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TOPIC HIGHLIGHT

2015 Advances in *Helicobacter Pylori*

Helicobacter pylori: Effect of coexisting diseases and update on treatment regimens

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Abstract

The presence of concomitant diseases is an independent predictive factor for non-*Helicobacter pylori* (*H. pylori*) peptic ulcers. Patients contracting concomitant diseases have an increased risk of developing ulcer disease through pathogenic mechanisms distinct from those of *H. pylori* infections. Factors other than *H. pylori* seem critical in peptic ulcer recurrence in end stage renal disease (ESRD) and cirrhotic patients. However, early *H. pylori* eradication is associated with a reduced risk of recurrent complicated peptic ulcers in patients with ESRD and liver cirrhosis. Resistances to triple therapy are currently detected using culture-based and molecular methods. Culture susceptibility testing before first- or second-line therapy is unadvisable. Using highly effective empiric first-line and rescue regimens can yield acceptable results. Sequential therapy has been included in a recent consensus report as a valid first-line option for eradicating *H. pylori* in geographic regions with high clarithromycin resistance. Two novel eradication regimens, namely concomitant and hybrid therapy, have proven more effective in patients with dual- (clarithromycin- and metronidazole-) resistant *H. pylori* strains. We aim to review the prevalence of and eradication therapy for *H. pylori* infection in patients with ESRD and cirrhosis. Moreover, we summarized the updated *H. pylori* eradication regimens.

Key words: Concomitant diseases; *Helicobacter pylori*; Culture susceptibility; Concomitant therapy; Hybrid therapy

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Core tip: The authors outline that patients contracting concomitant diseases have an increased risk of developing ulcer disease through pathogenic mechanisms distinct from those of *Helicobacter pylori* (*H. pylori*) infections. Early *H. pylori* eradication is associated with a reduced risk of recurrent complicated peptic ulcers in patients with end stage renal disease and liver cirrhosis. Two novel eradication regimens, namely concomitant

and hybrid therapy, have proven more effective in patients with dual resistant *H. pylori* strains. High-dose amoxicillin therapy is promising and superior to standard regimens. Finally, culture and susceptibility testing should be performed before third-line treatment.

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INTRODUCTION

Helicobacter pylori (*H. pylori*), a widespread human pathogen affecting more than 50% of the human population[1], has been implicated in the development of peptic ulcer disease (PUD), gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma[2-4]. Hopkins *et al*[5] reported that the recurrence of peptic ulcers can markedly decrease from 70% to 10% or lower following *H. pylori* eradication.

Interactions among hosts, pathogens, and environmental factors are crucial to *H. pylori* colonization[6,7]. The presence of concomitant diseases is an independent predictive factor for non-*H. pylori* peptic ulcers[8]. Patients contracting concomitant diseases have an increased risk of developing ulcer disease through pathogenic mechanisms distinct from those of *H. pylori* infections[9,10]. Another explanation for the reported association between concomitant diseases and *H. pylori*-negative peptic ulcers is that many patients with comorbid conditions require nonsteroidal antiinflammatory drugs (NSAIDs). Whether *H. pylori* eradication can protect all patients with concomitant diseases, such as end-stage renal disease (ESRD) and liver cirrhosis, from ulcer recurrence requires further exploration.

Triple therapy is one of the oldest methods for *H. pylori* eradication. Resistances to triple therapy are currently detected using culture-based and molecular methods. However, such methods are difficult to apply in clinical practice because of the long period necessary before obtaining results as well as the high costs of routine performance. No therapy regimen can cure *H. pylori* infections in all treated patients, and some patients remain infected despite several consecutive standard therapies[11]. Concomitant therapy is a combination of antibiotics, including amoxicillin, metronidazole, clarithromycin, and a proton pump inhibitor (PPI), for a period of 5-7 d. This is a novel regimen, regarding which only a few evaluation studies have been published. Thus, the optimal therapy duration and success rates in populations with high dual resistance remain undefined.

END-STAGE RENAL DISEASE

H. pylori prevalence among patients with end-stage renal disease

Studies on *H. pylori* infections in uremic patients have reported rates varying from 27% to 73.0%[12-20]. This variation may have been caused by small sample sizes, nonuniform duration of dialysis, and varying methodologies and enrollment criteria. The *H. pylori* infection rate is lower in chronic kidney disease (CKD) (58.52%) and ESRD (56.25%) patients with PUD than in PUD patients without CKD, according to a Taiwanese population-based study[21]. Sugimoto *et al*[20] reported an *H. pylori* infection rate of 38.3% in patients with ESRD receiving dialysis for 4 years, suggesting that longer durations of dialysis reduce the risk of *H. pylori* infection. Factors other than *H. pylori* seem critical to peptic ulcer recurrence in patients with ESRD patients. These results imply that the diverse gastric environment of ESRD patients. Factors such as reductions in mucosa prostaglandin[12], hypergastrinemia[22], drugs such as NSAIDs[23], and systemic and local circulatory failure[20] influence the onset of recurrent PUD in patients with ESRD.

H. pylori tests for patients with end-stage renal disease

Invasive and noninvasive methods are available to detect *H. pylori* infections. However, dialyzed patients are often reluctant to undergo invasive procedures such as endoscopies[24]. Because patients with ESRD receive antisecretory drugs and require multiple antibiotic treatments for septic complications, inadvertent eradication of *H. pylori* infections is possible. Therefore, many *H. pylori*-negative patients with positive serologies were previously infected with *H. pylori* and inadvertently cured. The 2007 Maastricht Consensus Report on the diagnosis and treatment of *H. pylori* infections does not recommend the serological determination of *H. pylori* infections in routine clinical practice[25]. Huang *et al*[26] proposed that the diagnostic accuracy of *H. pylori* detection in patients with ESRD can be improved by performing the ^{13}C-urea breath test (UBT) after hemodialysis therapy and assessing the UBT with a cutoff excess 13CO2/12CO2 ratio value exceeding 5. However, the diagnostic efficacy of the UBT for patients with ESRD remains less accurate than that for dyspeptic patients without renal impairment.

The UBT seems to be the most reliable diagnostic method for *H. pylori* infections in patients with chronic renal failure (CRF), and stool antigen tests show heterogeneous results, with substantial differences among manufacturers[24]. However, Wang *et al*[27] proposed that stool antigen is a noninvasive and reliable tool for screening *H. pylori* infections before therapy and assessing the success of eradication therapy in patients with ESRD. Establishing the reliability of diagnostic methods for *H. pylori* is crucial for managing infection[28]. Patients contracting CRF often have reduced gastric acid secretion and increased levels of urea in the blood and gastric juices[29-31], which may affect the density and distribution of *H. pylori* infections and, consequently, the reliability of diagnostic tests. Because no diagnostic tests for *H. pylori* infections are 100% reliable, the European *Helicobacter pylori* Study Group guidelines[32] recommend determining a gold standard from at

least two techniques. The approach of combining all techniques has been used in previous studies evaluating the methods of diagnosing *H. pylori* infections[24,33,34]. However, this approach is too costly for use in clinical practice.

H. pylori therapy in patients with end-stage renal disease

The optimal therapeutic regimen for *H. pylori* infection remains undefined in patients with ESRD. Few studies concerning triple therapy in uremic patients have been reported[27,35-39]. A 1-wk course of PPI-based triple therapy (omeprazole, 20 mg twice daily; amoxicillin, 1 g twice daily; and clarithromycin, 500 mg twice daily) achieved a high eradication rate of *H. pylori* infection in patients with CRF and a creatinine clearance (CrCl) of less than 30 mL/min per 1.73 m^2, similar to that of controls with normal renal function[35]. The regimen was tolerated favorably. Another study showed that 7-d triple therapy with a low-dose OAC (omeprazole, 40 mg daily; amoxicillin, 500 mg daily; and clarithromycin, 500 mg daily) regimen was effective and safe for eradicating *H. pylori* infections in hemodialysis patients[40].

Amoxicillin[41] and clarithromycin[42], which are primarily eliminated renally, necessitate dosage reduction in patients with renal impairment according to CrCl. Wang *et al*[27] used 7-d triple therapy with omeprazole (20 mg twice daily), amoxicillin (1 g twice daily), and clarithromycin (500 mg twice daily) and reported an eradication rate of 86.8% among 40 hemodialysis patients. Tsukada *et al*[38] reported an eradication rate of 82.0% among 39 hemodialysis patients using 7-d triple therapy with omeprazole (30 mg twice daily), amoxicillin (500 mg twice daily), and clarithromycin (400 mg twice daily). Itatsu *et al*[39] used 7-d triple therapy with lansoprazole (30 mg twice daily), amoxicillin (375 mg twice daily), and clarithromycin (200 mg twice daily) in 11 hemodialysis patients and achieved an eradication rate of 72.7%.

Ideal treatment regimens should be effective, simple, and safe with fewer adverse effects and high patient compliance. One of the main reasons for treatment failure is irregular therapy with low compliance[43]. The prevalence of resistance to antibiotics, particularly clarithromycin and nitroimidazoles varies with gender, ethnic group and country[44]. Resistance to amoxicillin does not appear to be a critical problem in *H. pylori*-infected ESRD and non-ESRD patients in Turkey. By contrast, rates of resistance to clarithromycin are high, particularly in the ESRD population[45]. Prospective studies on the optimal therapy protocol, including antibiotic combination, dosage, and duration, in ESRD patients are warranted.

H. pylori eradication and recurrent peptic ulcers in patients with end-stage renal disease

Patients with ESRD receiving hemodialysis often have various gastrointestinal (GI) problems such as nausea, dyspepsia, appetite loss, epigastric discomfort, and heartburn. Patients with ESRD exhibit a higher incidence of PUD than do patients without renal disease[12]. *H. pylori* is critical in the development of peptic ulcers[46]. Therefore, physicians must consider these two factors when treating ESRD in patients with upper GI disease.

ESRD is associated with a substantial health care burden in hospitalized patients with peptic ulcer bleeding (PUB). The presence of ESRD contributes to a higher mortality rate, longer hospital stay, and increased need for surgery among such patients[47]. A population-based study conducted in Taiwan[48] over a 10-year period revealed that PUD incidence was 10-12 times higher in patients with CKD than in those without CKD. Luo *et al*[49] reported that patients with ESRD receiving hemodialysis exhibited a high risk of PUB. Another study showed that patients with ESRD had a higher long-term risk of peptic ulcer rebleeding[50]. A crucial question is whether *H. pylori* eradication therapy is necessary for *H. pylori*-infected dialysis patients. Although *H. pylori* eradication is unequivocally effective in preventing peptic ulcer recurrence in the general population[3], such effectiveness has not been established in patients with ESRD. Tseng *et al*[12] conducted a prospective study in a single hospital and reported that *H. pylori* eradication in patients with ESRD reduces recurrent PUD. In addition, a higher recurrent peptic ulcer rate was noted after successful *H. pylori* eradication in *H. pylori*-infected ESRD patients. Sugimoto *et al*[20,51] reported that initiating hemodialysis treatment triggers a decrease in the prevalence of *H. pylori* infection. Moreover, receiving a maximum of 4 years of dialysis treatment has naturally cured *H. pylori* infection, thus supporting the practice of administering eradication therapy to *H. pylori*-infected dialysis patients, particularly those receiving dialysis for 5 years or more. However, a population-based study in Taiwan[52] revealed that early *H. pylori* eradication is associated with a reduced risk of recurrent complicated peptic ulcers in patients with ESRD; the authors recommended administering *H. pylori* eradication within 120 d after peptic ulcer diagnosis in *H. pylori*-infected ESRD patients who have developed peptic ulcers.

LIVER CIRRHOSIS

H. pylori prevalence in patients with liver cirrhosis

Cirrhotic patients with PUB have a 5-fold higher risk of complications or death[53]. *H. pylori* infection promotes the production of ammonia, which is an etiological factor involved in gastric mucosa disorders[54]. However, decompensated liver cirrhosis also involves hepatic encephalopathy because of higher serum ammonia levels. Thus, decompensated cirrhotic patients with *H. pylori* infections seem to have a higher risk of gastric mucosa lesions and GI complications.

Kim *et al*[55] revealed that *H. pylori* infection in cirrhotic patients may be inversely related to the severity of liver cirrhosis (Child-Pugh class A group: 51.5%, class B group: 30.5%, and class C group: 20%). Jung *et al*[56] also showed that the *H. pylori* infection rate

is approximately 71.1% (162 of 228 patients) in all cirrhotic patients with peptic ulcers; however, the rate is only 50.0% (17 of 34 patients) in the Child-Pugh class C group. By contrast, Siringo *et al*[57] used serum anti-*H. pylori* IgG antibody levels to confirm a higher *H. pylori* infection rate of 76.5% in cirrhotic patients and 95.1% in cirrhotic patients with peptic ulcers. Such variability is likely explained by differences in *H. pylori* prevalence inherent in different populations and methodological differences among studies, including the means of testing used to define the presence of infection.

Bhargava *et al*[58] showed that gastric mucosa from patients with portal hypertension exhibited typical vascular dilatation and congestion, whereas the *H. pylori* infection rate was significantly lower in patients with portal hypertension (51.5% *H. pylori* infection rate) with particularly marked vascular dilatation (only 18.8% *H. pylori* infection rate) compared with the controls (75.5% *H. pylori* infection rate). Factors other than *H. pylori* seem critical in peptic ulcer recurrence in cirrhotic patients. In addition, *H. pylori* is not the predominant etiology for liver cirrhosis, particularly the decompensated type, with PUD or recurrent ulcer disease, according to a population-based study conducted in Taiwan[59]. This is consistent with previous studies[55,60,61], and a 35.6% to 51.92% *H. pylori* infection rate in cirrhotic patients with peptic ulcers.

H. pylori eradication and recurrent peptic ulcers in patients with liver cirrhosis

The prevalence of *H. pylori* in patients with cirrhosis and PUD is generally less than 60%[60,62-65], suggesting that the pathogenesis of ulcer disease in a substantial proportion of cirrhotic patients may not be related to *H. pylori* infection[66-69]. Host environments are crucial to *H. pylori* colonization[7,70]. *H. pylori* adapts to humans, colonizing in children and remaining persistent throughout life[71]. The pathogenesis of the high peptic ulcer rate in cirrhotic patients is multifactorial. Cirrhotic patients have a higher risk of gastric mucosa damage because of reduced mucosal prostaglandin, which is crucial in the cytoprotection of gastric mucosa, which causes PUD. Other factors including increased serum gastrin concentration[72], impaired mucus secretion[73], and portal hypertensive gastropathy[74,75] may contribute to peptic ulcers and peptic ulcer recurrence in cirrhotic patients.

Compared with the general population, patients with cirrhosis have greater bleeding complications, delayed healing, and higher ulcer recurrence rates[68]. Luo *et al*[76] proposed that the risk of developing PUB in liver cirrhosis patients is 4-fold. A group of researchers from Taiwan found that 21 (58%) patients in whom *H. pylori* infections were eradicated developed recurrent duodenal ulcers within a year[60]. These results suggest that the pathogenesis of ulcer disease in a substantial proportion of patients with cirrhosis may not be related to *H. pylori* infection, a possibility proposed by researchers[65,67]. However, early *H. pylori* eradication is associated with a lower risk of recurrent peptic ulcers in cirrhotic patients, according to a Taiwan population-based study[77]. *H. pylori* eradication therapy is the primary method of treating cirrhotic patients with peptic ulcers.

H. pylori eradication and hepatic encephalopathy in patients with liver cirrhosis

A meta-analysis showed that *H. pylori* infections are associated with elevated blood ammonia levels in cirrhotic patients. In addition, the association seems more prominent in Asian patients than in Caucasian patients[78]. Addressing whether *H. pylori* eradication may benefit the long-term management of hepatic encephalopathy. Some studies have shown the benefit of eradication therapy[79-81]; however, other studies have reported negative results[82-84].

An ideal study protocol should also address a homogenous study population according to the severity of liver cirrhosis, assessment of psychometric tests, and measurements of ammonia levels in the blood. Currently, the demonstrated beneficial effect of eradication therapy in *H. pylori*-positive cirrhotic patients is insufficient for recommending the use of this therapy in clinical practice. An appropriately randomized study designed to assess the influence of *H. pylori* eradication on hepatic encephalopathy in cirrhotic patients is warranted.

ENTEROHEPATIC *HELICOBACTERS* AND LIVER DISEASE

Bile-tolerant *helicobacter* species such as *H. hepaticus* and *H. bilis* have frequently been reported to cause hepatitis in mice and other rodents[85]. The most comprehensively studied member of this group of enterohepatic *Helicobacter* species is *H. hepaticus*[86]. *H. bilis* has been found in species of inbred mice and reported to induce chronic hepatitis and hepatocellular carcinomas[87]. *H. hepaticus* was initially detected by immunofluorescence, electron microscopy, and culture in the livers of certain inbred mice and has been shown to cause multifocal necrotizing hepatitis, hepatic adenomas, and hepatocellular carcinomas[88,89]. The reason for further study of the possible role of these new helicobacter species in human liver disease has been to develop noninvasive serological assays for determining the seroprevalence of hepatic helicobacter infections[85].

Fox *et al*[90] stated that *H. hepaticus* infection increased the risk of liver cancer in hepatitis C virus and/or Hepatitis B virus infection. Fukuda *et al*[91] revealed that serum anti-*H. hepaticus* and/or *anti-H. bilis* antibody levels were significantly higher in patients with liver disease that in patients with other autoimmune hepatitis. Liver cirrhosis patients exhibited a substantially higher anti-*H. hepaticus* serum antibody level than other liver disease and health donors[92]. Although *Helicobacter* spp. have been identified in the liver of humans, their pathogenic role in human liver diseases remains largely unclear[93]. Kleine *et al*[94] established an *in vitro* model

for demonstrating the pathogenic effect of a *Helicobacter* spp. on human liver cells, resulting in an inflammatory response with increased synthesis of inflammatory mediators and consecutive monocyte activation. The higher prevalence of *Helicobacter* spp. associated with more advanced stages of liver disease supports the possibility of their role in the progression of chronic hepatitis toward cirrhosis and hepatocellular carcinoma. An interventional study aimed at eradicating *Helicobacter* spp. from the liver would elucidate this association between *Helicobacter* spp. and liver cirrhosis and is thus warranted[93].

UPDATED *H. PYLORI* THERAPY

Successful eradication of *H. pylori* is a major component in treating these conditions[95]. However, the rate of *H. pylori* eradication after triple therapy is decreasing, with standard amoxicillin plus clarithromycin-based triple therapy achieving eradication rates of only approximately 75% in many series[96,97]. Apart from the conventional first-line regimen (triple therapy), other therapies have been proposed (sequential, concomitant, quadruple, and miscellaneous) to face the growing problem of antibiotic resistance. Although unsuccessful eradication can be caused by increasing antimicrobial resistance, an additional critical contributor is the treatment-related side effects and resultant incomplete therapy. New treatment regimens for *H. pylori* infections should be optimized to achieve an eradication rate of ≥ 95%[98]. Patient allergies and the local availability of drugs should be considered when selecting a treatment. *H. pylori* eradication should be confirmed after treatment, and, if second-line therapy is required, clarithromycin or a fluoroquinolone should not be reused[99].

Sequential therapy

First developed in Italy in the 1990s, sequential therapy (5-d PPI and amoxicillin, followed by 5-d PPI, clarithromycin, and metronidazole), is a regimen that has proven more effective in eradicating *H. pylori* than has triple therapy in many studies[100-104]. Recent multicenter randomized trials conducted in Taiwan have shown the superiority of sequential therapy over standard triple therapy. These findings also support that the most effective eradication regimen should be chosen on the basis of the prevalence of antibiotic-resistant *H. pylori* in a region[105]. The ability of sequential therapy to eradicate clarithromycin-resistant bacteria has been demonstrated, and sequential therapy has been included in a recent consensus report as a valid first-line option for eradicating *H. pylori* in geographic regions with high clarithromycin resistance[106].

Hybrid and concomitant therapy

Two novel eradication regimens, namely concomitant and hybrid therapy, have proven more effective than triple and sequential therapy in the last few years, particularly in patients with dual- (clarithromycin- and metronidazole-) resistant *H. pylori* strains[107-111]. Meta-analyses have shown that the outcome of concomitant therapy is duration-dependent[112]. Molina-Infante *et al*[113] proposed that optimized nonbismuth quadruple hybrid (consisting of omeprazole 40 mg twice daily and amoxicillin 1 g twice daily for 14 d, plus clarithromycin 500 mg twice daily and nitroimidazole 500 mg twice daily for the final 7 d as a quadruple therapy) and concomitant (consisting of omeprazole 40 mg twice daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily, and nitroimidazole 500 mg twice daily, all concurrently for 14 d) therapies cured more than 90% of patients with *H. pylori* infections in areas of high clarithromycin and metronidazole resistance. In concomitant therapy, all four drugs are administered for the entire therapy duration, indicating that this regimen is less complex than sequential therapy because it does not involve changing the number or type of drugs halfway through the therapy. A recently proposed hybrid therapy has proven as effective as a 14-d concomitant regimen in a pilot study[106].

High-dose amoxicillin therapy

The efficacy of treatment for *H. pylori* infection has decreased steadily because of increasing resistance to clarithromycin, metronidazole, and levofloxacin. Resistance to amoxicillin is generally low, and high intragastric pH increases the efficacy of amoxicillin. Therefore, Yang *et al*[114] proposed that a combination of a high-dose PPI and amoxicillin (dual therapy), consisting of rabeprazole (20 mg, four times daily) and amoxicillin (750 mg, four times daily) for 14 d, is superior to standard regimens as empirical first-line or rescue therapies for *H. pylori* infection and has similar safety profiles and tolerability.

Bismuth-based quadruple therapy

During the initial development of bismuth quadruple therapy, the dose and duration of bismuth therapy were shown to be crucial variables, particularly in regions where metronidazole resistance was common[115]. However, many studies on these regimens have used suboptimal doses and durations of bismuth therapy, producing relatively poor results[116]. Bismuth-containing quadruple therapy is an alternative to standard triple therapy in areas with low clarithromycin resistance and the main first-line therapeutic option in areas with high prevalence of clarithromycin resistance. Using this regimen at full doses for 14 d produces a 95% or greater treatment success rate, irrespective of the level of metronidazole resistance[117].

Salvage therapy

Tailored antimicrobial therapy for an infectious disease is typically selected on the basis of susceptibility testing[99,118]. The treatment of *H. pylori* infection differs from that of most common infectious diseases because culture and susceptibility testing is generally not offered for *H. pylori* infections by hospital laboratories. In

addition, many *H. pylori* infections can be identified using noninvasive testing (such as UBT or stool antigen testing), indicating that endoscopies are neither necessary nor acceptable to patients, and clinicians must choose treatment empirically. Therefore, culture and susceptibility testing should be performed before third-line treatment[106]. Salvage therapy (after multiple treatment failures) should be chosen on the basis of susceptibility testing whenever possible[101].

Probiotic therapy

Song *et al*[119] proposed that supplementation with *Saccharomyces boulardii* could be effective for improving *H. pylori* eradication rates by reducing side effects, thus facilitating completion of eradication therapy. Probiotics are mostly administered by modulating the balance of its microflora[120]. Probiotic adjunct therapy is particularly useful in patients with a history of GI intolerance to antibiotic treatment[121]. These effects have been demonstrated for several species of probiotics, including *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Lactobacillus rhamnosus*, and *Bifidobacterium bifidum*, among others[122-124]. Proposed mechanisms include modulating the colonization of the gastric mucosa and the direct killing of *H. pylori* through secreted metabolites with antimicrobial properties[95]. The lack of protocol standardization is problematic, and interpreting the various results is difficult.

CONCLUSION

Although other factors influence the onset of peptic ulcer and recurrent peptic ulcer in ESRD and cirrhotic patients, *H. pylori* eradication therapy is the primary method of treating ESRD and cirrhotic patients with peptic ulcers. Culture susceptibility testing before first- or second-line therapy is unadvisable. The known obstacles to culture susceptibility testing include the need for endoscopic examination and the fact that culture is time-consuming, costly, and not 100% sensitive. Using highly effective empiric first-line and rescue regimens can yield acceptable results[100,107,125]. In the near future, *in vivo* and *in vitro* studies may possibly be grouped according to geographic area to identify the most effective therapy for eradicating *H. pylori*, which relates to the local habitat.

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REFERENCES

1 **Suerbaum S**, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]

2 **Thiede C**, Morgner A, Alpen B, Wündisch T, Herrmann J, Ritter M, Ehninger G, Stolte M, Bayerdörffer E, Neubauer A. What role does Helicobacter pylori eradication play in gastric MALT and gastric MALT lymphoma? *Gastroenterology* 1997; **113**: S61-S64 [PMID: 9394762 DOI: 10.1016/S0016-5085(97)80014-5]

3 **Van der Hulst RW**, Rauws EA, Köycü B, Keller JJ, Bruno MJ, Tijssen JG, Tytgat GN. Prevention of ulcer recurrence after eradication of Helicobacter pylori: a prospective long-term follow-up study. *Gastroenterology* 1997; **113**: 1082-1086 [PMID: 9322501 DOI: 10.1053/gast.1997.v113.pm9322501]

4 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1080/003655202760230793]

5 **Hopkins RJ**, Girardi LS, Turney EA. Relationship between Helicobacter pylori eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology* 1996; **110**: 1244-1252 [PMID: 8613015 DOI: 10.1053/gast.1996.v110.pm8613015]

6 **Amieva MR**, El-Omar EM. Host-bacterial interactions in Helicobacter pylori infection. *Gastroenterology* 2008; **134**: 306-323 [PMID: 18166359 DOI: 10.1053/j.gastro.2007.11.009]

7 **Wu MS**, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1878-1882 [PMID: 16103430 DOI: 10.1158/1055-9965.EPI-04-0792]

8 **Gisbert JP**, Calvet X. Review article: Helicobacter pylori-negative duodenal ulcer disease. *Aliment Pharmacol Ther* 2009; **30**: 791-815 [PMID: 19706147 DOI: 10.1111/j.1365-2036.2009.04105.x]

9 **Xia HH**, Phung N, Kalantar JS, Talley NJ. Demographic and endoscopic characteristics of patients with Helicobacter pylori positive and negative peptic ulcer disease. *Med J Aust* 2000; **173**: 515-519 [PMID: 11194733 DOI: 10.1093/ageing/27.4.427]

10 **Shahin WA**, Abdel-Baset EZ, Nassar AK, Atta MM, Kabil SM, Murray JA. Low incidence of Helicobacter pylori infection in patients with duodenal ulcer and chronic liver disease. *Scand J Gastroenterol* 2001; **36**: 479-484 [PMID: 11346200 DOI: 10.1080/003655201750153250]

11 **Ierardi E**, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change Helicobacter pylori treatment: A matter of geography? *World J Gastroenterol* 2013; **19**: 8168-8180 [PMID: 24363506 DOI: 10.3748/wjg.v19.i45.8168]

12 **Tseng GY**, Lin HJ, Fang CT, Yang HB, Tseng GC, Wang PC, Hung TL, Deng YC, Cheng YT, Huang CH. Recurrence of peptic ulcer in uraemic and non-uraemic patients after Helicobacter pylori eradication: a 2-year study. *Aliment Pharmacol Ther* 2007; **26**: 925-933 [PMID: 17767477 DOI: 10.1111/j.1365-2036.2007.03438.x]

13 **Kang JY**, Ho KY, Yeoh KG, Guan R, Wee A, Lee E, Lye WC, Leong SO, Tan CC. Peptic ulcer and gastritis in uraemia, with particular reference to the effect of Helicobacter pylori infection. *J Gastroenterol Hepatol* 1999; **14**: 771-778 [PMID: 10482427 DOI: 10.1046/j.1440-1746.1999.01947.x]

14 **Sotoudehmanesh R**, Ali Asgari A, Ansari R, Nouraie M. Endoscopic findings in end-stage renal disease. *Endoscopy* 2003; **35**: 502-505 [PMID: 12783348 DOI: 10.1055/s-2003-39672]

15 **Loffeld RJ**, Peltenburg HG, vd Oever H, Stobberingh E. Prevalence of Helicobacter pylori antibodies in patients on chronic intermittent haemodialysis. *Nephron* 1991; **59**: 250-253 [PMID: 1956486 DOI: 10.1159/000186560]

16 **Davenport A**, Shallcross TM, Crabtree JE, Davison AM, Will EJ, Heatley RV. Prevalence of Helicobacter pylori in patients with end-stage renal failure and renal transplant recipients. *Nephron* 1991; **59**: 597-601 [PMID: 1766499 DOI: 10.1159/000186650]

17 **Luzza F**, Imeneo M, Maletta M, Mantelli I, Tancre D, Merando G, Biancone L, Pallone F. Helicobacter pylori-specific IgG in chronic haemodialysis patients: relationship of hypergastrinaemia to positive serology. *Nephrol Dial Transplant* 1996; **11**: 120-124 [PMID: 8649619 DOI: 10.1093/oxfordjournals.ndt.a027026]

18 **Jaspersen D**, Fassbinder W, Heinkele P, Kronsbein H, Schorr W, Raschka C, Brennenstuhl M. Significantly lower prevalence of Helicobacter pylori in uremic patients than in patients with normal renal function. *J Gastroenterol* 1995; **30**: 585-588 [PMID: 8574329

DOI: 10.1007/BF02367783]
19 **Khedmat H**, Ahmadzad-Asl M, Amini M, Lessan-Pezeshki M, Einollahi B, Pourfarziani V, Naseri MH, Davoudi F. Gastroduodenal lesions and Helicobacter pylori infection in uremic patients and renal transplant recipients. *Transplant Proc* 2007; **39**: 1003-1007 [PMID: 17524875 DOI: 10.1016/j.transproceed.2007.03.034]
20 **Sugimoto M**, Sakai K, Kita M, Imanishi J, Yamaoka Y. Prevalence of Helicobacter pylori infection in long-term hemodialysis patients. *Kidney Int* 2009; **75**: 96-103 [PMID: 18843261 DOI: 10.1038/ki.2008.508]
21 **Chang SS**, Hu HY. Lower Helicobacter pylori infection rate in chronic kidney disease and end-stage renal disease patients with peptic ulcer disease. *J Chin Med Assoc* 2014; **77**: 354-359 [PMID: 24907021 DOI: 10.1016/j.jcma.2014.04.004]
22 **Gür G**, Boyacioglu S, Gül C, Turan M, Gürsoy M, Baysal C, Ozdemir N. Impact of Helicobacter pylori infection on serum gastrin in haemodialysis patients. *Nephrol Dial Transplant* 1999; **14**: 2688-2691 [PMID: 10534513 DOI: 10.1093/ndt/14.11.2688]
23 **Tseng GY**, Lin HJ. Aspirin prescription and outcomes in hemodialysis patients. *Am J Kidney Dis* 2008; **51**: 1070-1071; author reply 1071 [PMID: 18501791 DOI: 10.1053/j.ajkd.2008.01.035]
24 **López T**, Quesada M, Almirall J, Sanfeliu I, Segura F, Calvet X. Usefulness of non-invasive tests for diagnosing Helicobacter pylori infection in patients undergoing dialysis for chronic renal failure. *Helicobacter* 2004; **9**: 674-680 [PMID: 15610083 DOI: 10.1111/j.1083-4389.2004.00282.x]
25 **Malfertheiner P**, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772-781 [PMID: 17170018 DOI: 10.1136/gut.2006.101634]
26 **Huang JJ**, Huang CJ, Ruaan MK, Chen KW, Yen TS, Sheu BS. Diagnostic efficacy of (13)C-urea breath test for Helicobacter pylori infection in hemodialysis patients. *Am J Kidney Dis* 2000; **36**: 124-129 [PMID: 10873881 DOI: 10.1053/ajkd.2000.8284]
27 **Wang YL**, Sheu BS, Huang JJ, Yang HB. Noninvasive stool antigen assay can effectively screen Helicobacter pylori Infection and assess success of eradication therapy in hemodialysis patients. *Am J Kidney Dis* 2001; **38**: 98-103 [PMID: 11431188 DOI: 10.1053/ajkd.2001.25200]
28 **Chang SS**, Hu HY. Reply. *J Chin Med Assoc* 2014; **77**: 657-658 [PMID: 25443803]
29 **Ala-Kaila K**, Kataja M, Keyriläinen O, Pasternack A. The gastric secretion profile of patients with chronic renal failure. *Ann Clin Res* 1981; **13**: 65-70 [PMID: 7235612 DOI: 10.3109/00365528708991969]
30 **Ala-Kaila K**. Gastric secretion kinetics in chronic renal failure. *Scand J Gastroenterol* 1987; **22**: 1185-1192 [PMID: 3324296]
31 **Kim H**, Park C, Jang WI, Lee KH, Kwon SO, Robey-Cafferty SS, Ro JY, Lee YB. The gastric juice urea and ammonia levels in patients with Campylobacter pylori. *Am J Clin Pathol* 1990; **94**: 187-191 [PMID: 2371972 DOI: 10.1097/00004836-200205000-00020]
32 Guidelines for clinical trials in Helicobacter pylori infection. Working Party of the European Helicobacter pylori Study Group. *Gut* 1997; **41** Suppl 2: S1-S9 [PMID: 9404236 DOI: 10.1136/gut.43.5.e728]
33 **Calvet X**, Quesada M, Roselló M, Salceda F, Sanfeliu I, Dalmau B, Gil M. Stool antigen for the diagnosis of Helicobacter pylori infection in cirrhosis: comparative usefulness of three different methods. *Aliment Pharmacol Ther* 2003; **17**: 727-731 [PMID: 12641523 DOI: 10.1046/j.1365-2036.2003.01466.x]
34 **Thijs JC**, van Zwet AA, Thijs WJ, Oey HB, Karrenbeld A, Stellaard F, Luijt DS, Meyer BC, Kleibeuker JH. Diagnostic tests for Helicobacter pylori: a prospective evaluation of their accuracy, without selecting a single test as the gold standard. *Am J Gastroenterol* 1996; **91**: 2125-2129 [PMID: 8855734 DOI: 10.1016/0016-5085(95)23623-6]
35 **Mak SK**, Loo CK, Wong AM, Wong PN, Lo KY, Tong GM, Lam EK, Wong AK. Efficacy of a 1-week course of proton-pump inhibitor-based triple therapy for eradicating Helicobacter pylori in patients with and without chronic renal failure. *Am J Kidney Dis* 2002; **40**: 576-581 [PMID: 12200810 DOI: 10.1053/ajkd.2002.34916]
36 **Tamura H**, Tokushima H, Murakawa M, Matsumura O, Itoyama S, Sekine S, Hirose H, Mitarai T, Isoda K. Eradication of Helicobacter pylori in patients with end-stage renal disease under dialysis treatment. *Am J Kidney Dis* 1997; **29**: 86-90 [PMID: 9002534 DOI: 10.1016/S0272-6386(97)90012-3]
37 **Mak SK**, Loo CK, Wong PN, Lo KY, Tong GM, Lam EK, Wong AK. A retrospective study on efficacy of proton-pump inhibitor-based triple therapy for eradication of Helicobacter pylori in patients with chronic renal failure. *Singapore Med J* 2003; **44**: 74-78 [PMID: 14503780]
38 **Tsukada K**, Miyazaki T, Katoh H, Masuda N, Ojima H, Fukai Y, Nakajima M, Manda R, Fukuchi M, Kuwano H, Tsukada O. Seven-day triple therapy with omeprazole, amoxycillin and clarithromycin for Helicobacter pylori infection in haemodialysis patients. *Scand J Gastroenterol* 2002; **37**: 1265-1268 [PMID: 12465723 DOI: 10.1080/003655202761020524]
39 **Itatsu T**, Miwa H, Nagahara A, Kubota M, Miyazaki A, Sato N, Hayashida Y. Eradication of Helicobacter pylori in hemodialysis patients. *Ren Fail* 2007; **29**: 97-102 [PMID: 17365917 DOI: 10.1080/08860220601039122]
40 **Chang WC**, Jo YI, Park HS, Jegal J, Park JH, Lee JH, Jin CJ. Helicobacter pylori eradication with a 7-day low-dose triple therapy in hemodialysis patients. *Clin Exp Nephrol* 2010; **14**: 469-473 [PMID: 20632062 DOI: 10.1007/s10157-010-0319-7]
41 **Arancibia A**, Drouguett MT, Fuentes G, González G, González C, Thambo S, Palombo G. Pharmacokinetics of amoxicillin in subjects with normal and impaired renal function. *Int J Clin Pharmacol Ther Toxicol* 1982; **20**: 447-453 [PMID: 7141752 DOI: 10.1046/j.1365-2125.2000.00149.x]
42 **Fraschini F**, Scaglione F, Demartini G. Clarithromycin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25**: 189-204 [PMID: 8222460 DOI: 10.2165/00003088-199325030-00003]
43 **Wermeille J**, Cunningham M, Dederding JP, Girard L, Baumann R, Zelger G, Buri P, Metry JM, Sitavanc R, Gallaz L, Merki H, Godin N. Failure of Helicobacter pylori eradication: is poor compliance the main cause? *Gastroenterol Clin Biol* 2002; **26**: 216-219 [PMID: 11981460]
44 **Harris A**, Misiewicz JJ. Treating Helicobacter pylori--the best is yet to come? *Gut* 1996; **39**: 781-783 [PMID: 9038656 DOI: 10.1136/gut.39.6.781]
45 **Aydemir S**, Boyacioglu S, Gur G, Demirbilek M, Can FK, Korkmaz M, Yilmaz U. Helicobacter pylori infection in hemodialysis patients: susceptibility to amoxicillin and clarithromycin. *World J Gastroenterol* 2005; **11**: 842-845 [PMID: 15682477 DOI: 10.3748/wjg.v11.i6.842]
46 **McColl KE**. Clinical practice. Helicobacter pylori infection. *N Engl J Med* 2010; **362**: 1597-1604 [PMID: 20427808 DOI: 10.1056/NEJMcp1001110]
47 **Parasa S**, Navaneethan U, Sridhar AR, Venkatesh PG, Olden K. End-stage renal disease is associated with worse outcomes in hospitalized patients with peptic ulcer bleeding. *Gastrointest Endosc* 2013; **77**: 609-616 [PMID: 23357495 DOI: 10.1016/j.gie.2012.11.014]
48 **Liang CC**, Muo CH, Wang IK, Chang CT, Chou CY, Liu JH, Yen TH, Huang CC, Chung CJ. Peptic ulcer disease risk in chronic kidney disease: ten-year incidence, ulcer location, and ulcerogenic effect of medications. *PLoS One* 2014; **9**: e87952 [PMID: 24498412 DOI: 10.1371/journal.pone.0087952]
49 **Luo JC**, Leu HB, Huang KW, Huang CC, Hou MC, Lin HC, Lee FY, Lee SD. Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis. *CMAJ* 2011; **183**: E1345-E1351 [PMID: 22083684 DOI: 10.1503/cmaj.110299]
50 **Wu CY**, Wu MS, Kuo KN, Wang CB, Chen YJ, Lin JT. Long-term peptic ulcer rebleeding risk estimation in patients undergoing haemodialysis: a 10-year nationwide cohort study. *Gut* 2011; **60**: 1038-1042 [PMID: 21266725]
51 **Sugimoto M**, Yamaoka Y. Review of Helicobacter pylori infection

and chronic renal failure. *Ther Apher Dial* 2011; **15**: 1-9 [PMID: 21272246 DOI: 10.1111/j.1744-9987.2010.00851.x]
52 **Chang SS**, Hu HY. Association between early Helicobacter pylori eradication and a lower risk of recurrent complicated peptic ulcers in end-stage renal disease patients. *Medicine* (Baltimore) 2015; **94**: e370 [PMID: 25569660 DOI: 10.1097/MD.0000000000000370]
53 **Calvet X**, Navarro M, Gil M, Lafont A, Sanfeliu I, Brullet E, Campo R, Dalmau B, Rivero E, Mas P. Epidemiology of peptic ulcer disease in cirrhotic patients: role of Helicobacter pylori infection. *Am J Gastroenterol* 1998; **93**: 2501-2507 [PMID: 9860415 DOI: 10.1016/S0002-9270(98)00592-9]
54 **Tsujii M**, Kawano S, Tsuji S, Fusamoto H, Kamada T, Sato N. Mechanism of gastric mucosal damage induced by ammonia. *Gastroenterology* 1992; **102**: 1881-1888 [PMID: 1587407 DOI: 10.1016/S0016-5085(00)85070-2]
55 **Kim DJ**, Kim HY, Kim SJ, Hahn TH, Jang MK, Baik GH, Kim JB, Park SH, Lee MS, Park CK. Helicobacter pylori infection and peptic ulcer disease in patients with liver cirrhosis. *Korean J Intern Med* 2008; **23**: 16-21 [PMID: 18363275 DOI: 10.3904/kjim.2008.23.1.16]
56 **Jung SW**, Lee SW, Hyun JJ, Kim DI, Koo JS, Yim HJ, Park JJ, Lee HS, Chun HJ, Um SH, Choi JH, Kim CD, Ryu HS. Efficacy of Helicobacter pylori eradication therapy in chronic liver disease. *Dig Liver Dis* 2009; **41**: 134-140 [PMID: 18436489 DOI: 10.1016/j.dld.2008.03.005]
57 **Siringo S**, Vaira D, Menegatti M, Piscaglia F, Sofia S, Gaetani M, Miglioli M, Corinaldesi R, Bolondi L. High prevalence of Helicobacter pylori in liver cirrhosis: relationship with clinical and endoscopic features and the risk of peptic ulcer. *Dig Dis Sci* 1997; **42**: 2024-2030 [PMID: 9365129 DOI: 10.1136/gut.35.3.309]
58 **Bhargava N**, Venkateswaran S, Ramakrishna BS, Mathan M. Colonization by Helicobacter pylori and its relationship to histological changes in the gastric mucosa in portal hypertension. *J Gastroenterol Hepatol* 1994; **9**: 507-511 [PMID: 7827303 DOI: 10.1111/j.1440-1746.1994.tb01282.x]
59 **Chang SS**, Hu HY. Helicobacter pylori is not the predominant etiology for liver cirrhosis patients with peptic ulcer disease. *Eur J Gastroenterol Hepatol* 2013; **25**: 159-165 [PMID: 23044811 DOI: 10.1097/MEG.0b013e32835a1b26]
60 **Lo GH**, Yu HC, Chan YC, Chen WC, Hsu PI, Lin CK, Lai KH. The effects of eradication of Helicobacter pylori on the recurrence of duodenal ulcers in patients with cirrhosis. *Gastrointest Endosc* 2005; **62**: 350-356 [PMID: 16111950 DOI: 10.1016/S0016-5107(05)01633-0]
61 **Wang CH**, Ma LR, Lin RC, Kuo JY, Chang KK. Helicobacter pylori infection and risk of peptic ulcer among cirrhotic patients. *J Formos Med Assoc* 1997; **96**: 55-58 [PMID: 9033184]
62 **Chen LS**, Lin HC, Lee FY, Hou MC, Lee SD. Prevalence of duodenal ulcer in cirrhotic patients and its relation to Helicobacter pylori and portal hypertension. *Zhonghua Yixue Zazhi* (Taipei) 1995; **56**: 226-231 [PMID: 8548663 DOI: 10.1111/j.1440-1746.1996.tb00011.x]
63 **Wu CS**, Lin CY, Liaw YF. Helicobacter pylori in cirrhotic patients with peptic ulcer disease: a prospective, case controlled study. *Gastrointest Endosc* 1995; **42**: 424-427 [PMID: 8566632 DOI: 10.1016/S0016-5107(95)70044-7]
64 **Dore MP**, Mura D, Deledda S, Maragkoudakis E, Pironti A, Realdi G. Active peptic ulcer disease in patients with hepatitis C virus-related cirrhosis: the role of Helicobacter pylori infection and portal hypertensive gastropathy. *Can J Gastroenterol* 2004; **18**: 521-524 [PMID: 15372116 DOI: 10.1016/S1590-8658(01)80485-0]
65 **Calvet X**, Navarro M, Gil M, Mas P, Rivero E, Sanfeliu I, Brullet E, Campo R, Dalmau B, Lafont A. Seroprevalence and epidemiology of Helicobacter pylori infection in patients with cirrhosis. *J Hepatol* 1997; **26**: 1249-1254 [PMID: 9210611 DOI: 10.1016/S0168-8278(97)80459-X]
66 **Farinati F**, De Bona M, Floreani A, Foschia F, Rugge M. Helicobacter pylori and the liver: any relationship? *Ital J Gastroenterol Hepatol* 1998; **30**: 124-128 [PMID: 9615280 DOI: 10.1016/S0168-8278(98)80805-2]
67 **van Nieuwkerk CM**, Kuipers EJ. Liver cirrhosis and peptic ulcer disease; a correlation with Helicobacter pylori? *Neth J Med* 2000; **56**: 203-205 [PMID: 10821974 DOI: 10.1016/S0300-2977(00)00013-9]
68 **Saad RJ**, Chey WD. Peptic ulcer disease in patients with chronic liver disease: looking beyond bugs and drugs. *Gastrointest Endosc* 2005; **62**: 357-359 [PMID: 16111951 DOI: 10.1016/j.gie.2005.06.003]
69 **Gisbert JP**, Moreno-Otero R, Pajares JM. [Prevalence of Helicobacter pylori infection in chronic liver disease and relationship with its complications: systematic review and meta-analysis]. *Med Clin* (Barc) 2002; **119**: 464-474 [PMID: 12385656 DOI: 10.1016/S1590-8658(02)90225-2]
70 **Blaser MJ**, Atherton JC. Helicobacter pylori persistence: biology and disease. *J Clin Invest* 2004; **113**: 321-333 [PMID: 14755326 DOI: 10.1172/JCI20925]
71 **Atherton JC**, Blaser MJ. Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. *J Clin Invest* 2009; **119**: 2475-2487 [PMID: 19729845 DOI: 10.1172/JCI38605]
72 **Furuta T**, Baba S, Takashima M, Futami H, Arai H, Kajimura M, Hanai H, Kaneko E. Effect of Helicobacter pylori infection on gastric juice pH. *Scand J Gastroenterol* 1998; **33**: 357-363 [PMID: 9605256 DOI: 10.1080/00365529850170973]
73 **Suzuki H**, Ishii H. [Peptic ulcer disease complicated with liver cirrhosis]. *Nihon Rinsho* 2004; **62**: 532-540 [PMID: 15038099 DOI: 10.1016/S1590-8658(10)60366-0]
74 **Chen CT**, Wang TF, Chan CC, Lee FY, Chang FY, Lin HC, Hou MC, Lu RH, Chu CJ, Wang SS, Lee SD. Role of chronic Helicobacter pylori infection in hyperdynamic circulation of cirrhotic patients. *Hepatogastroenterology* 2002; **49**: 208-212 [PMID: 11941956]
75 **Kitano S**, Dolgor B. Does portal hypertension contribute to the pathogenesis of gastric ulcer associated with liver cirrhosis? *J Gastroenterol* 2000; **35**: 79-86 [PMID: 10680661 DOI: 10.1007/s005350050018]
76 **Luo JC**, Leu HB, Hou MC, Huang CC, Lin HC, Lee FY, Chang FY, Chan WL, Lin SJ, Chen JW. Cirrhotic patients at increased risk of peptic ulcer bleeding: a nationwide population-based cohort study. *Aliment Pharmacol Ther* 2012; **36**: 542-550 [PMID: 22817655 DOI: 10.1111/j.1365-2036.2012.05225.x]
77 **Chang SS**, Hu HY. H. pylori eradication lower ulcers in cirrhosis. [Corrected]. *J Dig Dis* 2014; **15**: 451-458 [PMID: 24825443 DOI: 10.1111/1751-2980.12159]
78 **Jiang HX**, Qin SY, Min ZG, Xie MZ, Lin T, Hu BL, Guo XY. Association of Helicobacter pylori with elevated blood ammonia levels in cirrhotic patients: a meta-analysis. *Yonsei Med J* 2013; **54**: 832-838 [PMID: 23709415 DOI: 10.3349/ymj.2013.54.4.832]
79 **Dasani BM**, Sigal SH, Lieber CS. Analysis of risk factors for chronic hepatic encephalopathy: the role of Helicobacter pylori infection. *Am J Gastroenterol* 1998; **93**: 726-731 [PMID: 9625117 DOI: 10.1016/S0002-9270(98)00094-X]
80 **Miyaji H**, Ito S, Azuma T, Ito Y, Yamazaki Y, Ohtaki Y, Sato F, Hirai M, Kuriyama M, Kohli Y. Effects of Helicobacter pylori eradication therapy on hyperammonaemia in patients with liver cirrhosis. *Gut* 1997; **40**: 726-730 [PMID: 9245925 DOI: 10.1136/gut.40.6.726]
81 **Agrawal A**, Gupta A, Chandra M, Koowar S. Role of Helicobacter pylori infection in the pathogenesis of minimal hepatic encephalopathy and effect of its eradication. *Indian J Gastroenterol* 2011; **30**: 29-32 [PMID: 21416318 DOI: 10.1007/s12664-011-0087-7]
82 **Miquel J**, Barcena R, Boixeda D, Fernández J, SanRoman AL, Martín-de-Argila C, Ramosa F. Role of Helicobacter pylori infection and its eradication in patients with subclinical hepatic encephalopathy. *Eur J Gastroenterol Hepatol* 2001; **13**: 1067-1072 [PMID: 11564957 DOI: 10.1097/00042737-200109000-00012]
83 **Scotiniotis IA**, Lucey MR, Metz DC. Helicobacter pylori infection is not associated with subclinical hepatic encephalopathy in stable cirrhotic patients. *Dig Dis Sci* 2001; **46**: 2744-2751 [PMID: 11768268]
84 **Quero JC**, Hartmann IJ, de Rooij F, Wilson JH, Schalm SW. Hyperammonaemia and Helicobacter pylori. *Lancet* 1995; **346**: 713-714 [PMID: 7658863 DOI: 10.1016/S0140-6736(95)92332-2]
85 **Nilsson I**, Lindgren S, Eriksson S, Wadström T. Serum antibodies

to Helicobacter hepaticus and Helicobacter pylori in patients with chronic liver disease. *Gut* 2000; **46**: 410-414 [PMID: 10673306 DOI: 10.1136/gut.46.3.410]

86 **Fox JG**, Ge Z, Whary MT, Erdman SE, Horwitz BH. Helicobacter hepaticus infection in mice: models for understanding lower bowel inflammation and cancer. *Mucosal Immunol* 2011; **4**: 22-30 [PMID: 20944559 DOI: 10.1038/mi.2010.61]

87 **Fox JG**, Yan LL, Dewhirst FE, Paster BJ, Shames B, Murphy JC, Hayward A, Belcher JC, Mendes EN. Helicobacter bilis sp. nov., a novel Helicobacter species isolated from bile, livers, and intestines of aged, inbred mice. *J Clin Microbiol* 1995; **33**: 445-454 [PMID: 7536217 DOI: 10.1099/jmm.0.032144-0]

88 **Ward JM**, Fox JG, Anver MR, Haines DC, George CV, Collins MJ, Gorelick PL, Nagashima K, Gonda MA, Gilden RV. Chronic active hepatitis and associated liver tumors in mice caused by a persistent bacterial infection with a novel Helicobacter species. *J Natl Cancer Inst* 1994; **86**: 1222-1227 [PMID: 8040890 DOI: 10.1093/jnci/86.16.1222]

89 **Fox JG**, Li X, Yan L, Cahill RJ, Hurley R, Lewis R, Murphy JC. Chronic proliferative hepatitis in A/JCr mice associated with persistent Helicobacter hepaticus infection: a model of helicobacter-induced carcinogenesis. *Infect Immun* 1996; **64**: 1548-1558 [PMID: 8613359 DOI: 10.1128/IAI.73.12.8449-8452.2005]

90 **Fox JG**, Feng Y, Theve EJ, Raczynski AR, Fiala JL, Doernte AL, Williams M, McFaline JL, Essigmann JM, Schauer DB, Tannenbaum SR, Dedon PC, Weinman SA, Lemon SM, Fry RC, Rogers AB. Gut microbes define liver cancer risk in mice exposed to chemical and viral transgenic hepatocarcinogens. *Gut* 2010; **59**: 88-97 [PMID: 19850960 DOI: 10.1136/gut.2009.183749]

91 **Fukuda Y**, Shimoyama T, Ohmura T, Sano Y, Nakabayashi N, Takahashi R, Fujioka T, Mitchell HM, Shimoyama T. Characterization and application of a new monoclonal antibody with high specificity for Helicobacter hepaticus. *Helicobacter* 2009; **14**: 66-71 [PMID: 19191899 DOI: 10.1111/j.1523-5378.2009.00652.x]

92 **Murakami K**, Takahashi R, Ono M, Watanabe K, Okimoto T, Kodama M, Abe D, Kimura M, Fujioka T. Serodiagnosis of Helicobacter hepaticus infection in patients with liver and gastrointestinal diseases: western blot analysis and ELISA using a highly specific monoclonal antibody for H. hepaticus antigen. *J Gastroenterol* 2011; **46**: 1120-1126 [PMID: 21656014 DOI: 10.1007/s00535-011-0414-x]

93 **Pellicano R**, Ménard A, Rizzetto M, Mégraud F. Helicobacter species and liver diseases: association or causation? *Lancet Infect Dis* 2008; **8**: 254-260 [PMID: 18353266 DOI: 10.1016/S1473-3099(08)70066-5]

94 **Kleine M**, Worbs T, Schrem H, Vondran FW, Kaltenborn A, Klempnauer J, Förster R, Josenhans C, Suerbaum S, Bektas H. Helicobacter hepaticus induces an inflammatory response in primary human hepatocytes. *PLoS One* 2014; **9**: e99713 [PMID: 24932686 DOI: 10.1371/journal.pone.0099713]

95 **Medeiros JA**, Pereira MI. The use of probiotics in Helicobacter pylori eradication therapy. *J Clin Gastroenterol* 2013; **47**: 1-5 [PMID: 23222208 DOI: 10.1097/MCG.0b013e3182702dbc]

96 **Scaccianoce G**, Zullo A, Hassan C, Gentili F, Cristofari F, Cardinale V, Gigliotti F, Piglionica D, Morini S. Triple therapies plus different probiotics for Helicobacter pylori eradication. *Eur Rev Med Pharmacol Sci* 2008; **12**: 251-256 [PMID: 18727457 DOI: 10.1016/j.ejim.2012.07.006]

97 **de Bortoli N**, Leonardi G, Ciancia E, Merlo A, Bellini M, Costa F, Mumolo MG, Ricchiuti A, Cristiani F, Santi S, Rossi M, Marchi S. Helicobacter pylori eradication: a randomized prospective study of triple therapy versus triple therapy plus lactoferrin and probiotics. *Am J Gastroenterol* 2007; **102**: 951-956 [PMID: 17313499 DOI: 10.1111/j.1572-0241.2007.01085.x]

98 **O'Connor A**, Gisbert JP, McNamara D, O'Morain C. Treatment of Helicobacter pylori infection 2011. *Helicobacter* 2011; **16** Suppl 1: 53-58 [PMID: 21896086]

99 **Rimbara E**, Fischbach LA, Graham DY. Optimal therapy for Helicobacter pylori infections. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 79-88 [PMID: 21293508 DOI: 10.1038/nrgastro.2010.210]

100 **Chuah SK**, Tsay FW, Hsu PI, Wu DC. A new look at anti-Helicobacter pylori therapy. *World J Gastroenterol* 2011; **17**: 3971-3975 [PMID: 22046084 DOI: 10.3748/wjg.v17.i35.3971]

101 **Rinaldi V**, Zullo A, Pugliano F, Valente C, Diana F, Attili AF. The management of failed dual or triple therapy for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 1997; **11**: 929-933 [PMID: 9354202 DOI: 10.1046/j.1365-2036.1997.00228.x]

102 **Gisbert JP**, Calvet X, O'Connor A, Mégraud F, O'Morain CA. Sequential therapy for Helicobacter pylori eradication: a critical review. *J Clin Gastroenterol* 2010; **44**: 313-325 [PMID: 20054285 DOI: 10.1016/S0016-5085(10)61541-7]

103 **Gatta L**, Vakil N, Vaira D, Scarpignato C. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013; **347**: f4587 [PMID: 23926315 DOI: 10.1136/bmj.f4587]

104 **Kate V**, Kalayarasan R, Ananthakrishnan N. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a systematic review of recent evidence. *Drugs* 2013; **73**: 815-824 [PMID: 23625272 DOI: 10.1007/s40265-013-0053-z]

105 **Liou JM**, Chen CC, Chen MJ, Chen CC, Chang CY, Fang YJ, Lee JY, Hsu SJ, Luo JC, Chang WH, Hsu YC, Tseng CH, Tseng PH, Wang HP, Yang UC, Shun CT, Lin JT, Lee YC, Wu MS. Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial. *Lancet* 2013; **381**: 205-213 [PMID: 23158886 DOI: 10.1016/S0140-6736(12)61579-7]

106 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499]

107 **Georgopoulos SD**, Papastergiou V, Karatapanis S. Current options for the treatment of Helicobacter pylori. *Expert Opin Pharmacother* 2013; **14**: 211-223 [PMID: 23331077 DOI: 10.1097/00001574-199801000-00012]

108 **Hsu PI**, Wu DC, Wu JY, Graham DY. Modified sequential Helicobacter pylori therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter* 2011; **16**: 139-145 [PMID: 21435092 DOI: 10.1111/j.1523-5378.2011.00828.x]

109 **Sardarian H**, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for Helicobacter pylori eradication in Iran: a prospective randomized trial. *Helicobacter* 2013; **18**: 129-134 [PMID: 23121338 DOI: 10.1111/hel.12017]

110 **Molina-Infante J**, Pazos-Pacheco C, Vinagre-Rodriguez G, Perez-Gallardo B, Dueñas-Sadornil C, Hernandez-Alonso M, Gonzalez-Garcia G, Mateos-Rodriguez JM, Fernandez-Bermejo M, Gisbert JP. Nonbismuth quadruple (concomitant) therapy: empirical and tailored efficacy versus standard triple therapy for clarithromycin-susceptible Helicobacter pylori and versus sequential therapy for clarithromycin-resistant strains. *Helicobacter* 2012; **17**: 269-276 [PMID: 22759326 DOI: 10.1111/j.1523-5378.2012.00947.x]

111 **Georgopoulos SD**, Xirouchakis E, Martinez-Gonzalez B, Sgouras DN, Spiliadi C, Mentis AF, Laoudi F. Clinical evaluation of a ten-day regimen with esomeprazole, metronidazole, amoxicillin, and clarithromycin for the eradication of Helicobacter pylori in a high clarithromycin resistance area. *Helicobacter* 2013; **18**: 459-467 [PMID: 23714140 DOI: 10.1111/hel.12062]

112 **Essa AS**, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication. *Helicobacter* 2009; **14**: 109-118 [PMID: 19298338 DOI: 10.1111/j.1523-5378.2009.00671.x]

113 **Molina-Infante J**, Romano M, Fernandez-Bermejo M, Federico A, Gravina AG, Pozzati L, Garcia-Abadia E, Vinagre-Rodriguez G, Martinez-Alcala C, Hernandez-Alonso M, Miranda A, Iovene MR, Pazos-Pacheco C, Gisbert JP. Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in populations with high rates of antibiotic resistance. *Gastroenterology* 2013; **145**: 121-128.e1 [PMID: 23562754 DOI:

10.1053/j.gastro.2013.03.050]
114 **Yang JC**, Lin CJ, Wang HL, Chen JD, Kao JY, Shun CT, Lu CW, Lin BR, Shieh MJ, Chang MC, Chang YT, Wei SC, Lin LC, Yeh WC, Kuo JS, Tung CC, Leong YL, Wang TH, Wong JM. High-dose dual therapy is superior to standard first-line or rescue therapy for Helicobacter pylori infection. *Clin Gastroenterol Hepatol* 2015; **13**: 895-905.e5 [PMID: 25460556 DOI: 10.1016/j.cgh.2014.10.036]
115 **van der Wouden EJ**, Thijs JC, van Zwet AA, Sluiter WJ, Kleibeuker JH. The influence of in vitro nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-Helicobacter pylori regimens: a meta-analysis. *Am J Gastroenterol* 1999; **94**: 1751-1759 [PMID: 10406231 DOI: 10.1016/S0002-9270(99)00258-0]
116 **Luther J**, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: Systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol* 2010; **105**: 65-73 [PMID: 19755966 DOI: 10.1038/ajg.2009.508]
117 **Liang X**, Xu X, Zheng Q, Zhang W, Sun Q, Liu W, Xiao S, Lu H. Efficacy of bismuth-containing quadruple therapies for clarithromycin-, metronidazole-, and fluoroquinolone-resistant Helicobacter pylori infections in a prospective study. *Clin Gastroenterol Hepatol* 2013; **11**: 802-807.e1 [PMID: 23376004 DOI: 10.1016/j.cgh.2013.01.008]
118 **Graham DY**. Helicobacter pylori eradication therapy research: Ethical issues and description of results. *Clin Gastroenterol Hepatol* 2010; **8**: 1032-1036 [PMID: 20656062 DOI: 10.1016/j.cgh.2010.07.002]
119 **Song MJ**, Park DI, Park JH, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI. The effect of probiotics and mucoprotective agents on PPI-based triple therapy for eradication of Helicobacter pylori. *Helicobacter* 2010; **15**: 206-213 [PMID: 20557362 DOI: 10.1111/j.1523-5378.2010.00751.x]
120 **Fuller R**. Probiotics in man and animals. *J Appl Bacteriol* 1989; **66**: 365-378 [PMID: 2666378 DOI: 10.1111/j.1365-2672.1989.tb05105.x]
121 **Wilhelm SM**, Johnson JL, Kale-Pradhan PB. Treating bugs with bugs: the role of probiotics as adjunctive therapy for Helicobacter pylori. *Ann Pharmacother* 2011; **45**: 960-966 [PMID: 21693698 DOI: 10.1345/aph.1Q104]
122 **Zou J**, Dong J, Yu X. Meta-analysis: Lactobacillus containing quadruple therapy versus standard triple first-line therapy for Helicobacter pylori eradication. *Helicobacter* 2009; **14**: 97-107 [PMID: 19751434 DOI: 10.1111/j.1523-5378.2009.00716.x]
123 **Canducci F**, Cremonini F, Armuzzi A, Di Caro S, Gabrielli M, Santarelli L, Nista E, Lupascu A, De Martini D, Gasbarrini A. Probiotics and Helicobacter pylori eradication. *Dig Liver Dis* 2002; **34** Suppl 2: S81-S83 [PMID: 12408448 DOI: 10.1016/S1590-8658(02)80172-4]
124 **Chenoll E**, Casinos B, Bataller E, Astals P, Echevarría J, Iglesias JR, Balbarie P, Ramón D, Genovés S. Novel probiotic Bifidobacterium bifidum CECT 7366 strain active against the pathogenic bacterium Helicobacter pylori. *Appl Environ Microbiol* 2011; **77**: 1335-1343 [PMID: 21169430 DOI: 10.1128/AEM.01820-10]
125 **Gisbert JP**. Is culture necessary before first-line treatment for Helicobacter pylori infection? *Intern Med* 2011; **50**: 2717; author reply 2719-2720 [PMID: 22041399 DOI: 10.2169/internalmedicine.50.5135]

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