (33). In automated analysis, swallows following RBM were sometimes misclassified as proximal GER events. Air in the esophagus after a swallow showed a pattern that was recognized as GER by the software.

As low baseline impedances are observed in esophagitis and motility disorders (27) it is not surprising that children with EA have baseline impedances that are approximately 75% lower than in symptomatic patients without EA (12). Even in EA patients without esophagitis baseline impedances are 44% lower than in control patients with esophagitis (28). Low baseline impedances impair bolus detection, resulting in an underestimation of the reflux burden in EA patients. This is a major limitation of pH-MII in EA patients.

Previous studies show high inter- and intra-observer variability in pH-MII analysis (34,35). The high percentage of deleted RBM raises the question how accurate pH-MII analysis in EA patients is. We believe this number is too high to ignore and to

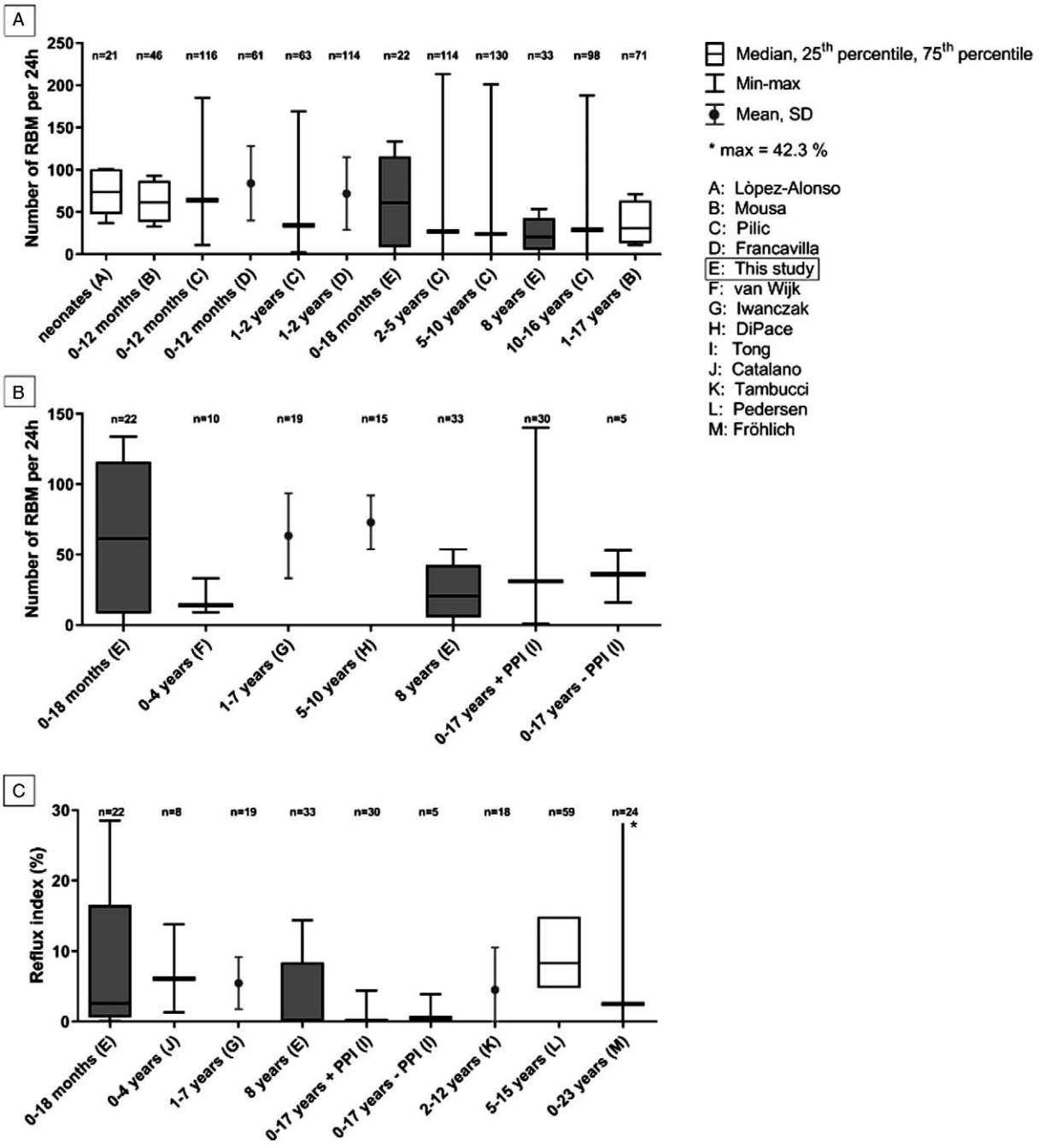

FIGURE 2. pH-MII parameters (number of retrograde bolus movements and reflux index) of study cohort compared with available reference values in (A) children without esophageal atresia (asymptomatic neonates or children with gastrointestinal, pulmonary or neurological symptoms) and (B and C) children with esophageal atresia.

perform automated analyses without manual revision. Manual revision, however, carries the risk of greater inter-observer variability. Refinement of automated software is needed to identify impedance reflux patterns in patients with complex motility disorders, such as EA.

The recent ESPGHAN-NASPGHAN Guideline recommends to treat all EA patients with antiacid treatment in the first year of life and to monitor GER with pH-MII monitoring and/or endoscopy at time of discontinuation (regardless of symptoms) and during long-term follow-up in symptomatic children (6). However, no studies have been performed to show benefit of routine pH-MII monitoring in EA patients and a recent SR showed evidence—albeit of low quality—that prophylactic antireflux medication does not prevent stricture formation after EA repair (36). As discussed above, reflux in our patients was mainly nonacid. These nonacid reflux events would be missed on pH monitoring without impedance tracing.

Impedance tracing has additional benefits to correlate extra-esophageal symptoms with reflux events (6). In infants, symptoms were mainly associated with nonacid RBM, whereas symptoms in older children were mainly associated with acid RBM (29). Treatment options of nonacid GER are limited. A small double-blinded placebo-controlled RCT in children showed that Baclofen inhibits transient lower esophageal sphincter relaxation and accelerates gastric emptying, but is dissuaded in guidelines as a first-choice therapy in children because of known side effects in adults (4,37). Surgical antireflux procedures are available, but have side effects and it is unclear, which patients would benefit. Further research is needed to determine the optimal duration of antiacid therapy after EA repair.

The strengths of our study are the manual evaluation of RBM, the inclusion of both symptomatic as well as asymptomatic children with EA, and both infants and older children. International guidelines recommend to monitor GER at time of discontinuation of antiacid treatment (around 1 year) and during long-term follow-up in symptomatic children with EA (6). Our study is the first to show pH-MII results in these 2 age-groups. Still, some limitations need to be mentioned. First, 2 different pH electrodes were used. Although significant differences have been found in acid exposure times between ISFET, glass, and antimony electrodes, our results from both catheters were similar (38). Second, only 52% of eligible children of our follow-up program were included. As demographics did not differ and the majority (79%) was asymptomatic, selection bias does not seem to be a major factor influencing our results. Third, only RBM recognized by the software were manually reviewed and modified. This method might have resulted in underreporting of reflux events. Although the software is designed to over-detect reflux events, we cannot exclude the option that episodes were missed. This is important to realize, and manual revision of pH-MII tracings should be considered in all EA patients, especially in case of unexplained symptoms or persistent growth impairment. Last, because of the lack of longitudinal data, we did not compare results between infants and older children. Infants seem to have worse pH-MII parameters compared with older children; however, differences in type of feeding (liquid vs solid food), body position during feeding, and other demographics (ie, thoracoscopic surgery, use of anti-reflux medication, and history of fundoplication surgery) would have made the comparison unreliable.

In conclusion, most infants and school-aged children with EA off medication have a normal RI, yet experience a significant number of nonacid RBM. After manual revision of the tracings, a high percentage of RBM was deleted. These were mainly nonacid swallows, which the software incorrectly identified as RBM. Our data show that automated impedance analysis software needs refinement for use in infants and children with EA and question the need for standard antiacid therapy in these patients.

Acknowledgments: The authors thank Marja van Schaik, Alwin van der Geer, Marjolein Spoel, and Saskia Gischler of the pediatric surgical long-term follow-up team of our hospital for acquisition of data. Ko Hagoort provided editorial advice.

REFERENCES

1. Pedersen RN, Calzolari E, Husby S, et al. Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. *Arch Dis Child* 2012;97:227–32.
2. van Wijk M, Knuppe F, Omari T, et al. Evaluation of gastroesophageal function and mechanisms underlying gastroesophageal reflux in infants and adults born with esophageal atresia. *J Pediatr Surg* 2013; 48:2496–505.
3. Tovar JA, Fragoso AC. Gastroesophageal reflux after repair of esophageal atresia. *Eur J Pediatr Surg* 2013;23:175–81.
4. Rosen R, Vandenplas Y, Singendonk M, et al. 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: 516–54.
5. Vergouwe FW, IJsselstijn H, Wijnen RM, et al. Screening and surveillance in esophageal atresia patients: current knowledge and future perspectives. *Eur J Pediatr Surg* 2015;25:345–52.
6. Krishnan U, Mousa H, Dall'Oglio L, et al. 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;63:550–70.
7. Vergouwe FWT, IJsselstijn H, Biermann K, et al. High prevalence of Barrett's esophagus and esophageal squamous cell carcinoma after repair of esophageal atresia. *Clin Gastroenterol Hepatol* 2018;16: 513.e6–21.e6.
8. Vergouwe FW, Gottrand M, Wijnhoven BP, et al. Four cancer cases after esophageal atresia repair: time to start screening the upper gastrointestinal tract. *World J Gastroenterol* 2018;24:1056–62.
9. de Benedictis FM, Bush A. Respiratory manifestations of gastro-oesophageal reflux in children. *Arch Dis Child* 2017;103:292–6.
10. Vergouwe FWT, Vlot J, IJsselstijn H, et al., DCEA Study Group. Risk factors for refractory anastomotic strictures after oesophageal atresia repair: a multicentre study. *Arch Dis Child* 2019;104:152–7.
11. Di Pace MR, Caruso AM, Catalano P, et al. 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;46:443–51.
12. Frohlich T, Otto S, Weber P, et al. Combined esophageal multichannel intraluminal impedance and pH monitoring after repair of esophageal atresia. *J Pediatr Gastroenterol Nutr* 2008;47:443–9.
13. Castilloux J, Bouron-Dal Soglio D, Faure C. Endoscopic assessment of children with esophageal atresia: lack of relationship of esophagitis and esophageal metaplasia to symptomatology. *Can J Gastroenterol* 2010;24:312–6.
14. Sistonen SJ, Pakarinen MP, Rintala RJ. Long-term results of esophageal atresia: Helsinki experience and review of literature. *Pediatr Surg Int* 2011;27:1141–9.
15. Gischler SJ, Mazer P, Duivenvoorden HJ, et al. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. *J Pediatr Surg* 2009;44:1382–9.
16. Gross RE. The surgery of infancy and childhood. Philadelphia: W. B. Saunders Company; 1953:441–444.
17. Talma H, Schönbeck Y, Bakker B, et al. Groeidiagrammen 2010: Handleiding bij het meten en wegen van kinderen en het invullen van groeidiagrammen Leiden: TNO innovation for life; 2010.
18. Manterola C, Munoz S, Grande L, et al. Initial validation of a questionnaire for detecting gastroesophageal reflux disease in epidemiological settings. *J Clin Epidemiol* 2002;55:1041–5.
19. Peetsold MG, Heij HA, Deurloo JA, et al. Health-related quality of life and its determinants in children and adolescents born with oesophageal atresia. *Acta Paediatr* 2010;99:411–7.
20. A standardized protocol for the methodology of esophageal pH monitoring and interpretation of the data for the diagnosis of gastroesophageal reflux. Working Group of the European Society of Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1992; 14:467–71.
21. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al., 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.
22. Pilic D, Frohlich T, Noh F, et al. Detection of gastroesophageal reflux in children using combined multichannel intraluminal impedance and pH measurement: data from the German Pediatric Impedance Group. *J Pediatr* 2011;158:650.e1–4.e1.

23. Lopez-Alonso M, Moya MJ, Cabo JA, et al. Twenty-four-hour esophageal impedance-pH monitoring in healthy preterm neonates: rate and characteristics of acid, weakly acidic, and weakly alkaline gastroesophageal reflux. *Pediatrics* 2006;118:e299–308.
24. Mousa H, Machado R, Orsi M, et al. Combined multichannel intraluminal impedance-pH (MII-pH): multicenter report of normal values from 117 children. *Curr Gastroenterol Rep* 2014; 16:400.
25. Francavilla R, Magista AM, Bucci N, et al. Comparison of esophageal pH and multichannel intraluminal impedance testing in pediatric patients with suspected gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2010;50:154–60.
26. Tong S, Mallitt KA, Krishnan U. Evaluation of gastroesophageal reflux by combined multichannel intraluminal impedance and pH monitoring and esophageal motility patterns in children with esophageal atresia. *Eur J Pediatr Surg* 2016;26:322–31.
27. Tambucci R, Thapar N, Saliakellis E, et al. Clinical relevance of esophageal baseline impedance measurement: just an innocent bystander. *J Pediatr Gastroenterol Nutr* 2015;60:776–82.
28. Pedersen RN, Markow S, Kruse-Andersen S, et al. Esophageal atresia: gastroesophageal functional follow-up in 5-15 year old children. *J Pediatr Surg* 2013;48:2487–95.
29. Catalano P, Di Pace MR, Caruso AM, et al. Gastroesophageal reflux in young children treated for esophageal atresia: evaluation with pH-multichannel intraluminal impedance. *J Pediatr Gastroenterol Nutr* 2011;52:686–90.
30. Iwanczak BM, Kosmowska-Miskow A, Kofla-Dlubacz A, et al. Assessment of clinical symptoms and multichannel intraluminal impedance and pH monitoring in children after thoracoscopic repair of esophageal atresia and distal tracheoesophageal fistula. *Adv Clin Exp Med* 2016; 25:917–22.
31. Rosen R, Amirault J, Giligan E, et al. Intraesophageal pressure recording improves the detection of cough during multichannel intraluminal impedance testing in children. *J Pediatr Gastroenterol Nutr* 2014; 58:22–6.
32. Dalby K, Nielsen RG, Markoew S, et al. Reproducibility of 24-hour combined multiple intraluminal impedance (MII) and pH measurements in infants and children. Evaluation of a diagnostic procedure for gastroesophageal reflux disease. *Dig Dis Sci* 2007;52:2159–65.
33. de Bortoli N, Martinucci I, Savarino EV, et al. Manually calculated oesophageal bolus clearance time increases in parallel with reflux severity at impedance-pH monitoring. *Dig Liver Dis* 2015;47:1027–32.
34. Loots CM, van Wijk MP, Blondeau K, et al. Interobserver and intraobserver variability in pH-impedance analysis between 10 experts and automated analysis. *J Pediatr* 2012;160:441.e1–6.e1.
35. Pilic D, Hofs C, Weitmann S, et al. Inter- and intraobserver agreement in 24-hour combined multiple intraluminal impedance and pH measurement in children. *J Pediatr Gastroenterol Nutr* 2011;53:255–9.
36. Miyake H, Chen Y, Hock A, et al. Are prophylactic anti-reflux medications effective after esophageal atresia repair? Systematic review and meta-analysis. *Pediatr Surg Int* 2018;34:491–7.
37. Omari TI, Benninga MA, Sansom L, et al. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. *J Pediatr* 2006;149:468–74.
38. Hemmink GJ, Weusten BL, Oors J, et al. Ambulatory oesophageal pH monitoring: a comparison between antimony, ISFET, and glass pH electrodes. *Eur J Gastroenterol Hepatol* 2010;22:572–7.