Reflux disease and achalasia: Failure of the gatekeeper
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Chapter 7

Effect of Azithromycin on acid reflux, hiatus hernia and proximal acid pocket in the postprandial period

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ABSTRACT

Background and Aims:
The risk for acidic reflux is mainly determined by the position of the gastric acid pocket. We hypothesized that compounds affecting proximal stomach tone might reduce gastro-oesophageal reflux by changing the acid pocket position. Therefore, we studied the effect of Azithromycin (Azi) on acid pocket position and acid exposure in patients with gastro-oesophageal reflux disease (GERD).

Methods:
Nineteen patients with GERD were included of whom 7 had a large hiatal hernia (≥3cm) (L-HH) and 12 had a small or no hiatal hernia (S-HH). Patients were randomized to Azi 250 mg/day or placebo during 3 days in a cross-over manner. On each study day, reflux episodes were detected using concurrent HRM and pH-impedance monitoring after a standardized meal. The acid pocket was visualized using scintigraphy, and its position was determined relative to the diaphragm.

Results:
Azi reduced the number of acid reflux events (placebo 8.0±2.2 vs Azi 5.6±1.8, p<0.01) and postprandial acid exposure (placebo 10.5±3.8% vs Azi 5.9±2.3%, p<0.05), in all patients without affecting the total number of reflux episodes. Acid reflux occurred mainly when the acid pocket was located above or at the level of the diaphragm, in contrast to below the diaphragm. Treatment with Azi reduced hiatal hernia size and resulted in a more distal position of the acid pocket compared to placebo (below the diaphragm 39% vs 29%, p=0.03). Azi reduced the rate of acid reflux episodes in S-HH patients (38% to 17%) to a larger extent than in L-HH patient (69% to 62%, p=0.04).

Conclusion:
Azi leads to a reduction in acid reflux episodes and esophageal acid exposure. This effect was associated with a smaller hiatal hernia size and a more distal position of the acid pocket, further indicating the importance of the acid pocket in the pathogenesis of GERD.
INTRODUCTION

Gastroesophageal reflux is a physiological phenomenon in which gastric contents flow back into the esophagus. When reflux causes symptoms such as heartburn or regurgitation and/or esophageal damage, it is referred to as gastroesophageal reflux disease (GERD), a very common chronic condition affecting 10-20% of the adult population.\textsuperscript{1,2}

Most reflux episodes occur after a meal, when the stomach is filled with ingested food. In contrast to the belief that meal ingestion buffers gastric acid, acid reflux episodes occur even in the early postprandial period.\textsuperscript{3} Fletcher et al elegantly showed that gastric acid floats on top of the meal acting as a reservoir from which acid can enter the esophagus during episodes of opening of the esophagogastroduodenal junction. This unbuffered pool of gastric acid is referred to as the gastric acid pocket.\textsuperscript{4}

The position of the acid pocket relative to the crural diaphragm is an important determinant of the acidity of the reflexate. We previously showed that 74-85% of reflux episodes is acidic when the acid pocket is located above or at the level of the diaphragm. In contrast, only 7-20% of reflux episodes is acidic if the acid pocket is located below the diaphragm.\textsuperscript{3} The position of the pocket relative to diaphragm on the other hand is largely determined by presence of a hiatal hernia. Especially in patients with a large HH, the acid pocket is frequently located above the diaphragm, facilitating the occurrence of acid reflux events.\textsuperscript{1,3} This insight implies that drugs affecting the position of the acid pocket (hiatal hernia) may alter acid exposure.

Prokinetic agents like macrolides increase gastric emptying and in addition increase proximal stomach tone and LES pressure, presumably via a cholinergic pathway mediated by motilin receptors or possibly by serotonin receptors.\textsuperscript{6} These properties make these compounds interesting candidates to alter the acid pocket position. Recently, Mertens et al. indeed reported that the macrolide Azithromycin (Azi), a macrolide similar in structure and function to erythromycin\textsuperscript{7}, reduced the rate of reflux episodes in lung transplant patients.\textsuperscript{6} Interestingly, Azi mainly affected the rate of acidic reflux leaving the number of weakly acid reflux events unchanged. As the acidity of the reflexate is mainly determined by the position of the acid pocket, we hypothesized that this action of Azi was mediated by a reduction in hiatal hernia size thereby leading to an alteration in the position of the acid pocket. To evaluate this hypothesis, we examined the effect of Azi on gastroesophageal reflux and the acid pocket position in patients with GERD.
PATIENTS AND METHODS

Patients
The study was performed in 19 patients with proven GERD, defined by the presence of esophagitis observed during upper endoscopy and/or pH-metry with an acid exposure of >4.5%, in combination with typical GERD symptoms. None of the patients had undergone previous gastrointestinal surgery or was taking medication known to influence esophageal motor function. Hiatal hernia size was measured by high resolution manometry (HRM), and patients were divided in large HH (≥3cm) or small or no HH (<3cm) according to the size of the hiatal hernia. One patient withdrew consent after the first study day due to discomfort. The study was approved by the Medical Ethics Committee of the Academic Medical Center. Written informed consent was obtained from all subjects before enrolment in the study.

Study design
The study had a randomized double blind, crossover design. Patients were randomised to Azi 250 mg or Placebo by the pharmacy where the code was stored until the end of the study. Both the investigators and the patients were blinded to the treatment. Study medication was taken during a three day course ending on the study day, with comparable dosing of Azi used in the earlier study by Mertens et al. Acid suppressive medication was stopped at least 7 days before each study day. The study day protocol was repeated after a minimal wash-out period of two weeks.

Study day protocol
Subjects were studied after an overnight fast of at least 12 h. Reflux episodes were detected using concurrent HRM and pH-impedance monitoring, and scintigraphy was performed to localize the acid pocket relative to the crural diaphragm.

At 30 minutes before insertion of the catheters, 350 MBq $^{99m}$Tc-pertechnetate was injected intravenously. Pertechnetate behaves as a chloride ion, and is secreted by the parietal cells of the stomach. Using this technique, acid distribution in the stomach can be visualized scintigraphically as validated previously.

Before introduction of the HRM catheter, two sealed markers impregnated with $^{99m}$Tc-pertechnetate were attached to the catheter, one to the distal end of the catheter and one between sensor 13 and 14 to visualize the exact location of the catheter during scintigraphy. These markers were used to integrate manometry and scintigraphy as described below in more detail.

The HRM catheter and the pH-impedance catheter were inserted transnasally. The HRM catheter was positioned with the most distal 5 sensors positioned in the stomach. The pH-sensor of the pH/
impedance catheter was placed 5 centimetres above the upper border of the LES. Subsequently, the patients were positioned in upright position in front of the scintigraphy camera. First, a baseline fasting recording was obtained during 5 minutes. Then subjects consumed a standardized meal in 10 minutes consisting of 200 ml orange juice and two pancakes with jam (510 kcal). After the meal scintigraphic, HRM and pH-impedance recordings were performed for 105 minutes.

**Recording methods**

High resolution manometry was performed using a solid state high-resolution manometry catheter (Unisensor, Attikon, Switzerland) with 36 solid state pressure transducers spaced 1 cm apart. Pressure sensors were zeroed before insertion. The sample rate was 50 Hz and data was collected and analyzed with the MMS Solar system (MMS, Enschede, the Netherlands).

For pH-impedance measurement a Unisensor pH-impedance catheter (Unisensor, Attikon, Switzerland) containing one ISFET pH sensor and 8 impedance electrodes was used, allowing impedance recordings at 3, 5, 7, 9, 15 and 17 cm above the upper border of the lower esophageal sphincter (LES). Data was collected using the MMS Solar system. Before each study the pH electrode was calibrated with pH 4.0 and pH 7.0 solutions (Medtronic A/S, Skovlunde, Denmark).

Dynamic scintigraphic images were acquired on a gamma camera system (Diacam; Siemens Medical Solutions, Illinois, USA), equipped with a low-energy all purpose collimator. Dynamic recordings were made for 2 hours (720 views, 10 s/view, 120 min total acquisition time). Every acquisition was processed on a Hermes processing station (Hermes Medical Solutions, Stockholm, Sweden) for further analysis.

**Data analysis**

Reflux episodes were detected using pH-impedance and each liquid or mixed reflux event was defined as acidic reflux when pH < 4, as weakly acidic when pH ≥ 4 and pH < 7 and as non-acidic when pH ≥ 7. A liquid reflux was defined as a fall in impedance of ≥ 40% of baseline impedance starting at the most distal segment and propagating retrograde to at least the next measuring segment. Pure gas reflux was defined as a rapid (>3000 Ω s⁻¹) rise in impedance, occurring simultaneously in at least two impedance sites, in the absence of swallowing. Mixed reflux was defined as gas reflux occurring during or immediately before liquid reflux. Esophageal clearance time and proximal extent of refluxate was determined for each reflux episode.

For each reflux episode, HRM recordings were used to determine the exact distance from the crural diaphragm to the markers on the catheter for the position of the acid pocket and to the LES for hiatal hernia size. The lower and upper border of the crural diaphragm and the middle of the LES zone were determined. (Figure 1.) Hiatal hernia size was defined as the distance from...
the lower end of the diaphragm to the middle of the LES. Additionally, we determined whether the hiatal hernia was in the reduced (1 high pressure zone) or non-reduced state (2 high pressure zones), as described and validated by Bredenoord et al.\textsuperscript{11} For the non reduced state, a trough with a pressure of at least 10 mmHg lower than the two high pressure zones had to be present.

Figure 1 | Figure 1A represents a schematic view of the study set-up. Two radionuclide markers are attached to the HRM catheter, which can be observed on the scintigraphic images (B), on the proximal and distal end of the acid pocket. The representative image of the HRM and pH-impedance recording is shown in figure 1C, with a mixed reflux episode as a result of a TLESR in a patient with a large hiatal hernia. The LES is marked with 1, and the upper and lower border of the crural diaphragm are marked with 2 and 3 respectively.

Subsequently, calibrated Hermes software was used to measure the distance of the proximal end of the gastric acid pocket to the markers on the catheters on one image prior to the reflux event to calculate the distance between the acid pocket and the crural diaphragm. The position of the acid pocket was classified in three categories relative to the crural diaphragm: below the diaphragm, at the level of the diaphragm or above the level of the diaphragm.

Measurements of the distances between the acid pocket and the diaphragm were made through a straight line in a planar posterior view of the stomach. A pocket was considered as present when a clear pool of radiolabelled activity was distinguishable in the proximal stomach. The radiolabelled markers on the catheter were scintigraphically visualised as clear dots. Acid pocket length and
width were determined for each reflux event by measuring the distance from the proximal to the distal end of the radiolabelled activity for the length and between both lateral ends for the width respectively.

For each reflux episode the underlying mechanism was classified using previously described criteria (12) as a TLESR, swallow induced, low LES pressure, abdominal straining or with unknown cause. Briefly, a TLESR was defined as a decrease in LES pressure with a rate of ≥ 1 mmHg/s, with a duration of 10 seconds, a nadir pressure ≤ 2mmHg, and absence of swallowing from 4 seconds before to 2 seconds after the start of the relaxation. Swallow induced reflux was defined similarly to TLESRs but with the presence of a swallow. Low LES pressure was defined as a period of at least 30 seconds with end-expiratory LES pressure of ≤ 3mmHg. Abdominal straining was detected as a sharp and brief increase in gastric pressure of at least 30 mmHg with a simultaneous elevation in esophageal pressures.

**Statistical analysis**

Based on data from previous studies a mean number of postprandial acid reflux episodes of 10 per study day was assumed in patients with GERD. To detect a difference of 30% in acid reflux episodes with a statistical power of 80% and a two-sided alpha of 0.05, a total of 16 patients was required in a cross-over design. Thirty percent reduction in reflux episodes is a clinically relevant difference and is observed in studies with a comparable design. To compensate for drop-outs, we decided to include 19 patients.

Statistical analysis was performed using SPSS 20.0 software (IBM corporation, Somers, NY, United States). Data are presented as mean ± SEM. Continuous data were compared using a paired t-test or with a linear mixed model (LMM) in case of multiple measurements per patients. Comparisons of proportions were performed using a generalised estimating equations (GEE) logistic regression model, with subject as clustering factor, and treatment as independent variable. Pearson’s correlation was used for correlations. All p-values were two-tailed and a p-value < 0.05 was considered as statistically significant.

**RESULTS**

**Patients**

Nineteen patients with GERD (13 male; median age 56 yrs, range 45-67 yrs) were included. HRM analysis showed that 7 patients had a large hiatal hernia (L-HH) (≥ 3 cm) and 12 had a small hiatal hernia (S-HH) (< 3 cm).
Acid reflux episodes and esophageal acid exposure

In the 19 patients studied, a total of 494 reflux episodes was detected, of which 245 (49.6%) episodes were acidic. The total number of reflux episodes per patient was not altered by Azithromycin in comparison to placebo (13.8 ± 2.0 versus 14.0 ± 1.7, p = 0.79) (Figure 2). However, the number of acid reflux events and postprandial acid exposure were significantly reduced by Azithromycin compared to placebo (8.0 ± 2.2 vs 5.6 ± 1.8, p < 0.01 and 10.5 ± 3.8% vs 5.9 ± 2.5%, p = 0.01 respectively). Conversely, the number of weakly acid reflux episodes was increased in Azithromycin in comparison to placebo. (Figure 2) A TLESR was the underlying cause in 328 (66%) of the 494 reflux episodes recorded. The number of TLESRs did not differ between Azithromycin and placebo.
Acid pocket position prior to a reflux event
The acid pocket was scintigraphically visible in all patients within 15 minutes after meal ingestion. Acid reflux occurred mainly when the acid pocket was located above (117 of 129 reflux episodes [91%]) or at the level (106 of 171 [62%]) of the diaphragm, but seldom when the pocket was located below the diaphragm (18 of 168 [11%]). (Figure 3)

During treatment with Azi, the acid pocket was more often located below the diaphragm (39±9 vs 29±8%, p=0.03, GEE). (Figure 4) The mean acid pocket length did not differ between Azi and placebo (4.2 ± 0.5 cm and 4.6 ± 0.5 cm respectively, p=0.76, LMM).

Figure 3 | The acidity of the refluxate is mainly determined by the position of the acid pocket relatively to the crural diaphragm (A). When the crural diaphragm and the LES are spatially separated, the acid pocket is located significantly more often above or at the level of the diaphragm compared to when the hiatal hernia is in the reduced state (B). The hiatal hernia size in all patients correlates with the distance of the acid pocket relative to the diaphragm. (C)

Hiatus hernia size and acid reflux
Hiatal hernia size was measured using HRM as the distance from the lower end of the diaphragm to the middle of the LES, as shown in Figure 1. The size of the hiatal hernia varied during the study impacting on the acidity of the refluxate, as previously shown by Bredenoord et al. When reflux episodes were acidic, the mean hiatus hernia size was larger compared to when reflux episodes were weakly or non-acidic (acid 2.8 ± 0.2 vs non acid 2.4 ± 0.2 cm, p<0.05, LMM). Moreover, when
the hiatus hernia was in non-reduced state (spatial separation between diaphragm and LES), the risk for acid reflux was significantly increased compared to in the reduced state (59 ± 7% compared to 30 ± 8% of reflux events respectively, p<0.001, GEE). The distance of the acid pocket to the crural diaphragm correlated significantly with hiatal hernia size (r=0.61, p<0.0001 Pearson’s correlation), with a larger hiatal hernia size thus leading to a more proximal position of the acid pocket. (Figure 3) In the reduced state, hiatal hernia size was never more than 2.0 cm.

Proximal extent and esophageal clearance time
In the total group, the proximal extent of liquid and mixed reflux episodes varied between 5 and 17 cm. During treatment with AZI, the proximal extent was significantly reduced compared to placebo (9.9 ± 0.50 cm vs 8.6 ± 0.44 cm, p<0.01). As acid exposure is also determined by clearance of the refluxate, we assessed the effect of AZI on acid clearance time. Mean clearance time was not significantly altered by AZI (13 ± 1.5 s with AZI vs 17 ± 2.1 s with placebo (p=0.10)).

Small versus large hiatal hernia
Motilides increase proximal stomach tone thereby reducing the volume of the proximal stomach. We hypothesized that this would affect the position of acid pocket, particularly in patients with a small HH, by reducing the size of the hiatal hernia. In patients with a large HH, however, the acid pocket is continuously positioned above the diaphragm, reducing the potential of AZI to affect the position of the acid pocket. Based on previous findings, patients were divided in large HH (≥3cm) or small or no HH (<3cm) according to the size of the hiatal hernia. Seven patients had a large HH whereas 12 had a small HH.

The total number of reflux episodes is comparable in the two groups (249 in L-HH patients, and 245 in S-HH patients). In L-HH patients, the acid pocket was located above the diaphragm in 45% of reflux episodes, and 99 (91%) of these reflux episodes were acidic. In S-HH patients however, the acid pocket was mostly located below (63%) or at the level (29%) of the diaphragm.

In large hiatal hernia patients AZI reduces the rate of acid reflux from 69% to 62%. In small hiatal hernia patients, AZI reduces the rate of acid reflux from 38% to 17%, which is a significantly larger effect compared to in large hiatal hernia patients. (p<0.05, GEE). (Figure 5)

In S-HH patients treatment with AZI led to a significantly smaller mean hiatal hernia size prior to reflux episodes compared to placebo (2.5 ± 0.3 cm vs 2.1 ± 0.2 cm, p<0.05 LMM). In line with this, the hiatus hernia was more often in the reduced state during AZI treatment compared to during placebo. (Figure 5) As a result, the acid pocket in S-HH patients was more often located below the diaphragm during treatment (69 ± 8% vs 53 ± 8% of reflux episodes respectively, p=0.01, GEE). (Figure 4)
Most acid reflux episodes occur starting from 10-15 minutes postprandial till 60 minutes postprandial (A). In this period, the acid pocket has its most proximal position. Azithromycin leads overall to a more distal position of the acid pocket compared to placebo (B). In figure 3C the acid pocket position relative to the crural diaphragm is shown when the subdivision in small and large hiatal hernia is made, demonstrating that the observed effect on altered acid pocket position mainly results from patients with a small hiatal hernia.

Figure 4
**DISCUSSION**

In the present study we showed that Azithromycin reduces acid reflux episodes and esophageal acid exposure in GERD patients. This effect is mainly caused by a more distal position of the acid pocket, probably resulting from a reduction of the hiatal hernia size. These findings provide further insight in the role of the acid pocket and its position in the composition of the refluxate, and provide an additional mechanism explaining the beneficial effect of motilides and perhaps other prokinetics on gastroesophageal reflux.
After meal intake, gastric acid floats on top of the ingested food also referred to as the acid pocket. We recently provided evidence supporting the hypothesis that this pocket functions as a reservoir from which acid refluxes into the esophagus, especially if the pocket is located above the diaphragm or in the hiatus.\textsuperscript{5} The present study confirms that the risk for having acid reflux is strongly determined by the position of the acid pocket relative to the diaphragm. We indeed found that only 11\% of the reflux episodes were acidic when the acid pocket is located below the diaphragm, in contrast to 91\% when the pocket is positioned above. As we previously demonstrated that the position of the acid pocket is largely determined by the presence of a hiatal hernia, accurate recording of the position of the hiatal hernia is of great importance when evaluating the interaction between hiatal hernia, acid pocket and reflux. This is particularly of importance in patients with a small or no hiatal hernia, as concurrent pH-impedance and HRM recording elegantly showed that a hiatal hernia is a dynamic entity, i.e. it appears and disappears in time, thereby largely determining the risk to have acidic reflux.\textsuperscript{11,17} When the hiatal hernia is in the reduced state, i.e. no separation between LES and diaphragm, the risk to have acidic reflux is 2 to 4-fold lower compared to when the hernia is in non-reduced state.\textsuperscript{11,17} Using the same methodology, but combined with continuous recording of the acid pocket, we were able to study the dynamics of the acid pocket (in contrast to pH pull-through studies) and hiatus hernia in great detail during a prolonged period of time. Hence, we could demonstrate that spatial separation of the LES and crural diaphragm (hiatal hernia size) is indeed larger prior to acid reflux events compared to weakly acid reflux events, and that a reduction in hiatal hernia size results in a more distal position of the acid pocket relative to the diaphragm. When the hiatal hernia is in the reduced state, the acid pocket is more often located below the diaphragm, and the risk for acidic reflux is lower (30\%) compared to when the hernia is in a non-reduced state (59\%). These data confirm that the position of the acid pocket and the size of the hiatal hernia are closely related and are major risks factors to have acid reflux or GERD.

Clinically, the relation between GERD and a hiatal hernia is evident as hiatal hernia size correlates excellent with esophageal acid exposure and esophageal damage.\textsuperscript{11,18,20} Accepting that the position of the acid pocket largely determines acidity of the refluxate, drugs reducing the hiatus hernia or move the acid pocket more distally should result in reduced acid exposure. To this end, GERD patients were treated with Azi, a broad spectrum antibiotic with prokinetic properties, previously shown to reduce acid reflux in lung transplant patients.\textsuperscript{6} In the present study, we showed that also in GERD patients Azi treatment decreased the number of acid reflux episodes and acid reflux exposure, but increased non-acid reflux. Hence, the total number of reflux events remained unchanged, in line with the finding that Azi had no effect on TLESRs, the main mechanism underlying GOR.\textsuperscript{12} Instead, Azi significantly reduced hiatal hernia size. This effect was mainly observed in patients with a small hiatal hernia (<3 cm). This was confirmed by the observation
that hiatal hernia was in a reduced state in 59% of reflux episodes during Azi compared to 33% during placebo in these patients. In patients with a large hiatal hernia (≥3 cm) Azi however failed to affect the hiatal hernia (reduced vs separated) or alter the position of the acid pocket, most likely explaining the larger effect on acid reflux rates in patients with a small hiatal hernia.

The exact mechanism by which Azi affects the hiatal hernia and acid pocket position is unclear. Motilides such as Azi and erythromycin act on motilin receptors on nerves and smooth muscle cells mediating an overall prokinetic effect.6,12 In the proximal stomach and distal esophagus motilides therefore enhance motility leading to increased proximal gastric tone and LES pressure, presumably via a cholinergic pathway.22-24 One could speculate that increased tone reduces proximal stomach volume, thereby reducing hiatal hernia size forcing the gastric content and acid pocket more distally. This effect is mainly observed in patients with a small HH, as illustrated by the increase in the reduced state of the HH. In contrast, in patients with a large HH, the separation of the LES and the crural diaphragm is too large for the HH to be reverted into the reduced state.25-27 Alternatively, Azi accelerates gastric emptying and improves mixing of stomach contents, potentially affecting acid pocket properties.24,28 Lastly, reduction in acid secretion by Azi could have contributed to the reduced number of acidic reflux events. However, no effect of Azi on acid pocket width and length was observed in our study. It should be emphasized though that our scintigraphic technique is not sensitive enough to detect subtle changes in acid secretion. Hence, we cannot exclude this possibility. A limitation of our study is that we only analysed one dose of Azi. However, due to the nature of the recording methods and the burden of these techniques, we choose to use one low dose comparable to the earlier study on this subject.8 Another possible limitation of our study is that we did not assess gastric emptying.

Our findings provide additional evidence for the importance of the position of the gastric acid pocket as a risk factor for acidic reflux. In addition, our study confirms that the gastric acid pocket may represent a possible target for GERD therapy.28-30 Finally, we provide evidence that distal migration of the acid pocket and increased time of the hiatal hernia in the reduced state are new potential explanations for the effect of prokinetics on acid exposure, although the effect of affecting the pocket position was rather limited and primarily observed in patients with a small hiatal hernia. The effect of motilin agonists and other prokinetics on gastroesophageal parameters has been investigated more extensively in earlier studies showing a reduction in proximal extent of the refluxate, accelerated gastric emptying and increased LES pressure as potential mechanisms explaining the reduction in acid exposure.8,31-35 Although a 30% reduction in acid reflux episodes and esophageal acid exposure as observed in our study is a large beneficial effect, earlier therapeutic studies with prokinetics have demonstrated a rather small effect on GERD symptoms.36-38 Our results indeed provide evidence for a new potential explanation of the effect of prokinetics on
acid exposure, but whether treatment with prokinetics in GERD leads to a reduction in symptoms remains to be studied.

In theory, therapeutic strategies directly intervening with the composition of the acid pocket may possibly prove more efficient in preventing acid reflux events. Recent studies indeed show that antacid-alginate formulations effectively eliminate or displace the acid pocket, by formation of a raft in the proximal stomach.\textsuperscript{30,40} We hypothesize that this intervention will be successful in S-HH as well as in L-HH patients, as antacid-alginate formulations reduce acid reflux events in patients with and without a hiatal hernia.\textsuperscript{41}

In conclusion, this study demonstrates that Azi reduces the number of acid reflux events and esophageal acid exposure in GERD patients, especially in patients with a small HH. We hypothesize that this effect results from relocation of the acid pocket to a more distal position and a concomitant reduction in hiatal hernia. These data indicate that modulation of the position of the acid pocket has an impact on the acidity of the refluxate, further confirming the importance of the acid pocket in the pathogenesis of GERD.
REFERENCE LIST


