

## ***Helicobacter pylori: What's Left?***

**Alan F. Cutler, MD**

**Wayne State University, Farmington Hills, Michigan**



*Alan F. Cutler, MD is a gastroenterologist with Digestive Health Associates, PLC in Farmington Hills, Michigan and is a Clinical Associate Professor of Medicine at Wayne State University.*

*Dr. Cutler's expertise in the field of gastroenterology has allowed him to serve on many medical committees including the Nominating Committee for Esophageal, Gastric and Duodenal Section of the American Gastroenterological Association Institute Council, and Chairman on the AGA Institute's research forum: Update on H. pylori Treatment: New Strategies and Continuing Issues of Resistance.*

*In addition, Dr. Cutler served on the editorial board of the American Journal of Gastroenterology and Gastroenterology & Endoscopy News. Dr. Cutler is also the member of many professional associations, including the American Gastroenterological Association Institute, American College of Gastroenterology, American Society of Gastrointestinal Endoscopy, American Digestive Health Foundation, American College of Physicians and the Michigan Society of Gastrointestinal Endoscopy, where he served as president from 2003-2005.*

*Dr. Cutler completed a gastroenterology fellowship at Henry Ford Hospital in Detroit and his graduate and undergraduate studies at the University of Michigan.*

My name is Alan Cutler. Welcome to *H. pylori: What's Left?* Today I will talk about abstracts related to diagnosis, disease association, treatment resistance, and rescue therapy.

### ***Abstract 219207: "In vivo diagnosing of Helicobacter pylori with confocal laser endomicroscopy – Prospective evaluation in comparison with conventional histology and urease testing"***

Confocal laser endoscopy has been developed recently. It allows subsurface and surface imaging during endoscopy. This study used the Pentax endomicroscopy scope. They applied fluorescein intravenously as well as a topical acriflavine hydrochloride and attempted to see if they could "see" gastritis and see *Helicobacter pylori*. They took targeted biopsies of these areas where they thought they saw the *H. pylori* to try to increase their yield on histology and urease testing. They could see bacteria with their shapes and flagella. They could see the gastritis with cell alterations. *Helicobacter pylori* was proven in all cases except one using histology and urease together as a gold standard for diagnosis. Thus endomicroscopy had a sensitivity of 91% and a specificity of 97%. Endomicroscopy allows evaluation of the stomach. You can look at it, you can do a histological diagnosis of gastritis and immediate diagnosis of *H. pylori* and the authors conclude that it is as accurate as our conventional *H. pylori* testing techniques of histology and urease testing. This is a pretty straightforward abstract. I don't know if it is anything controversial. It's interesting. How it will compare cost-wise will be interesting.

The next thing we are looking at is disease association.

### ***Abstract 223429: "Signs of H. pylori infection in autoimmune atrophic gastritis patients by immunoblotting"***

The authors start off by saying, look we can use Western blot to evaluate for *H. pylori* infection. We can look for the seroreactivity in one of the *H. pylori* specific antigens. They took a group of patients and looked at immunoblotting against specific *H. pylori* antigens to detect past *H. pylori* infection in patients with autoimmune atrophic gastritis. There were 138 patients with atrophic body gastritis classified either

as autoimmune when histology and ELISA serology were negative or as *H. pylori* related when there is evidence for *H. pylori* infection. Twenty three percent of the patients had autoimmune atrophic gastritis, 21% had *H. pylori*-related atrophic gastritis with active infection and 56% had previous *H. pylori* infection. Every patient with autoimmune atrophic gastritis shows immunoblotting seroreactivity against at least one of the *H. pylori* specific antigens. Think about this for a second. Every patient who has autoimmune atrophic gastritis had evidence of *H. pylori* infection. The number of mean seroreactive antigens of autoimmune atrophic gastritis was similar to those with past *H. pylori* infection, but lower than those with active infection. Active infection has more reactivity and CagA and VacA were not different between the three groups. The authors don't quite get there, but get close and say there is a close relationship between *H. pylori* infection and autoimmune atrophic gastritis and that there is an underestimate of the infection. If you read their abstract another way, you could say there is no such thing as autoimmune atrophic gastritis and it is all *H. pylori*. If this holds up and further research is done to confirm this data, it will certainly change our thinking pattern. It is pretty interesting as far as disease association goes.

***Abstract 223644: "In children eradication of Helicobacter pylori does not promote gastroesophageal reflux disease: A multichannel pH-impedance study"***

The authors looked at *H. pylori* and reflux disease in children. They looked at the effects of eradicating *H. pylori* on acid and non-acid exposure by looking at a 24-hour multichannel intraluminal impedance and pH monitoring. They had 17 patients who had *H. pylori* infection and no reflux esophagitis on endoscopy. They underwent endoscopy with histology and 13C testing. MII-pH was performed before and eight weeks after eradication of *H. pylori*. They used a standard *H. pylori* eradication technique (omeprazole, amoxicillin, and clarithromycin) and then measured number of reflux episodes, acid reflux episodes, non-acid reflux episodes with impedance, the percentage time esophageal pH < 4, the longest duration of acid exposure, acid clearing time, all the things we normally look at in adults. After *H. pylori* eradication there was no significant change in any of the MII-pH parameters evaluated. Of the eight patients who had some abnormal esophageal exposure prior to the study, four became normal afterwards and four persisted abnormal. Of the nine patients with normal baseline acid exposures, two developed a little bit of abnormality. Basically, eradication of *H. pylori* in children at least by eight weeks, did not show any significant change in reflux disease and did not show positive association. Children are obviously a little bit different than adults. This concept of *H. pylori* and GERD has pretty much met its doom. Sometimes getting rid of *H. pylori* can make reflux worse, sometimes getting rid of it makes it better, and sometimes it doesn't do anything. There are no predictable factors that we can find. Most of us who are "HPologists" have said this is not something you should go looking for or worrying about.

We're moving on to management.

***Abstract 221051: "Clinical practice patterns for the management of Helicobacter pylori infection, dyspepsia, and gastroesophageal reflux disease"***

This looks at the medical and pharmacy claims of a national sample of two million, non-elderly individuals continuously enrolled in managed care from 2002 to 2004. This is a longitudinal, cohort study. They grouped the patients by their initial diagnosis. There were 3,400 with ulcer disease, 14,000 with non-ulcer dyspepsia, and 36,000 with reflux disease. They looked for triggers (claims for antisecretory medications, *H. pylori* tests, endoscopies, *H. pylori* treatment) which would trigger them to the fact of what was being done and what has happened before and after. Unfortunately, practice was frequently contrary to guidelines, even basic guidelines. Twenty-five percent of suspected ulcer disease patients were not checked for *H. pylori* infection. Only 25% of those who were *H. pylori* infected were treated in the face of ulcer disease. Fifteen percent had endoscopy as their first clinical event. One-third

received *H. pylori* infection treatment without being tested for the infection. Serology was used appropriately in the pretreatment testing, but was inappropriately repeated in a posttreatment setting to confirm eradication. Nineteen percent of GERD patients were checked for *H. pylori* and patterns of care varied little by type of medical practice or geographical region. Every year we see these abstracts. We don't know if there are gastroenterologists involved. That is always one of my questions. I suspect that the subspecialists are probably not the problem. We all know *H. pylori*, we're comfortable with it, we all know what to do, and here we're looking at a 25% adherence rate to guidelines. It would be important to know who we had to educate better.

***Abstract 215812: "Comparison study on effectiveness of established triple therapy with its modified therapies for Helicobacter pylori eradication"***

This is a prospective study with 355 *H. pylori* infected patients mean age 48 years. There was functional dyspepsia in about half and ulcer disease in the other half. The study was performed March 2003 to August 2005. They were randomly assigned to one of three groups. They either received a proton pump inhibitor (rabeprazole) plus clarithromycin BID, or they received that same therapy plus an H2 blocker (roxatidine) given twice a day, or they received double dose of PPI (instead of 10 mg of rabeprazole, they got 20 mg) and each treatment arm was for one week. They underwent follow up endoscopy or breath testing at four weeks, so it's an either/or. In the per protocol analysis eradication rates were 83% in our standard therapies, 92% in our PPI plus H2 blocker, and 81% in our double dose PPI. Obviously, there was significant difference (p-value =.019). Intention to treat analysis was 74%, 84%, and 69% respectively. Doubling the PPI dose from 10 to 20 mg did not make a difference. Adding an H2 blocker away from the proton pump inhibitors improved eradication rates. This was interesting. We've done a lot of things. We've played with bismuth and H2 blockers, we've double dosed our PPIs, we've done once daily things, and we've had people put balloons in the stomach. I have not seen an H2 blocker and a PPI together, not in a while. This will need to be supported by other research, but it is interesting.

***Abstract 218477: "Effect of 2 weeks furazolidone – or 2 weeks metronidazole – or combination of 1 week furazolidone +1 week metronidazole-based anti Helicobacter pylori regimens in peptic ulcer: A randomized-controlled multicenter trial"***

They looked at three different *H. pylori* regimens, either one or two weeks of furazolidone. Group 1 received omeprazole, amoxicillin, and furazolidone plus bismuth for two weeks. Group 2 received the same but metronidazole replaced the furazolidone and Group 3 received the regimen from Group 1 for the first week and the regimen from Group 2 for the second week. Patients were followed at two and 10 weeks. Compliance and side effects were checked and a single breath test was performed at 10 weeks to verify *HP* eradication. Three hundred and fourteen patients were enrolled. They had a few people drop out. Side effects were most common in the patients receiving two full weeks of furazolidone (Group 1). Per protocol eradication was 95% if you received furazolidone for two weeks, it was 83% if you received metronidazole, and it was 95% if you had one week of furazolidone and one week of metronidazole. Intention to treat was 87% in Group 1, 74% in Group 2, and 87% in Group 3. They conclude that furazolidone given for one week followed by metronidazole has the same efficacy as furazolidone for two weeks with fewer side effects.

The reason I chose this abstract was sequential therapy. In the last few years, we've seen a lot of this. Physicians call me and ask me what they do with their failures. One of the things you can do is sequential therapy. You can do a week of one thing and a week of another for three weeks. The concept of sequential therapy has actually shown up really well. What you're probably doing is targeting different populations of *H. pylori* as you move your antibiotics around. This is not rocket science. It's the same thing we do in other disease states. Sequential therapy is not unusual but it's a nice thing to think about.

Moving on to resistance.

**Abstract 215689: “Antimicrobial resistance for primary and secondary *Helicobacter pylori* strains isolated from Korean patients”**

These authors found 65 strains of *H. pylori* from 65 patients who had not received antibiotics, PPI, or non-steroidals in the last three months. They found 324 strains of *H. pylori* in 67 patients who had taken PPIs, post treatment. That is the big point of this study. After therapy you're going to end up with mixed colonies. People look at resistance rates, they get cultures of a single spot in the stomach and they give us resistance facts. A number of us have argued for years that with multiple strains, you are going to have a mixed infection with antibiotic susceptible and resistant strains and what you grab is what you're going to see. This is a nice abstract if it holds up. I mean 324 strains – it's just amazing. That's quite a mixed bag of trouble in there. Not surprisingly, the MIC values of the isolates in the post treatment patients all went up to higher concentrations and required more antibiotics. This stands out because of the concept of the mixed colonies and mixed infections. It's something that is really understated in the literature. Again, it's an argument for sequential therapy in some ways as a concept.

The next three abstracts look at rescue therapy which is always a question. How many people here only treat *H. pylori* once? How many stop after two treatments? How many go on to a third treatment? How many stop after the third treatment? How many go to a fourth treatment? Fifth treatment? Sixth treatment? I use a "three strikes and you're out" rule for no good reason.

**Abstract 217042: “Levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure: Systematic review and meta-analysis”**

We've seen a lot at the last two DDWs on levofloxacin. My answer for any new antibiotic that works for *H. pylori* is use it while it is still effective. Use it early! The authors looked at levofloxacin based rescue therapies. It was a meta-analysis and they compared it to patients who received quadruple therapy. They were treatment failures, probably from a clarithromycin-based therapy who were either going on to a bismuth based quadruple therapy or to levofloxacin. The mean eradication rate with levofloxacin based regimens was 80%. Ten day regimens were more effective than 7 day regimens with a p-value of <.01 and the meta-analysis showed better results with levofloxacin than with the quadruple therapy (81% versus 70% with an odds ratio of 1.8). Their difference reached statistical significance when a single outlier study was excluded. Adverse effects in general and severe adverse effects were 18 and 3%. The meta analysis showed less adverse effects with levofloxacin than with quadruple therapy, and it looks like levofloxacin based rescue therapy is more effective and better tolerated than what we consider the bismuth based quadruple therapy, and 10 days is better than 7 days. When you are retreating the second time through, expand your days. Every time you treat them, add days. My second time through, I never go less than 14 days. If I get to a third one, they are going 21 days. When I use quadruple therapy I will go 21 days in patients who have failed previous trials. The levofloxacin has shown some resistance. Our colleagues in Canada first reported a 12% resistance rate, I believe. It is nudging its way up there a little bit.

**Abstract 217065: “Third-line rescue therapy with levofloxacin after two *H. pylori* treatment failures”**

Again, this is looking at levofloxacin. They looked at it as a third-line regimen after two previous failures. It was a prospective, multicenter study. The first treatment had been performed with omeprazole, clarithromycin, and amoxicillin and the second with omeprazole, bismuth, tetracycline, and metronidazole or ranitidine bismuth citrate if it was available. The third regimen was levofloxacin 500 BID which is

reasonable dosing, amoxicillin 1 gm BID which is standard, omeprazole 20 BID. They did this for 10 days. Eradication was assessed by a single breath test four to eight weeks after therapy. There were 100 patients included, nine were lost to follow up. Per protocol and intention to treat eradication was 66% per protocol and 60% intention to treat. That's actually pretty darn good considering these patients failed previous therapies and probably have clarithromycin and metronidazole resistance at this point. I presented this one because where I come from, this is what we tend to use as a third-line therapy. I favor clarithromycin first line, bismuth second line, and levofloxacin third line. That's nice information. I'm betting you all still get calls from your primary care docs and family practitioners asking you what to use next. It's nice to know three lines and increasing the length of treatments.

***Abstract 214491: "One-week once-daily triple therapy with esomeprazole, moxifloxacin and rifabutin is effective in the treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin"***

These people haven't just failed therapy. They are resistant to metronidazole and clarithromycin. This was a prospective, open-label study. The esomeprazole was given at 40 mg, moxifloxacin 400 gm, rifabutin 300 mg, all standard doses given orally once daily in the morning for seven days. Follow-up endoscopy rather than a breath test was used including histology and cultures six to eight weeks after treatment. They are doing a very nice study here. They've done all the right things. Eighty-six patients were enrolled and that is a fair number if you consider they found people resistant to both metronidazole and clarithromycin. Three patients discontinued therapy due to adverse events. Successful eradication was confirmed in 80% of patients which is impressive. In the patients with clinical failures, ones who did not eradicate the infection, post-treatment resistance to both rifabutin and Cipro were detected in five patients.

It's interesting.

Thank you for your attention.

## Abstracts Discussed

**219207: *In Vivo* Diagnosing of *Helicobacter pylori* with Confocal Laser Endomicroscopy - Prospective Evaluation in Comparison with Conventional Histology and Urease Testing.** Ralf Kiesslich, Martin Goetz, Arthur Hoffman, Constantin Schneide,r Katharina Lammersdorf, Michael Vieth, Manfred Stolte, Peter R Galle, Markus F Neurath

Abstract: Confocal laser endomicroscopy (CLE) enables surface and subsurface imaging of living tissue during ongoing endoscopy. Currently, *in vivo* diagnosis of *Helicobacter pylori* with acriflavine aided CLE was described. The aim of the current prospective study was the *in vivo* detection of *Helicobacter pylori* in patients with dyspepsia and the correlation with histologic findings and urease testing. Methods: Endomicroscopy (Pentax, Tokyo, EC-3870CIFK) of the stomach was performed by using two different contrast stains. Fluorescein was applied intravenously to enable confocal endomicroscopy of the gastric mucosa. Confocal image data were collected at a scan rate of 1.6 sec/frames (1024x1024 pixels) using an optical slice thickness of 7µm (lateral resolution ≤1µm). Subsequently, acriflavine hydrochloride was applied topically onto the surface of the gastric mucosa with the help of a spraying catheter. Acriflavine netted the surface and allowed identification of focal accumulation of *Helicobacter pylori* at the surface and in deeper layer of the gastric epithelium. Targeted biopsies of the examined areas were performed at the antrum and corpus for urease testing and histology (Warthin-Starry silver). Results: In 11 out of 30 patients *Helicobacter pylori* infection could be diagnosed by CLE. Accumulated as well as single bacteria with bright contrast could be observed including the distinct shape and flagella of *Helicobacter pylori*. In addition gastritis could be graduated due to visible vessel and cell alterations. *Helicobacter pylori* infection was proven in all except one case by histology and urease testing (Sensitivity 90.9%, Specificity 96.7%). The single false positive result was seen in a patient with extremely few germs detected by endomicroscopy. Furthermore, 4 patients were re-examined after eradication. CLE correctly proved the absence of *Helicobacter pylori*. Conclusions: Endomicroscopy allows simultaneously endoscopic images of the stomach, *in vivo* histology of gastritis and immediate diagnosis of *Helicobacter pylori* infection during ongoing upper endoscopy. The diagnostic accuracy is comparable with conventional histology and urease testing.

**223429: Signs of *H Pylori* Infection in Autoimmune Atrophic Gastritis Patients by Immunoblotting.** Edith Lahner, Annalisa Santucci, Dino Vaira, Amelia Pasquali, Roberta Mini, Natale Figura, Gianfranco Delle Fave, Bruno Annibal

Background: Two mechanisms are generally considered able to induce atrophic body gastritis (ABG): autoimmunity and *H pylori* infection. The most characteristic clinical presentation of autoimmune ABG is pernicious anemia (PA). No sign of *H pylori* infection is detectable in about 30% of ABG patients, who are thus considered having autoimmune ABG. Western blotting permits an accurate exposure classification to *H pylori* infection. Aim: to assess the strength of *H pylori*-ABG relationship by using immunoblotting against specific *H pylori* antigens to detect past *H pylori* exposure in patients with autoimmune ABG. Methods: Case-series consisted of 138 ABG outpatients, classified as autoimmune when histology and ELISA serology were negative, and as *H pylori*-related, when histology and ELISA serology were positive (active infection) or only serology was positive (past infection). Immunoblotting against *H pylori*-specific antigens (CagA, VacA, HspB, UreA and UreB) was performed. Results: 22.5% of patients had autoimmune ABG, 21% had *H pylori*-related ABG with active infection and 56.5% with past infection. All autoimmune ABG patients showed immunoblotting seroreactivity against at least one of the *H pylori*-specific antigens. The number of mean seroreactive antigens of autoimmune ABG patients was similar to those of patients with past *H pylori* infection (3.6±0.2 vs 3.5±0.1 ns), but lower than that of patients with active infection (4.3±0.2, p<0.001). Seroreactivity against CagA and VacA antigens was not different between the three groups (80.6% and 93.5% of autoimmune patients; 86.2% and 96.6% in active and 67.9% and 89.7% in past *H pylori* infection, respectively). Some classic features of gastric autoimmunity, as PA and corpus-restricted atrophy were observed more frequently among patients with autoimmune ABG, whereas others as positivity to autoantibodies against parietal cells and intrinsic factor and the association of other autoimmune diseases were similarly distributed among patients with autoimmune and *H pylori*-related ABG. Conclusions: *H pylori* immunoblotting reveals a close relationship between *H pylori* and autoimmune ABG, suggesting a misclassification of exposure and an underestimation of infection in this condition.

**223644: In Children Eradication of *Helicobacter Pylori* Does Not Promote Gastroesophageal Reflux Disease: A Multichannel pH-Impedance Study.** Osvaldo Borrelli, Caterina Anania, Letizia Cordischi, Felicia Galos, Marina Aloi, Manuela Cirulli, Valeria Labalestra, Valentina Mancini, Salvatore Cucchiara

Background. Conflicting data on the relationship between *Helicobacter Pylori* (*H. pylori*) infection and gastroesophageal reflux disease (GERD) have been reported, and only few studies on this issue have been performed in children. Aim. We aimed at assessing the effect of eradication of *H. pylori* on both acid and non-acid esophageal exposure, as measured with 24-hr multichannel intraluminal impedance and pH (MMI-pH) monitoring in children without reflux esophagitis. Patients and Methods. 17 consecutive patients (pts) (median age:10.2 years; range: 4-15) with *H.Pylori* infection and no reflux esophagitis were enrolled into the study. Diagnosis was performed by endoscopy with histology and 13C-urea breath test. MMI-pH

monitoring was performed before and 8 weeks after eradication of H. Pylori, which was achieved using standard triple therapy (omeprazole, amoxicillin and clarithromycin for 14 days) and confirmed by 13C-urea breath test. The MII-pH parameters evaluated were: total numbers of reflux episodes (TN), numbers of acid reflux episodes (AR), numbers of non-acid reflux episodes (NAR), % of time with esophageal pH < 4 (ARI), numbers of long-lasting (> 5 min) acid reflux episodes (LAR) and acid clearance time (ACT)(sec). Esophageal acid exposure was considered abnormal when 24-hour ARI was > 5%. Results (mean±SD). At baseline ARI was abnormal only in 8 pts; MII-pH TN, AR, NAR, ARI, LAR and ACT were 62.59±31.92, 41.2±21.3, 20.9±19.8, 4.9±3.1, 2.0±2.3 and 87.1±48.9 respectively. After H. Pylori eradication, there was no significant change in all MII-pH parameters evaluated (TN: 61.7±35.5; AR: 43.7±27.8; NAR: 17.9±14.6; ARI: 5.2±4.1; LAR: 2.6±2.4; ACT: 101.9±35.1; NS). Of the 8 pts with abnormal ARI, the latter became normal in 4 and persisted abnormal in 4 (in 2 with a reduction of the acid exposure); of the 9 pts with normal baseline ARI the latter became abnormal only in 2. Conclusions. In children with H. Pylori infection, eradication of the organism is not associated with significant change in the pattern of gastroesophageal reflux. Our results fail to show a positive association between anti-H. Pylori therapy and occurrence of de novo GERD

**221051: Clinical Practice Patterns for the Management of *Helicobacter pylori* Infection, Dyspepsia, and Gastroesophageal Reflux Disease.** *Steven W Blume, Colin W Howden, Gregory de Lissovoy*

Background Since the recognition of *Helicobacter pylori* (*H. pylori*) as the major cause of peptic ulcer, clinical guidelines for the testing and treatment of *H. pylori* infection have been widely disseminated. One of the key recommendations has been that clinicians use non-invasive testing for *H. pylori* infection, reserving prompt endoscopy for older patients or those with alarm symptoms. Eradication therapy should be administered to all patients testing positive. Little is known about adherence to these recommendations and actual medical practice patterns. Methods Medical and pharmacy claims of a national sample of two million non-elderly individuals continuously enrolled in managed care plans from 2002 to 2004 were the basis of a longitudinal cohort study. We selected patients with claims for antisecretory medication, *H. pylori* tests, or endoscopies but having no disease-related claims in the first six months of the study period and having at least six months of follow-up. Patients were grouped by their initial clinical diagnosis: peptic ulcer disease (PUD) (n = 3456), non-ulcer dyspepsia (n = 14,593), or GERD (n = 36,233). The proportions of patients treated contrary to guidelines, diagnostic procedures and medications received, and the sequencing of key procedures and medications were examined by initial diagnosis, age, and physician type. Results Two-thirds of the study population were enrolled in health maintenance organizations and almost half were located in the Midwest census region. Several practices contrary to guidelines were common. Twenty-five percent of suspected PUD patients were not checked for *H. pylori* infection, and only 25% were treated with eradication therapy. Of all patients aged 18-49, 15% had an endoscopy as their first clinical event. A third of those receiving antibiotics for *H. pylori* infection had not been first tested for the infection. Serology was used for 87% of pre-treatment tests in 2004 and was improperly used by primary care practitioners for post-treatment testing. Nineteen percent of GERD patients were tested for *H. pylori*. Patterns of care varied little by type of medical plan or geographic region. Conclusions The study demonstrated substantial non-compliance with guidelines. A better understanding by physicians of the indications for *H. pylori* testing and endoscopy would improve patient care and resource use.

**215812: Comparison Study on Effectiveness of Established Triple Therapy With Its Modified Therapies For *Helicobacter Pylori* Eradication.** *Taewoon Park, Jae Eun Lee, Chang Woo Gha, m Ja Sung Choi, Chang Hwan Choi, Ki Joon Han, Hyeon Geun Cho*

Background: The rate of *Helicobacter pylori* infection as well as related morbidity are relatively high in Korea. *H. pylori* eradication is becoming an essential treatment not only for peptic ulcer patients but also for functional dyspepsia patients. However, the eradication rate by the established triple therapy (PPI + amoxicillin + clarithromycin, PAC) is still around 80%. In this study, we compared the efficacies of the established triple therapy with its modified therapies for *H. pylori* eradication in order to obtain a better eradication rate. Methods: This prospective study included a convenience sample of 355 *H. pylori* infected patients (mean age 48.4±12.4 years) with functional dyspepsia (n=189) or peptic ulcer (n=166)(table 1). From March 2003 to August 2005, the patients were randomly assigned to PAC group (PPI: rabeprazole 10mg, bid + amoxicillin 1g, bid + clarithromycin 500mg, bid), PACR group (PAC + roxatidine 75mg, bid at different timing from PPI), or DPAC group (doubling PPI dose in PAC). The patients in three groups underwent each eradication treatment for one week and the eradication was confirmed through follow-up endoscopy or urea breath test at least four weeks after the completion of treatment. Results: Tests for homogeneity demonstrated no significant differences between groups in age, gender, and diagnosis. In per protocol analysis, the eradication rates were 83.2% in PAC group, 92.6% in PACR group, and 81.6% in DPAC group. Significantly higher eradication rate was noted in PACR group than the other two groups (p=0.034; p=0.019, respectively). Intent-to-treat analysis also showed similar findings; 74.2% in PAC group, 84% in PACR group, and 69.0% in DPAC group (p=0.043; p=0.003, respectively). In terms of drug tolerance, only seven patients out of 355 patients failed to complete the treatment, but there were no differences between groups. Conclusion: While doubling PPI dose in PAC did not change *H. pylori* eradication rate, adding H2RA(roxatidine) to PAC did significantly increase the eradication rate. Further

studies with a large sample are recommended to support these results and drug interaction between PPI and H2RA needs to be examined.

Table 1. Characteristics of Patients

	PAC (n=120)	PACR (n=119)	DPAC (n=116)	Total (n=355)
Sex (M/F)	63/57	62/57	62/54	187/168
Age (Mean±SD)	50.3±11.5	47.8±11.9	47.0±13.8	48.4±12.4
PUD/FD	65/55	65/54	59/57	189/166

P: proton pump inhibitor (rabeprazole), A: amoxicillin, C: clarithromycin, R: roxatitidine, DP: double dose PPI PUD: peptic ulcer disease, FD: functional dyspepsia

**218477: Effect of 2 Weeks Furazolidone- or 2 Weeks Metronidazole- or Combination of 1Week Furazolidone+ 1 Week Metronidazole-based anti Helicobacter Pylori Regimens in Peptic Ulcer: A Randomized-controlled Multicenter Trial.** *Y Ajvadi, R Malekzadeh, S Nasser-Moghaddam, N E Daryani, H Vahedi, N Zendehdel, R Sotoudehmanesh, S Agah, J Mikaeli, A Pourshams, M Khatibian, A Ali Asgari, Sadegh Massarraf*

Background: Metronidazole or Clarithromycin combined with Amoxicillin, a Bismuth compound and Omeprazole are commonly used to treat Helicobacter pylori (HP). There is a high bacterial resistance to Metronidazole and high cost for Clarithromycin. Iranian studies show that Furazolidone is effective against HP, with no resistance, but intolerable side-effects are common in 2weeks therapy. We compared efficacy and side-effects profile of three different anti-HP regimens with 1 or 2 weeks Furazolidone administration. Materials and Methods: Consenting, HP positive peptic ulcer patients were randomly allocated in three groups. Group 1 received Omeprazole 20mg BID+ Amoxicillin 1 g BID + Furazolidone 200 mg BID + Bismuth-subcitrate 240 mg BID for 2 weeks. Group 2 received the same but Furazolidone was replaced with Metronidazole 500 mg BID. Group 3 received regimen 1 for the first week and regimen 2 for the 2nd week. Patients were followed at weeks 2 and 10. Compliance and side-effects were checked at week 2. 13C Urea breath test (UBT) at week 10 verified HP eradication. Results: 314 patients were enrolled, 299 followed at week 2 and 276 took the UBT. There were 100, 102, and 97 patients in groups 1-3 respectively. Seven, 3, and 6 patients discontinued medication prematurely in groups 1-3 respectively. Side-effects were more common in group 1 (7 patient with high fever, 10 vomiting and 19 weakness) than group 2 (4 with fatigue) and group 3 (1with fever, 7 fatigue, and 4 vomiting) (p<0.05). Per protocol eradication rates were 95.2%, 83.1% and 95.3% in groups 1 to 3 respectively (p=0.005). Intention to treat eradication rates were 87.0%, 74.5%, and 86.6% in groups 1-3 respectively (p=0.02). Conclusion: Furazolidone given for one week followed by Metronidazole has the same efficacy for HP eradication as Furazolidone for 2 weeks with fewer side effects. Furazolidone-based regimens are superior to Metronidazole based ones.

**215689: Antimicrobial Resistance for Primary and Secondary Helicobacter Pylori Strains Isolated from Korean Patients.** *Jung Mogg Kim, Joo Sung Kim, Nayoung Kim, Sang Gyun Kim, Hyun Chae Jung, In Sung Song*

BACKGROUND and AIMS: The aim of this study was to assess MIC values and resistance rates of several antibiotics in primary and secondary H. pylori isolates from Korean patients. MATERIALS AND METHODS: Sixty-five strains of H. pylori were isolated from 65 patients that had not received antibiotics, PPI or nonsteroidal anti-inflammatory drugs during the preceding three months. Three hundred twenty-four strains of H. pylori were isolated from 67 patients who had taken PPI triple therapy consisting of amoxicillin and clarithromycin for one week. The MIC values of H. pylori isolates to the antibiotics were determined using the serial two-fold agar dilution method. The resistance breakpoints for amoxicillin, metronidazole, and tetracycline were defined as  $\geq 0.5$ ,  $> 8$ , and  $> 4$   $\mu\text{g/ml}$ , respectively. The breakpoint for clarithromycin was set at  $> 1.0$   $\mu\text{g/ml}$ , and those for azithromycin, ciprofloxacin, levofloxacin, and moxifloxacin were provisionally defined as  $> 1.0$   $\mu\text{g/ml}$ . The mutation of penicillin-binding protein 1A (pbp1A) was determined by PCR amplification and nucleotide sequencing. RESULTS: The overall MIC values of secondary isolates showed a shift to high concentrations compared with those of primary isolates. Primary resistances to amoxicillin, clarithromycin, metronidazole, tetracycline, azithromycin, ciprofloxacin, levofloxacin and moxifloxacin were 18.5%, 13.8%, 66.2%, 12.8%, 32.3% 33.8%, 21.5% and 21.5%, respectively. Secondary resistances to amoxicillin, clarithromycin, metronidazole, tetracycline, azithromycin, ciprofloxacin, levofloxacin and moxifloxacin were 31.3%, 85.1%, 70.1%, 0%, 89.6% 35.8%, 32.8% and 32.8%, respectively. Sequence analysis of pbp1A in H. pylori strains with more than 2  $\mu\text{g/ml}$  of amoxicillin MIC revealed C206T (Asp69 to Val), C1667G (Thr556 to Ser), A1684T (Asn562 to Tyr), A1777G (Thr593 to Ala), and C1798A (Pro600 to Thr). In contrast, the activity of  $\beta$ -lactamase was detected in neither the amoxicillin-resistant strains nor amoxicillin-susceptible strains. Eleven out of 67 treatment-failure patients (16.4%) showed mixed infections with both antibiotic-susceptible and -resistant H. pylori. The most common multidrug resistance was to clarithromycin, metronidazole and azithromycin. CONCLUSIONS: These results indicate that MIC

values of secondary isolates were higher than those of primary isolates and that resistance to amoxicillin is likely mediated through mutations in *pbp1A*.

**217042: Levofloxacin-Based Rescue Regimens after Helicobacter Pylori Treatment Failure: Systematic Review and Meta-Analysis.** *Javier P Gisbert, Felipe de la Morena*

**OBJECTIVE:** To systematically review the efficacy and tolerance of levofloxacin-based rescue regimens, and to conduct a meta-analysis of studies comparing these regimens with the quadruple therapy for H. pylori eradication failures. **METHODS:** Selection of studies: levofloxacin-based rescue regimens. For the meta-analysis, randomized controlled trials comparing levofloxacin-based and quadruple regimens were included. Search strategy: electronic and manual bibliographical searches. Assessment of study quality: independently by two reviewers. Data synthesis: "intention-to-treat" eradication rate. Meta-analysis combining the Odds Ratios (OR) of the individual studies. **RESULTS:** Mean eradication rate with levofloxacin-based regimens was 80%. 10-day regimens were more effective than 7-day combinations (81% vs. 73%;  $p < 0.01$ ). The meta-analysis showed better results with levofloxacin than with the quadruple combination (81% vs. 70%;  $OR = 1.80$ ; 95%  $CI = 0.94-3.46$ ). This difference reached statistical significance and heterogeneity markedly decreased when a single outlier study was excluded or when only high-quality studies were considered. Incidence of adverse effects in general, and severe adverse effects in particular, in levofloxacin treated patients was 18% and 3%. The meta-analysis showed less adverse effects with levofloxacin than with quadruple regimen, both overall (19% vs. 44%;  $OR = 0.27$ ; 95%  $CI = 0.16-0.46$ ) and regarding severe adverse effects (0.8% vs. 8.4%;  $OR = 0.20$ ; 95%  $CI = 0.06-0.67$ ). **CONCLUSION:** After H. pylori eradication failure, levofloxacin-based rescue regimen is more effective and better tolerated than the generally recommended quadruple therapy. A 10-day combination of levofloxacin-amoxicillin-proton pump inhibitor constitutes an encouraging second-line alternative.

**217065: Third-Line Rescue Therapy with Levofloxacin after Two H. Pylori Treatment Failures**

*Javier P Gisbert, Manuel Castro-Fernandez, Fernando Bermejo, Angeles Perez-Aisa, Julio Ducons, Miguel Fernandez-Bermejo, Felipe Bory, Angel Cosme, Luis-Miguel Benito, Laureano Lopez-Rivas, Eloisa Lamas, Manuel Pabon, David Olivares*

**AIM:** Eradication therapy with proton pump inhibitor, clarithromycin and amoxicillin fails in a considerable number of cases. A rescue therapy still fails in more than 20% of the cases. Our aim was to evaluate the efficacy and tolerability of a third-line levofloxacin-based regimen in patients with two consecutive H. pylori eradication failures. **METHODS:** Design: Prospective multicenter study. Patients: in whom a first treatment with omeprazole-clarithromycin-amoxicillin and a second with omeprazole-bismuth-tetracycline-metronidazole (or ranitidine bismuth citrate with these antibiotics) had failed. Intervention: A third eradication regimen with levofloxacin (500 mg b.i.d.), amoxicillin (1 g b.i.d.) and omeprazole (20 mg b.i.d.) was prescribed for 10 days. Outcome: Eradication was confirmed with  $^{13}C$ -urea breath test 4-8 weeks after therapy. **RESULTS:** One-hundred patients were initially included, and 9 were lost for follow-up. All patients but 5 took all the medications correctly. Per-protocol and intention-to-treat eradication rates were 66% (95%  $CI = 56-75%$ ) and 60% (50-70%). Adverse effects were reported in 25% of the patients, mainly including metallic taste (8%), nausea (8%), myalgia/arthritis (5%), and diarrhea (4%); none of them were severe. **CONCLUSION:** Levofloxacin-based rescue therapy constitutes an encouraging empirical third-line strategy after multiple previous H. pylori eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole and tetracycline.

**214491: One-Week Once-Daily Triple Therapy with Esomeprazole, Moxifloxacin and Rifabutin Is Effective in the Treatment of Helicobacter Pylori Resistant to Both Metronidazole and Clarithromycin**

*Stephan Miehke, Wulf Schneider-Brachert, Andrea Morgner, Ahmed Madisch, Christian Kirsch, Elke Baestlein, Christian Haferland, Claus Jebens, Holger Knoth, Manfred Stolte, Norbert Lehn*

**Objectives:** Failure of standard triple therapy aiming at eradication of H. pylori often leads to post-treatment resistance to metronidazole (MET) and/or clarithromycin (CLA). Subsequent treatment of these patients remains a clinical challenge. We evaluated the efficacy and tolerability of a convenient triple therapy using esomeprazole, moxifloxacin and rifabutin for eradication of H. pylori resistant to both MET and CLA in a prospective open-label study. **Methods:** Consecutive patients with H. pylori infection resistant to both MET & CLA (Etest<sup>®</sup>) were treated with esomeprazole 40 mg, moxifloxacin 400 mg and rifabutin 300 mg, each given orally once daily in the morning for 7 days. Follow-up endoscopy including histology and H. pylori culture was performed 6 to 8 weeks after treatment. **Results:** Between January 2004 and October 2005, 86 patients were enrolled (56 female, 30 male, median age 52 years. 62 patients (72.1%) had a history of two or more previous treatment failures. Three patients (3.5%) discontinued treatment prematurely due to adverse events). 73 patients (85%) are currently available for per protocol efficacy analysis. Successful eradication was confirmed in 58 patients (79.5 %). In the patients with clinical failure (n=15), post-treatment resistance to the test drugs rifampicin and ciprofloxacin were detected in 5 and in 3 patients, respectively. **Conclusion:** One-week once-daily triple therapy with esomeprazole, moxifloxacin and rifabutin is effective and safe for eradication of H. pylori resistant to both metronidazole and clarithromycin in patients with a history of previous treatment failures.

**Additional Reading: Helicobacter pylori: What's Left?**

**220113: Dose Atrophic Gastritis Affect the Accordance between Stool Antigen Test and Serology to Determine Helicobacter Pylori Infection in the Mass Survey?** *Tadashi Shimoyama, Takao Oyama, Shinsaku Fukuda, Shigeyuki Nakaji, Akihiro Munakata*

**Background:** In Japan, infection of *Helicobacter pylori* is often tested in the mass screening for gastric cancer along with the level of serum pepsinogen (PG) I and II. Although infection of *H. pylori* is usually examined by serology, a stool antigen test (EIA) using monoclonal antibody to catalase is now available. We examined *H. pylori* infection by both serology and this stool antigen test in a mass survey and studied whether age of subjects or atrophic gastritis affect the results of the two tests. **Methods:** 994 healthy adults who received mass survey in April 2005 were tested. There were 379 males and 615 females, and the mean age was 57.7±13.9 years old. Stool samples were used to test the prevalence of *H. pylori* antigen by EIA using monoclonal antibody to *H. pylori* catalase. Serum samples were tested for the prevalence of IgG antibody to *H. pylori* by ELISA. The level of PG I and II was also measured and atrophic gastritis was considered significant if both PG I less than 70 µg/L and PGI/II less than 3.0 were observed. **Results:** The prevalence of *H. pylori* infection was defined as 60.7% by serology and 55.4% by stool antigen test. There were 22 subjects who were positive only by stool antigen test and 75 subjects were positive only by serology. The concordance of both tests was not affected by age of the subjects (91.7% in <50 years old, 88.1% in 50s, 92.1% in 60s, and 91.2% over 70 years old). The concordance of these tests was not also different in subjects with atrophic gastritis (91.1%, n=418) and without atrophic gastritis (90.1%, n=576). **Conclusions:** Both age and atrophic gastritis did not have significant effect on the results of serology and stool antigen test. The discrepancy of the results seemed to depend on the sensitivity and specificity of individual tests. Since stool antigen test have been shown to have better sensitivity and specificity, it would be better non-invasive test to determine *H. pylori* infection in the mass survey.

**216740: Seroprevalence of Helicobacter pylori in Two Asymptomatic Dutch Populations.** *A. J van Vuuren, R. A de Man, H. F van Driel, M. Ouwendijk, J. G Kusters, E. J Kuipers, J. H Richardus, P. D Siersema, M. Blankenstein*

**Background:** *Helicobacter pylori* (*Hp*) infection poses a potential risk for developing upper gastrointestinal disorders ranging from peptic ulcers to gastric malignancies. The *Hp* prevalence is thought to be declining in Western countries, probably reflecting a birth cohort effect resulting from improvements in hygiene. **Aims:** To examine the secular trends in the *Hp* seroprevalence in a native Dutch population and in non-Western immigrants by determining the age specific *Hp* seroprevalence in representative groups from both populations. **Methods:** Plasma samples were collected from 794 native Dutch blood donors living in the South-Western Netherlands, which includes Rotterdam. Information concerning age, gender, and geographic region was available, but no donor identity. Another 287 serum samples were collected from asymptomatic volunteers from an urban district of Rotterdam, predominantly populated by non-Western immigrants. All samples were tested for IgG antibodies against *Hp* by a commercial ELISA (Orion Diagnostica), the results were divided into ten-year age groups. **Results:** are summarized in the Table. *Hp* seroprevalence was overall 32% in the native Dutch population: 34% in males, and 30% in females. Logistic regression within donors reveals a higher age specific *Hp* prevalence compared to the younger age groups (p<0,001): odds ratios (95% CI) are respectively 2,1 (1,22-3,57) group II, 2,4 (1,40-4,03) group III, 2,4 (1,38-4,00) group IV, and 4,7 (2,79-7,86) group V. In contrast, in the urban district *Hp* seroprevalence was far higher in all age groups, 72% in males, 66% in females, 69% overall (p< 0.001 Chi-square test), without signs of an age specific increase. No gender differences were observed in either population. **Conclusions:** The secular trend towards lower *Hp* infection rates was observed in the native Dutch population, but not in volunteers of the urban district, with many non-Western immigrants. However, both populations are living in the same region, *Hp* seroprevalence varies. These ethnical differences are of obvious importance to public health authorities planning interventions to lighten the burden of *Hp* associated disease.

Donors				Volunteers		
Age Groups	<i>Hp</i> pos male (%)	<i>Hp</i> pos female (%)	<i>Hp</i> pos total (%)	<i>Hp</i> pos male (%)	<i>Hp</i> pos female (%)	<i>Hp</i> pos total (%)
I = 18-28 y	12/5 (20%)	15/101 (15%)	27/160(17%)	14/19 (74%)	21/38 (55%)	35/57 (61%)
II = 29-38 y	23/8 (27%)	24/73 (33%)	47/158 (30%)	23/35 (66%)	36/47 (77%)	59/82 (72%)
III = 39-48 y	31/9 (34%)	21/69 (30%)	52/160 (33%)	18/26 (69%)	24/36 (66%)	42/62 (68%)
IV = 49-58 y	32/101 (32%)	19/57 (33%)	51/158 (32%)	23/28 (82%)	22/33 (66%)	45/61 (74%)
V = 59-70 y	49/101 (49%)	28/57 (49%)	77/158 (49%)	11/15 (73%)	6/10 (60%)	17/25 (68%)

**220326: Accuracy of Monoclonal Stool Antigen Test for the Diagnosis of *H. Pylori* Infection: a Systematic Review and Meta-Analysis.** *Javier P Gisbert, Felipe de la Morena, Victor Abraira*

**OBJECTIVE:** To perform a systematic review and a meta-analysis of accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection. **METHODS:** Selection of studies: assessing the accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection. Search strategy: electronic and manual bibliographical searches. Data extraction: independently done by two reviewers. Data synthesis: meta-analyses of the different tests were performed combining the sensitivities, specificities, and likelihood ratios (LRs) of the individual studies. **RESULTS:** Pre-treatment studies: Twenty-two studies, including a total of 2,499 patients, evaluated the monoclonal stool antigen test for the diagnosis of *H. pylori* infection before therapy. Pooled sensitivity, specificity, LR+ and LR- were, respectively, 0.94 (95% CI, 0.93-0.95), 0.97 (0.96-0.98), 24 (15-41) and 0.07 (0.04-0.12). The accuracy of both the monoclonal and the polyclonal stool antigen tests was evaluated together in 13 pre-treatment studies, where a higher pooled sensitivity was demonstrated with the monoclonal technique (0.95 vs. 0.83). Post-treatment studies: Twelve studies, including a total of 957 patients, assessed the monoclonal stool antigen test to confirm eradication after therapy. Pooled sensitivity, specificity, LR+ and LR- were 0.93 (95% CI, 0.89-0.96), 0.96 (0.94-0.97), 17 (12-23) and 0.1 (0.07-0.15). The accuracy of both the monoclonal and the polyclonal stool antigen tests was evaluated together in 8 post-treatment studies, where, again, a higher pooled sensitivity was demonstrated with the monoclonal technique (0.91 vs. 0.76). Although heterogeneity among studies was initially present, it disappeared when a single outlier study was excluded. When subanalysis depending on the reference method (gold standard based on only one diagnostic method vs. at least two reference methods) or on the study population (adults vs. children) was performed, the results of the meta-analysis were similar. **CONCLUSION:** Monoclonal stool antigen test is an accurate non-invasive method both for the initial diagnosis of *H. pylori* infection and for the confirmation of its eradication after treatment. The monoclonal technique has a higher sensitivity than the polyclonal one, especially in the post-treatment setting.

**221473: *H. Pylori* Re-Infection in Insulin Dependent Diabetes Mellitus Patients: A Five Years Follow-Up.** *Veronica Ojetti, Dario Pitocco, Alessio Migneco, Michele Santoro, Ilir Leka, Giovanni Gasbarrini, Giovanni Ghirlanda, Antonio Gasbarrini*

**Objective:** Previous data show that diabetic patients (pts) have a low *H. pylori* eradication and a high re-infection rate after 1 year of follow-up. The increased susceptibility of diabetics to infections are based probably on many mechanisms (reduced lymphocyte activity, neutrophil dysfunction, failure of chemotaxis, frequent hospitalization and dental plaque as *H. pylori* reservoir). Aim of our study was to evaluate the *H. pylori* re-infection rate in insulin dependent diabetes mellitus (IDDM) pts and in dyspeptic controls five years after successful eradication, and the impact of *H. pylori* re-infection on glycaemic control. **Methods:** 40 pts (23 males, 17 females; mean age 48 +/- 9) affected by IDDM and 50 dyspeptic control matched for sex and age, previously treated for *H. pylori* infection and successfully eradicated, were submitted to 13C urea breath test (UBT) after five years of follow-up. Daily insulin requirement, glycosylated haemoglobin (HbA1c) expressions of glycaemic metabolic control and the development of organ damage were evaluated. **Results:** We found a significantly higher incidence of *H. pylori* re-infection in IDDM pts compared to controls. In particular, 11 of 40 (27%) IDDM pts vs 2 of 50 (4%) controls resulted re-infected after 5 years ( $p < 0.001$ ). Among IDDM pts, re-infection occurrence was not affected by sex or age. At five years follow-up in the re-infected diabetic pts an increased levels of HbA1c compared to values at enrolment (8.26 vs 7.48,  $p < 0.01$ ) was observed, while no significant increase in HbA1c was found in the negative group. Furthermore, the *H. pylori* positive group showed increased insulin requirements compared to negative pts (0.69/Kg vs 0.61/Kg). These data reached not statistical significance. Finally, we found statistical significant higher prevalence of diabetic organ damages in the re-infected group compared to negative pts: neuropathies: 42 % vs 10 % ( $p < 0.01$ ); nephropathies: 42 % vs 15 % ( $p < 0.01$ ); retinopathies: 28.6% vs 5 % ( $p < 0.05$ ), respectively. **Conclusions:** IDDM pts show higher *H. pylori* re-infection rates compared to dyspeptic controls. *H. pylori* re-infection in IDDM pts is associated with poorer glycaemic control and higher incidence of organ damage compared to not re-infected diabetic patients. UBT as follow-up screening in successfully eradicated IDDM pts seems therefore a useful tool in order to detect re-infected pts and optimize glycaemic control.

**220347: Efficacy of *Helicobacter pylori* Eradication Treatment in Gastric MALT Lymphoma: a Systematic Review.** *Javier P Gisbert, Laura Martin-Asenjo*

**Objective:** To perform a systematic review of studies evaluating the effect of *H. pylori* eradication treatment on the histological regression of gastric MALT lymphoma. **Methods:** Bibliographical searches were conducted in MedLine, and studies evaluating the effect of *H. pylori* eradication treatment on the histological regression of gastric MALT lymphoma were included. **Results:** Forty-one studies were identified, including a total of 1446 patients. After *H. pylori* eradication, complete remission was achieved in 74% of the cases, partial remission in 10%, and no response in 16%, during a mean follow-up of 23 months (range 12 to 35 months). After complete remission, tumoral relapse was detected in 6% of the cases; of these, 25% were associated with *H. pylori* reinfection, and in 15% a high grade MALT lymphoma component was identified. When only patients with MALT lymphoma stage EI (confined to stomach) and with purely low-grade histological type were included, complete

remission was achieved in 80% (95% CI, 77-82%) of the cases. In stage E11 (confined to mucosa or submucosa), the response to eradication treatment was higher than in stage E12 (beyond submucosa): 84% vs. 31%;  $p < 0.0001$ . Conclusion: *H. pylori* eradication in patients with gastric low-grade MALT lymphoma and stage E1 achieves complete remission in 80% of the cases. This figure increases up to 84% in E11 lymphomas, but is of only 31% in E12 ones.

**223626: Three and Seven Days Levofloxacin/Azithromycin-Based Triple Therapies as First-Line Treatment for Helicobacter Pylori Eradication.** Rosalba Finizio, Enrico C Nista, Marcello Candelli, Giovanni Cammarota, Giovanni Gasbarrini, Antonio Gasbarrini

Background and aim: The failure of first-line anti-*H. pylori* therapies is due to primary antibiotic resistance and poor compliance. For this reason it is essential to investigate new antibiotic associations and simple therapeutic schemes. Levofloxacin and azithromycin are broad spectrum antibiotics with long half life administrable in single daily dose that could increase patients compliance. Aim of the study is to compare the efficacy of a 3- and 7-days levofloxacin/azithromycin based *H. pylori* eradication regimen against standard 7-days triple therapy. Material and methods: Ninety Hp-positive patients (infection was assessed by histology and 13-C UBT) were randomized to receive: Group A (30 pts): levofloxacin (500 mg od), azithromycin (500 mg od) and esomeprazole (20 mg bid) for 3 days; Group B (30 pts): levofloxacin (500 mg od), azithromycin (500 mg od) and esomeprazole (20 mg bid) for 7 days; Group C (30 pts) clarithromycin (500 mg bid), amoxicillin (1 gr bid) and esomeprazole (20 mg bid). Hp status was re-checked by 13-C UBT six weeks after end of therapies. Results: *H. pylori* eradication rate in Group A was 86.7% (26/30 pts), in Group B was 93.3% (28/30 pts), in Group C was 70% (21/30) in either ITT or PP analysis. Eradication rate of 7-days levofloxacin/azithromycin-based triple therapy was significantly higher than that observed using standard triple therapy (93.3% vs 70%;  $p < 0.05$ ). Eradication rate of 3-days levofloxacin/azithromycin-based triple therapy was higher even if not significantly than that showed by standard therapy (86.7% vs 70%  $p = 0.06$ ). Incidence of side effects were lower in groups A and B than in group C. Moreover, prevalence of side effects resulted higher in the group B than in group A. Conclusions: According to the present data a 7-days levofloxacin/azithromycin-based triple therapy may be considered a high effective therapy for *H. pylori* eradication.

**217237: Recurrence of H. pylori Infection after Eradication: 5-year Follow-up Study of 1,000 Patients.** Javier P Gisbert, Marta Luna, Blas Gomez, Juan-Manuel Herrerias, Joan Mones, Manuel Castro-Fernandez, Pilar Sanchez-Pobre, Angel Cosme, David Olivares, Jose-Maria Pajares

AIM: To study the incidence of *H. pylori* recurrence, its chronological aspects, and the variables that might influence it. METHODS: 1,000 patients in whom *H. pylori* had been eradicated were prospectively studied. Therapies were classified as low and high efficacy regimens. Four to eight weeks after completion of therapy, 13C-urea breath test was performed, and it was repeated yearly up to 5 years. In some patients, endoscopy with biopsies was also performed to confirm *H. pylori* eradication. RESULTS: 1,000 patients were included, giving 2,744 patient-years of follow-up. Seventy-one *H. pylori* recurrences were observed (2.6% per patient-year). Probability of being *H. pylori*-negative at 1 year was 94.7%, and at 5 years 90.7%. In the multivariate analysis, low age (OR: 1.84; 95% CI: 1.04-3.26) and low efficacy therapies (OR: 2.5; 1.23-5.04) correlated with 1 year *H. pylori* recurrence. Differences were observed when Kaplan-Meier curves were compared depending on age and therapy regimen. CONCLUSION: Risk of post-eradication *H. pylori* recurrence is higher during the first year, which suggests that most recurrences during this period are recrudescences and not true reinfections. *H. pylori* recurrence is more frequent in younger patients and in those treated with low efficacy therapies, but is exceptional if high efficacy therapies are used, in which case post-therapy eradication can be safely confirmed at 4 weeks with 13C-urea breath test.

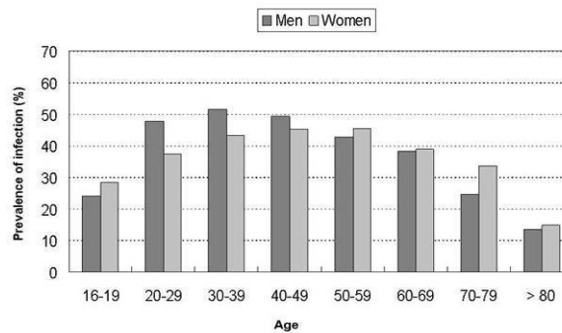
**218215: Where Does the Antimicrobial Resistance of Helicobacter Pylori Come From, Acquired after Birth or Inherited from Parents? : Different Mechanism between Clarithromycin And Levofloxacin.** Naomi Torio, Mutsuko Konno, Ikuya Miki, Daisuke Shirasaka, Yoshinori Morita, Yuko Matsumoto, Hideyuki Miyachi, Takao Tamura, Nobuo Aoyama

Background; Many reports revealed that most *Helicobacter pylori* (*H. pylori*) infection might be transmitted during childhood, mainly from their parents, and however, only a few reports clarified the different acquisition mechanism of antimicrobial resistance of *H. pylori* in childhood between antibiotics. Clarithromycin (CAM)-resistance is a major issue in standard anti-*H. pylori* both in children and adults, in which situation levofloxacin (LVFX) is considered one of alternative agents showing a good efficacy and tolerance. CAM can be used both for children and adults for many infectious diseases, while LVFX cannot for children. Aim; We revealed the mutation pattern and rate of *H. pylori* in the genes associated with CAM- and LVFX-resistance in Japanese children, and focusing on the difference of antibiotics used between children and adults, we clarified whether *H. pylori* antimicrobial resistance in children might depend on their usage of antibiotics after birth or on the inheritance from their parents. Methods; Forty *H. pylori* strains were isolated from 26 Japanese children and 14 parents using biopsy specimens obtained through endoscopy. In order to confirm CAM- and LVFX-resistance, mutations were analyzed in the 23S rRNA gene (A2142G and A2143G) and the *gyrA* gene performing amplification by PCR and direct sequencing, and mutation patterns of *H. pylori* in children were compared to those in their parents. Results; Mutant strains in the 23S rRNA gene

were found in 7 children (26.9%), and none of their parents harbored mutants in this gene. Mutants in the *gyrA* gene were found in 3 children (11.5%), and 2 of their parents harbored the same type of mutation point in this gene (Asn to Lys at amino acid 87). Conclusion; CAM-resistance rate of *H. pylori* is very high in Japanese children compared to that in Japanese adults previously reported, which may depend mainly on its frequent use in childhood. In contrast, LVFX-resistance is often found although LVFX cannot be used for children, which suggests that LVFX-resistance may be originated from their parents. We have to realize the importance of proper usage of antibiotics in consideration of not only acquired but also inherited antimicrobial resistance of *H. pylori*.

**214961: Lower Prevalence of *Helicobacter pylori* Infection in Young Women: a 9-year Observational Study.** Sun-Young Lee, Sang Kyun Yu, In-Kyung Sung, Hyung-Seok Park, Choon-Jo Jin, Won Hyeok Choe, So Young Kwon, Chang Hong Lee, Kyoo Wan Choi

**Background and Aim:** Although many studies have reported on the trends of changes since *Helicobacter pylori* was first discovered in 1982, detailed information is still lacking. We surveyed the detailed information on the trends of changes in the prevalence of *Helicobacter pylori* infection relative to age and gender. **Methods:** A total of 8646 subjects aged 16 years or older (4099 men and 4547 women) who submitted to a rapid urease test during upper gastrointestinal endoscopy, from January 1997 to July 2005, were included in this study. We investigated how the prevalence of *H. pylori* infection varied with gender and age at the date of examination. **Results:** *H. pylori* infection was noted in 3747 cases (43.3%) of all cases. The infection rate was 50.0% in 1997, but declined gradually down to 40.6% in 2005 ( $P < 0.001$ ). In addition, the prevalence was higher in men (49.0%) than in women (41.6%) before the age 50 years ( $P < 0.001$ ) in any of the years studied. In contrast, there was no difference in the prevalence of *H. pylori* infection between the men (39.2%) and women (41.1%) after the age 50 years ( $P = 0.28$ ). **Conclusions:** *H. pylori* infection has gradually decreased over the past decade, and there is a lower rate of infection among young women aged less than 50 years old when compared to men. Female sex hormone might be the cause of this gender-related difference in the prevalence of *H. pylori* infection, which explains indirectly the lower prevalence of intestinal-type gastric cancer among young women. **Key Words:** *Helicobacter pylori*, Prevalence, Young, Women



**225760: Influence of Polymorphisms in the *NOD1/CARD4* and *NOD2/CARD15* Genes on the Clinical Outcome of *H.pylori* Infection.** Philip C Rosenstiel, Stephan Hellmig, Jochen Hampe, Wolfgang Fischbach, Hany Sahly, Ralph Lucius, Dana Philpott, Stefan Schreiber

**Background:** Host immune response influences the clinical outcome of *H.pylori* infection leading to ulcer disease, gastric carcinoma and MALT-lymphoma. A genetic risk profile for gastric cancer has been identified, but genetic susceptibility to develop MALT-lymphoma is still unclear. We investigated the role of NOD1 and NOD2 as intracellular recognition molecules for pathogen-associated molecules in *H.pylori* infection in vitro and analysed the influence of single nucleotide polymorphisms on susceptibility to ulcer disease and MALT-lymphoma. **Methods:** The influence of NOD1 and NOD2 expression on *H.pylori*-induced NF- $\kappa$ B activation was assessed using luciferase reporter gene assays. Expression of NOD1 and NOD2 protein in the gastric mucosa was investigated using Western Blot of isolated gastric epithelial cells and by immunohistochemistry of biopsy material. 534 healthy blood donors, 440 *H.pylori* infected patients with chronic gastritis and gastric ulcer and 153 patients with gastric MALT-lymphoma were genotyped for NOD1 and NOD2 polymorphisms by Taqman technology. Associations were tested in a case-control setting. **Results:** Expression of NOD1 and NOD2 significantly sensitized HEK293 cells to *H. pylori*-induced NF- $\kappa$ B activation in a *cagPAI*-dependent manner. In cells carrying the Crohn-associated NOD2 variant R702W the NF- $\kappa$ B response was significantly diminished. NOD1/NOD2 expression levels were induced in the gastric epithelium in *H.pylori*-positive patients. No mutations were found to be associated with gastritis or gastric ulcer development. However, the R702W mutation in the NOD2/CARD15 gene was significantly associated with gastric lymphoma. Carrier of the rare allele T had a more than doubled risk to develop lymphoma than controls (OR: 2.4, 95CI: 1.2-4.6;  $p < 0.044$ ). **Conclusions:** *H.pylori*-

induced upregulation of NOD 1 and NOD2 in vivo may play a critical role in the recognition of this common pathogen. A missense mutation in the leucine-rich region of CARD15 is associated with gastric lymphoma.

**225688: Induction of Autophagy, A Novel Effect of *H. pylori* Vacuolating Toxin VacA.** Mauricio R Terebiznik, Cristina L Vazquez, Karl Torbicki, Noboru Mizushima, Tamotsu Yoshimori, Maria I Colombo, Nicola L Jones

Autophagy is an evolutionarily conserved mechanism for the degradation of cellular components in the cytoplasm. It has multiple physiological functions including protein degradation, organelle turnover and autophagic type II cell death. In addition disruption of autophagy has also been implicated in carcinogenesis. Although bacteria and viruses are vulnerable to autophagy, several intracellular pathogens have developed strategies to utilize this pathway for their own benefit. Current evidence indicates that *H. pylori* can invade epithelial cells in the gastric mucosa and survive inside large vacuolar compartments. However, relatively little is known about the biology of *H. pylori* invasion and survival in host cells. In AGS cells invaded with *H. pylori*, bacteria containing vacuoles originate through the fusion of late endosomal-lysosomal organelles by a mechanism based on the ability of the VacA toxin to hijack the small GTPase Rab7 at the membrane of the bacterial compartment. Since the scission of Rab7 from its functional locations disrupts the host's endocytic pathway, we hypothesized that *H. pylori* could induce a nutritional stress that triggers autophagy. To assess this possibility, we monitored the outcome of autophagy by expressing the autophagic protein markers Rab24 and LC3 in AGS cells. *H. pylori* infection caused the recruitment of GFP-LC3 and Rab24 to a sub-population of intracellular compartments where *H. pylori* resides. To further confirm this observation, we utilized embryonic fibroblast cells defective for autophagy (*atg5*<sup>-/-</sup> MEFs). In *atg5*<sup>-/-</sup> MEFs *H. pylori*-containing vacuoles were not labeled with LC3 indicating that autophagy is responsible for the recruitment of LC3 to the *H. pylori* vacuolar membrane. Importantly, the engagement of the autophagic pathway was totally dependent on the presence of the bacterial toxin VacA since autophagy was not detected when isogenic VacA mutant bacteria were utilized. Furthermore, our findings indicate that autophagy contributes to vacuolation since the vacuolating phenotype was impaired in autophagy deficient mutant cells infected with *H. pylori* or exposed to VacA positive bacterial supernatants. Our results describe a novel interaction of *H. pylori* with the host cell. Since modulation of autophagy has been linked with carcinogenesis these findings may have relevance for the development of *H. pylori* associated pathologies.

**224940: CD4+CD45RB<sup>lo</sup>CD25+ Regulatory Lymphocytes Protect against Induction of *Helicobacter pylori* Gastritis in C57BL/6 Mice through an IL10 Dependent Mechanism.** Chung-Wei Lee, Varada P Rao, Susan E Erdman, Arlin B Rogers, James G Fox

Mouse models of *Helicobacter pylori* (Hp)-induced gastritis and associated lesions are valuable for the study of immunopathogenesis of gastric cancer in humans. Gastritis due to Hp involves CD4+CD45RB<sup>hi</sup> effector T cells both in mice and humans, whereas T cell populations of CD4+CD45RB<sup>lo</sup> CD25+ phenotype are known to be protective against Hp-induced gastritis. Interestingly, IL10-deficient C57BL/6 mice develop more severe Hp-induced gastritis than wild-type (WT) mice. We hypothesized that IL-10, a potent immunosuppressive cytokine of regulatory T cells, is critical for the control of gastritis in the host. In the present study, we assessed regulatory function of CD4+CD45RB<sup>lo</sup>CD25+ T cells from WT or IL10-deficient donors in Hp-infected C57BL/6 Rag2<sup>-/-</sup> mice that have received CD4+CD45RB<sup>hi</sup> effector T cells (Table 1). Severe gastritis and wasting occurred in Hp-infected Rag2<sup>-/-</sup> mice 10-12 weeks post transfer with effector T cells (inflammatory score 2.7+/-0.11). In contrast, Hp-induced gastritis was ameliorated in mice that received co-transfer of effector T cells and regulatory T cells from WT donors (1.0+/-0.15, p<0.001). Suppression of gastritis, however, was not observed when regulatory T cells from IL10<sup>-/-</sup> donors were used (inflammatory score 2.0+/-0.35, p=0.146), suggesting that IL10 is critical for regulatory T cell function of CD25+ cells in this model. Similarly, adoptive transfer of WT regulatory T cells was effective in ameliorating pan-gastritis observed in mice that have received effector T cells in the absence of Hp infection. We observed a significant decrease in Hp colonization in mice reconstituted with effector T cells compared to non-transferred control animals. Compared to the non-transferred group, mice that have received co-transfer of effector and regulatory T cells also had lower levels of Hp colonization. These data support previous studies demonstrating that mounting an immune response against Hp reduces Hp colonization in the gastric compartment. These findings highlight the important protective role of IL10-competent CD4+CD45RB<sup>lo</sup>CD25+ regulatory T cells in Hp pathogenesis, and suggest that approaches aimed at selectively enhancing regulatory T cell function in humans may prevent Hp-induced gastritis and gastric cancer.

Table 1

Group	<i>H. pylori</i>	TE	TR	Inflammation score	Colonization log (CFU/g)
Hp	+	-	-	0.7+/-0.10 <sup>†</sup>	5.73+/-0.24
Hp+TE	+	+	-	2.7+/-0.11	1.26+/-0.52*
Hp+TE+wt TR	+	+	WT	1.0+/-0.15 <sup>†#</sup>	2.77+/-0.89*
Hp+TE+IL10 <sup>-/-</sup> TR	+	+	IL10 <sup>-/-</sup>	2.0+/-0.35	2.06+/-1.19*

<sup>†</sup>p<0.001 when compared to Hp+TE group, <sup>#</sup>p<0.05 when compared to Hp+TE+IL10<sup>-/-</sup>TR group \*p<0.001 when compared to Hp group