

GERD

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Good morning everyone. My name is Nick Shaheen. I'm from the University of North Carolina. I picked ten abstracts to discuss and then another ten that I thought made for interesting reading. The ones I selected for you today I picked based on two criteria. I thought they challenged a current paradigm and had a decent chance of changing your clinical practice if not immediately, then some years down the road.

Abstract 219189: "What is the optimal initial therapy duration for patients with suspected GERD-related laryngitis?"

This is by Mike Vaezi's group. Mike has been trying to sort out the horrible morass of extraesophageal reflux disease. He is first author of a randomized controlled trial of high-dose proton pump inhibition vs. placebo in patients with ENT symptoms who did not have heartburn and showed that high dose proton pump inhibition was no better than placebo. It was published in the journal *Laryngoscope*. The question he asks is, "How long do you really need to give a therapeutic trial of PPI in extraesophageal reflux?" As you know, the standard dictum is to give an empiric trial of PPI for an extraesophageal reflux symptom for three to six months. Extraesophageal symptoms - hoarseness, chronic cough, lump in the throat - do not respond as quickly as heartburn to proton pump inhibitors. We're in a quandary because we don't have a good diagnostic test for extraesophageal reflux disease. Twenty-four hour pH has only a weak correlation to symptom response so we can't use traditional parameters like we use for classic heartburn. Proximal pH probe analysis is almost no better than a coin flip. A pharyngeal pH electrode; a three-channel probe that measures pharyngeal acid exposure, is not helpful either.

Investigators in this trial took 47 patients with ENT symptoms. These consisted of throat clearing, hoarseness, cough, etc. and patients were put on BID PPI for four months. These patients kept symptom diaries. They also used (this is one of the weaknesses of this study) a scale of 1-4 for symptom severity. They could have probably done a little better with that because there are some validated scales looking at some of the symptomatology. They had a 92% symptom response for primary throat symptoms, which is better than most studies. There is a high degree of heartburn and regurgitation in this group so that probably accounts for the high response. The most important finding is that it occurred at 30 days. What this group is saying, at least for these throat symptoms is 30 days of empiric therapy is probably enough. If you're not seeing improvement, you can probably stop. The major weakness of the study is the lack of a validated symptom score. Tough to use for multiple symptoms but it would have strengthened this study.

Abstract 218337: “Acidification of distal esophagus increases cough reflex sensitivity in patients with gastroesophageal reflux disease (GERD) and chronic cough”

This is by a group from Slovakia. This was funded by the Slovak National Research Grant. This group asked the question, “What’s the mechanism of GERD-induced cough?” By way of background, what we know so far about GERD-induced cough is that it occurs by one of two mechanisms. One is microaspiration, which is probably a minority of patients. The second, probably more common cause is a vagally mediated reflex by which patients reflux acid in the distal esophagus, activate the vagus nerve, get bronchoconstriction, and get a cough reflex on the basis of that. That is also perhaps the same mechanism for GERD induced asthma. At any rate, those are the two postulated mechanisms. This group had eight patients with GERD plus cough and 18 patients with GERD without cough. They infused the patients with either 0.1N hydrochloric acid or saline through an NG tube. They asked the question, “Does it matter what fluid the distal esophagus is seeing in terms of how easy these patients cough?” They also did capsaicin inhalation. If anybody in this room inhales enough capsaicin, they will cough. Our pulmonary colleagues use this as an inducing test for cough variant asthma. The question was, “How much capsaicin does it take to induce cough based on what is infused?” This is a bit complex. The outcome of interest was how much capsaicin it takes to cough. They found that in the GERD plus cough patients, it took half as much capsaicin to make them cough as the patients who had GERD without cough when their distal esophagus sees acid. The take-home point is that if you acidify the distal esophagus in the patients that have GERD and cough, you can get them to cough much easier. This fits in well with the literature that’s out there and further clarifies this vagal reflex.

Abstract 215958: “Targeted esophageal biopsies: What you see is what you get (WYSIWYG) or not?”

The question here is an important one. I do a lot of studies in Barrett’s esophagus and one thing we commonly will do is targeted biopsies, usually as part of a surveillance protocol. The question here is, “How much can you rely on the accuracy of the biopsies?” Somebody says, well we biopsied around the Z line – how good are we at that? How likely is that to be reproducible? This work is still in progress so this is interim data. Fifty patients with erosive esophagitis, 150 patients with GERD, and 150 patients with dysphagia were biopsied at seven sites. In the abstract, they don’t outline all seven sites but what they do tell us is that they take two from the Z line and one from any mucosal breaks that they see in the esophagus. They rate whether or not the biopsies from the Z line have both columnar and squamous epithelium and if a biopsy from the mucosal breaks had signs of inflammation. They found that in only 18% of patients, both of the Z line biopsies had columnar and squamous tissue. Overall, only about one third of the biopsies from the Z line hit both sides of the Z line. The numbers were similar for mucosal breaks. About one-third of the patients that were biopsied in the mucosal break actually had the biopsy hit the mucosal break. The implication of this is that we are not very good at this. Secondly, if you get somebody referred to you or you see someone that you’ve evaluated previously, where you’ve taken a biopsy and the biopsy doesn’t yield the nodular tissue that you thought you had, sampling error is probably a bigger risk than you first appreciated, and it may be worth going back again. This may be very important in Barrett’s surveillance.

Abstract 216880: “The diagnostic value of proton pump inhibitor test for gastroesophageal reflux disease: A population-based study”

For the vast majority of primary care physicians in the United States, when a patient comes to their office complaining of uncomplicated GERD symptoms – empiric proton pump inhibitor is prescribed. The idea is that a therapeutic trial of proton pump inhibitors is as good as any other diagnostic test we have for diagnosing GERD. The question this group in The Netherlands is asking is, “How good is the PPI test in terms of sensitivity and specificity?” If a test is very sensitive, that means that the test is positive in the

vast majority of those who have disease. If the test is specific, the test is negative in the vast majority of those who don't have disease. Obviously, you want good operating characteristics – you want both a high sensitivity and specificity. This group entered 90 patients with GERD symptoms for at least two times a week for three months. Most of these patients were recruited by advertisement. They did 24-hour pH probe testing. From that testing, they calculated the symptom association probability (SAP). If you are not familiar with this, you should be. The symptom index is the number of symptoms associated with reflux divided by the total number of symptoms. So, if I cough 20 times during a pH probe study and 15 of those coughs are accompanied by a reflux event, my symptom index is 75% - 15 divided by 20. The problem with symptom index is if I cough once during that study and it is accompanied by reflux, my symptom index is 100%. If you go to get a pH test from your gastroenterologist tomorrow, he or she will likely send a symptom index to your primary care doctor. This is what is popular in America because it is easily understood. Perhaps a better way to look at symptomatology is SAP. What SAP does is it asks the question, for every interval, for each very short period in this test (sometimes intervals are two minutes long, sometimes five minutes long) we can classify that interval in one of four boxes. It can be reflux – yes/no, it can be symptoms – yes/no. You're having a test. Five minutes of the test is timed. During that five minutes, you have no symptoms. You have no reflux. That five-minute interval goes in the no/no box. You have cough. With that cough, you have a reflux event. That interval goes into the yes/yes box. For the whole study, it is calculating and putting ticks into these boxes. At the end of the day, looking at these bins – how many intervals have been classified – what we want to see, if the symptoms are caused by reflux, is all the ticks being concentrated into these two boxes – yes/yes, no/no. That indicates a high symptom association probability that this patient has a symptom that is being caused by reflux. Generally speaking, a symptom association probability of greater than 95% is significant. That's what they did for these studies. In the 90 patients, the SAP was calculatable in only 74. I'm not sure why they failed in so many.

The questions they had were, “What's the sensitivity and specificity of the PPI therapy? Did the SAP correlate with the patient's ability to get better on PPI therapy?” They found that the sensitivity was actually pretty good. If the pH probe said that you had disease, the likelihood was that you were going to respond to PPI therapy – 92%. On the other hand, unfortunately, the specificity was poor. The specificity in this group was only 28%. In other words, the PPI test said yes to a lot of people without disease. That has some implications when you think about it. What primary care physicians do now is they hand you a script and say here, take this for one month or two months. If you respond, you have GERD and we will continue it chronically. If you don't respond, you don't have GERD and we'll put you on a treadmill and do other tests for cardiac work up, etc. The point of this study is that at least in this high prevalence group, this is probably inappropriate therapy. If your PPI test is positive, there is still a good chance you do not have pathologic reflux. We'll see how this plays out. People have looked at this a variety of times before and it punched a few holes in this whole PPI test idea. I'm not too sold on this data. I think it is probably still the best thing to do, but it is clearly not as good a test as we initially thought it was.

Abstract 221233: “The relevance of duodenogastroesophageal reflux and its diagnosis”

The idea behind this abstract is looking at the importance of duodenal gastroesophageal reflux (DGER). We debate how much bile really has to do with reflux disease. The question behind this abstract was, “Can you tease out the differences between bile exposure and acid exposure in terms of the mucosal abnormality they cause?” It's difficult to do. The reason it is difficult is that bile almost always accompanies acid. As disease severity goes up, the likelihood that you reflux bile goes up, but the amount of acid you reflux goes up too. They march hand in hand. If you reflux very little acid, you're not likely to reflux much bile. If you reflux a lot of acid, you are probably refluxing bile and you are probably going to have a more severe mucosal lesion. Is the bile causing that lesion or is the bile along for the ride? We know that the main mechanism by which the bile gets up into the esophagus is gastric secretions. If you

have a lot of gastric secretions refluxed, you're going to have a lot of bile reflux. If you have relatively little acid reflux, you're not going to get too much bile. It's difficult to know if bile is just a bystander or if bile is really a causative agent here. You can see why both might be possible. What does bile do? Bile is a detergent. Bile breaks down phospholipid bilayers. So, a lot of bile in the chest could be a bad thing. On the other hand, how many of you clinicians have gone down in the stomach and seen a bile stained stomach? They've had absolutely no GERD. We do know that lots of people just get bile in their stomach. It's not hard to imagine that this is just along for the ride. So, if you think about it for a second, the patients that are going to be informative are those with lots of acid and no bile in their esophagus and patients with lots of bile and no acid in their stomach. If you want to tease apart the effect, you're going to want to see the extremes of patients that only have one entity in their esophagus to see if it does have a difference.

They looked at 217 patients evaluated for GERD symptoms, tested with 24-hour pH Bilitec testing, 63 of the 217 had acid reflux alone, 20 had bile reflux alone, and 70 had bile and acid reflux and 64 had no reflux. Interestingly, there was no difference in bile exposures with respect to the likelihood of developing Barrett's esophagus or erosive disease. Those who had erosive disease had more bile than if you had NERD. The take home point here was that DGER, in this study, was not a factor in the development of mucosal pathology. This is a little bit at odds with data from the Cleveland Clinic and some other places that have suggested that there are increased amounts of bile after controlling acid amounts in patients who have Barrett's esophagus.

Abstract 220246: "Do we finally understand the underlying mechanism of increased reflux during TLESRs in GERD patients?"

This is a study from The Netherlands and Australia. The authors looked at pressure gradients across the EG junction during and three minutes prior to a transient lower esophageal sphincter relaxation (TLESR). They had 18 healthy controls, 17 patients with GERD, studied with high-resolution manometry catheter and esophageal pH. They monitored pressure in the chest and pressure in the stomach. Remember that intrathoracic pressure is below gastric. They are looking at the seconds leading up to a TLESR. What you see is that the patients with GERD and the healthy controls have about the same pressures in the chest. That makes sense unless you are grossly obese and have a lot of fat; you're not going to have to generate real negative pressures to get a breath so you have relatively small intrathoracic pressures whether you have GERD or whether you do not. What they noticed, though, which was interesting is that the GERD patients have higher intragastric pressure and thus, a greater difference in intragastric pressure relative to intrathoracic than controls during and up to 180 seconds before a TLESR. Water rolls downhill. It rolls down a pressure gradient. TLESR, the pressure gradient, was greater in GERD patients, which they postulate is responsible for reflux. There are a lot of questions about this study. The immediate one is how obese are these people? Maybe there are other mechanisms at play here. Maybe this is an anatomic issue. We've become much more interested in intraabdominal fat. Maybe not so much how fat you are, but where you wear your fat that may be important. This opens up at least as many questions as answers. For years we've known about this issue about TLESRs being more likely to have reflux associated in GERD patients, but we haven't known why. These are the first guys that, to my knowledge, have made an effort to understand this.

Abstract 222856: "Effects of high dose PPI (rabeprazole) on laryngopharyngeal reflux disease: A prospective, double blind, randomized controlled study"

The Vaezi study discussed before is probably the best data in this field. This was a randomized controlled trial in 30 laryngopharyngeal reflux (LPR) patients. Each LPR symptom - hoarseness, lump in the throat, cough, clearing throat, sore throat, burning throat, breathing difficulties or choking, and mucus in the

throat was scored 0-5 using VAS before and at the end of treatments. They all had 24-hour pH monitoring and videolaryngoscopy. After 12 weeks of BID rabeprazole, the symptom score for the treatment group was 4.2 ± 1.6 , significantly improved when compared to placebo (8.7 ± 1.3 , $p < 0.05$). However, all of the improvement that they did see occurred in those who had a positive 24 hour pH probe. There was no significant improvement in the group with normal esophageal acid exposures. Additionally, the laryngoscopy was not helpful in differentiating placebo and treatment group – they both improved similarly after the 12 weeks.

Taken with the results of the earlier study from Vaezi et al., I think that it is fair to guess that if subjects have only a possible extra-esophageal symptom of reflux, with no heartburn and a normal pH study, the likelihood of a response better than placebo to therapy with PPI is small.

Abstract 217140: “Positive association between intragastric and intraesophageal acid control and healing of Los Angeles Grade C and D erosive esophagitis: Results of a prospective, controlled clinical trial”

This is a study that needed to be done for a long time. There’s a large amount of data with PPI’s that shows how well intragastric acid is suppressed. What we haven’t had until now were data linking intragastric acid control with esophageal mucosal healing. Every time we refer to one of these intragastric pH studies, we would always have to include the caveat that these surrogate marker studies don’t tell us how this impacts esophageal healing. So, this study was designed to do look at that. Patients with erosive disease were randomized to 10 mg or 40 mg of esomeprazole. These two doses were picked to be sure that some patients, especially those on 10 mg, would still have acidic gastric contents. It was expected that both groups would heal but some probably slower. The authors found that patients who healed their erosive esophagitis had better acid control over 24 hours than those who did not. It correlates, for the first time, intragastric studies to esophageal healing.

Abstract 225811: “Predictive factors of long-term outcome after antireflux surgery (ARS). A community practice experience”

Antireflux surgery has been increasing in the U.S. There are many places in the country that have formed heartburn centers where you come in, you see a gastroenterologist, you see a surgeon, and the likelihood of getting a Nissen is quite high. The number of proficient laparoscopic surgeons in this field is increasing. The question is, “How good are the outcomes?” Most of the studies we have on outcomes come from tertiary care centers who do Nissens very well and do many. Their results are spectacular. Two years out, 90% of these patients are off medicine, and have very high satisfaction rates. We have relatively few community studies in low volume centers; people that do five procedures or less a year. These are incredibly important because although the number per surgeon is low, the total number done in the U.S. in the low volume centers is higher than the high volume centers. We have only a couple of studies looking at community experience. There was a community-based study in the *American Journal of Medicine* several years ago which showed poorer results, lower satisfaction rates, and higher rates of recurrent reflux than tertiary centers.

This is a study from France asking the same kind of question. What kind of outcomes do you get with this in a community practice? One hundred and twenty-one patients referred from 33 surgeons had a pH probe, calculated symptom association probability and the symptom index, had a Nissen fundoplication, and were followed for a mean of 43 months. Only 58% of patients reported good or excellent outcome. They also looked at the predictors of a good and bad outcome. They included a number of predictors and after they adjusted, the only two predictors of good outcome are male gender and abnormal esophageal acid exposure on pH study.

The take homes are that we should only operate on patients with GERD who have an abnormal pH in particular. It is not clear whether the authors specifically looked at PPI response as a predictor.

Abstract 219280: “New Barrett’s epithelium after the healing of erosive oesophagitis – Prospective endoscopic and histological assessments”

They took 120 patients that had esophagitis, endoscoped them after they healed their esophagitis, excluded 15 patients who already had Barrett’s and followed the remaining 105 patients prospectively, to determine their likelihood of developing new Barrett’s. The authors found pathologic evidence of Barrett’s in six patients (8.6%) with median follow up of 52 months. What the authors do not tell us are the endoscopic findings in the group or where they were biopsied.

Abstract 209783: “Predictors for treatment failure of on-demand proton pump inhibitor (PPI) therapy in gastroesophageal reflux disease (GERD)”

The question here was, “If you want to give patients on demand PPI therapy, who is going to do well with it and who is not?” Patients with weekly heartburn or regurgitation and erosive esophagitis grade A or normal were included. Esomeprazole 20 mg was given for eight weeks. Those with complete resolution of symptoms were enrolled in an open-label on demand treatment for 26 weeks. Treatment failure was defined as the need for esomeprazole for greater than or equal to 75% of the time for satisfactory control of symptoms at 26 weeks. What they found was that those with coexistent functional dyspepsia, daily symptoms, or a positive Bernstein test were likely to relapse with on demand therapy. NERD patients relapsed more frequently (36.3%) compared to grade A erosive patients (20.3%, p=0.02).

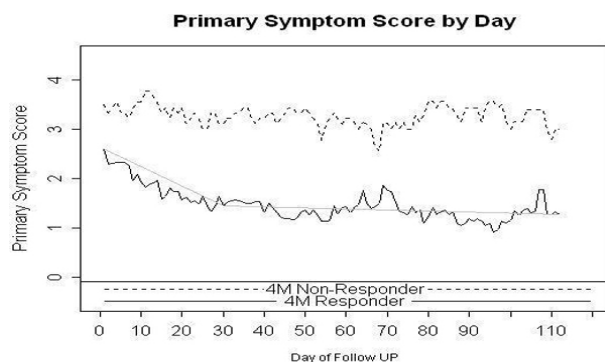
The take home points of this are that many of the patients who try on-demand are going to end up going back to daily or at least three to four days/weeks of treatment. There are predictors of patients in whom it may not even be worth trying on demand therapy.

We’ve come to the end of the session. Thank you for coming.

Abstracts discussed

219189: What is the Optimal Initial Therapy Duration for Patients with Suspected GERD-Related Laryngitis? Michael F Vaezi, Rocio Lopez, Douglas Hicks, Thomas Abelson, Claudio Milstein

Objective: ENT and GI literatures currently recommend initial PPI therapy of at least 3-4 months in pts suspected with GERD-related laryngitis. However, there are currently no well designed studies in support of such recommendations. Thus, the aim of our study was to assess the optimal treatment response duration for this group of patients. Methods: Pts with suspected GERD-related laryngitis based on chronic throat symptoms and laryngoscopic findings were enrolled. Questionnaire assessed the presence/severity of throat symptoms and heartburn. Symptom severity scored using a scale of 1 to 4 [1=rare (once a month or less); 2=occasional (once a week or less); 3=frequent (several times a week); 4=all the time (several times daily)]. Subjects kept daily symptom diaries of the primary throat symptom and heartburn during 4-months of BID PPI therapy. Greater than 50% primary symptom improvement from baseline defined symptom response. Results: 47 Patients enrolled (median age: 49 yrs, IQR: 44.0 - 65.0; 76% Caucasian; 34% male). Daily symptom diaries were complete in 43 (91%) patients. 34/43 (79%) patients responded to therapy. The most common presenting throat symptoms (prevalence, median severity score) included: throat clearing (84%, 2.8), hoarseness (80%, 3.0), and cough (71%, 2.3). Heartburn (65%, 2.4) and regurgitation (55%, 2.1) were present in nearly half of pts. Maximum (92%) symptom response to therapy was achieved by 30 days for the primary throat symptoms (Figure) and by 18 days for heartburn (Figure 2). Conclusions: 1) In patients with suspected GERD-related laryngitis one month of therapy is adequate to assess response to therapy. 2) In those unresponsive to PPI therapy after one month the likelihood of symptomatic response with continued PPI therapy does not justify the cost.

**218337: Acidification of Distal Esophagus Increases Cough Reflex Sensitivity in Patients with Gastroesophageal Reflux Disease (GERD) and Chronic Cough.** Nikolaeta Javorkova, Renata Pecova, Silvia Varechova, Michal Demeter, Rudolf Hyrdel, Dusan Balaz, Milos Tatar, Marian Kollarik

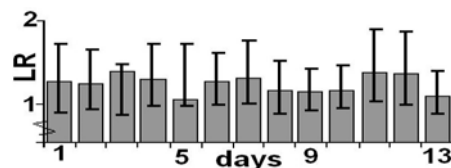
BACKGROUND & AIMS: Gastroesophageal reflux ranks among the most important causes of chronic cough, however, the mechanisms by which gastroesophageal reflux initiates coughing are incompletely understood. It is generally accepted that hyperexcitability of the cough reflex (increased cough reflex sensitivity) results in coughing. Here we address the hypothesis that acidification of distal esophagus increases the cough reflex sensitivity in patients with GERD and chronic cough. **METHODS:** Eight consecutive patients with GERD complaining of chronic cough (cough persisting for >8 weeks) and 18 gender- and age- matched patients with GERD without cough were recruited. GERD was confirmed by positive fibroscopy and/or pH monitoring. In a randomized double blind study, saline and acid (HCl 0.1M) were separately infused into distal esophagus via nasoesophageal catheter (10ml/min, 15 min). The infusions were separated by at least 20 min. Cough reflex sensitivity was determined immediately after completion of each infusion using standard capsaicin inhalation challenge (single-breath inhalation of the aerosols of capsaicin solutions with doubling concentrations, from 0.49 μ M to 500 μ M). The cough reflex sensitivity was expressed as the lowest concentration of capsaicin evoking 2 coughs (C₂). Group data were expressed as median (interquartile range). **RESULTS:** Infusion of acid but not saline into distal esophagus induced mild heartburn and/or chest discomfort in 7/26 patients. In patients with GERD and chronic cough, infusion of acid into distal esophagus increased cough reflex sensitivity [1.95 (0.98-15.6) μ M after saline vs. 0.98 (0.49-1.95) μ M after acid, $p < 0.05$]. In contrast, infusion of acid into distal esophagus in patients with GERD without cough had no effect on the cough reflex sensitivity [15.6 (7.81-46.88) μ M after saline vs. 31.25 (4.88-125) μ M after acid, $p > 0.5$]. **CONCLUSIONS:** We conclude that acidification of distal esophagus induces the cough reflex hyperexcitability in patients with GERD and chronic cough. We speculate that this phenomenon (likely mediated by vagal nerves) underlies chronic cough due to gastroesophageal reflux. Absence of this phenomenon in patients with GERD who do not complain of cough further supports this notion. Supported by Slovak National Research Grant VEGA 1/2273/05.

215958: Targeted Esophageal Biopsies: What You See Is What You Get (WYSIWYG) - Or Not? Robert H Riddell, Vijay Mann, Paul Moayyedi, SJO Veldhuyzen van Zanten, Janusz Jankowski, Marc Bradette, Jacob Louw, Garth Noad, Robert J White, David Armstrong

Background: Evaluation of esophageal epithelial histology for features of gastroesophageal reflux disease (GERD) has shown regional variations related to the distance from the Z-line, anterior or posterior location and proximity to mucosal breaks (MB). Discrepancies between histological and endoscopic findings for MB and Barrett's esophagus (BE) have been attributed to deficits in endoscopic recognition of lesions but discrepancies may also indicate the difficulty of acquiring targeted biopsies in the esophagus. If the latter is true, the accuracy of biopsies from the Z-line (readily recognized at endoscopy) and MB should be equivalent. Aim: To assess the accuracy of biopsy acquisition from the esophagus in GERD patients. Methods: An ongoing 6-month, open-label, multicentre trial planned to recruit patients from tertiary care with heartburn and erosive esophagitis (EE: n=50), nonerosive reflux disease (NERD: n=150) and heartburn non-dominant dyspepsia (HND: n= 150). At baseline endoscopy, biopsies were obtained from 7 sites, including 1 each from the Z-line anterior & posterior locations, and, in EE patients, from the edge of an MB. Histological assessment evaluated the accuracy of acquisition of biopsies by determining the proportions of (a) Z-line biopsies that contained both columnar mucosa (CM) and squamous epithelium (SE) and (b) MB biopsies that showed features of an erosion or MB. Results: To date, 145 patients have been enrolled - EE: 50, NERD: 50, HND: 45. Evaluable Z-line biopsies are available from 145 patents (290 biopsies) and MB biopsies from 49 patients (49 biopsies). In 26/145 patients (18%), both Z-line biopsies showed both CM and SE and in another 45 (31%), one Z-line biopsy showed CM and SE; overall, 97/290 (33%) of biopsies were acquired accurately from the Z-line. In 3/49 (6%) patients, histology showed fibrinopurulent exudates consistent with an erosion and in another 12 (24%), there were features of regeneration; overall, 15/49 (31%) were acquired accurately from an MB. Conclusions: "WYSINotWYG" Although the accuracy of biopsy acquisition from the Z-line and MB was comparable, acquisition of targeted biopsies in the esophagus was accurate in only about one-third of cases; this appears to be related to technical difficulties in targeting specific lesions rather than failure to recognize the lesions although a true mismatch between the endoscopic and histological features or mucosal breaks cannot be excluded. These results have implications for the conduct of clinical studies, for accurate biopsy acquisition from the lower esophagus and cardia, for endoscopic surveillance in patients with BE and, possibly, for endoscopy training.

216880: The Diagnostic Value of the Proton Pump Inhibitor Test for Gastroesophageal Reflux Disease: A population-based study. Marissa C Aanen, Bas L Weusten, Mattijs E Numans, Niek J de Wit, Andre J Smout

Introduction General practice guidelines often suggest as diagnostic tool for GERD the symptomatic response to a short course of proton pump inhibitor (PPI test). Our aim was to re-determine the diagnostic abilities of the PPI test by using the most relevant reference test, the symptom association probability (SAP), in a primary care population. Methods Subjects suspected of GERD who had heartburn complaints for at least twice a week during at least 3 months were recruited from primary care, either during consultation or by advertisement. After a 24h pH recording with calculation of the SAP, subjects started using 40 mg esomeprazole once daily for 13 days. The PPI test was considered positive when the subjects reported that their symptoms were adequately suppressed. Sensitivity, specificity and positive likelihood ratios (LR) were determined daily for each PPI test day. Results A total of 90 subjects were included (1/3 consultation, 2/3 advertisement). Successful 24h pH recording was accomplished in 84 subjects and the SAP was calculable in 74. The median age was 51 yr (IQR 41- 62), and 62% was male. The SAP was positive in 70% of the subjects. The sensitivity of the PPI test was 92.2% (87.4-93.5) and the specificity was 28.6% (19-33.3). The LR was low (1.3 (1.2-1.4)) and fairly constant during the 13 days (figure). Conclusion The sensitivity of the PPI test for diagnosing GERD is high, but its specificity low. The low LRs observed from day 1 to day 13 indicate that the PPI test does not change the high pre-test probability (70%) of GERD found in primary care patients with heartburn. Thus the additional value of short term treatment with a PPI for diagnosing GERD in primary care is relatively poor even with the most adequate reference test SAP.



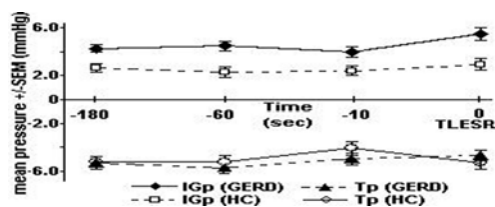
221233: The Relevance of Duodenogastroesophageal Reflux And Its Diagnosis. Ulrich Muller, Patrick Darb-Esfahani, Thomas Fiedler, Sarah Johanssen, Daniel Kottler, Heike Muller, Herbert Lochs, Winfried A Voderholzer

Introduction: Duodenogastroesophageal reflux (DGER) is a common finding in patients suffering from gastroesophageal reflux (GER) symptoms and has been accused to be an important factor in the pathogenesis of Barrett's esophagus. However, data on large samples are rare. Aim: To elucidate whether or not DGER results in specific symptoms or Barrett's esophagus. Methods: We conducted a retrospective analysis of patients undergoing semiquantitative esophageal 24h-bilirubin measurement

(Bilitec™) for evaluation of GERD between 2000 and 2005. All patients were evaluated by a standardized reflux symptom questionnaire (which included heartburn, regurgitation, dysphagia, odynophagia, nausea, vomiting, cough, asthma, sore throat, thoracic pain, problems with nose and ears, abdominal pain, and other problems) and underwent esophageal manometry, 24hour pH-metry (partially double probe measuring), and esophagogastroduodenoscopy (EGD). Pathologic DGER was defined as the percentage time with bilirubin absorption > 0.2 exceeding 10.7%. Results: We included 217 patients (54.4±12.9 years; 95 female, 139 male). Sixty-three of them had isolated acid reflux, 20 isolated biliary reflux, 70 combined reflux, and 64 had no reflux at all. There was no significant difference between patients in each group with regard to the development of erosive esophagitis (ERD) or Barrett's esophagus. In 42% of patients a pathologic DGER was found (mean DGER 31.0±17.6 %). On EGD, DGER positive and negative patients did not differ with respect to ERD (37.8% of all patients with DGER vs. 26.5% without, p=0.056) nor with respect to short segment Barrett (10.9% with DGER vs. 9.8 % without DGER, p=0.68) or long segment Barrett (13.9% with DGER vs. 8.3% without DGER, p=0.13). As expected, patients with ERD (n=122) had a significantly higher DeMeester Score than patients without esophageal erosions (65.3±60.0 for ERD vs. 30.6±36.7 for NERD, p=0.0001). However, ERD-patients suffered from significantly more DGER than NERD-patients (17.6±18.4% for ERD vs. 10.1±15.5% for NERD, p=0.004). DGER correlated with distal esophageal acid exposure time (r=0.432;p<0.0001) but not with proximal reflux (r=0.206;p=0.07 Spearman-rho test). Symptom evaluation did not find any association of DGER with reflux symptoms. Conclusions: Our data confirm the positive correlation of DGER with acid GER. Although DGER can be found in almost half of the patients with reflux symptoms there is no symptom indicative of DGER. Our study does not support the hypothesis that DGER is a relevant factor in the development of Barrett's esophagus.

220246: Do We Finally Understand the Underlying Mechanism of Increased Reflux During TLESRs in GERD patients? R Frankhuisen, MA van Herwaarden, RCH Scheffer, HG Gooszen, GS Hebbard, M Samsom

Background: Increased pressure gradients across the esophagogastric junction (Δ EGJp) are pivotal for the occurrence of reflux during TLESR. It remains unclear if Δ EGJp differs between GERD patients and healthy controls (HC). Aim: To investigate Δ EGJp (=intragastric (IGp) - intrathoracic (ITp) pressures), during and 3 min preceding a TLESR in HC and GERD patients. Patients and methods: 18 HC (10 men, mean age 28 (18-53)) and 17 GERD patients (10 men, mean age 50 (29-69)) were enrolled. One hour before and 2 hr after a liquid meal (500 ml/300kcal) combined esophageal pH and high-resolution manometry, using an assembly with 11 side holes spaced by 1 cm, positioned across the EGJ, was performed. The 2 side holes proximal to the upper and distal to the lower border of the EGJ were used to calculate mean ITp and IGp. Δ EGJp was analyzed during TLESRs and at 180, 60 and 10 seconds before. Statistics: repeated measures ANOVA. Results: Δ EGJp and IGp were increased in GERD compared to HC at all points in time for TLESRs irrespective of reflux and both for TLESRs with and without reflux (Δ EGJp: all p<0.05, IGp: all p=0.001). ITp was comparable in both groups at all intervals. Conclusion: An increased Δ EGJp caused by a higher intragastric pressure is responsible for the increased prevalence of GER during TLESRs in GERD patients. Lowering intragastric pressure might be a new strategy for the treatment of GERD.



222856: Effects of High Dose PPI (rabeprazole) on Laryngopharyngeal Reflux Disease: A Prospective, Double Blind, Randomized Controlled Study. Apichart Suramethakul, Permsarp Isipradit, Supinda Saengpanich, Sutep Gonlachanvit

Background : The role of high dose PPI on laryngopharyngeal reflux disease has not been well established. We performed a randomized, placebo-controlled, double blind, single center study to evaluate the effect of high dose PPI in patients with chronic laryngopharyngeal reflux symptoms. Methods: Thirty patients(8M, age 45±2 yrs, mean±SEM) with suspected of having laryngopharyngeal reflux disease for >12 weeks(median durations 15 mo(3-120) by ENT doctors were included. Each patient underwent a video laryngoscopy and a dual channel(15 cm apart), 24 hr esophageal pH testing before receiving either rabeprazole(R) 20 mg bid or placebo(P) for 12 wks. Each laryngopharyngeal reflux symptom including, hoarseness, lump in the throat, cough, clearing throat, sore throat, burning throat, breathing difficulties or choking, and mucous in the throat was scored 0-5 using modified visual analog scales before and at the end of treatments. Positive pH monitoring results for lower and upper esophagus were defined as %time pH<4 at lower esophagus >4 % and upper esophagus >1%, respectively. A positive pH test was defined as a positive result in either lower or upper esophagus. Results: The main symptoms were lump in the throat(n=20), sore throat(4), burning throat(5), and hoarseness(1). 16 patients had weekly typical GERD symptoms. 15, 15, and 18 patients had positive esophageal pH tests at lower, upper, and either lower or upper esophagus, respectively. The baseline symptom score for R(12.7±1.8) was similar to P(13.5±1.3, p>0.05). At the end of the 12th week, the symptom score for R was

4.2±1.6, significantly improved compared to P(8.7±1.3, $p<0.05$). Baseline symptom scores for patients with positive pH test in R and P group were similar(11.4±1.9 vs 14.2±1.9, $p>0.05$). R significantly improved the symptom scores compared to P at the end of the 12th wk(2.9±1.2 vs 9.7±1.7, $p<0.01$) in patients with positive pH tests. In contrast, the symptom scores for R and P group in patients with negative pH tests were similar at both baseline (14.5±3.4 vs 12.3±1.7, $p>0.05$) and the 12th wk(6.0±3.4 vs 7.2±2.4, $p>0.05$). Reflux finding scores(RFS) evaluated by video endoscopies were improved similarly in both R and P($p>0.05$). There was no significant different of RFS improvements after R or P irrespective of the pH results ($p>0.05$). Conclusions: High dose rabeprazole is superior to placebo for relieving ENT symptoms in patients with laryngopharyngeal reflux disease especially in patients with positive pH tests, but not in patients with negative pH tests. The dual channel, 24-hour esophageal pH monitoring is helpful for identifying patients who will have benefits from high dose PPI therapy.

217140: Positive Association Between Intra-gastric and Intraesophageal Acid Control and Healing of Los Angeles Grade C and D Erosive Esophagitis: Results of a Prospective, Controlled Clinical Trial. Philip O Katz, Gregory G Ginsberg, Paul Hoyle, Mark B Sostek, John Monyak, Debra G Silberg

BACKGROUND & AIM: Acid control has been considered to be a surrogate marker for clinical efficacy (EE [erosive esophagitis] healing and symptom control). However, the relationship between efficacy for EE healing and acid control has not been prospectively established. This study's aim was to assess the relationship between the percentage of time intra-gastric pH is >4 and the healing of EE, using an acid suppression drug. Also assessed was the relationship between intra-gastric acid control and gastroesophageal reflux disease (GERD) symptom control. **METHODS:** In this 28-site, double-blind, exploratory study (D9612L00062), adult patients with endoscopically verified Los Angeles grade C or D EE were randomly assigned to oral esomeprazole 10 or 40 mg once daily for 4 weeks. At treatment day 5, patients underwent a dual-electrode, intraesophageal and intra-gastric, catheter-based, 24-hour pH study. The electrodes were placed 5 cm above and 10 cm below the proximal border of the lower esophageal sphincter (15 cm apart). At 4 weeks, an endoscopist blinded to the pH study results assessed EE healing status. Investigators scored GERD symptoms before treatment and at 4 weeks, before the final endoscopy, as none (0), mild (1), moderate (2), or severe (3). Analyses included patients who satisfactorily completed the pH study and final endoscopy, and met predetermined protocol criteria. A t-test was used to compare the percentage of time pH was >4 for healed vs unhealed patients. Spearman rank correlations (r) and tests of significance were done for percentage of time pH was >4 and investigator-assessed symptom scores. **RESULTS:** Of 103 patients who had evaluable data (mean age, 48.7 years; 65% men), EE was healed in 69.9% at 4 weeks. Mean percentages of time intra-gastric pH was >4 at day 5 in patients with healed and unhealed EE were 61.3% and 42.1%, respectively ($P = .0002$). EE healing rates were positively related to the percentage of time intra-gastric pH was >4 . A post hoc analysis showed a significant difference in the percentages of time intraesophageal pH was >4 between healed and unhealed patients (95.2% and 88.9%, respectively; $P = .0059$). Better control of gastric acid was also correlated with lower final heartburn and acid regurgitation symptom scores ($r = -29\%$ and -21% ; $P = .003$ and $.032$, respectively). **CONCLUSION:** This is the first prospective study to show a positive relationship between intra-gastric and intraesophageal acid control and the clinical outcomes of EE healing and symptom control. These data support the importance of intra-gastric pH as a surrogate marker for drug efficacy. Supported by AstraZeneca LP

225811: Predictive Factors of Long-Term Outcome after Antireflux Surgery (ARS). A Community Practice Experience. Ronan Thibault, Sylvie Sacher-Huvelin, Veronique Seville, Stanislas Bruley des Varannes, Jean-Paul Galmiche

Background: Data about predictive factors of clinical outcome after ARS are scarce. Most studies were performed in tertiary referral centers. Quality of life (QOL) is considered as the main end-point for ARS assessment. We aimed to determine the factors predicting outcome after ARS in GERD patients managed in community practice. We choose QOL as the primary end-point for long-term assessment. Methods: We selected all consecutive patients referred to our laboratory between the 1st January 1995 and 31 December 2002 for 24-hour pH monitoring before ARS. Patients were referred by 33 surgeons, most working in district hospitals or private surgical centers. Patients were included only if there was clear evidence that acid reflux was responsible for symptoms, i.e. symptom index (SI) $\geq 50\%$ and symptom-association probability (SAP) $\geq 95\%$. Esophageal acid exposure (EAE) could be normal or abnormal ($\geq 4.2\%$). We included 121 patients (49 women, mean age 47±13 yr, 61 with erosive disease and 60 with non-erosive GERD). The laparoscopic approach was chosen in 96% and Nissen procedure in 85%. After ARS, QOL was measured with the French validated GERD-specific questionnaire, REFLUX-QUAL. QOL was considered good or excellent when REFLUX-QUAL global score was above 80. After univariate statistical analysis, variables independently associated with a score >80 were determined by a stepwise logistic regression. Results: After an average 43±19 month follow-up, 58% of patients reported a good or excellent post-operative QOL. Male gender (72% with score >80 vs 28% with score ≤ 80 , $P<0.001$), abnormal EAE (62% vs 38%, $P=0.02$), preoperative regurgitation (54% vs 46%, $P=0.04$), absence of preoperative dysphagia (63% vs 37%, $P=0.02$), PPI-dependence (68% vs 32%, $P=0.007$), SI $\geq 75\%$ (68% vs 32%, $P=0.02$) and history of GERD symptoms ≥ 4 yr (67% vs 33%, $P=0.04$) were significantly associated with a postoperative QOL score >80 . Only two factors were significantly and independently associated with an excellent post-operative QOL, namely male gender (OR=4.4; 95%CI [2.00-9.80], $P<0.001$) and abnormal EAE (OR=3.0; 95%CI [1.03-8.69], $P=0.04$). Conclusion: In community practice, good or excellent surgical results are reported in less than 2/3 of patients. These results are consistent with a similar study conducted in US*. Although only 2 variables were independently predictive of long-term outcome, our results strongly

support the recommendation of preoperative pH-monitoring assessment. 3) Patients with hypersensitive esophagus (normal EAE but positive SAP) are not good candidates for surgery especially those of the female gender (the most frequent situation in this case). *Vakil N et al. Am J Med 2003;114:1-5.

219280: New Barrett's Epithelium after the Healing of Erosive Oesophagitis - Prospective Endoscopic and Histological Assessments. *Ali S Taha, Margaret Balsitis, Wilson J Angerson, Frances Gallagher, Christopher G Morran*

BACKGROUND Epidemiological studies have considered a number of risk factors for Barrett's oesophagus including oesophagitis. However, prospective assessments have been lacking. We, therefore, aimed at studying the possible development of new Barrett's epithelium in patients with a history of oesophagitis while considering other risk factors including gastro-duodenal disease and H pylori. **PATIENTS & METHODS** After the endoscopic healing of oesophagitis in 120 patients, 15 (12.5%) found to have Barrett's oesophagus were excluded. The remaining 105 patients were followed-up for the development of new Barrett's epithelium for a median (range) of 52 (38-77) months. They included 67 men (64%), 38 women (36%), 39 smokers (37%), 67 alcohol drinkers (64%), and had a median (range) age of 52 (19-83) years. Baseline endoscopic findings included 41 patients (39%) with non-erosive and 64 (61%) with erosive oesophagitis, 9 (9%) with gastric ulcers or erosions, 25 (24%) with duodenal ulcers or erosions, and 66 (63%) with H pylori gastritis. Eradication therapy was given to 43 patients. Using recent criteria (Coad RA, Shepherd NA. Current Diagnostic Pathology 2003; 9: 218-227), histological features diagnostic of Barrett's oesophagus (category 1) included the presence of native oesophageal structures such as oesophageal gland ducts with juxtaposition to glandular mucosa. Less diagnostic or normal categories (2-4) were also noted. The endoscopist and pathologist were not aware of patient's baseline characteristics. **RESULTS** Diagnostic features (category 1) of newly developed Barrett's oesophagus were found in 9 patients (8.6%) after a median (range) of 52 (35-83) months, with a median (interquartile range) length of 3 (1-3.5) cm. There was a negative correlation between the length of Barrett's epithelium and the histological categories ($r = -0.28$; $p = 0.004$). Six of the new Barrett's cases developed in those with baseline erosive oesophagitis (6/64, 9.4%) and 3 in non-erosive disease (3/41, 7.3%). Five of 43 patients (12%) given H pylori eradication therapy developed Barrett's epithelium, compared with 3/23, 13% whose infection was not treated. Taking all histological categories into account, males had greater tendency to develop Barrett's oesophagus ($X^2 = 5.69$; $df = 1$; $p = 0.017$). No significant tendency was seen with other risk factors including gastro-duodenal abnormalities H pylori, or eradication therapy. **CONCLUSIONS** New Barrett's epithelium can develop after the exclusion of baseline cases in patients with oesophagitis. It is more likely to develop in men, and does not seem to be influenced by baseline gastro-duodenal disease, H pylori or its eradication.

209783: Predictors For Treatment Failure of on-Demand Proton Pump Inhibitor (PPI) Therapy in Gastroesophageal Reflux Disease (GERD). *Justin Wu, Carrian Cheung, Vincent Wong, Joseph Sung*

BACKGROUND: It is unclear whether on-demand PPI is equally effective as step-down therapy in patients with non-erosive reflux disease (NERD) and reflux esophagitis (RE). **AIM:** To compare the efficacy of on-demand PPI therapy in NERD and RE patients and identify the predictors for treatment failure. **METHODS:** We prospectively recruited consecutive patients with weekly attacks of heartburn or acid regurgitation. HP eradication was completed before recruitment. Exclusion criteria included high grade (B or above) RE, previous gastric surgery, recent use of NSAID or PPI, and peptic ulcer. All patients completed a self-administered questionnaire for baseline assessment of reflux symptom. Diagnosis of concomitant functional dyspepsia (FD), irritable bowel syndrome (IBS) and psychological disorders (PD) were recorded. RE and hiatus hernia (HH) were assessed by EGD. Esophageal manometry (EM), Bernstein test (BT) and 24-hour pH metry were performed for all patients. Esomeprazole 20 mg daily were given for 8 weeks after baseline assessment. Patients with complete symptom resolution were then enrolled to open-label, on-demand Esomeprazole 20 mg for 26 weeks. Treatment failure was defined as need of Esomeprazole in $\geq 75\%$ of time for satisfactory symptom control at 26 weeks. NERD and RE patients were compared for treatment failure rates after 26-week on-demand PPI therapy. Potential predictors (age, gender, RE, HH, baseline reflux severity, FD, IBS, PD, positive BT, abnormal pH study, ineffective esophageal motility (IEM: failed peristalsis $\geq 30\%$) and weak lower esophageal sphincter (LESP <10 mmHg)) were determined using multivariate logistic regression model. **RESULTS:** 182 patients (NERD: 113, RE: 69; mean age 52.16.8, male: 48%) were studied. NERD patients had significantly higher prevalence of FD (65 Vs 42%, $p=0.003$) and positive BT (41 Vs 20%, $p=0.004$) than RE patients. Both groups had comparable symptom resolution rate after 8-week daily PPI (NERD Vs RE: 92.0 Vs 97.1%, $p=0.16$). However, NERD patients had significantly higher treatment failure rates after 26-week on-demand PPI therapy (36.3% Vs 20.3%, $p=0.023$) than RE patients. Multivariate analysis showed that daily reflux symptom (OR: 2.1, $p=0.001$), FD (OR: 1.7, $p=0.02$) and positive BT (OR: 1.6, $p=0.03$) were the significant predictors for treatment failure of on-demand PPI. NERD was not a predictor (OR: 1.1, $p=0.73$). **CONCLUSION:** Daily reflux symptom, concomitant FD and positive BT are associated with failure of on-demand PPI therapy in GERD patients. Although NERD apparently has higher treatment failure rate, it is actually confounded by higher prevalence of FD and esophageal sensitivity.

Additional Reading: GERD

226317 Nighttime GERD and More Severe GERD Symptomatology Are Associated With Greater Work Productivity Loss. Adam B Elfant, Stephen M Lange, Quan V Doan, Lynda S Welage, Stephen Brunto, Richard B Lynn, Robert W Dubois

OBJECTIVE: To assess the relationship between work productivity loss and GERD-related severity among daytime (DG) and nighttime GERD (NG) cases. **METHODS:** A survey was conducted among adults. A screening questionnaire assessed frequency and severity of GERD symptoms during the past 12 months and past 7 days and identified GERD cases and controls. GERD was assessed using the validated GERD Symptom & Medication Questionnaire (GERD-SMQ). Symptomatic GERD was defined as GERD-SMQ score >9 and =>1 episode of heartburn or acid reflux during the past 7 days. Symptomatic NG was defined as individuals with GERD reporting =>2 nights with symptoms (whether or not daytime symptoms are present) or 1 night with symptoms (in absence of daytime symptoms). A maximum value from 4 severity ratings of heartburn and acid regurgitation (each based on a 10-point Likert scale) was used as the severity score to stratify patients into the following severity groups: mild (1-4), moderate (5-7) and severe (8-10). Among the DG and NG cases, the severity score was based solely on the 2 nighttime severity ratings and solely on the 2 daytime severity ratings, respectively. GERD-specific productivity losses were assessed using the validated Worker Productivity & Activity Impairment Questionnaire (WPAI), which measures work time absenteeism and impairment while working. Mean percent reductions in Work Productivity Scores (WPS) were calculated for all GERD, NG and DG cases and differences were assessed using statistical test. **RESULTS:** 13,231 (21.4%) of 65,001 invited to participate responded; 1,515 satisfied the study criteria (mean age 44.3 years; 57% women). Of these, 1002 were symptomatic GERD cases (475 NG vs 469 DG) and 513 were non-GERD controls. More severe symptoms were associated with statistically greater work productivity loss among GERD, DG, and NG cases. Overall, patients with NG suffered significantly greater work productivity loss compared with DG cases (P<0.05). Patients with NG in moderate or severe strata had statistically greater work impairment than DG cases. **CONCLUSIONS:** GERD-related symptom severity is strongly associated with work impairment. Patients with NG reported substantially greater work impairment in every severity stratum compared with DG cases.

GERD-specific Work Productivity Loss

Severity	Mean % Reduction			DG vs NG Difference
	GERD* (n=1002)	DG* (n=469Φ)	NG* (n=475Φ)	
Mild	4.6	3.3	6.6	3.3
Moderate	11.4	7.7	14.5	6.9ψ
Severe	15.3	11.5	16.4	4.9ψ
Overall	9.0	5.6	12.2	6.8ψ

* P<0.05 Φ 58 cases w/missing data excluded ψ P<0.05, comparison of DG and NG

217885: The Seattle Protocol For High-Grade Dysplasia In Barrett’s Esophagus-It May Not Be As Good As We Think. Revital Kariv, Thomas P Plesec, Mary P Bronner, John R Goldblum, Mary Oldenburgh, Thomas W Rice, Gary W Falk

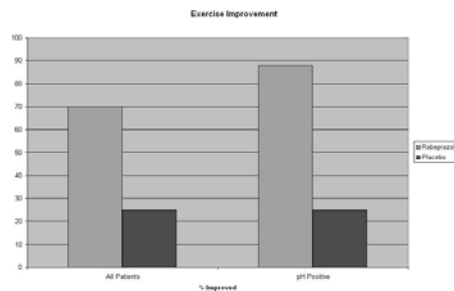
Background: The optimal management of high-grade dysplasia (HGD) in Barrett’s esophagus (BE) remains controversial. A biopsy protocol consisting of 4 quadrant jumbo biopsies at 1 cm intervals plus biopsies of any mucosal abnormalities no matter how trivial (Seattle protocol) is thought to be a reliable method to detect early cancers in HGD patients. However, this protocol has never been validated outside of Seattle. **Aim:** To validate the Seattle protocol in a cohort of BE patients who underwent esophagectomy for a diagnosis of HGD. **Patients and Methods:** This is a single center study of 32 consecutive BE patients with a biopsy diagnosis of HGD who underwent esophagectomy between 1999-2005. None had mass lesions suggestive of obvious malignancy at the time of preoperative endoscopy. All biopsies were confirmed by expert GI pathologists prior to surgery. Patients were divided into 2 groups: Group 1 had preoperative surveillance biopsies done according to the Seattle protocol as described above; Group 2 had 4 quadrant biopsies every 2 cm. Postoperative pathology findings confirmed by expert GI pathologists were compared to preoperative findings in both groups. **Results:** There were 21 patients in Group 1 and 11 patients in Group 2. Age and hiatal hernia size were not significantly different between the 2 groups. Median [IQR]BE length was greater in Group 2 (10.0 cm [4.0,10.0] vs 4.0 cm [2.0,5.0](P= 0.01)). Postoperatively, unsuspected intramucosal cancer was found in 7/21(33.3%) Group 1 vs 3/11(27.3%)in Group 2 (P=0.99). No patients in either group had a postoperative diagnosis of submucosal cancer or lymph node metastases. **Conclusions:** Intensive preoperative surveillance biopsies using the Seattle protocol does not reliably predict the presence of intramucosal carcinoma at the time of esophagectomy any better than a less intensive surveillance biopsy protocol. This calls into question the concept that the Seattle protocol consistently detects early cancer arising in BE patients with HGD.

218482: Natural History of High Grade Dysplasia in a Regional Veterans Administration Barrett's Cohort. *Gareth S Dulai, Dennis M Jensen, Fasiha Kanwal, Brennan M Speigel, Ian M Gralnek, Paul G Shekelle*

OBJECTIVES: Published data on the natural history of high grade dysplasia (HGD) in Barrett's esophagus (BE) give widely varying estimates of risk for esophageal cancer. The risk of cancer and related mortality may be greater in prevalent than incident cases due to detection of early stage disease in surveillance or bias. Our primary aim was to describe the natural history of prevalent and incident HGD in a large cohort of BE patients. A secondary aim was to compare outcomes in those with prevalent vs. incident cancer. **METHODS:** Consecutive BE cases from 1988-2002 were identified via pathology databases in a regional VA healthcare system and medical record data were abstracted. The risk of progression to cancer as well as mortality was measured and compared in cases with prevalent vs. incident HGD/cancer using survival analysis. **RESULTS:** There were 30 cases of prevalent HGD, six of whom developed cancer over 70 patient-years of follow-up. Three of thirteen cases with incident HGD developed cancer over 136 years of follow-up. The crude rate of cancer was 1 in 12 years for those with prevalent vs. 1 in 45 years with incident HGD ($p=0.085$). Ten cases with prevalent and five cases with incident HGD died, but only 20% were due to cancer. Mortality was 1 in 7 years for those with prevalent vs. 1 in 27 years with incident HGD ($p=0.005$). There were 45 prevalent and 11 incident cancers. Cancer was early stage in 16% of prevalent vs. 45% of incident cases ($p=0.03$). Twenty-eight cases with prevalent and six with incident cancer died. Death was due to cancer in 96% of prevalent vs. 50% of incident cases ($p=0.01$). Mortality rates were 1 in 4 years for those with prevalent vs. 1 in 16 years for incident cancers ($p=0.02$). **CONCLUSIONS:** In a large cohort study of Barrett's, high-grade dysplasia was associated with a high rate of progression to cancer. The risk of overall mortality was significantly higher in those with prevalent vs. incident high-grade dysplasia and cancer. The reduction in risk may be an effect of surveillance and/or other factors including bias.

219795: The Role of Gastroesophageal Reflux (GER) in Exercise-Triggered Asthma. *Kathryn Peterson, John Fang, Christopher Canale, Darin Ruyjin, David Young, Wayne Samuelson*

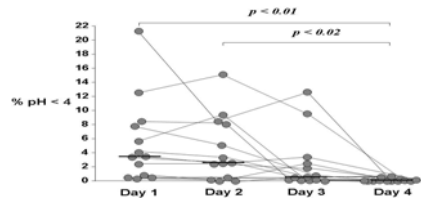
Background: Exercise-triggered asthma develops when vigorous physical activity triggers symptoms of cough, wheezing, dyspnea, and/or chest tightness during or directly after exercise. ETA can occur both in people with chronic asthma and in otherwise healthy individuals. In patients prone to symptoms of supra-esophageal reflux, exercise may trigger GER, resulting in shortness of breath and cough. **Aims:** (1) To determine the prevalence of abnormal pH in patients with exercise-triggered asthma, (2) To determine whether acid suppression improves respiratory symptoms during exercise in ETA patients. **Methods:** We performed a randomized, double blind trial of rabeprazole versus placebo in the treatment of patients (both asthmatic and non-asthmatic) with exercise-triggered asthma. Patients reported "heartburn" less than 2x/week. Upon enrollment, subjects underwent 24 hour pH testing while undergoing 30 minute treadmill program exercising them at pre-determined 60-65% of their VO₂max. They were subsequently randomized to rabeprazole 20mg Qam and placebo QPM, rabeprazole 20 mg po BID, or placebo BID for 12 weeks. At the end of 12 weeks, exercise testing was repeated. Subjects reported whether their treadmill symptoms improved or did not improve at the end of the study. **Results:** 37 total patients were recruited. A total of 30 patients completed the study in its entirety (20 asthmatics, 10 non-asthmatics). 22/30 (73%) subjects had abnormal pH studies. For all subjects, rabeprazole improved symptoms more often than placebo ($p=0.04$). In the pH+ group, rabeprazole resulted in even greater improvement ($p=0.02$). **Discussion:** Acid reflux is common in ETA patients. Many patients with exercise-related respiratory symptoms are under-diagnosed (or misdiagnosed) as chronic asthmatics. In addition, exercise related symptoms improve with the use of acid suppression. Such patients may benefit from an empiric trial of high dose acid suppression.



222545: Four-Day Bravo pH Recording Combining 48-hour Periods On and Off Proton Pump Inhibitor Therapy. *Pai-Wain C Lo, Qing Zhang, Nirmala Gonsalves, Ikuo Hirano*

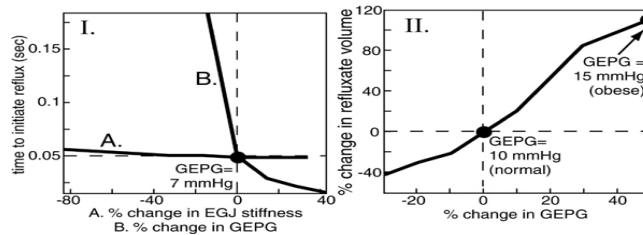
Background & Aims: Bravo monitoring increases the sensitivity of pH testing by allowing for 48 rather than 24 hour recordings. Controversy exists as to whether pH studies are optimally done off or on proton pump inhibitor (PPI) therapy. The aim of this study was to determine the feasibility of 4-day pH recordings using the Bravo pH system to encompass 2 day periods both before and during PPI therapy. **Methods:** 16 patients underwent 4-day pH recordings (2 day off; 2 day on) using 2 separate receivers calibrated to a single Bravo capsule. Indications for pH testing were refractory heartburn, chest pain, and

chronic cough. Patients were off PPI therapy for days 1 & 2. Rabeprazole 20mg orally twice a day was administered on days 3 & 4. **Results:** 13 patients completed the 4 day study and were included in the analysis. Off therapy, 5 patients (38%) had esophageal acid exposure values exceeding 5.3%. On therapy, all patients showed significant and progressive acid reduction (Fig). By day 4, esophageal acid exposure value was 0% in 8 patients and < 1% in 5 patients. The symptom index was significantly higher off (median 50%) than on (median 0%) PPI therapy ($p < 0.001$). 2 patients with capsule detachment on day 3 and one on day 2 were excluded. Of the excluded patients, two had normal off PPI acid exposure and the lack of day 4 data did not change the overall test interpretation. **Conclusions:** Prolonged recordings using the Bravo pH system are feasible and allow for combined testing both off and on therapeutic trial of PPI. The initial 2 day off PPI allows for increased sensitivity and symptom association for the diagnosis of GERD compared with on PPI testing. Such combined studies may allow for acquisition of information useful in the evaluation of refractory and atypical reflux symptoms.



224860: Obesity and GERD: is Increased Intra-gastric Pressure the Mechanism of Linkage? *Sudip K Ghosh, James G Brasseur, John E Pandolfino, Peter J Kahrilas*

AIM: Obesity (BMI>30) is epidemiologically linked to GERD, but the causal mechanism is argued. Recent data show that intra-gastric pressure and, particularly, the median gastroesophageal pressure gradient (GEPG) at inspiration, when reflux events are most likely to occur, are significantly greater in the obese than in the non-obese (Pandolfino JE et al. *Gastroenterology*; In Press). Reflux volume is also increasingly recognized as a key determinant of GERD. Our aim was to use computer simulations to explore the mechanical significance of the increased GEPG observed in obesity (15 vs 10 mmHg) on reflux events and reflux volume. **METHODS:** Anatomic and physiologic properties of the esophagogastric junction (EGJ) were obtained from physiological data and, along with Newton's laws, used to develop a computer model of the EGJ. Simulations were done to examine the sensitivities of: 1) EGJ opening (reflux) to changes in EGJ stiffness and GEPG, and 2) reflux volume to changes in GEPG, assuming stiffness constant. Refluxate volume was calculated for 0.5 seconds of flow. GEPG was varied between the median values of non-obese (n=129) and obese subjects (n=75). **RESULTS:** Opening of the relaxed EGJ occurred almost instantaneously (0.02-0.19 sec), strongly driven by increases in GEPG but relatively insensitive to changes in EGJ stiffness (Figure I). EGJ radius as well as the refluxate volume showed a strong dependency on changes in GEPG. As GEPG increased from 10 to 15 mmHg, reflux volume increased more than two-fold, from 6.7 to 14.1 ml (Figure II). **CONCLUSION:** Our computer simulations suggest that: 1) opening of the relaxed EGJ is primarily driven by the GEPJ rather than EGJ stiffness, 2) an increased GEPG of the magnitude observed with obesity doubles the volume of reflux and halves the time to initiate reflux, all other variables held constant. These findings suggest that the increased GEPG with obesity may be a key mediator in the causal pathway linking obesity with GERD.



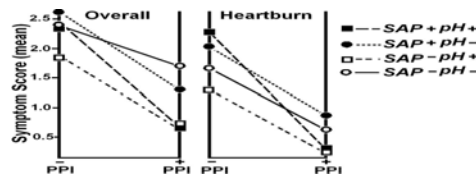
215316: Does Gastric Leptin in the Refluxate Contribute to Healing of the Esophageal Mucosa? *Fritz Francois, Adam J Goodman, Jatin Roper, Michelle Mourad, Asalia Z Olivares de Perez, Guillermo I Perez-Perez, Zhiheng Pei, Martin J Blaser*

BACKGROUND: Although heartburn is a hallmark of GERD, only a subset of affected individuals develop mucosal injury. Leptin, a hormone produced in the human stomach, stimulates cell growth in vitro and inhibits gastric ulcer formation in rats. We hypothesized that gastric leptin in the refluxate may contribute to the healing of the esophageal mucosa. Our aims were to evaluate whether leptin receptors are present in the esophagus and to determine whether regional gastric leptin levels correlate with esophageal pathology (esophagitis and/or Barrett's). **METHODS:** Patients referred for EGD were enrolled if they reported heartburn for ≥ 6 months in the prior year. A detailed medical history, height, and weight were obtained, and BMI calculated. Serum was collected, and biopsies obtained from antrum, fundus, and esophagus were reviewed by a blinded GI pathologist. Based on endoscopic and histologic findings, patients were classified as having esophageal pathology (EP+) or not (EP-), and immunohistochemistry was performed on representative sections from both groups to determine density and localization of

leptin receptors. Leptin levels in plasma and gastric biopsy samples were determined by specific ELISA, and gastric concentrations were normalized according to biopsy protein (pg/mg protein). RESULTS: Among 48 patients enrolled with heartburn, 27 were EP- and 21 were EP+. The two groups did not differ significantly in ethnicity, mean age, BMI, and gastric pH, or in proportions using PPIs, or with H. pylori, or in plasma leptin. Receptors for leptin were highly expressed on esophageal epithelial cells, with similar density and staining pattern in the EP- and EP+ specimens. The EP- group had significantly higher antral leptin levels than the EP+ group (median 94 pg/mg IQR (40-156) vs. 49 pg/mg (34-98); $p=0.047$). Similarly, the EP- group had significantly higher fundic leptin levels than the EP+ group (median 221 pg/mg IQR (93-357) vs. 103 pg/mg (72-163); $p=0.003$). Although the groups did not differ in symptom chronicity, the duration of heartburn was significantly correlated with fundus leptin levels in the EP- group ($r=0.59$, $p=0.005$), but not the EP+ group. CONCLUSIONS: Extensive expression of the leptin receptor on esophageal epithelial cells suggests that they are susceptible to leptin-mediated signal transduction. Differences in gastric leptin levels between EP+ and EP- persons could provide a mechanism for differential esophageal healing after reflux-induced injury. These data support the hypothesis that gastric leptin plays a protective role against esophageal pathology among patients with heartburn.

216900: Effect of Acid Inhibition on Reflux Symptoms Depends on Symptom Association Probability. *Marissa C Aanen, Bas L Weusten, Mattijs E Numans, Niek J de Wit, Melvin Samsom, A.J.P.M. Smout*

Introduction In patients with heartburn the symptomatic response to a proton pump inhibitor (PPI) is variable. We hypothesized that the highest response to PPI treatment can be expected in patients in whom a proven relationship exists between symptoms and reflux events. **Methods** Seventy-four heartburn patients were categorized into 4 groups according to presence or absence of pathological reflux, defined as $\text{pH}<4 >6\%$ of the time ($\text{pH}+/\text{pH}-$) and positive and negative SAP ($\text{SAP}+/\text{SAP}-$). During 7 days off and 13 days on esomeprazole 40 mg daily subjects kept a diary in which overall symptoms (O) and heartburn (H) were scored from 0 [absent] to 5 [very bad]. Data are presented as mean (7 days off PPI vs. last 7 days on PPI) and analysis was performed with Kruskal-Wallis tests. **Results** The 4 groups ($\text{SAP}+/\text{pH}+$ ($n=40$); $\text{SAP}+/\text{pH}-$ ($n=12$); $\text{SAP}-/\text{pH}+$ ($n=10$); $\text{SAP}-/\text{pH}-$ ($n=10$)) were similar in age and gender. Pre-treatment scores were highest in the $\text{SAP}+/\text{pH}+$ and $\text{SAP}+/\text{pH}-$ subgroups. In all subgroups of patients a reduction in reflux symptoms was seen. The greatest reduction was achieved in $\text{SAP}+/\text{pH}+$ subjects (ΔO $p<0.01$, ΔH $p<0.02$). The residual symptom scores on treatment were lowest in $\text{SAP}+/\text{pH}+$ and $\text{SAP}-/\text{pH}+$ subjects (O $p<0.01$, H ns) and relatively high in the $\text{SAP}+/\text{pH}-$ subjects. **Conclusion** The best response to PPI treatment was found in patients with positive SAP and pathological reflux. Subjects with a positive SAP and physiological reflux responded less favorably, presumably reflecting the element of visceral hypersensitivity in these patients.



213525: Discontinuation of Proton Pump Inhibitors in Patients on Long-Term Therapy: A Double-Blind, Placebo-Controlled Trial. *Einar Bjornsson, Hasse Abrahamsson, Magnus Simren, Niklas Mattsson, Pia Agerforz, Anders Kilander*

Background: The proportion of PPI users on long-term therapy who could discontinue PPIs without developing symptoms is unknown. It has been suggested that acid rebound following treatment with PPIs can make it more difficult to stop PPIs due to exacerbation of symptoms. We aimed to study what proportion of long-term PPI users is able to discontinue their medication and whether tapering down the PPIs makes it easier to stop PPIs. **Method:** Patients buying PPIs on prescription at the pharmacy were asked to complete a questionnaire concerning the indication for the medication and their symptomatology. Patients using PPIs for at least two months, without a history of peptic ulcer or esophagitis were asked to participate and examined with upper endoscopy. If an ulcer or esophagitis was observed the patient was excluded. Remaining patients were randomized double-blindly to taper down or continue with a constant dosage of omeprazole for three weeks. Thereafter, all patients discontinued PPI therapy. **Results:** A total of 115 patients underwent endoscopy, 19 patients were excluded due to organic GI disease (16 had esophagitis). Of the 96 enrolled (median age 63 years, 52 females), who had used PPI for a median time of 48 months (IQR 22-87; range 4-180 months), 23 (24%) had helicobacter pylori, 75 (78%) had GERD and 21 (22%) other indications. A total of 26 patients (27%) did not use PPIs during the year after discontinuation. A total of 31% randomized to tapering discontinued PPIs whereas 22% of those who did not taper PPIs could discontinue therapy (NS). Sex, age, duration of PPI therapy or HP status did not predict PPI requirement. GERD patients were more prone to resume PPI therapy than those with other indications. Only 16 (21%) of GERD patients were off PPIs compared with 48% of patients without GERD ($p<0.05$). GERD patients resumed their PPI therapy after a median time of 18 days (4-34; range 4-193) whereas the non-GERD patients resumed therapy 95 days (17-114; range 22-203) after the three week study drug period ($p<0.0001$). Serum gastrin was higher at baseline in GERD patients who resumed PPIs vs. those who did not (59pmol/L (36-81) vs. 38 (25-57); $p=0.03$). GERD and serum gastrin were independent predictors of PPI requirement. **Conclusions:** Discontinuation of PPIs was successful in 27% of long-term PPI

users. Patients with GERD were less likely to discontinue PPIs than those with non-GERD. Tapering down the PPIs did not significantly increase the possibility of a successful discontinuation. Hypergastrinaemia appeared to be an important predictor of PPI requirement in GERD patients.