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Position Paper

Esophageal pH-impedance monitoring in children: position paper on indications, methodology and interpretation by the SIGENP working group

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ABSTRACT

Multichannel intraluminal impedance pH (MII-pH) monitoring currently represents the gold standard diagnostic technique for the detection of gastro-esophageal reflux (GER), since it allows to quantify and characterize all reflux events and their possible relation with symptoms. Over the last ten years, thanks to its strengths and along with the publication of several clinical studies, its worldwide use has gradually increased, particularly in infants and children. Nevertheless, factors such as the limited pediatric reference values and limited therapeutic options still weaken its current clinical impact. Through an up-to-date review of the available scientific evidence, our aim was to produce a position paper on behalf of the working group on neurogastroenterology and acid-related disorders of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) on MII-pH monitoring technique, indications and interpretation in pediatric age, in order to standardise its use and to help clinicians in the diagnostic approach to children with GER symptoms.

1. Introduction

Multichannel intraluminal impedance pH (MII-pH) monitoring currently represents the gold standard diagnostic technique for the detection of gastro-esophageal reflux (GER), since it allows to quantify and characterize all reflux events and their possible relation with symptoms [1]. MII-pH monitoring provides an accurate assessment of the number of both acid and non acid GER episodes, the acid esophageal exposure percent time, the height and composition of the refluxate (liquid, gas, or mixed contents). It also recognizes swallows from reflux episodes, measures the bolus and acid clearance time, and assesses the temporal association between reflux episodes and symptoms occurring during the study period. Over the last ten years, thanks to its strengths and along with the

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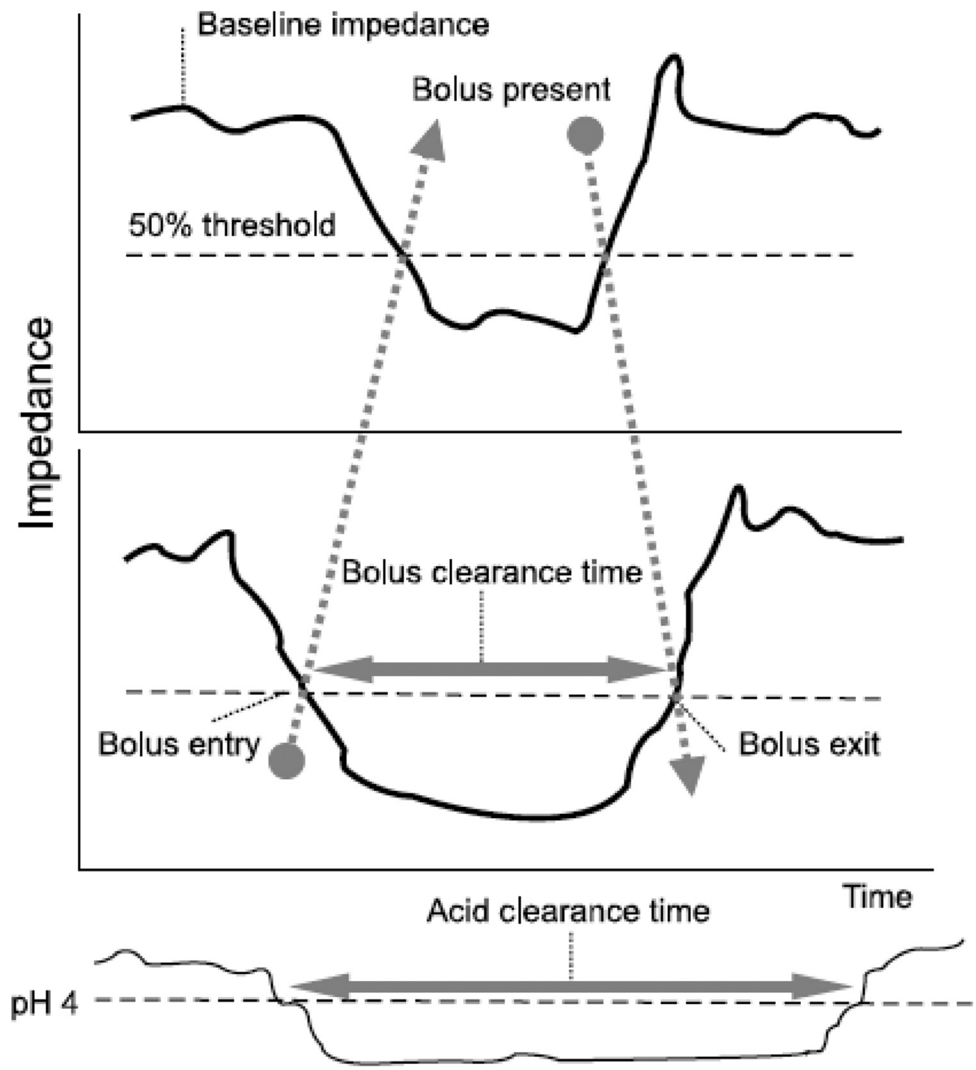

Fig. 1. Change of impedance in 2 channels: the figure shows a reflux episode, followed by a return of impedance to the baseline.

publication of several clinical studies its worldwide use has gradually increased, particularly in infants and children.

Although MII-pH monitoring provides a great amount of esophageal data, yet the limited reference and normative values, the lack of therapeutic choices for non acid GER and the cost of the device and catheters currently reduce its clinical impact.

The aim of the current paper is to present an updated summary of MII-pH monitoring technique, indications, and interpretation in pediatric age to help clinicians in the diagnostic approach to children with GER disease. Therefore, an exhaustive search for eligible studies was performed in MEDLINE (via PubMed), EMBASE and Cochrane Library databases. The following headings were used: "pH monitoring technique", "gastroesophageal reflux", "multichannel intraluminal impedance (MII) pH monitoring technique". Proper Boolean operators "AND" "OR" were also included to be as comprehensive as possible. English language restriction was applied while geographical restrictions were not. All relevant articles detected were further scrutinized for additional references which did not appear in the initial search. Search limits were set for studies on human subjects published between January 1990 and December 2018. When the scientific evidence was lacking, the reccomendations were formulated according to the authors' personal experience.

2. Technical and methodological aspects

MII-pH monitoring was first described by Silny et al. in 1991 for the study of esophageal motility, providing information on the presence of esophageal bolus movements and type of esophageal content (solids, liquids, gas) by changes in intraluminal electrical conductivity [2]. The basic component of MII technology is an impedance circuit, including an alternating current generator (located in the recording device) and multiple metal rings placed across a catheter, which acts as an electrical isolator. The electrical circuit is closed by electrical charges in the esophageal mucosa surrounding the catheter.

The test is based on the measurement of impedance (changes in resistance to electrical current in a circuit), which is inversely correlated to the ionic concentration of luminal content. A liquid bolus with a high ionic content (e.g. swallows, refluxate) has a high conductivity and therefore a low impedance measure, whilst in the presence of air the content of ions is low, resulting in a poor conductivity and hence a high impedance. At rest, in an empty esophagus, the conductivity and the so called baseline impedance are stable, ranging between 2000 and 4000 ohm. When a liquid bolus enters the esophagus, the impedance rapidly drops and remains low as long as the bolus lies between the 2 electrodes, then raises and returns to the baseline values once the bolus has passed (Fig. 1).

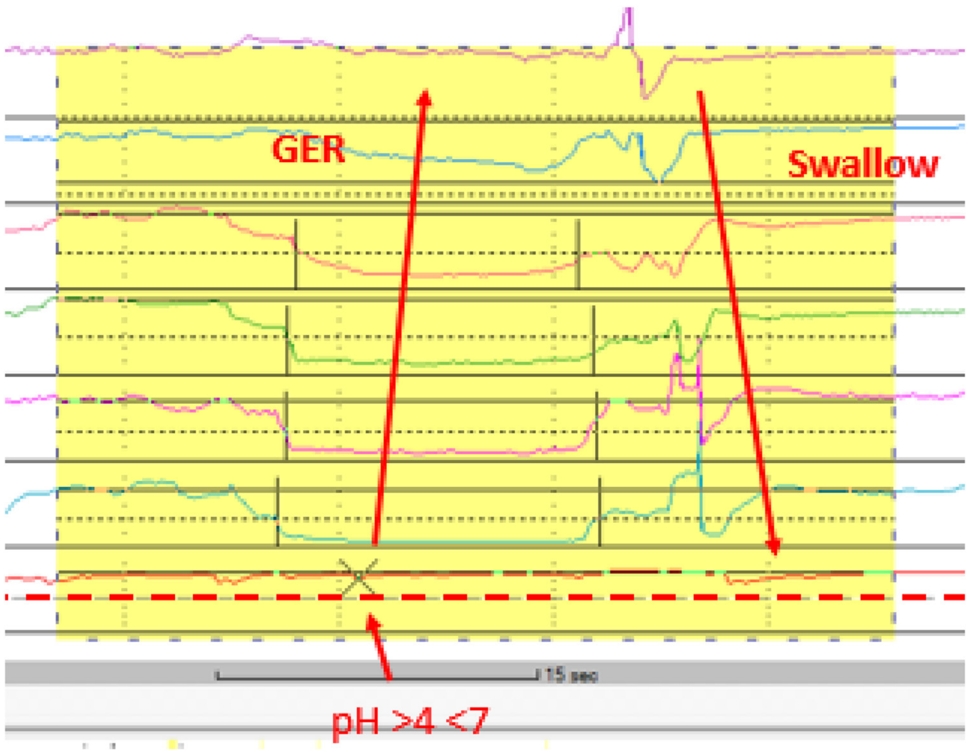

Fig. 2. Reflux episode followed by a swallow.

In the presence of a gas bolus, a typical impedance spike above 5000 ohm is observed.

The presence of multiple channels on the same catheter allows the measurement of sequential transitory impedance changes (drop or rise) involving consecutive channels, determines the direction of bolus flow, and hence allows to discriminate between antegrade flow (swallow) from retrograde movement from the stomach (reflux) as well as the esophageal location (height) of the refluxate. Combining MII with pH monitoring enables the identification and classification of acidic (pH < 4), weakly acidic (pH 4–7) and weakly alkaline (pH > 7) episodes (Fig. 2).

3. The recording device

Many ambulatory and stationary devices from different brands are now available and used in children of all ages. Portable ambulatory devices are very small and allow recording during normal daily activities and sleeping period. These devices, which are the most commonly used, are comfortable for the patients and have a simple interface with internal clock, event buttons and recumbent indicators for easy viewing. Conversely, stationary devices are less comfortable but enable to evaluate additional parameters, such as heart and respiratory rate, oxygen saturation, and esophageal motility with high-resolution manometry. Each device has specific catheters [3].

4. Catheters

MII-pH catheters are thin flexible polyvinyl catheters usually 2.13 mm diameter-wide (6.4 Fr). Single or multiple-use catheters are available and can be used according to investigator or patient choices, national regulations, and hygiene protocols. Multiple-use catheters must be sterilized according to the manufacturer's recommendations. Therefore disposable catheters are often preferred. Catheters have 7–12 impedance rings/sensors positioned along the length of the catheters resulting in 6–11 corresponding impedance channels, as every channel is created by two consecutive rings/sensors. Various age (height)-appropriate impedance catheters are available: infant (height <75 cm), pediatric (height >75 cm and <150 cm), and adult (height >150 cm) type. The probes differ for the spacing between the impedance rings and the position of the pH sensor. In infant catheters, the space between two electrodes is 1.5 cm, whist in pediatric and adult catheters the distance is 2 cm due to the increased esophageal length. Combined MII-pH and (simplified) manometry catheters have been developed and may provide important additional information in selected patients (e.g. children with chronic cough or candidates to anti-reflux surgery).

5. pH electrodes

MII-pH catheters include 1 or 2 pH electrodes (for proximal and distal esophagus, esophageal and gastric, or pharyngeal and esophageal or gastric monitoring). Many different pH electrodes are commercially available, based on antimony, glass, ion-sensitive field-effect transistor (ISFET), each with their own advantages and disadvantages. However, although antimony electrodes are less sensitive than glass or ISFET electrodes, these are the most frequently used because of lower costs, ease to use characteristics, and smaller size. Differently from adult catheters, both in infant and pediatric catheters the pH sensor lies in the middle of the most distal impedance channel.

6. Calibration of the catheter

A correct calibration of the catheter is critical for an accurate registration of pH and impedance changes. The MII-pH catheter should be calibrated according to the manufacturer's instructions, clearly displayed on the screen during the procedure, with 2 different buffer solutions (usually pH 4.0 and 7.0) at either room or body temperature, until stabilization is reached. If the catheter has the external reference, the calibration has to be done with the external reference electrode fixed on the skin of the child, and his finger immersed in the buffer solution together with the electrode. This method is not necessary for catheters with internal reference electrodes which are nowadays preferred.

7. Computer software

MII monitoring data can be manually read or automatically analysed by software. Several analytical software packages from different manufacturers are currently available. The software provides summary data for reflux occurrence and clearance, as well as calculations of symptom reflux temporal association indexes.

The new software also supplies additional functions that magnifies, colours, and improves the vision of each event helping the observer to distinguish artefacts, swallowing and reflux. It also calculates the mean esophageal impedance value of all tracing or selected periods and segmental or total bolus transit time during swallowing. Moreover, nowadays wireless Bluetooth® technology may be applied to view data while recording.

8. Indications for testing

Despite its acknowledged drawbacks, the role of MII-pH monitoring has gradually increased over the last years, especially in children in the early stages of life. MII-pH currently represents the gold standard diagnostic technique for measuring acid and non acid GER and symptom association, thus tailoring therapeutic intervention. Nevertheless, due to its burden in terms of patient discomfort, time analysis and costs, the indications for testing should be carefully evaluated. Combining NICE [4], ESPGHAN and NASPGHAN recommendations [1] MII-pH monitoring should be considered for the following conditions:

- Infantile non-epileptic seizure-like events
- Purported Sandifer's syndrome [5]
- Feeding refusal in infant with failure to thrive in the absence of other diagnosis
- Persistent unexplained crying despite conservative treatment and before considering acid-suppressive therapy in infants
- Unexplained respiratory symptoms, such as:
  - ○ Recurrent infantile apnoeas or oxygen desaturations [6,7]
  - Recurrent BRUEs or idiopathic ALTEs
  - Chronic or recurrent cough [8–10]
  - Recurrent purported aspiration pneumonia
  - Chronic laryngeal disorders [11]
- Feeding disorders in children with neurodisability [12]
- Dental erosions in children with neurodisability
- Assessment and follow-up of esophageal surgical conditions [13–15]
- Assessment of the efficacy of antireflux therapy in patients with persisting symptoms
- Evaluation of preadolescent children with unreliable GERD clinical picture [16,17]
- Confirmation of rumination and aerophagia diagnosis (in combination with manometry)
- Persistent heartburn or epigastric pain on acid suppressive treatment
- Recurrent otitis media [18]
- Unexplained bradycardia or cardiac arrhytmia [19]

The overall outcomes of MII-pH monitoring for all the above listed conditions are to qualify and quantify reflux episodes and to ascertain their association with the reported symptoms. The latter outcome is crucial for the assessment of specific discontinuous symptoms, such cough, apnoea, oxygen desaturations, bradycardia or cardiac arythmias, pain or crying, which can be associated with acid, weakly acid, non-acid GER.

As MII-pH monitoring detects reflux irrespective of pH, it can be carried out on or off reflux therapy such as acid inhibitors [20]. Furthermore, children on enteral nutrition fed via continuous or bolus regimen can be accurately tested only with MII-pH, because of the majority of non acid GER episodes due to the buffering effect of feeding.

Because MII-pH cannot determine and distinguish mucosal complications, upper endoscopy should also be performed in cases of suspect esophagitis, stenosis or Barrett esophagus.

9. Preparation of the patient and positioning of the probe

9.1. Preparation of the patient

Before starting MII-pH monitoring is important to assess and report any clinical information about patient's medical treatment and diet. In particular, histamine H_2 receptor antagonist (H_2 blockers) and prokinetics should be stopped at least 72 h before the study, whereas alginates can be suspended up to 4 h before the investigation [1]. The washout period must be prolonged for at least 2 weeks for proton pump inhibitors (PPIs) if the test would be performed off acid treatment for diagnostic purposes. H2-blockers or PPIs should be continued only when the MII-pH monitoring is performed to evaluate their effectiveness on esophageal acid exposure and to titrate the appropriate dose for the individual patient based on associated symptoms. Although various medications can alter LES function and esophageal pH (such as diazepam, smooth muscle relaxants, antiasthmatic drugs, etc.), their cessation is not necessary. The procedure should be carefully explained to parents and possibly to the child (if he/she is old enough) to obtain the child's collaboration and to increase his/her comfort. Infants must be fasting for at least 3 h and children from at least 6 h before the procedure, to avoid nausea, vomiting, and aspiration during the insertion of the catheter. Before starting MII-pH testing, a written informed consent should be obtained from the parents.

9.2. Positioning of the probe

The catheter is passed transnasally, preferably without sedation. Intranasal anesthetic spray or gel could be used to decrease child's discomfort during the insertion. It is advised not to place the gel directly on the electrodes or metallic rings to avoid inaccuracy of recording. The pH probe tip should be ideally positioned in the lower esophagus at 87% of the total esophageal length, in order to avoid the LES region and the displacement into the stomach during the registration. The tip position is crucial for the correct measurement of pH and the detection of acid reflux episodes.

Several methods have been suggested to identify the correct placement of pH electrodes: calculation of esophageal length, fluoroscopy, manometry, and endoscopy. Manometry is the most accurate method for localizing the LES and defining pH probe placement, but its use is very limited since it is invasive, time-consuming, and not widely available. Endoscopy may be necessary for the esophageal assessment and directly localizes the LES. However, it is invasive, not easily available, particularly for newborns and infants, and it cannot accurately provide the distance between the anterior nares and the gastroesophageal junction. The MII-pH probe can be placed during endoscopy but displacement of the catheter is still possible while retrieving the endoscope. Hence, different non invasive mathematic methods have been proposed with the Strobel's formula ($5 + 0.252 \times$ length of the child) as the most commonly used, particularly in infants and preterm newborns [21]. However, in children over 1 meter in height the formula may be inaccurate since it tends to overestimate the esophagus length with increasing body height, and the placement can result too close to the gastroesophageal junction. Recently Mutalib et al. proposed a new formula which seems able to accurately estimate the catheter position based on children's body length [22]. Fluoroscopy or X-ray are commonly performed and recommended by the working group on GER of the ESPGHAN to check the position of the pH electrode [3]. The exact position of the pH-sensitive point is debated but it mainly depends on the age of the patient: in infants and newborns it should be placed on the second vertebral body above the diaphragm wall to avoid the proximal extension of the catheter in the pharynx causing discomfort of the little patient and artifacts on the tracings; in older children and adult it is recommended to place it above the third vertebral body above the diaphragm throughout the respiratory cycle, in order to avoid the proximity to the gastroesophageal junction [23,3]. The disadvantage of this method is that it can be inaccurate in the presence of severe thoracic malformation, previous esophageal or thoracic surgery, and in the presence of hiatal hernia.

10. Monitoring conditions and event recording

The type and amount of ingested food, the daily habits and the body position, have been shown to affect the duration and the extent of GER episodes and esophageal acid exposure [24–26]. In the prone position reflux episodes occur less frequently than in the left and right side or supine position, while more reflux is recorded when infants are sitting than when they lay down, due to an increased intra-abdominal pressure [27]. Despite these considerations, it is commonly recommended that the monitoring conditions should be as unrestricted as possible, with emphasis placed on allowing daily habits that replicate normal daily life and the patient symptoms. However, it is advised to avoid very hot or very cold beverages or food, acid juices, and carbonated beverages because they can interfere with the sensitivity of the catheter and with recording. As for adolescent patients, smoking and use of chewing gums should be limited and recorded on the diary because of the increased number of swallows that they produce. In infants or neonates the use of pacifiers should be limited: if that is not possible, the tracing needs to be carefully reviewed avoiding misinterpretation of continual swallowing.

Education of patient, caregivers, and staff is critical for the success of the examination. It is necessary to note down feeding time and duration, body positionings, and all the symptoms that the child complains about during the procedure. An accurate diary is essential to recognize and control the effects of all variables and to obtain a good quality and correct data interpretation. It is also necessary to synchronize the caregiver and device clocks, to obtain simultaneous registration, or to instruct the caregivers to use the device clock when recording symptoms.

Before starting the procedure, relevant symptoms are established and assigned to "event" buttons on the recording device. The caretakers should be instructed to press the labelled symptoms buttons, start and stop feeding buttons, and supine and upright position button for their child. In addition or in alternative, a written symptom diary can be completed recording the time shown on the recorder at the time of the occurrence of symptoms and any other relevant events (e.g. dislocation of catheter, time of acid-suppression medication).

Different authors showed that both written diary and "event" buttons have limited accuracy in recording symptoms, thus affecting the analysis of the temporal relationship between the events and the GER episodes [28]. In selected patients (e.g. patients with recurrent apnoea/desaturations or cough) specific combined catheters (e.g. with manometry) or simultaneous investigations (e.g. with polysomnography or cough recording devices) have been introduced to exactly marker the time of the symptoms but synchronization between the different devices should be guaranteed before starting the procedures.

Traditionally, ambulatory MII-pH recording is performed over a 24-h period. A 18-h minimum period, including a daily and nightly recording and different postprandial periods, is recommended by ESPGHAN-NASPGHAN working group on GER [3]. A reduced monitoring period is questionable, whilst a prolonged recording (18–24 h) optimizes diagnostic sensitivity, specificity, and reproducibility, without deterioration of acceptability and compliance. Finally, there is no requirement of an hospital stay unless other simultaneous monitoring (e.g. polysomnography) is performed. After the probe has been positioned and the parents have been trained on recording daily activities and symptoms, the patient can go home and return the following day to have the probe removed and the diary reviewed.

11. Data analysis

11.1. Manual and software automated analysis

After the recording data are downloaded on the dedicated software, the tracing should be visually inspected (e.g. by a 30 min time window) to ensure the technical validity of the study and to exclude all artefacts, such as impedance and/or pH signal failure. To avoid inappropriate estimation of the symptom association analysis, duplicated symptoms over a few minute period window should be deleted. If a written symptom diary has been completed, all documented events such as mealtimes, body position, and symptoms should be manually checked accordingly [3].

Afterwards, data analysis is generally started with the automated software, but accurate visual-manual re-analysis throughout the tracing (by a 3 to 5-min time window) is mandatory to confirm/modify, add and/or delete reflux events [3]. Meal periods are generally excluded from the analysis. However, according to the patient's history and type of nutrition (e.g. continuous enteral feeding), mealtimes should be considered if relevant [3].

11.2. Definition of reflux episodes

Liquid reflux is defined as a retrograde drop in impedance below 50% from the baseline impedance value in at least 2 distal impedance channels (approximately 4 cm or 6 cm above the LES for infant or pediatric probes, respectively). By convention, reflux episodes start when the impedance drops at the 50% value from (previous) baseline, and ends at the 50% recovery point from nadir to baseline, recorded at the distal channel. Gas reflux is defined as a rapid and simultaneous increase in impedance above 3000 ohms in 2 or more channels, with 1 site having an absolute value >7000 ohms. Mixed liquid/gas reflux is defined as gas reflux occurring during or immediately before liquid reflux. The reflux episode is considered to be proximal if one or both the uppermost impedance channels (channels 1 and/or 2) are reached [29,30].

MII reflux episodes are further categorized according to the pH value of the refluxate. Reflux episodes are defined as acid when pH falls <4.0, weakly acidic when pH remains $\geq$4.0 but <7.0, and weakly alkaline when pH does not drop below 7.0 (pH $\geq$ 7.0). A superimposed or re-reflux is defined as a MII reflux episode that occurs after a previous acid reflux episode and before the esophageal pH has recovered to a value $\geq$4 (during the acid clearing interval). Finally, pH-only reflux is defined as a drop in pH below 4 for at least 5 s, in the absence of a detectable bolus reflux on the MII tracing [31].

Table 1
Reference values for the interpretation of MII-pH results in infants and children

MII-pH parameters	Definition	Interpretation	Note	Reference
RI (AET)	The percent time of the entire duration of the study with esophageal pH < 4.0	• >7% abnormal • <3% normal • 3–7% indeterminate	Applicable for pH antimony-based sensor	Vandenplas JPGN 2009
GER episodes	Total number of GER episodes with bolus reaching the two most distal impedance channels	• Abnormal if >100/24 h • Abnormal if >70/24 h	In infants (0-12 months) In children (>12 months)	Lopez-Alonso Pilic 2011 Mousa 2014
Proximal GER episodes	Number of GER episodes reaching the two most proximal impedance channels	• 44 for acid, 57 for non acid GER • 43 for acid, 20 for non acid GER (95th percentile)	In infants In children	Mousa 2014
BEI	The total percent time that a bolus is present in the esophagus	• 2.4 – 2.9% • 1.8 – 2.4% (90th–95th percentile)	In infants In children	Mousa 2014
BCT	(Mean) time (in seconds) needed for retrograde bolus to be cleared from the (distal) esophagus	• 18–20 s • 25–32 s (90th–95th percentile)	In infants In children	Mousa 2014
IB	Mean value of impedance tracing in (an empty) esophagus	1000–1500 ohm for both distal and proximal channels (3rd percentile)	<or>6 months	Salvatore 2013
SI	Number of GER related symptoms out of the total number of symptom episodes × 100	Positive if ≥50%	Temporal window between reflux and symptoms (generally considered within 2 min)	Wenzl 2012 Omari 2011 Rosen 2018
SAP	The likelihood that the patient's symptoms are related to GER, computed analysing consecutive 2-min segments through Fisher contingency table	Positive if ≥95%		

RI: reflux index.
AET: acid esophageal exposure.
BEI: bolus exposure index.
BCT: bolus clearance time.
BI: mean impedance baseline.
SI: symptom index.
SAP: symptom association probability.

11.3. pH parameters

Although pH monitoring alone has become an obsolete technique for GER assessment over the last decades, pH parameters are still of pivotal importance in clinical practice. The pH sensors are of different types, of which the most popular are made by glass and antimony [32].

The reflux index (RI) (or acid exposure time, AET), defined as the percent time of the entire duration of the study with esophageal pH < 4.0, the total number of acid reflux episodes, the number of acid reflux episodes lasting >5 min, and the duration of the longest acid reflux episode are the classical parameters obtained from pH monitoring [33]. Moreover, the mean acid clearance time (MACT) is determined by the pH electrode and is defined as the time needed for acid to be cleared from the esophagus (time with esophageal exposure to a pH < 4 during the reflux episode).

Of all the above-mentioned parameters, the RI is considered as the most important parameter in clinical practice. Based on pH-based acid indexes, various composite scoring systems, such as the DeMeester or Boix-Ochoa scores, have been developed but no one is superior compared to the RI alone [34–36].

11.4. Impedance-based parameters

Quantitative MII analysis consists on the analysis of retrograde bolus movements with liquid or mixed contents. The number of total reflux events, the number of acid, weakly acidic and weakly alkaline GER and the number of reflux episodes reaching the most proximal impedance segment are all calculated by the automatic software. According to the clinical need, gas episodes can be eventually added into the final report although a high inter-observer variability in interpreting gas events has been highlighted [37].

MII testing provides also data on the single episode and mean time needed for retrograde bolus to be cleared from the esophagus, according to the pre-setting definition of 50% drop and rise of the impedance value, and is defined as the bolus clearance time (BCT), expressed in seconds. The median bolus clearance time (BCT) (seconds) is the period during which intraluminal impedance in the distal esophagus is <50% of baseline impedance. Consequently, the bolus exposure index (BEI) is the total percent time that a bolus is exposed in the esophagus. The BEI is mostly computed for all reflux episodes (total BEI), but may be also calculated according to the chemical content (acid and nonacid GER) [38].

11.5. Normal values

Normative data are essential to guide the interpretation of results. However, for an invasive procedure such as MII-pH monitoring it is ethically unacceptable to obtain data from healthy infants and children. As a consequence, no real normal pediatric ranges are available for both pH (antimonium-based) and impedance parameters. Normal values in healthy individuals have been determined only for adults for both pH- and impedance-based parameters [38–40]. If the results in adolescents could be likely assimilated to the ones reported in adults, this is clearly not correct for younger patients. As already highlighted before, published pediatric data is rather limited and no truly healthy and asymptomatic children have ever been enrolled. However, in the last years, an increasing effort has been made to produce reference values based on different population of infants and children referred for possible GERD (Table 1).

Several studies showed that infants generally present more reflux episodes and more non acid content compared to older children and adults, partially explained by more frequent feeding time and post-prandial periods.

The 2009 joint NASPGHAN and ESPGHAN guidelines on reflux pointed out that normal or reference ranges should be used as guidelines for interpretation rather than absolute "cut-off" values. In pH studies performed with antimony electrodes, a RI >7% can be considered abnormal, a RI <3% normal, and a RI between 3 and 7% indeterminate. An attempt to identify normal MII-pH values has been first reported in a study conducted in preterm infants, who were unable to be fed orally but were otherwise healthy. Overall, the total number of reflux episodes differed significantly from adult data with the upper limit identified at 100 events in 24 h and a wide range of subset percentage of GER (from 52% of acid to 98% nonacid reflux). However, the small and peculiar sample size (21 preterm newborns with tube feeding nutrition) limited the clinical application of these results [36]. In 2011 the German Pediatric Impedance Group published a large series of pediatric impedance tracings (700 MII-pH) with aged patients ranging from 3 weeks to 16 years. All infants and children were referred for symptoms suggestive of GERD. In this report abnormal MII-pH was defined when Symptom Index (SI) was ≥50% or in case of high number of (bolus) reflux episodes in 24 h, arbitrarily fixed as >70 episodes in patients aged ≥1 year and >100/24 h episodes in those <1 year [28]. In 2014 other authors selected 46 infants and 71 children referred for reflux testing but found to have normal acid-based indices (<6% in infants and <3% in children), negative GER symptom asoociation (SI and SAP)and no previous GER treatments. The 95th percentile for total reflux episodes in infants (age ≤12 months) resulted 93, while in children it was 71 [33]. Percentage and frequency of total, proximal, acid and non acid GER, and BCT were also calculated as mean, 90th and 95th percentile for both age groups.

11.6. Symptom association analysis

If symptoms are accurately registered during the study, MII-pH has also the potential of assessing the temporal relationship between them and reflux episodes. Conventionally, a time interval of 2 min before and after a reflux episode is used as time frame to demonstrate a time association with symptoms. Despite widely accepted, this 2-min window is not evidence based, but it derives from adult data on reflux-related non-cardiac chest pain [41]. Moreover, the optimal time window for association analysis may vary depending on the symptom of interest; for example, for the symptom "apnea" the time frame has been suggested to be as short as 30 s, while for "crying" should probably be longer, up to 5 min [42]. Noteworthy, the registration of symptoms during the study may be inaccurate in the absence of other specific recorders or a simultaneous manometric catheter. The fact that patients or parents are asked to press the event button or write the symptoms down in a diary may lead to an underscoring of the number of symptoms (particularly during the night) or in a delayed recording. In some circumstances, to address this limitation, the MII-pH monitoring can be paired with simultaneous measurement of esophageal pressure or with a noninvasive acoustic recording to detect cough episodes and, especially in infants with apnoeas, should be synchronized with cardiorespiratory events monitoring [43,44]. This allows for a more precise and objective assessment of reflux and symptoms, but the applicability of these techniques is far from routine practice.

Several symptom-reflux association analysis indexes have been developed to express the relationship between symptoms and reflux, such as the symptom index (SI), the symptom sensitivity index (SSI) and the symptom association probability index (SAP). The SI is the percentage of symptom episodes that is related to reflux (% of reflux-associated symptoms divided by the total number of symptoms.). It should be reported separately for each symptom and is regarded as positive if ≥50% [45]. The main limitation of the SI is that it does not take into account the total number of reflux episodes. Consequently it may overestimate the relationship between reflux and symptoms when there is a high number of reflux episodes. The SSI is the proportion of reflux episodes that are symptomatic (% of symptom-associated reflux events divided by the total number of reflux events). A value ≥10% for each symptom is generally accepted as positive [46]. The SSI is likely to produce false positive results when there is a high number of reported symptoms. To overcome both SI and SII drawbacks, a third index has been developed, the SAP. The SAP index uses two-tailed Fisher's exact test to determine the probability that the association between 2 sets of events is not casual. For SAP calculation, total measuring time is subdivided into 2-min intervals and, based on the number of intervals with and without reflux events and symptoms, the probability that symptoms and reflux events are related is calculated based on a Fisher's contingency table. A SAP index >95% indicates a significant association between reflux and symptoms [47].

The minimum number of symptoms to produce a reliable analysis is still debated and it is likely to differ for different symptoms. Omari et al showed that, for instance in infants, reflux symptom associated statistics can be optimized by applying a minimum of 5 cough and 20 crying symptoms. The best agreement in SAP was reached using time intervals of 2 min for cough and 5 min for crying [42].

Although the SAP index is currently recognized as the strongest statistical parameter for symptom association analysis, it is important to remember that this parameter indicates the statistical probability of the symptom/reflux association. Indeed, it is worth to highlight that temporal association does not prove causal relationship, which is the key limitation to symptom association analysis [3]. Only the follow-up of the patient can clarify whether the GER treatment, based on MII-pH results, benefit the patient, reducing the symptoms. Data on median and long term evaluation of infants and children submitted to MII-pH are currently very scarce.

11.7. Novel impedance variables

Over the past decade, attention has been drawn to the determination of the baseline impedance (BI), that is the mean impedance value of the empty esophagus (in the absence of swallowing or reflux events). The BI is lower in the distal esophagus in patients with esophagitis and values measured at distal level are inversely correlated with acid reflux parameters [48–52]. Low BI values at both proximal and distal levels are present in patients with esophageal atresia and esophageal motor abnormalities, likely because of liquid stasis into the esophagus [53–55].

It is worth to notice that BI is age-dependent with significantly lower values in the first months of life compared with older infants and children [56]. BI is generally obtained by averaging BI values calculated during the first stable minute period (in the absence of swallowing or reflux events) every 1–4 h. Nevertheless, this method is too time-consuming and BI can more easily be measured over the entire 24-h study, which has been shown to be statistically not different [57]. Recently, mean nocturnal BI (three stable 10-min nighttime periods) has been also proposed as an accurate surrogate of the total BI because nighttime period is less influenced by swallowing activity and may identify patients to submit to endoscopy [58]. Recently, MII monitoring has also been proposed as an indirect test to evaluate esophageal bolus transit, through the assessment of the bolus presence time (BPT) at various levels (time between bolus entry and bolus exit at each impedance channel) and the total bolus transit time (TBTT) (time between bolus entry at the most proximal channel and exit at the most distal channel) of swallowing [59]. By MII testing, swallows can be classified as having complete bolus transit if the bolus enters the proximal channel and exits from all distal impedance-measuring segments. Conversely, if impedance detects bolus retention in any of the distal channels bolus transit is defined as incomplete. The esophageal clearance represents a key defense mechanism following refluxes and a protective reflex response characterized by a peristaltic wave induced by swallow (primary peristalsis) that permits the clearance of the retrograde bolus and, by delivering salivary bicarbonate, allows the buffering of refluxate [60,61]. Studies in adults found that low post-reflux swallow induced peristaltic wave (PSPW) index accurately discriminates erosive esophagitis from nonerosive GERD and from healthy controls [62]. Furthermore, in a study of patients with Barrett's esophagus, PSPW was the only impedance parameter associated with incident dysplasia at 3-year follow-up [63]. To date no studies assessing PSPW in pediatric age have been published.

12. Reporting

The report of MII-pH monitoring should be standardized, in order to ensure homogeneous interpretation of the study results and to facilitate both clinical practice and research purposes. In 2012 the ESPGHAN European pediatric impedance working group first provided pediatric consensus about MII-pH reporting, suggesting that it should include patient information, indication for testing, interpretation of the main MII and pH results and and recommendations for treatment or further investigations. Based on the available evidence, current international guidelines and recent studies we suggest to include in the study report the following data:

12.1. Patient baseline informations

Reports should use common terminology and should be easily readable and interpretable for not specialized readers. The report should include patient's demographic data, relevant information on medical history (e.g. underlying diseases or previous endoscopy findings) and indication for testing. Moreover, a list of current medications, including whether possible acid suppressive drugs were withdrawn (specifying the timing) or continued during the study, and information about feeding (normal diet, use of extensively hydrolyzed or amino acid formula) should be added. As for patients on enteral feeding, delivery methods for enteral nutrition (nasogastric, nasojejunal, gastrostomy, or jejunostomy tube feeding) and schedules timing of administration (bolus or continuous feeds) should be detailed.

12.2. pH parameters

Report should include all the following pH-based parameters: total acid exposure time (AET) (%) (also known as reflux index), number of long-lasting reflux episodes (episodes lasting over 5 min), the duration of the longest episode (min), the mean acid clearance time (s), and the number of only-pH reflux episodes.

12.3. Impedance-based parameters

The impedance results should include: the total number of reflux events, specifying the number of acid, weakly acidic, and weakly alkaline episodes, number and percentage of reflux episodes reaching the most proximal impedance channels, total bolus exposure index (%), and median bolus clearance time (in seconds).

It should be also specified whether artifacts were present and excluded from the analysis, whether other technical problems (i.e. very low impedance baseline) were noted and whether mealtimes were considered, according to the patient history and indication for testing (e.g. symptoms during meals, continuous enteral feeding).

12.4. Symptoms association indexes

In the report the overall number of symptoms occurring during the investigation and the proportion of symptoms temporally associated with reflux episodes, along with SI and SAP results should be detailed.

12.5. Adjunctive parameters

MII-pH report may also include baseline impedance value when levels are below the available percentiles for age group. Although there are no pediatric reference values, in selected patients a generic comment on swallowing, according to esophageal bolus transit parameters and swallows with complete bolus transit, on air swallow and belching and on PSPW index may be considered.

12.6. Interpretation of results

The lack of true normal pediatric values for MII-pH does not allow drawing any definitive conclusions in terms of pathologic MII-pH findings. The available reference ranges may guide in the study interpretation, but final impressions of the test, recommendation for treatment or further investigations should derive by the combination of MII-pH findings and patient clinical history.

13. Impact on clinical practice

According to the latest GERD guidelines no studies have yet been performed in pediatrics that convincingly demonstrate that the results of pH-MII testing influences clinical outcomes [1]. Conversely, several studies in adults have shown that pH-MII may predict a clinical response to therapy including proton-pump inhibitors [64,65]. Francavilla and coworkers showed that the addition of impedance to conventional pH monitoring increase the diagnostic yield in detecting reflux events in infants and revealing an association between refluxes and respiratory symptoms in the same group of patients [66]. One pediatric study evaluated the role of MII-pH monitoring compared to pH parameters alone in managing GERD: out of 50 MII-pH tsestings, the impedance parameters changed the clinical management in an additional 22% of the patients (62% vs 40%) [67]. The limited effect of pH-MII on clinical management may be more related to the lack of therapies for nonacid reflux rather than a weakness of the technique itself. In a study of children undergoing pH-MII monitoring prior to fundoplication, the test results suggest that no reflux parameter other than the amount of full column reflux could predict symptom resolution after fundoplication [68]. Finally, in a recent study of 116 children undergoing MII-pH monitoring, abnormal reflux parameters did not predict hospitalization risk even in high-risk patients with aspiration [69].

Cresi et al recently showed that pathological MII-pH results were significantly related to the post-test duration of symptoms in infants [70]. Further outcome studies are needed to prove the impact of MII-pH monitoring in clinical practice in infants and children.

What emerges from the currently available evidences are the following points:

1. MII-pH monitoring has much higher sensitivity in the detection of GER episodes compared to pH-monitoirng alone, in children with both extra- or esophageal symptoms and up to 50% of children with GERD would not be recognized analyzing only acid parameters [25,16]. The ability of pH-MII monitoring to detect all kind of reflux episodes may be important to correlate persistent troublesome symptoms with acid and non-acid gas-

troesophageal reflux events in patients off or on acid suppression and during postprandial time [71].

2. MII-pH monitoring can differentiate NERD, hypersensitive esophagus, and functional heartburn, when performed off therapy. The new Rome IV esophageal criteria now define a variety of nonerosive esophageal phenotypes based on the results of diagnostic testing including MII-pH monitoring. Symptomatic patient with a negative endoscopic finding may be classified into 3 distinct phenotypes: (a) non-erosive reflux disease (NERD), with abnormal esophageal acid exposure regardless of symptom correlation, (b) esophageal hypersensitvity, with normal esophageal acid exposure but a positive symptom association to acid or nonacid reflux and (c) functional heartburn, with normal esophageal acid exposure and a negative symptom association. Appropriate categorization of patients into these subgroups has important therapeutic implications, because patients with similar GER symptoms may require different medical (PPI vs neuromodulators) or surgical interventions. Mahoney et al. first demonstrated in a group of 45 children with negative endoscopy that 27% were categorized with NERD, 29%, with reflux hypersensitivity and 44% with functional heartburn [72].
3. MII-pH monitoring may provide new insights in the pathophysiology of acid and non acid GERD and new parameters (such as impedance baseline and swallow indices) that helps in identifying children with motility or esophageal mucosal complications to submit to other investigations like manometry and endoscopy. While a low impedance baseline may alert the clinician to the presence of esophagitis (peptic and eosinophilic in nature), it does not prevent the need for endoscopy [54,72,73].
4. Conflicting data are available on the role of pH-MII monitoring in predicting fundoplication outcome. Adult studies have found that MII-pH may predict which patients respond symptomatically to fundoplication [74,75], whilst data in children are limited and are less encouraging 6 [67]. Rosen et al. did not identify single reflux or symptom marker be able to predict post-operative outcome. In contrast Mauritz et al. have recently showed that laparoscopic antireflux surgery obtained a better reflux reduction in children with higher number of reflux episodes on preoperative pH-MII monitoring [76]. More recently, adult studies have suggested the post-fundoplication MII-pH studies may predict who responds to reoperation, but again there is no pediatric data to confirm this [77,78].

14. Current limitations

Despite the above-mentioned clinical relevance and further possible potentials, MII-pH esophageal monitoring still carries some drawbacks and limitations, which should be taken into account. As already highlighted, although there are increasing published pediatric data, the lack of true pediatric normal reference values is a major issue. As a consequence, the interpretation of the obtained data should be mainly based on the analysis between reported symptoms and objective findings rather than the quantitative reflux assessment. Moreover, the current restricted therapeutic options, particularly for non acid reflux episodes, unavoidably lessen the impact of MII-pH monitoring on clinical practice. In our opinion, both issues demand further development in order to optimize the test yield.

Finally, performing MII-pH test and the subsequent data analysis require both specific medical training and significant costs in terms of time and money which should not be overlooked (we emphasize that the reading of a single tracing takes from 30 min to 2 h for the most complex ones). Even the inter-observer agreement on data interpretation has recently become a matter of debate, being higher for simple tracings and lower for difficult cases. Therefore, we agree that the automatic software analysis should be considered as a background analysis and manual reading should be performed by an investigator with good expertise, according to shared settings and with possible assistance by a more expert referral center for selected difficult patients.

15. Special patients

15.1. Newborns and small infants

15.1.1. Background and indications

In the first months of life GER is a physiological phenomenon. However, the association with troublesome symptoms and complications may lead to the diagnosis of GERD in about 5% of cases [79,36]. In newborns and small infants (1–6 months) non-acidic refluxes are prevalent and cardiorespiratory (CR) events are the most reported symptoms [80]. The frequent coexistence of CR and GER symptoms in infants gives caregivers and neonatologists the perception of a causal association between these 2 events and has become the basis for an over-prescription of acid suppressive drugs, which may increase the risk of infections, sepsis and necrotizing enterocolitis [81,82]. Hence, an early assessment of GER episodes is important to prevent over-prescription of antacid drugs and prolonged hospital stay.

As in older children, in newborns and infants MII-pH monitoring is able to identify both acid and non-acid GER events and to evaluate their association with symptoms [1]. The presence of atypical or extraesophageal symptoms of GER and no response to conservative or pharmacological treatment are the main indications for MII-pH in the early stages of life [1].

15.1.2. Patient preparation and catheter positioning

Infants undergoing MII-pH monitoring should be almost 3-h fasting, to avoid vomiting during catheter insertion. Indications for acid suppressive drug continuation or suspension are similar to those previously reported for older children. MII-pH catheters are of 2.13 mm diameter-wide (6 F), with impedance rings set 1.5 cm apart and should be inserted trans-nasally, without sedation and with the infant in supine position. The use of saline solution could ease the passage of the catheter as well as the use of pacifiers, which are known to induce sequential swallows. Glucose administration by mouth just before the insertion of the probe may also decrease the discomfort and pain of the patient. The correct position of the catheter has been described before. Because of the short esophageal length of infants, the fluoroscopic/X-ray check should be used to identify the pH sensor and the number of impedance rings actually into the esophagus, which is critical for reporting. During MII-pH monitoring infants should be clinically stable, without respiratory support and preferably fully oral fed (by bottle or breastfeeding). The presence of a nutritional probe, any respiratory supports, associated diseases and the use of drugs influencing GER do not represent an absolute contraindication to the monitoring but should be carefully considered in the analysis.

15.1.3. Caregivers' instruction and protocol

During MII-pH monitoring the caregivers play a key role, as they should monitor the correct execution of the examination. They should be trained to assure the maintenance of the correct position of the MII-pH catheter and carefully observe and note behaviours and symptoms. Substantial changes in positioning should be noted down in the specific diary as they are reported to influence the number of GER events and gastric emptying time. A detailed and properly completed diary with eventual cardiorespiratory events and feeding changes is mandatory to obtain good-quality data for correct reporting. MII-pH monitoring showed to be safe and generally well tolerated even in preterm newborns. However, hospitalization of the patient is advised because of the need of a careful monitoring and the frequent association with CR events. Since infants present circadian rhythm that influence GER characteristics and frequency, a MII-pH monitoring at least 20-h long is necessary to obtain complete data on day and night periods. To evaluate the association between symptoms and GER events, MII-pH monitoring could be easily combined with other type of monitoring and tests (e.g. polysomnography, video-recording, EEG, etc. . .). The synchronization of the instruments should be carefully set before the beginning of recording.

15.1.4. Reflux characteristics and reporting

Chronological and gestational age should be indicated within the study report, along with the type of milk and feeding modality (e.g. breastfeeding, bottle or nasogastric tube), drugs that can influence GER (e.g. caffeine, steroids, antibiotics), number of impedance channels considered for the analysis, and duration of the recording. For the association between CR and GER events a time window of 30 s is suggested as the most appropriate time frame and the following CR events should be considered: blood oxygen saturation <80%, bradycardia with heart rate <80 beats per minute, and apnea >20 s or >5 s, if followed by desaturation or bradycardia [82,83].

The frequent feedings, the buffering effect of milk and the immaturity of esophageal and gastric motility explain the higher frequency and longer duration of GER events observed in newborns, especially in preterms, and lead to a higher proportion of non-acidic GER, which show a decreasing trend from newborns to later ages. GER characteristic are also influenced by fasting/feeding periods and by sleep/awake status. GER frequency is significantly reduced during fasting periods, with an increased frequency of acid GER events in newborns, and significantly increased in awake periods [84–86].

Some MII-pH variables (e.g. bolus exposure index and proximal reflux frequency) are positively correlated with the duration of symptoms, thus showing a prognostic value [83]. These features should be considered in the analysis of MII-pH tracings and could be helpful in tailoring clinical management and treatment. Moreover, the possibility to use MII technique to study esophageal swallows as well could be interesting to better characterize reflux and identify patients with impaired esophageal motility [87].

15.2. Patients on enteral feeding

Considering its ability in detecting nonacid or weakly acid GER, MII-pH can be performed on either continuous or bolus-based enteral feeding [88]. However, if the study is performed with a nasogastric (NG) tube in place, the number of reflux episodes may be artificially increased. It has been shown that the presence of a NG tube through the esofagogastric junction (EGJ) increases the postprandial reflux by nearly 70% [89–91], which could be explained either by the fact that the EGJ is held open by the stiff tube or that the NG tube impairs esophageal clearance [91–94].

15.3. Patients on GER treatment

Ambulatory 24-h pH monitoring is usually performed after the discontinuation of acid-suppressive therapy for several days, as the test allows the detection only of acid reflux, being hence useless when gastric acidity is pharmacologically suppressed. Conversely, MII-pH monitoring detects reflux irrespective of pH and thus can be carried out both on or off anti-reflux therapy. Nevertheless, pH assessment is still a part of the test evaluation and the use of drugs affecting gastric pH needs to be taken into account. If the goal of testing is to determine the efficacy of therapy in persistently symptomatic patients, testing should definitely be performed on acid suppression in order to evaluate the possible ineffectiveness of drugs in swabbing gastric acidity or the possible role of non-acid reflux on symptom genesis. Conversely, if the aim is to evaluate the frequency, severity, and pH characteristics of reflux events in a patient with GER symptoms, the test should be performed before starting acid suppressive therapy. Nevertheless, it is not uncommon that the patient is already on anti-reflux therapy at the time of testing due to the strong suspicion of GERD. In this case, we suggest not stopping the treatment immediately before the MII-pH recording in order to avoid the rebound iperacidity. In particular, PPIs should be gradually stopped at least 2 weeks before MII-pH monitoring. In patients on acid suppressive agents a catheter with two pH-sensors (the distal one positioned in stomach and the proximal one in esophagus) allows both the calculation of gastric buffering and esophageal acid exposure, relevant to titrate eventual increase of drug dose.

15.4. Patients with neurological impairment

The increased frequency and severity of GERD among children with neurologic impairment is widely reported [95–100]. Chronic GERD in these fragile patients is multifactorial in etiology and several underlying mechanisms have been proposed, including hiatus hernia, adoption of a prolonged supine position, and increased intraabdominal pressure secondary to spasticity, scoliosis or seizures. Nevertheless, central nervous system (CNS) dysfunction is likely to be the leading cause of GERD [101–103].

Recent ESPGHAN guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with NI recommend the use of objective measures for the diagnosis of GERD in these children. Moreover, as severely neurologically disabled children cannot adequately report symptoms, diagnostic tests are suggested for monitoring whether GERD is successfully controlled by therapy or not [100]. It is worth to underline that in NI children upper gastrointestinal and respiratory manifestations secondary to GERD may overlap with those associated to oropharyngeal and esophageal dysphagia. MII-pH allows both quantitative analysis of different parameters and qualitative assessment of the symptom association. Moreover, since MII-pH is able to assess both antegrade and retrograde bolus movement, it offers the possibility to distinguish the different components of esophageal dysmotility. In this context, impedance measurements combined with manometry have shown valuable information in assessing the aspiration risk by detecting alterations of pharyngeal swallow in children with cerebral palsy [104].

One of the limitations of MII-pH monitoring is that both esophagitis and motility disorders lower impedance baseline values. Therefore, as for other conditions such as achalasia or esophageal atresia, also for NI children the automated analysis is often inaccurate, leading to a significant underestimation of the amount of reflux, and, despite challenging, manual analysis is firmly required [105].

15.5. Patients with surgical conditions

Patients with some congenital diseases (esophageal atresia, congenital diaphragmatic hernia) or previous surgical procedures (lung transplantation, Heller myotomy or Per-Oral Endoscopic Myotomy-POEM-for esophageal achalasia) are at greater risk for developing gastro-esophageal reflux disease (GERD).

15.6. Esophageal atresia

Esophageal atresia (EA) is one of the most common congenital gastrointestinal (GI) malformation occurring in 1 in 2.400–4.500 births world-wide [106]. The prognosis has significantly improved in the last decades due to the advances in medical care, however patients with EA need a systematic long term follow-up because of GI and nutritional life-long consequences [107]. In 2016 ESPGHAN-NASPGHAN guidelines for the management of GI complications in children with EA defining the diagnostic and therapeutic pathways both for asymptomatic and symptomatic patients [108].

As for GI problems, GERD represents the most frequent sequela with a prevalence ranging from 22% to 45% according to age, patient selection, and diagnostic tools [109]. Post-surgical anatomical alterations such as a shorter intra-abdominal esophagus and/or deformity of gastro-esophageal junction and esophageal dysmotility depending on congenital abnormal extrinsic innervation at birth and/or surgical repair (i.e. iatrogenic vagal nerve lesion) may contribute to the physiopathology of GER in EA patients [110–112].

According to the international guidelines, all EA patients have to be treated with PPIs up to the first year of life or longer, due to the high prevalence of GER-related GI and pulmonary conditions [108]. Indeed, recurrent or late esophageal anastomotic stricture, peptic or eosinophilic esophagitis, Barrett's esophagus, or recurrent respiratory problems (atelectasis, aspiration pneumonia, asthma/increased airway reactivity, bronchiectasis and worsened tracheomalacia) can be frequently observed as GERD complications within the first 5 years of life, but also during adolescence and adulthood [113–116]. Therefore, in this cohort of patients a careful assessment of GERD is mandatory to ensure a correct management and follow-up.

Multichannel Intraluminal Impedance and pH (MII-pH) monitoring, considered as the gold standard in GER evaluation, plays a relevant role especially for the study of children with EA, because this technique is also able to demonstrate the presence of an impaired esophageal motility, to dectect weakly acidic/alkaline reflux episodes and to correlate symptoms with non-acid reflux events in symptomatic patients on PPI therapy or on continuous feeds or with extra-esophageal symptoms [108–117].

In comparison to other groups of patients with GERD, in fact it has been documented that EA subjects have an impedance pattern characterized by: longer mean acid clearing time and mean bolus clearing time [113]; higher number of non acidic reflux episodes [113]; 75% lower baseline impedance than control patients, related to esophageal dysmotility and/or severe acid reflux [55]; poorer correlation between symptoms and MII-pH study findings [118]. Low baseline impedance, often associated with an abnormal esophageal motility typical of this cohort of subjects, makes it difficult for automated analysis to detect reflux events, thus it is necessary to manually review the tracing to avoid underreporting of reflux episodes.

As for gastro-esophageal symptoms, EA patients seem to be insensitive or, to some extent, accustomed to (chronic) GER or dysphagia even if MII-pH monitoring or/and endoscopy plus histology result pathological [118–120]. Furthermore, it has been documented that the extraesophageal symptoms are frequently caused by GER and up to 50% of these are associated with non acidic events [121–122]. For all these reasons, the evaluation and treatment of EA patients in a referral pediatric centre are recommended.

MII-pH monitoring should be preferred to pH-probe testing in the assessment of GERD and it should be performed in all asymptomatic and symptomatic patients with EA at time of discontinuation of PPI treatment and repeated in the long term follow-up to choose between medical or surgical therapy when GERD is suspected [108].

15.7. Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a rare malformation characterized by a defect of diaphragmatic development that allows abdominal viscera to herniate in the chest. The most frequent type of CDH is a posterolateral defect, generally located on the left side of the diaphragm.

CDH is a predisposing condition for GERD development, with a prevalence ranging from 12% to 86% [120]. Several anatomical factors as the mediastinal shift and compression during fetal life, the abnormal hiatal anatomy at the gastro-esophageal junction, the lack of an angle of His, the herniation of the stomach into the chest and the closure of the diaphragmatic defect under excessive tension, could contribute to GER onset. In addition, a prenatal diagnosis of CDH, herniation of liver or stomach in the chest and need for ECMO or patch closure have been identified as potential risk factors of GERD occurrence [123–125].

Even if a rate of CDH patients ranging from 8 to 21% needs antireflux surgery, the incidence and the severity of GER symptoms show a decreasing trend with aging [126–132]. However, some studies have demonstrated that in CDH survivors GER may be asymptomatic or likely underrated because patients probably attribute the symptoms to their primary defect [132–133].

Vanamo et al. observed esophagitis in 54% and Barrett esophagus in 12% of patients 20 years after CDH repair [134]. Recently Morandi et al. found esophagitis in 12 pediatric patients with CDH enrolled and endoscopically studied; one of the 12 children had a diagnosis of Barrett's esophagus. These data do not correlate with the clinical manifestations as typical symptoms were present in only 25% of the children [135].

If a high incidence of esophagitis in adult and pediatric survivors with CDH suggests that long-term endoscopic surveillance is required, as well MII-pH testing should be performed to ensure an early GERD diagnosis and to prevent pulmonary morbidity by aspiration. Indeed a few studies evaluated GER using MII-pH monitoring in CDH children, confirming a high incidence of GER with a predominance of non-acidic reflux also in the asymptomatic patients (about the 50% of subjects enrolled) [132,133]. So far, though, the right timing and type of investigations (endoscopy, MII-pH monitoring) for GERD detection in CDH still need to be defined. According to the recent findings, it should be recommended to perform upper endoscopy plus MII-pH testing when CDH patients are symptomatic or before transition to adulthood when they are asymptomatic [134,135].

15.8. Lung transplantation

Lung transplantation is an effective therapeutic option for the treatment of some end-stage pulmonary disorders, i.e. cystic fibrosis and idiopathic pulmonary fibrosis (IPF), improving the quality of life and extending the survival rate for the recipients [136].

Several studies have documented both a high prevalence of GERD in patients with an end-stage lung disease prior to transplantation and a relationship between GERD and lung transplant outcomes, including acute rejection and lymphocytic bronchiolitis, and chronic rejection associated with bronchiolitis obliterans syndrome (BOS) [137]. It has been shown that patients with IPF have increased prevalence of GERD in comparison to patients with other chronic lung diseases [138–140], a higher prevalence of abnormal reflux compared to those with chronic obstructive pulmonary disease [141] and a higher total reflux episodes and total proximal reflux episodes compared to both non-IPF chronic lung disease patients and healthy volunteers [142].

The most accredited etiopathogenetic hypothesis states that GERD may increase micro-aspiration episodes, resulting in activation of an inflammatory cascade in lung tissue, which induces fibrotic changes that characterize IPF [143–145]. The mechanisms that have been proposed to explain GERD development after surgery are a post-operative iatrogenic vagal innervation, impaired cough reflexes and muco-ciliary clearance and reduced gastric motility induced by immunosuppressive drugs (i.e. calcineurin inhibitors) [146]. Moreover, the micro-aspiration of gastric contents has been identified as a potential non-immune risk factor for allograft injury, as it may cause repetitive epithelial injury and worsening of pulmonary function [147–150].

According to the international guidelines for diagnosis and management of BOS, MII-pH monitoring can be routinely used to diagnose motility abnormalities and abnormal acid and/or non-acid GER in the evaluation of lung transplant recipients who develop a decline in FEV1 (FEV1 <90% of baseline) consistent with the onset of BOS [151,152]. If GERD is confirmed, the patient should be referred to an experienced surgeon to be evaluated for potential fundoplication.

15.9. Esophageal achalasia

Esophageal achalasia (EAc) is a rare, chronic and progressive motility disorder manometrically characterised by absence of esophageal peristalsis and incomplete or absent relaxation of the lower esophageal sphincter (LES) [153]. The estimated incidence of EAc in children is 0.11 per 100.000, without racial or gender predilection [154].

Heller myotomy has always been considered the treatment of choice also for children, as it provides more durable outcomes in a long-term follow-up in comparison to endoscopic pneumatic dilations. Per-Oral Endoscopic Myotomy (POEM) is a minimally invasive procedure, recently developed for the treatment of EAc and that incorporates the endoscopic approach with the principles of the Natural Orifice Transluminal Endoscopic Surgery (NOTES) to perform a myotomy [155–157]. A systematic review on the efficacy of POEM for achalasia reported technical and clinical success of 97% and 93%, respectively [158].

The development of GERD after myotomy is a frequent problem and whether an antireflux procedure should be performed has been the subject of extensive debate, especially given concerns for increased postoperative dysphagia after a fundoplication.

The achalasia guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons recommend that patients who undergo myotomy should have a fundoplication to prevent reflux. One of the main POEM drawbacks may be represented by the development of gastroesophageal reflux, when considering that – differently from LHM – no anti-reflux intervention is performed [159]. Some authors replied that the advantage of this procedure is indeed the selective myotomy of the internal circular muscular fibers without dissection of the diaphragmatic hiatus and division of the crura, typically required to perform an adequate surgical myotomy [160].

To date, limited data report the trend towards the development of GER years after POEM, and it remains unclear whether its incidence increases or decreases. A recent systematic review and meta-analysis comparing the reported results of POEM to LHM for the treatment of EAc found that patients undergoing POEM were more likely to develop GERD symptoms (17.5% after LHM vs 18.5% after POEM), that GERD evidenced by erosive esophagitis was observed in 11.5% and 22.4% of patients receiving LHM and POEM respectively, that GERD-pH was observed in 11.1% of LHM patients and in 47.5% of POEM patients. It is important to note, however, that the majority of studies of both modalities did not perform routine pH-monitoring [161].

The odds between patient-reported symptoms versus pH results suggests that the majority of patients could be asymptomatic, therefore it is necessary to perform objective post-procedure testing in all subjects treated. The management algorithm and goals of therapy are unclear when GER is identified, and the extent of intervention necessary to manage these patients needs to be ascertained by future studies.

In literature, a few cases of pediatric patients with AEc have been described to date. Caldaro et al. compared the conventional laparoscopic technique and the POEM procedure in a cohort of 18 children affected by EAc, demonstrating that POEM was characterized by a rate of iatrogenic GERD that was very low and similar in both procedures [162]. However, the difference in follow-up length between the two groups could underestimate the onset of GERD in POEM cohort, therefore a tight follow-up with systematic symptom assessment, manometric study, endoscopic evaluation, and MII-pH testing is recommended.

It is worth remembering that achalasia patients may have false positive pH studies owing to stasis (poor clearance of acid in the absence of peristalsis) and fermentation of retained food causing a decrease in pH due to lactic acid. Thus, expert assessment of the overall clinical situation is needed to diagnose GERD.

In summary, patients treated with LHM or POEM should have close follow-up with MII-pH monitoring and upper endoscopy because GERD is the most common adverse event after both procedures and patients often need PPIs. Studies comparing the long-term results of POEM with LHM are awaited.

16. Conclusions

MII-pH monitoring is the current investigation of choice for diagnosing GERD in infants, children and adolescents due to its ability both in detecting all types of reflux episodes and evaluating the association of symptoms with reflux events. With proper indications, monitoring conditions and data analysis, MII-pH provides the clinicians with important information for diagnostic and therapeutic purposes. However, certain limitations are still unresolved. First of all, the limited pediatric normative values are a drawback in the interpretation of the results. Moreover, the restricted therapeutic options, particularly for non acid reflux episodes, unavoidably lessen the impact of MII-pH monitoring on clinical practice. Both issues demand further development. The analysis of MII-pH data is time consuming and requires specific training. The urgent need to standardize data analysis and reporting has been addressed by the present position paper. Further studies on the possible clinical utility of different MII-pH parameters are welcomed.

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