Third-line Rescue Therapy with Levofloxacin Based Protocol for H. pylori Eradication in Children

Çocuklarda Tedaviye Yanıtsız H. Pylori Eradikasyonunda 3. Basamak Levofloksasin İçeren Kombinasyon Tedavisi

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Abstract

Objective: Triple therapy is the preferred regimen for *H. pylori* eradication in children. Levofloxacin included regimens are one of the treatment choices for adult patients in whom the first line triple therapy has failed.However, limited data is available for children.

Methods: This is a prospective, open-label, follow-up study to evaluate the efficacy of different therapeutic regimen for *H. pylori* infected children. The primary end point was to determine the rate of treatment failure of *H. pylori* infected children with first (ACL; amoxicillin, lansoprozole, clarithromycin) and second (MDBL; metranidazole, doxycycline, bismuth subcitrate, lansoprozole) line therapy regimens. The secondary end point was to evaluate the eradication rate and safety of levofloxacin based regimen (LML, including levofloxacin, metronidazole, lansoprozole) in *H. pylori* infected children who were non-responders to first or second line regimens.

Results: 61 symptomatic children who were infected with *H. pylori* were treated with ACL protocol and 36 (59%) were cured. Fifteen (60%) of the remaining 25 patients were cured with MDBL protocol. All the remaining patients in whom therapy had failed (n=10) were successfully treated with a third line therapy of LML protocol. No side effects were observed during treatment and follow up period.

Conclusion: Levofloxacin based triple therapy seems safe and effective as a third line rescue therapy in *H. pylori* infected children who failed to respond to triple or quadruple therapies. Further larger randomized controlled trials are needed to test the potential clinical efficacy and also safety of levofloxacin based regimens in *H. pylori* infected children.

(J Pediatr Inf 2009; 3: 98-103)

Key words: *H. pylori*, children, levofloxacin

Özet

Amaç: Çocuklarda *Helicobacter pylori* eradikasyon tedavisinde üçlü ilaç tedavisi tercih edilmektedir. İlk basamak tedavilere yanıt vermeyen erişkin hastalarda levofloksasin içeren kombinasyon tedavi seçeneği olarak kullanılabilmektedir ancak çocuklarda bu konu ile ilgili yeterli bilgi bulunmamaktadır

Yöntemler: Prospektif, açık-etiketli, izlem çalışmasında *H. pylori* infeksiyonu olan semptomatik çocuklarda farklı tedavi protokollerinin değerlendirilmesi planlandı. Çalışmanın birinci amacı birinci (ACL; amoksisilin, lansoprazol, klaritromisin) ve ikinci (MDBL; metranidazol, doksisiklin, bizmut sitrat, lansoprazol) basamak eradikasyon tedavilerinin etkinliğinin değerlendirilmesi idi. Birinci ve ikinci basamak tedaviye yanıt alınamayan olgularda levofloksasin içeren tedavi protokolünün (LML, levofloksasin, metronidazol, lansoprazol) etkinliği ve yan etki profilinin değerlendirilmesi planlandı.

Bulgular: *H. pylori* ile enfekte olan 61 semptomatik çocuğa ACL protokolü verildi ve olguların 36'sında (%59) eradikasyon sağlandı. Yanıt alınamayan 25 olgudan 15'inde (%60) MDBL protokolü ile eradikasyon sağlandı. İlk iki basamak tedavi ile yanıt alınamayan 10 olgunun tamamı levofloksasin içeren LML kombinasyonu ile başarı ile tedavi edildi. Tedavi süreci ve takip dönemimde herhangi bir yan etki gözlenmedi.

Sonuç: Levofloksasin içeren üçlü tedavi birinci ve ikinci basamak tedavilere yanıt alınamayan *H. pylori* ile enfekte çocuklarda etkin ve güvenilir bir tedavi seçeneği olarak görülmektedir. Ancak çocuklarda levofloksasin içeren protokolün etkinliği ve güvenirliği ile ilgili daha geniş çalışmalara gereksinim duyulmaktadır. *(Çocuk Enf Derg 2009; 3: 98-103)*

Anahtar kelimeler: *H. pylori*, çocuk, levofloksasin

Geliş Tarihi: 01.07.2009
Kabul Tarihi: 03.08.2009

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Introduction

Helicobacter pylori (H. pylori) infection is common worldwide. Seropositivity rates in Turkey vary between 23.9% and 78.5% (1-2). *H. pylori* colonizes the gastric mucosa and leads to clinical manifestations ranging from asymptomatic infection to peptic ulcer and gastric cancer (3-4). Although gastric mucosal colonization begins mostly in early childhood, *H. pylori* related diseases are rare in children. Clinical trials have generated contradictory results about the management of *H. pylori* infection in children and different protocols are used in different countries. As a first line regimen, the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommended triple therapy consisting of ta wice daily proton pump inhibitor (PPI) combined with two antibiotics, either clarithromycin-amoxicillin or metronidazole-amoxicillin, for 1-2 weeks. For patients in whom initial treatment has failed, a second line of quadruple therapy was recommended. In this quadruple therapy, a bismuth preparate and metronidazole is combined with either a PPI or ranitidine , with an additional antibiotic (tetracycline or clarithromycin in the former and clarithromycin in the latter) (5). Nevertheless antibiotic resistance is a growing problem worldwide and both triple and quadruple therapy modalities seem to be insufficient in some cases. Up to 20-30% of treatment failures have been reported for both triple and quadruple regimens. Regimens including levofloxacin have been demonstrated to be effective protocols in *H. pylori* treatment in adults, showing an eradication rate of 73-82% (6).

The primary end point of this study was to determine the resistant *H. pylori* infected children with firstly, triple and secondly, quadruple therapy regimens. The secondary end point was to evaluate eradication rate and safety of levofloxacin based regimen (LML, including levofloxacin, metronidazole, lansoprozole) in *H. pylori* infected children who were non-responders to first or second line regimens. To the best of our knowledge, this is the first study that uses levofloxacin in *H. pylori* eradication regimens in children.

Patients and Methods

This is a prospective, open-label, follow-up study for the evaluation of therapy regimens for *H. pylori* in children who were admitted to our Pediatric Gastroenterology, Hepatology outpatient clinic in Turkey with various dyspeptic symptoms. The presence of *H. pylori* infection was assessed first with a ^{14}C urea breath test (UBT) (since we do not have the opportunity of using ^{13}C in our institution) (7). An upper gastrointestinal endoscopy (performed by Olympus XQ260N Olympus Optical, Tokyo, Japan) was then performed for all children, after informed consent was obtained, and at least two biopsies were taken from the antrum. Patients were accepted as *H. pylori* infected when *H. pylori* were demonstrated histologically and the ^{14}C urea breath test was positive. Unfortunately *H. pylori* culture and antibiotic sensitivity tests could not be performed. Patients with *H. pylori* associated endoscopic findings (chronic gastritis, gastric or duodenal ulcer) and diagnosed with *H. pylori* infection were treated with a first line regimen composed of lansoprozole (1-1.4 mg/kg/day), amoxicillin (30mg/kg/day), and clarithromycin (15 mg/kg/day) (ACL) for a two- week period. They were reevaluated four weeks after treatment with ^{14}C UBT. Those who were still symptomatic (epigastric pain, vomiting, dyspepsia such as early satiety, feeling of indigestion) and still had *H. pylori* infection detected by ^{14}C UBT, underwent a second line regimen consisting of lansoprozole (1-1.4 mg/kg for 14 days), metronidazole (30 mg/kg for 7 days), doxycycline (2 mg/kg/day for 7 days), and bismuth subcitrate (8 mg/kg/day for 7 days) (MDBL). Patients in whom first and second line therapy had failed to eradicate *H. pylori* infection and who were still suffering from the same symptoms were offered treatment and were administered a third line rescue treatment composed of lansoprozole (1-1.4 mg/kg/day), levofloxacin (10 mg/kg/day twice daily), and metronidazole (30 mg/kg/day three times a day) (LML) prospectively. Therapy failure was defined as positive ^{14}C UBT four weeks after each treatment regimen (6,8). Metronidazole was chosen in the LML regimen since amoxicillin and clarithromycin were the most frequently used antibiotics in this study group according to the parent questionnaire and medical prescription record of the children. Patients and parents were asked to write and note any side effects they noticed as a result of the levofloxacin regimen. They were especially warned about arthralgia, arthritis, rash, and vomiting and were asked to contact us in the case of these adverse events, which may be attributed to levofloxacin. In order to control compliance, parents were advised to give the drugs. Treatment protocol was approved by the institutional ethics committies, patients and parents were asked for voluntary participation, and parents gave their written consent. Patients were re-evaluated and invited for recurrent visits to check for possible chondrotoxicity for six months duration at two- month intervals or when they had any skeletal complication.

The primary end point of this study was to determine the treatment failure of *H. pylori* infected children with first (ALC; amoxicillin, lansoprozole, clarithromycin) and second (MDBL; metranidazole, doxycycline, bismuth subcitrate, lansoprozole) line therapy regimens. The secondary end point of this study was to evaluate the eradication rate and safety of the levofloxacin based regimen (LML, including levofloxacin, metronidazole, lansoprozole) in *H. pylori* infected children who were non-responders to first or second line regimens.

Çocuk Enf Derg 2009; 3: 98-103
J Pediatr Inf 2009; 3: 98-103

Statistical Analysis: SPSS for Windows 13.0 package was used for statistical tests. The χ-square test was used to compare the gender distribution and histopathology of the eradication rate. Independent *t* test was used for comparison of age between responders and non-responders to treatment. Values are presented as mean±standard deviation. p values below 0.05 were considered significant.

Results

Recruited children and therapy protocols were summarized in Figure 1. Between November 2006 and November 2007, 110 consecutive patients with dyspeptic symptoms and abdominal pain underwent upper endoscopy, and 61 of them (43 girls, 18 boys) aged between 6 to 18 years (mean age 13.3±2.9 years) were found to be *H. pylori* infected.

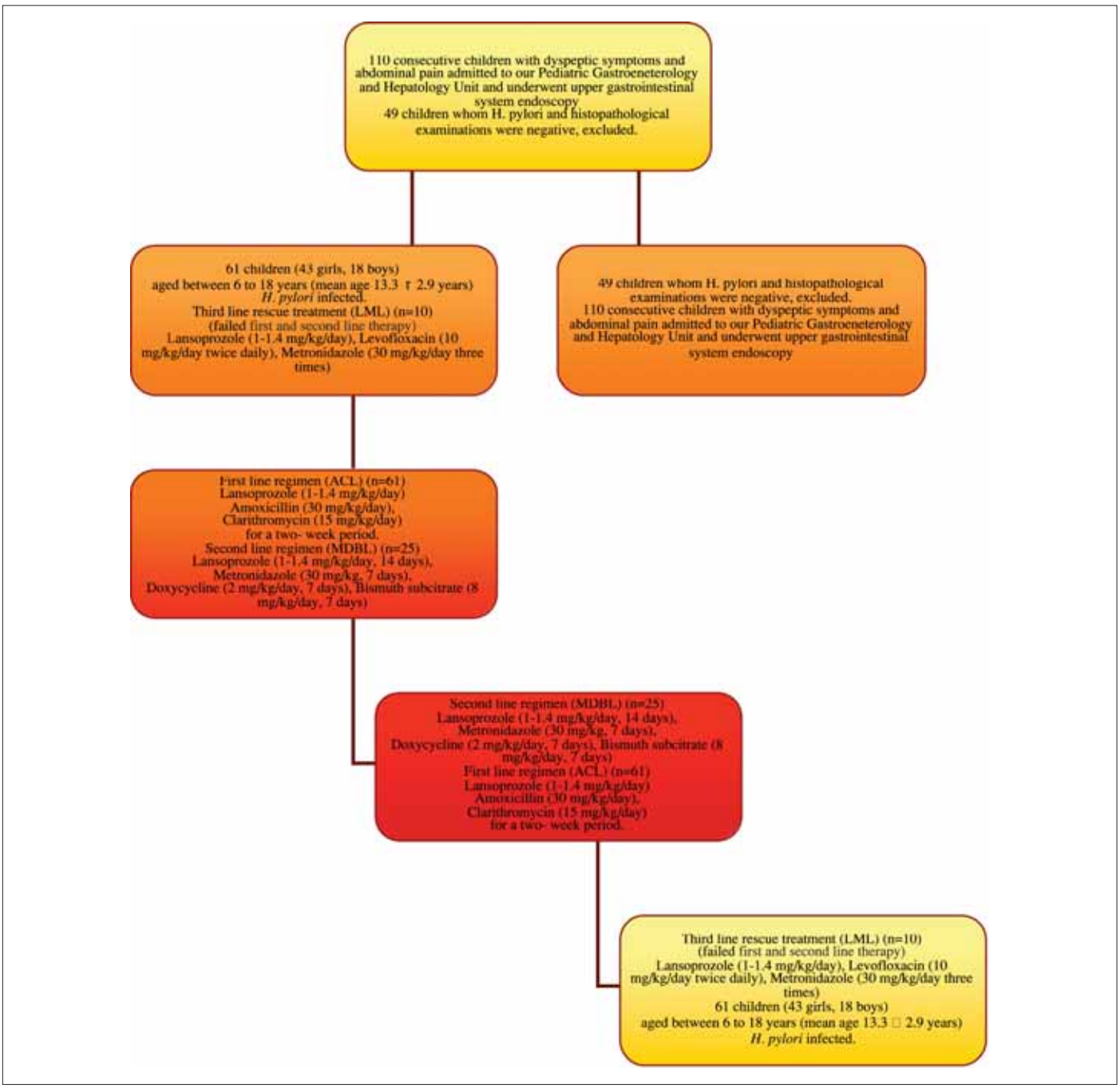

Figure 1. Study design and characteristics of enrolled children

Table 1. Symptoms on admission of children (n=61)

Symptoms	% (n)
Epigastric pain	67.2% (n=41)
Dyspepsia	41.0 % (n=25)
Regurgitation	39.3% (n=24)
Heartburn	32.8 % (n=20)
Vomiting	26.2% (n=16)
Dysphagia	3.3 % (n=2)
Odynophagia	3.3 % (n=2)

All of these 61 children were naive for *H. pylori* treatment. Their chief complaints were epigastric pain in 41 (67.2%) children, and dyspepsia (early satiety and feeling of indigestion) in 25 (41.0%) children. Other symptoms and clinical findings are summarized in Table 1. The main findings on upper endoscopy were antral gastritis in 44 (72.1%) cases, duodenitis in 12 (19.7%) cases, pangastritis in 10 (16.4%) cases, esophagitis in nine (14.8%) cases, duodenal ulcer in two (3.3%) cases, erosive gastritis in two (3.3%) cases and no pathology in two (3.3%) patients. On histopathological examination, 26 patients (42.6%) had activated chronic gastritis, 20 (32.8%) patients had chronic gastritis, 15 (24.6%) patients had duodenitis and one (1.6%) had acute gastritis. Intestinal metaplasia was noted in one patient, as was intestinal atrophy.

All of these 61 children had received ACL therapy protocol as a first line regimen (Figure 1). Fifty nine percent (n=36) of these patients were cured with the ACL regimen, whereas 25 (41%) of them had a failed treatment. These 25 children had received MDBL regimen as a second line regimen. Fifteen of these 25 resistant patients (60%) were treated successfully with MDBL regimen. So 51 patients (83.6%) were cured with the first and second line regimens. The overall treatment failure with the two most preferred treatment regimens (ACL+MDLB) was 16.4% (n=10). These10 patients have been treated with the 3rd line (LML) treatment protocol. Eradication was achieved in all of them.

All of the cases of duodenal ulcer and acute gastritis were cured with first line treatment (ACL). However, only 50% of chronic gastritis, 57.7% of activating chronic gastritis and 60% of duodenitis cases were cured with ACL protocol (Table 2). In terms of ACL treatment failure, there was no difference between the presence chronic gastritis, activated chronic gastritis and duodenitis ($p>0.05$ for all). Gender distribution and age were similar between responders and non-responders to ACL treatment ($p>0.05$ for both). During the follow-up period *H. pylori* - associated symptoms disappeared completely in all children, but 10 out of 61 children (16.4%) still had symptoms which were attributed to gastroesophageal reflux (retrosternal pain, dysphagia, odynophagia, and heartburn) in spite of eradication achievement. Among these ten patients, nine complained of heartburn in addition to epigastric pain at application. The remaining patient developed heartburn after eradication.

Two patients complained of nausea during treatment with ACL regimen, whereas no side effects were observed with MDLB and LML regimens. During the 6 months of follow up period after treatment, no side effects were observed in children who had received levofloxacin based regimen.

Discussion

H. pylori is a gram-negative flagellated microorganism that colonizes the gastric mucosa in nearly half the world. Acquisition starts early in life, and 78% of Turkish children become infected with this microorganism by 16 years of age (9). Spontaneous clearance is possible but rare and varies with geographical region, with a 5 ,5% rate in Turkey (10). European *H. pylori* study groups and Canadian *H. pylori* study groups have reported a consensus statement concerning who to investigate, how to

Table 2. Demographic, histopathologic and endoscopic findings of patients treated with three different regimens

	First line treatment ACL (n=61)	Second line treatment MDBL (n=25)	Third line treatment LML (n=10)
Age (years)	13.2±3.6	13.5±2.8	13.3±2.9
Gender (F/M)	25/11	12/3	6/4
Therapy results	Cured/Total	Cured/Total	Cured/Total
Chronic gastritis	10/20	5/10	5/5
Activated chronic gastritis	15/26	7/11	4/4
Duodenitis (histopathologically)	9/15	4/6	2/2
Acute gastritis	1/1	0	0
Duodenal ulcer	1/1	0	0
Erosive gastritis	1/2	0	1/1

investigate and who to treat for *H. pylori* infection in children (11-12). According to these statements there is no specific clinical picture of *H. pylori* infection, Children should be investigated for *H. pylori* only when their symptoms are indicative of organic disease (chronic gastritis, peptic ulcer) and upper GI endoscopy is the preferred method. They also stated that physicians should offer treatment for the infection if a child undergoes endoscopy and *H. pylori* is identified without peptic ulcer but with information to the parents that eradication of *H. pylori* does not necessarily lead to relief of symptoms. NASPGAN stated that an initial treatment regimen should comprise two antibiotics, PPI or H2 antagonist, for 7-14 days, the so called triple therapy. When the first line regimen fails they recommended a second line option consisting of two antibiotics, bismuth perpetrate and PPI or H2 blocker, the so called quadruple therapy (5). Various different regimens are used in children worldwide and the best treatment regimen still needs to be clarified in children. The Pediatric European Register for Treatment of *Helicobacter pylori* (PERTH) study identified 27 different regimens (13). According to the results of a meta-analysis performed by Khurana et al (14) triple therapies where two antibiotics were combined with a PPI or bismuth for a 2 week period appeared to be the most efficacious option. Addition of PPI to amoxicillin and clarithromycin increased the eradication rate (15). On the other hand, this was not the case with the amoxicillin- tinidazol combination. Dual therapy with these two antibiotics and triple therapy comprising lansoprozole in addition to these antibiotics seemed equally effective (16). Bismuth containing triple therapies were found to be more effective in the PERTH analysis. But a two week treatment course was not found to be more effective than a one week regimen (13-14). In the meta analysis of Khurana et al. (14) the most commonly used triple regimen was PPI-clarithromycin-amoxicillin for a 2 week period, but with this regimen treatment success was lower in developing countries than in Europe (67% vs. 80%) (18). With the same regimen Faber et al. (17) and Gottrand et al. (15) achieved an eradication rate of 63%-74%, respectively. In our study, children diagnosed with *H. pylori* infection were treated with a first line regimen composed of amoxicillin, clarithromycin, lansoprozole (ACL) for a 2-week period. and only (59%) of the patients achieved eradication, which is much lower than previous reports (18). But Usta at al also reported a 60.5% eradication rate with the same regimen and equal duration in a neighbouring region. This may be due to the clarithromycin resistance which was reported to be 18.2% in our region (19).

Patients with peptic ulcer cases respond better than chronic gastritis, as in our study all the children with peptic ulcers and acute gastritis were cured with the ACL regimen (3, 20). However, neither histopathological differences nor gender and age were correlated with eradication rate.

In quadruple therapies where PPI was combined with three different antibiotics (metronidazole, clarithromycin, amoxicillin, or furazolidone or probiotics), the eradication rate has been reported as 80-94% (18). Protocols with bismuth are found to be more effective (13). Our result with quadruple therapy (MDBL; metronidazole, doxycycline, lansoprozole, bismuth subcitrate), with which we achieved a 60% eradication rate, was not satisfactory. Also Usta et al. (8) reported a 66.7% eradication rate in 89 patients.

In our study, 16.4% of patients failed to respond to treatment with the quadruple regimen using the same antibiotics and duration as both triple and quadruple therapy, pointing to the need for third line rescue treatment. The best approach in antibiotic selection is to decide the treatment according to an antibiotic susceptibility test when possible. However, when impossible, a logical approach is to choose the antibiotics according to the knowledge about the antibiotic susceptibility of *H. pylori* strains in that geographical region. Levofloxacin is a member of the fluoroquinolones, and it has broad spectrum antibiotic activity against gram negative/positive strains. The *H. pylori* eradication rate of levofloxacin included regimens was 66% in adults (6,21,22), whereas in our study all of the children were eradicated. The use of fluoroquinolones in children has been limited due to concern about their experimental chondrotoxicity. The limited use of levofloxacin in childhood could explain its high eradication rate (6-23). Although they have potential chondrotoxicity, demonstrated in laboratory animals, levofloxacin and other fluoroquinolones have been used in children with other indications in several clinical trials without any signs of chondrotoxicity (24). In our study, the mean age of our patients was 13years, but with the same levofloxacin dose and duration (10 mg/kg/day, 10 days) cartilage damage has not been documented in prospective and retrospective clinical trials even in children aged 1-3 years of age. Radiological imaging has not been performed in our patients, but none of them complained of arthritis, arthralgia or tendinopathy during their therapy or after six months of follow up. Ten days of a levofloxacin- including regimen was well tolerated and no serious side effects were observed.

The limitation of our study was that it consists of results of only ten children on the levofloxacin based regimen. Further larger randomized controlled trials are needed for assessing the potential clinical efficacy and also safety of levofloxacin based regimens in *H. pylori* infected children.

In conclusion, this clinical study demonstrated that current regimens used to eradicate *H. pylori* are not satisfactory. A ten-day rescue therapy with a triple combination of levofloxacin, metranidazole and lansoprozole constitutes an encouraging third line regimen. It may be used as a rescue therapy in symptomatic *H. pylori* infec-

ted children when the benefit is judged to be greater than the potential cartilage damage. Treatment of asymptomatic and resistant *H. pylori* infected children needs to have a consensus and remains an issue for further study.

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