Table 2.7. Impact of *helicobacter pylori* eradication on gastric mucosal associated lymphoid tissues (MALT) lymphoma

Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Wotherspoon *et al.* (1993), UK, Italy	6 patients (3m/3f, age range 37-76 years) with primary gastric low-grade β-cell MALT lymphoma. Gastric MALT lymphoma diagnosed as unequivocal partial destruction of gastric glands or crypts by groups of centrocyte like cells. *H. pylori* assessed by H & E stains with negative findings confirmed by modified Giemsa	Ampicillin with metronidazole or tripotassium dicitrobismuthase in 5 cases and 1 case received metronidazole and omeprazole. Dose/duration not reported	6/6 (100%)	5/6 complete remission 1/6 residual infiltrate within lamina propria suspicions for lymphoma	Endoscopy 1-2 months and 4-10 months later. An average of 10 paired biopsisis (range 3-15) for molecular genetic studies and routine histology	
Stolte *et al.* (1994), Germany	16 patients with low grade MALT lymphoma and *H. pylori*	80 mg omeprazole and 2 g amoxicillin per day for 10 days	Not specified	12/16 treated patients regression was found at follow-up In 6 of 12 sparse residual lymphoma answered	Endoscopic and histologic assessment prior to therapy and at 4 weeks and 3 months post therapy. Some patients followed 6 to 12 months.	98.3% of specimens from 205 surgical specimens containing primary malignant MALT b-cells lymphomas had chronic active gastritis, typical of *H. pylori* induced gastritis.
Bayerdörffer *et al*. (1995) Germany	33 patients with primary gastric low-grade MALT lymphoma, histologically confirmed; 18 men, 15 women, aged 31-84 years with a mean age of 58	14-day course of omeprazole 120mg/day in 3 doses and amoxicillin2.25g/day in 3 doses. One patient with allergy and another who did not respond were given 250 mg clarithromycin and 1200 mg metronidazole (both in 3 doses/day) and 40 mg omeprazole daily for 10 days	97% eradicated (94% by intent to treat) for final course of omeprazole and amoxicillin	Complete remission 23 (70%) Partial regression 4 (12%) No change 6 (18%)	All patients followed-up for median of 12.5 months (range 6-18.0). No relapse of low grade MALT occurred; however 1 patient had a high grade lymphoma of nasal concha detected 5 months after successful treatment of primary gastric MALT lymphoma. No reinfection of *H. pylori* detected	4 of 5 patients referred for surgery because no cure was achieved showed transition to high grade lymphoma and should have been staged $\geq$ EII

Table 2.7. Impact of *helicobacter pylori* eradication on gastric mucosal associated lymphoid tissues (MALT) lymphoma

Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Pinotti *et al*. (1997), Italy	93 patients with histologically diagnosed low-grade β-cell MALT lymphoma, median age 63 years, range 21-89, 46 f/47 m Stage I 82 (88%) Stage II 4 (4%) Stage IV 7 (87%)	49 patients treated with antibiotics and 45 were evaluable (other lymphoma treated by chemotherapy or combined modalities) 1st line treatment: 2 weeks of amoxicilline (500 mg, 3 doses/day) plus metronidazole (480 mg, 4 doses/day) coloidal bismuth (120 mg, 4 doses/day) or omeprazole (20 mg, 2 doses/day)	44/45 (97%) complete eradication but 9/45 required second line antibiotics to achieve eradication	81 patients with stage I disease Complete remission 52/81 (64%) Partial regression 5/81 (6%) No change 18/81 (22%) Not evaluable 6/81 (8%) 49 patients treated with antibiotics Complete remission 30/49 (61%) Partial regression 4/49 (8%) No change 11/49 (23%) Not evaluable 4/49 (8%)	Antibiotics treatment group followed by regular endoscopic biopsies every 3-6 months and responses histologically evaluated and graded by Woltherspoon histological score. Post-treatment score < 3 evidence of complete remission. Data analyzed at median follow-up of 34 months	
Neubauer *et al*. (1997), Germany	50 patients with stage E1 low-grade gastric MALT lymphoma, 22 f, 28 m. The 50 patients include 17 new patients and 33 patients previously described in Bayerdorffer *et al*, 1995	Amoxicillin, 2.25 g/day and omeprazole, 120 mg/day in 3 doses for 2 weeks	50/50 (100%)	Complete remission 40/50 (80%) Partial regression 4/50 (8%) No change 6/50 (12%)	Median follow-up 24 months (729 days, range 135-411 days). Relapse: 5/40 with complete remission 4 of 6 patients whose lymphoma did not respond to *H. pylori* eradication showed high grade lymphoma at surgery	

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Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Savio *et al*. (2000), Italy (1991-1997)	109 patients with low-grade gastric MALT lymphoma diagnosed histologically and scare by Wotherspoon system 101 stage IE	101 stage IE patients treated with antibacterial therapy	Eradication assessed 6 weeks post therapy	Complete histologic remission 71/76 Remission achieved in 3 months 61 cases 12 months 5 cases 24 months 2 cases Indeterminate time 8 cases	99 of 101 patients to be followed every 6 months for 5 years and annually there after; only 76 were followed for more than a year and included in analysis	
Chen *et al* (2001), Taiwan	16 cases of high grade gastric MALT 6 men, 10 women; median age 55.0 years	Amoxicillin 500 mg and metronidazole 250 mg qid with either bismuth subcitrate 120 mg qid or omeprazole 20 mg bid for 4 weeks. Later changed to amoxicillin 500 mg bid and clarithromycin 500 mg bid, plus omeprazole 20 mg bid for 2 weeks.	15/16	10/15 (62.5%, 35.8-89.1%)	Mean 43.5 months, range 21.1-67.4. First follow-up endoscopy 4-6 weeks post-treatment and every 6-12 weeks until histologic evidence of remission obtained. 4 to 6 biopsies taken for *H.pylori* evaluation and a minimum of 6 biopsies taken from each tumour and suspicious area. Patients with complete histologic remission had repeat endoscopy and computed tomography every 3 to 6 months.	All 10 patients who achieve complete histologic remission after eradication alive and disease free for mean duration of 31.2 months, range 14.4 to 49.1 months.

Table 2.7. Impact of *helicobacter pylori* eradication on gastric mucosal associated lymphoid tissues (MALT) lymphoma

Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Fischbach *et al* (2004), Germany and Austria	95 patients will newly diagnosed marginal zone B-cell lymphoma of MALT. 5 lost to follow-up, 90 followed for at least 12 months. Mean age 54.3 years(range 22-85 years)	Triple therapy omeprazole 20 mg twice daily, metronidazole 400mg twice daily and clarithomycin 250mg twice daily for one week (OMC) or omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily for one week (OAC)	88/90 (98%)	Complete 56 (62%) Minimal residual 17 (18%) Partial remission 11 (12%) No change 4 (4%) Progressive disease 2 (2%)	Median follow-up 44.6 months (range 12-89 months). Relapse occurred in 4 patients, 3 with low grade lymphoma after 8.8 and 15 months and one with high grade lymphoma after 6 months. At relapse only 1 patient infected with *H.pylori.*	Relatively large prospective series with a median follow-up of more than 4 years.
Wündisch *et al*. (2005), Germany (multicenter trial)	120 patients with low grade MALT lymphoma (stage I_{1E}), 63 females, 57 males, age 62 years, range 29-88 years	2 weeks course of amoxicillin (3 x 750 mg/day) and omeprazole (3 x 40 mg/day). Second line treatment was omeprazole (2 x 20 mg/day), metronidazole (3 x 400 mg/day) and claritromicin (2 x 250 mg/day) for 10 days	116 patients (97%) cured with 1st course of treatment; 4 (3%) cured after 2nd course	96/120 (80%) complete histologic remission	Median follow-up 75 months (range 1-116 months). Estimated 90% patients survived at least 5 years. 71% (CI41-81%) in continuous complete remission after 5 years and after 114 months, 68% in continuous complete remission	

Table 2.7. Impact of *helicobacter pylori* eradication on gastric mucosal associated lymphoid tissues (MALT) lymphoma

Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Nakamura *et al* (2005), Japan 1994–2003	96 patients with gastric MALT lymphoma, including 17 with areas of diffuse large B-cell lymphoma 45 men, 51 women with mean age of 61.7 years (age range 16-84 years). 7 of 96 patients not infected with *H.pylori*.	All 96 treated for 14 days with proton pump inhibitor (40 mg/day omeprazole, 60 mg/day lansoprazole or 20 or 40 mg/day rabeprazole) and a combination of antibiotics 1500 mg/day amoxicillin plus 600 mg/day clarithomycin with or without 750 mg/day metronidazole. In 7 patients and additional regimen of high dose dual therapy necessary to cure infection.	*H.pylori* eradicated in 89/89 initially infected patients determined by ^{13}C urea breath test and histology	Complete remission 62 (65%) Partial remission 4 (4%) Transient histologic disease recurrence 4 (6.5%) of 62 pts with complete remission. Overall survival 96% and disease-free survival 80% after 5 years.	Median follow-up after eradication was 38 months (range 3-119 months). Follow-up every 4-6 weeks until confirmation of complete disease remission (CR). Repeated every 3-6 months after CR. CT scans of abdomen and/or chest performed every 6 months when extragastric involvement present at initial staging. CR=complete disappearance of clinical evidence of lymphoma and absence of lymphoma cells on endoscopic biopsy specimens. Partial remission PR= tumour reduction of $\geq$ 50%. Failed eradication if neither CR nor PR achieved.	

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Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Chen *et al* (2005), Taiwan	Patients from two multicenter prospective studies of anti *H.pylori* therapy; 34 patients (enrolled 1996-1999) with low grade MALT lymphoma. (MALT) 24 patients (enrolled 1995-2004) with high grade transformed tumours (diffuse large B-cell lymphoma with features of MALT lymphoma) (MALT,DLBCL) MALT lymphoma cases had median age 60 years (age range 30-84 years) with M:F ratio of 15:19. 94.1 % (32/34) infected with *H.pylori*. MALT, DLBCL cases had median age of 56 years (range 21-83 years, M:F ratio of 9:15 100% (24/24) infected with *H.pylori.*	For patients with MALT, DLBCL: amoxicillin (500 mg) and metronidazole (250 mg) 4 times per day, with either bismuth subcitrate (120 mg) 4 times per day or omeprazole (20 mg) twice a day for 4 weeks. After March 1996 MALT, DLBCL cases and all low grade MALT received: amoxicillin (500 mg) 4 times per day, clarithromycin (500 mg) twice a day plus omeprazole (20 mg) twice a day for two weeks.	MALT lymphomas 30/31 (96.8%) MALT, DLBCL lymphoma 22/24 (91.7%) Low grade predominant: 11/13 (84.6%) DLBCL predominant 11/11 (100%)	Complete remission <u>MALT lymphoma</u> 24/30 (80%) of *H.pylori* eradicated patients <u>MALT, DLBCL</u> 14/22 (63.6%) of *H.pylori* eradicated patients: Low grade predominant 7/11 (63.6%) DBLCL 7/11 (63.6%) Relapse rate 3/24 (12.5%) of MALT lymphoma only	First F-U endoscopy 4-6 weeks after completion of therapy and F-U every 3-6 months until complete remission (CR) achieved or treatment failed. 4 to 6 biopsies taken at each endoscopy for *H.pylori* evaluation. A minimum of 6 biopsies taken from each tumour and suspicious area. *H.pylori* infection status determined by histologic exam, biopsy urease test, bacterial culture. CR defined as Wotherspoon's score of $\leq$2 on every histologic section of every biopsy. Partial remission (PR) defined as presence of lesions with scores of 4 or 5 on any histologic section.	All numbers refer to evaluated patients. Follow-up time of complete responders, range of median 63.8 months to 80.4 months.

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Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Hong *et al*. (2006), Korea 1996-2003	90 *H. pylori* infected patients with log grade MALT lymphoma were treated with anti-*H. pylori* therapy. Median 49 years (range 22-78 years); M:F ratio 46:39.	Proton pump inhibitor (PPI) based triple therapy for 14 days: PPI usual dose, clarithromycin (500 mg) and amoxicillin (1000 mg) twice a day.	85 (94.4%)	Complete (CR) remission of low grade MALT lymphoma by 24 months 85 (100%) CR at 6 months 66 (77.6%) CR at 12 months 79 (92.9%)	Endoscopy every 3 months until CR and every 6 month thereafter. Follow-up biopsies taken of all macroscopically abnormal lesions and macroscopically normal-looking antrum, body and fundus. Median follow-up of 45 months (range 15-109) after CR. Disease recurred in 8 (10.4%) of 77 patients with no evidence of disease at 6 months. Mean interval to recurrence 17 months (range 11-26)	
El-Zahabi *et al* (2007), Lebanon 1999-2005	19 cases of histologically confirmed MALT lymohoma infected with *H.pylori* identified through retrospective chart review. Cases had a Wootherspoon histologic score of 5 and *H.pilory* determined by histopathologic exam and immunohistochemistry. All cases underwent endoscopic ultrasound (EUS) by a single endoscopist. 15(68.2%) male, 7 female (32.8%); mean age at diagnosis 52 years (range 33 to 80)	H. pylori treated with proton pump inhibitors (omeprazole, lansoprazole or rabeprazole) together with a combination of antimicrobial agents (amoxicillin, clarithromycin, metromidazole). Dose and duration not specified.	18/19 eradicated after 1 course of treatment. 1/19 eradicated after second course of treatment.	Complete response by tumour stage: T1m 7/9 (78%) T1sm 1/8 (12.5%) T2NO,T2N1,T3N1 0/5 (0%) T1m vs.> T1m (p=0.003)	First FU 3 months after diagnosis and every 3 to 4 months subsequently. Varying lengths of FU for patients: range 6 to 55 months, median 12 months, mean (SD) 21 months (15). Evaluation and staging by physical exam, lab test, chest radiographs, bone marrow aspiration, CT and EUS.	Retrospective single center study. Depth of mucosal invasion predictive of complete response to therapy in H.pylori treated uses.

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Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Nakamura *et al*. (2008), Japan 1993-2006	92 consecutive patients with gastric MALT lymphoma: 70 *H.pylori* positive and 87 received *H.pylori* eradication therapy; remaining 5 were API2-MALT1 positive and were not treated. Histological diagnosis of gastric MALT lymphoma based on Isaacson's histopathologic diagnostic criteria. M:F ratio, 44:48; average age 56.7 years (range 26-87 years). Clinical stage determined by Lugono's classification. *H.pylori* infection diagnosed on basis of culture and histology (H+E and /or immunostaining) of gastric biopsies, serum anti *H.pylori* IgG titer and urea breath tests. *H.pylori* infection positive when 1+ tests positive and negative when all tests negative.	87 of 92 cases administered 2-week course of proton pump inhibitor (lansoprazole) and a combination of antibiotics (amoxicillin, clarithromycin and/or metronidazole). when eradication not successful a secondline regimen of clarithromycin 400 mg/day, metronidazole 1000 mg/day, and omeprazole 20 mg/day for 7 days was given.	*H.pylori* positive at baseline: 65/70 eradicated with 1st course of treatment, 5/5 eradicated with second course of therapy.	*H. pylori* positive: 55/70 (78.6%)responders *H.pylori* negative: 2/17(11.8%)responders	H. pylori eradication FU performed 6 wks after treatment. When 2 or more tests were negative, *H.pylori* considered eradicated. MALT regression was evaluated by upper gastrointestinal endoscopy and abdominal CT every 3 months in year 1, every 4 months in year 2 and every 6 months in year 4 and beyond. Histology of biopsy specimens evaluated by Wotherspoon's criteria: responders, grade 3 or less; nonresponders, grade 4 or higher.	Retrospective study at single institution API2-MALT1 positive MALT lymphoma cases did not respond to *H.pylori* eradication treatment.

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Reference, study location and period	Cases treated	Treatment	*H. pylori* eradication rate	MALT regression rate	Follow-up	Comments
Terai *et al* (2008), 1995-2006	74 patients (70 *H. pylori+*, 4 *H.pylori-*) followed endoscopically for at least 12 months after anti-*H.pylori* therapy. Mean age 63years (range 35-80 yrs). Diagnosis of gastric MALT lymphoma based on WHO classifications and scoring system of Wotherspoon by histological examination of biopsy specimens, immunohistochemically stained for CD3 and CD20/CD79a to confirm monoclonal expansion of B-cells. *H. pylori* status diagnosed by rapid urease test, histologic exam, serum anti-*H.pylori* antibody, and ^{13}C urea breath test, status positive if positive on 1 or more tests.	All patients received combination of proton pump inhibitor and antibiotics (1500 mg/day amoxicillin plus 800 mg/day clarithromycin or 1000 mg/day metronidazole) for 7 days, even if H.pylori infection was not detected.	Not stated.	Complete regression (CR) 66/74 (89%) at last exam. Median time to CR was 6 months. 63/70 (93%) *H.pylori* positive patients and 1/4 (25%) *H.pylori* negative pts. Pretreatment achieved CR of 12 patients who achieved hRD at 12-months post-eradication, 11 achieved CR after a median FU of 22 months.	FU endoscopic exams with multiple biopsies from lesions performed at 1 month after eradication then every 1-3 months until reaching CR and every 6 months thereafter. Patients with hRD (histologic residual disease) followed with no additional treatment. hRD equivalent to minimal residual disease.	
Stathis *et al*. (2009), Switzerland (1990-2000)	105 patients with localized gastric MALT lymphoma Stage I 100 Stage II_1 5 diagnosed based on morphological and immunophenotypic analysis of paraffin-emhedded section (51 f/54 m)	Antibiotics: Amoxicillin and claritromicin in 36%; metronidazole and claritromicin in 24%; amoxicillin and metrodanizole in 15% and others in 16% plus Proton pump inhibitors: omeprazole or less commonly pantoprazole or lansoprazole	*H. pylori* detected by histology and/or histochemistry in 85 patients (81%) *H. pylori* confirmed by serology or breath' test in 14 patients. No data on *H. pylori* at diagnosis available for 10 patients. *H. pylori* eradicated in 85/85 (100%)	Complete remission (Wotherspoon scores 0-2) 64 Partial regression (Wotherspoon scores 0-2) 12 No change 7	At regular 6 months intervals by endoscopic exam with multiple biopsies. At median follow-up of 3.6 years histological remission confirmed in 33/74 assessable patients	