

HELİKOBAKTER PYLORİ TANISI VE TEDAVİ ENDİKASYONLARI

37. BÖLÜM

Derya Salim UYMAZ¹

ÖZET

Helikobakter pylori dünya nüfusunun yaklaşık yarısını enfekte etmesi, ısrarcı bakteriyel enfeksiyona sebep olması, peptik ülser, gastrik ülser, mukoza ilişkili lenfoid doku lenfomasına ve mide kanserine sebep olabilmesi nedeni ile tedavi edilmesi gereken bir ajandır. Maliyet, hastanın yaşı, ulaşılabilirlik gibi birçok faktöre bağlı olarak hastalığın tanı yöntem seçenekleri değişmektedir. Helikobakter pylori enfeksiyonu tespit edilince verilmesi gereken karar tedavi edilip edilmeyeceğidir. Standart üçlü tedavi ile hala yüksek oranda eradikasyon sağlanmasına rağmen dirençli olgularda çeşitli tedavi alternatifleri bulunmaktadır.

GİRİŞ

Helikobacter pylori (H. pylori), dünya çapında en sık ve kalıcı bakteriyel enfeksiyondan sorumlu mikroorganizmadır. H. pylori enfeksiyonu dünya nüfusunun neredeyse yarısını etkiler. Gelişmekte olan ülkelerde enfeksiyon prevalansı %90'a kadar çıkarken, Japonya dışındaki gelişmiş ülkelerde prevalans %40'ın altındadır (1). H. pylori enfeksiyonunu tespit etmek için tanı yöntemleri çeşitlidir ve bir yöntemin veya diğerinin seçimi, tanısal testlerin mevcudiyeti, endoskopi yapma gerekliliği, maliyet, erişilebilirlik, hastaların yaşı her yöntemin avantajları ve dezavantajları gibi birkaç faktöre bağlıdır.

Üçlü terapi, H. pylori için standart tedavidir. Üçlü terapi kabul edilebilir tedavi oranları sunsa da çeşitli ilaç kombinasyonlarını, ardışık tedavileri ve eşzamanlı terapileri kullanan dörtlü te-

daviler, H. pylori tedavisi için etkili alternatifler olarak tanıtılmıştır.

ENFEKSİYONUN TANISI

H. pylori'nin varlığını tespit etmek için her biri kendi avantajları, dezavantajları ve sınırlamaları olan birkaç yöntem mevcuttur. Yöntemleri sınıflandırmanın klasik bir yolu, endoskopinin gerekli olup olmadığına göre. Biyopsi temelli testler histolojik değerlendirme, kültür, polimeraz zincir reaksiyonu (PCR) ve hızlı üreaz testini (HÜT) içerir ve bunların tümü endoskopi sırasında elde edilen doku üzerinde gerçekleştirilir. Alternatif olarak, üre nefes testi (ÜNT), seroloji ve dışkı antijen testi (DAT), invazif olmayan prosedürler olarak gerçekleştirilebilir. Bu testleri sınıflandırmanın ikinci bir yolu, H. pylori eradikasyon tedavisinden önce mi sonra mı kullanıldığına göre.

¹ Uzm. Dr. Derya Salim UYMAZ, Koç Üniversitesi Genel Cerrahi AD deryauymaz@yahoo.com

lerin insidansının havuzlanmış OR'si, probiyotik takviyesi alan grupta önemli ölçüde azalmıştır (OR = 0.305; %95 CI: 0.117-0.793). Yetişkinlerde *Lactobacillus* ve *Bifidobacterium* içeren bir probiyotığın başlangıçtaki *H. pylori* eradikasyon tedavisi ile birleştirilmesinin eradikasyon hızı ve toplam yan etkilerin insidansı üzerinde yararlı etkileri olabileceği sonucuna varmışlardır.

Başka bir çalışma, standart bir anti-*H. pylori* rejimine probiyotik eklendiğinde yan etkilerin prevalansının azaltılabileceğini ve eradikasyon oranının artırabileceği amaçlandı. Çift kör, randomize, plasebo kontrollü bir çalışmada, HÜT veya histoloji ile teşhis edilen 66 *H. pylori* pozitif çocuk, üçlü bir ilaç tedavi protokolü (omeprazol, amoksisilin ve furazolidon) ile tedavi edildi ve rastgele probiyotik veya bir plasebo tedaviye eklendi (100). Tüm hastalara özofagogastroduodendoskopi yapıldı. *H. pylori* durumu, tedavinin tamamlanmasından 4 ila 8 hafta sonra DAT tarafından değerlendirildi. *H. pylori* eradikasyon oranı probiyotik alan grupta anlamlı olarak daha yüksekti ($P = 0.04$). Ayrıca, tedavi sırasında, probiyotik verilen çocuklarda plasebo ile tedavi edilen çocuklara göre daha düşük bulantı / kusma ($P = 0.02$) ve ishal ($P = 0.039$) oranı görülmüştür. Yazarlar, probiyotiklerin *H. pylori* enfeksiyonunun ortadan kaldırılması ve *H. pylori* tedavisinin yan etkileri üzerinde olumlu bir etkiye sahip olduğu sonucuna varmışlardır.

SONUÇ

H. pylori enfeksiyonu, dünya çapında en sık görülen ve kalıcı bakteriyel enfeksiyon olmaya devam etmektedir; bu nedenle, enfeksiyonun doğru teşhisi zorunludur. *H. pylori* enfeksiyonunun teşhisi ve tedavi sonrası eradikasyonun tespiti için birkaç alternatif vardır. Ek olarak, tedavi için kullanılan birkaç seçenek vardır. Her hasta için kullanılacak tanı yönteminin ve tedavilerin belirlenmesi, diğerlerinin yanı sıra hastanın klinik durumu, enfeksiyon prevalansı ve klaritromisin direncinin yaygınlığı gibi çeşitli faktörlere bağlıdır.

KAYNAKLAR

1. Tonkic A, Tonkic M, Lehours P, Mégraud F. Epidemiology and diagnosis of *Helicobacter pylori* infection. *Helicobacter* 2012; 17 Suppl 1: 1-8 (PMID: 22958148 DOI: 10.1111/j.1523-5378.2012.00975.x)
2. Genta RM, Graham DY. Comparison of biopsy sites for the histopathologic diagnosis of *Helicobacter pylori*: a topographic study of *H. pylori* density and distribution. *Gastrointest Endosc* 1994; 40: 342-345 (PMID: 7794303)
3. Satoh K, Kimura K, Taniguchi Y, Kihira K, Takimoto T, Saifuku K, Kawata H, Tokumaru K, Kojima T, Seki M, Ido K, Fujioka T. Biopsy sites suitable for the diagnosis of *Helicobacter pylori* infection and the assessment of the extent of atrophic gastritis. *Am J Gastroenterol* 1998; 93: 569-573 (PMID: 9576449 DOI: 10.1111/j.1572-0241.1998.166_b.x)
4. van IJendoorn MC, Laheij RJ, de Boer WA, Jansen JB. The importance of corpus biopsies for the determination of *Helicobacter pylori* infection. *Neth J Med* 2005; 63: 141-145 (PMID: 15869042)
5. Lan HC, Chen TS, Li AF, Chang FY, Lin HC. Additional corpus biopsy enhances the detection of *Helicobacter pylori* infection in a background of gastritis with atrophy. *BMC Gastroenterol* 2012; 12: 182 (PMID: 23272897 DOI: 10.1186/1471-230X-12-182)
6. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; 20: 1161-1181 (PMID: 8827022)
7. Laine L, Lewin DN, Naritoku W, Cohen H. Prospective comparison of H& E, Giemsa, and Genta stains for the diagnosis of *Helicobacter pylori*. *Gastrointest Endosc* 1997; 45: 463-467 (PMID: 9199901)
8. Fallone CA, Loo VG, Lough J, Barkun AN. Hematoxylin and eosin staining of gastric tissue for the detection of *Helicobacter pylori*. *Helicobacter* 1997; 2: 32-35 (PMID: 9432319)
9. El-Zimaity HM, Segura AM, Genta RM, Graham DY. Histologic assessment of *Helicobacter pylori* status after therapy: comparison of Giemsa, Diff-Quik, and Genta stains. *Mod Pathol* 1998; 11: 288-291 (PMID: 9521477)
10. Eshun JK, Black DD, Casteel HB, Horn H, Beavers-May T, Jetton CA, Parham DM. Comparison of immunohistochemistry and silver stain for the diagnosis of pediatric *Helicobacter pylori* infection in urease-negative gastric biopsies. *Pediatr Dev Pathol* 2001; 4: 82-88 (PMID: 11200495)
11. El-Zimaity HM, Graham DY. Evaluation of gastric mucosal biopsy site and number for identification of *Helicobacter pylori* or intestinal metaplasia: role of the Sydney System. *Hum Pathol* 1999; 30: 72-77 (PMID: 9923930)
12. Morgner A, Lehn N, Andersen LP, Thiede C, Bennedsen M, Trebesius K, Neubauer B, Neubauer A, Stolte M, Bayerdörffer E. *Helicobacter heilmannii*-associated primary gastric low-grade MALT lymphoma: complete remission after curing the infection. *Gastroentero-*

- logy 2000; 118: 821-828 (PMID: 10784580)
13. Carvalho MA, Machado NC, Ortolan EV, Rodrigues MA. Upper gastrointestinal histopathological findings in children and adolescents with nonulcer dyspepsia with *Helicobacter pylori* infection. *J Pediatr Gastroenterol Nutr* 2012; 55: 523-529 (PMID: 22684348 DOI: 10.1097/MPG.0b013e3182618136)
 14. Trebesius K, Panthel K, Strobel S, Vogt K, Faller G, Kirchner T, Kist M, Heesemann J, Haas R. Rapid and specific detection of *Helicobacter pylori* macrolide resistance in gastric tissue by fluorescent in situ hybridisation. *Gut* 2000; 46: 608-614 (PMID: 10764702)
 15. Rüssmann H, Kempf VA, Koletzko S, Heesemann J, Autenrieth IB. Comparison of fluorescent in situ hybridization and conventional culturing for detection of *Helicobacter pylori* in gastric biopsy specimens. *J Clin Microbiol* 2001; 39: 304-308 (PMID: 11136788 DOI: 10.1128/JCM.39.1.304-308.2001)
 16. Camorlinga-Ponce M, Romo C, González-Valencia G, Muñoz O, Torres J. Topographical localisation of *cagA* positive and *cagA* negative *Helicobacter pylori* strains in the gastric mucosa; an in situ hybridisation study. *J Clin Pathol* 2004; 57: 822-828 (PMID: 15280402 DOI: 10.1136/jcp.2004.017087)
 17. Windsor HM, Abioye-Kuteyi EA, Marshall BJ. Methodology and transport medium for collection of *Helicobacter pylori* on a string test in remote locations. *Helicobacter* 2005; 10: 630-634 (PMID: 16302991 DOI: 10.1111/j.1523-5378.2005.00355.x)
 18. Velapatiño B, Balqui J, Gilman RH, Bussalleu A, Quino W, Garza-González E et al. Diagnosis and treatment of *H. pylori* infection 1447 February 14, 2014|Volume 20|Issue 6|WJG |www.wjgnet.com Finger SA, Santivañez L, Herrera P, Piscocoya A, Valdivia J, Cok J, Berg DE. Validation of string test for diagnosis of *Helicobacter pylori* infections. *J Clin Microbiol* 2006; 44: 976-980 (PMID: 16517886 DOI: 10.1128/JCM.44.3.976-980.2006)
 19. Whitmire JM, Merrell DS. Successful culture techniques for *Helicobacter* species: verification of *Helicobacter* identity using 16S rRNA gene sequence analysis. *Methods Mol Biol* 2012; 921: 37-40 (PMID: 23015489 DOI: 10.1007/978-1-62703-005-2_6)
 20. Hirschl AM, Makristathis A. Methods to detect *Helicobacter pylori*: from culture to molecular biology. *Helicobacter* 2007; 12 Suppl 2: 6-11 (PMID: 17991170 DOI: 10.1111/j.1523-5378.2007.00560.x)
 21. Ramis IB, de Moraes EP, Fernandes MS, Mendoza-Sassi R, Rodrigues O, Juliano CR, Scaini CJ, da Silva PE. Evaluation of diagnostic methods for the detection of *Helicobacter pylori* in gastric biopsy specimens of dyspeptic patients. *Braz J Microbiol* 2012; 43: 903-908 (PMID: 24031905 DOI: 10.1590/S1517-83822012000300008)
 22. Choi YJ, Kim N, Lim J, Jo SY, Shin CM, Lee HS, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Jung HC. Accuracy of diagnostic tests for *Helicobacter pylori* in patients with peptic ulcer bleeding. *Helicobacter* 2012; 17: 77-85 (PMID: 22404437 DOI: 10.1111/j.1523-5378.2011.00915.x)
 23. Sudraba A, Daugule I, Rudzite D, Funka K, Tolmanis I, Engstrand L, Janciauskas D, Jonaitis L, Kiudelis G, Kupcinskas L, Ivanauskas A, Leja M. Performance of routine *Helicobacter pylori* tests in patients with atrophic gastritis. *J Gastrointest Liver Dis* 2011; 20: 349-354 (PMID: 22187698)
 24. Mendoza-Ibarra SI, Perez-Perez GI, Bosques-Padilla FJ, Urquidi-Rivera M, Rodriguez-Esquivel Z, Garza-González E. Utility of diagnostic tests for detection of *Helicobacter pylori* in children in northeastern Mexico. *Pediatr Int* 2007; 49: 869-874 (PMID: 18045288 DOI: 10.1111/j.1442200X.2007.02488.x)
 25. Perez-Perez GI. Accurate diagnosis of *Helicobacter pylori*. Culture, including transport. *Gastroenterol Clin North Am* 2000; 29: 879-884 (PMID: 11190072)
 26. Ndip RN, MacKay WG, Farthing MJ, Weaver LT. Culturing *Helicobacter pylori* from clinical specimens: review of microbiologic methods. *J Pediatr Gastroenterol Nutr* 2003; 36: 616-622 (PMID: 12717085)
 27. Ogata SK, Godoy AP, da Silva Patricio FR, Kawakami E. High *Helicobacter pylori* resistance to metronidazole and clarithromycin in Brazilian children and adolescents. *J Pediatr Gastroenterol Nutr* 2013; 56: 645-648 (PMID: 23403439 DOI: 10.1097/MPG.0b013e31828b3669)
 28. Kato S, Fujimura S. Primary antimicrobial resistance of *Helicobacter pylori* in children during the past 9 years. *Pediatr Int* 2010; 52: 187-190 (PMID: 19563459 DOI: 10.1111/j.1442200X.2009.02915.x)
 29. Rimbara E, Sasatsu M, Graham DY. PCR detection of *Helicobacter pylori* in clinical samples. *Methods Mol Biol* 2013; 943: 279-287 (PMID: 23104297 DOI: 10.1007/978-1-60327-3534_19)
 30. Duš I, Dobosz T, Manzin A, Loi G, Serra C, Radwan-Oczko M. Role of PCR in *Helicobacter pylori* diagnostics and research--new approaches for study of coccoid and spiral forms of the bacteria. *Postepy Hig Med Dosw (Online)* 2013; 67: 261-268 (PMID: 23619225)
 31. Owen RJ. Molecular testing for antibiotic resistance in *Helicobacter pylori*. *Gut* 2002; 50: 285-289 (PMID: 11839700)
 32. Schweizer HP. Understanding efflux in Gram-negative bacteria: opportunities for drug discovery. *Expert Opin Drug Discov* 2012; 7: 633-642 (PMID: 22607346 DOI: 10.1517/17460441.2012.688949)
 33. Lewis JD, Kroser J, Bevan J, Furth EE, Metz DC. Urea-based tests for *Helicobacter pylori* gastritis. Accurate for diagnosis but poor correlation with disease severity. *J Clin Gastroenterol* 1997; 25: 415-420 (PMID: 9412940)
 34. Moon SW, Kim TH, Kim HS, Ju JH, Ahn YJ, Jang HJ, Shim SG, Kim HJ, Jung WT, Lee OJ. United Rapid Urease Test Is Superior than Separate Test in Detecting *Helicobacter pylori* at the Gastric Antrum and Body Specimens. *Clin Endosc* 2012; 45: 392-396 (PMID: 23251887 DOI: 10.5946/ce.2012.45.4.392)
 35. Monteiro L, de Mascarel A, Sarrasqueta AM, Bergery B, Barberis C, Talby P, Roux D, Shouler L, Goldfain D, Lamouliatte H, Mégraud F. Diagnosis of *Helicobacter pylori* infection: noninvasive methods compared to invasive methods and evaluation of two new tests. *Am J Gastroenterol* 2001; 96: 353-358 (PMID:

- 11232675 DOI: 10.1111/j.1572-0241.2001.03518.x)
36. Tseng CA, Wang WM, Wu DC. Comparison of the clinical feasibility of three rapid urease tests in the diagnosis of *Helicobacter pylori* infection. *Dig Dis Sci* 2005; 50: 449-452 (PMID: 15810624)
 37. Harris P, Perez-Perez G, Zylberberg A, Rollán A, Serrano C, Riera F, Einisman H, García D, Viviani P. Relevance of adjusted cut-off values in commercial serological immunoassays for *Helicobacter pylori* infection in children. *Dig Dis Sci* 2005; 50: 2103-2109 (PMID: 16240223 DOI: 10.1007/s10620-005-3015-9)
 38. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, Elomar 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)
 39. Hirschl AM, Rotter ML. Serological tests for monitoring *Helicobacter pylori* eradication treatment. *J Gastroenterol* 1996; 31 Suppl 9: 33-36 (PMID: 8959515)
 40. Breslin NP, O'Morain CA. Noninvasive diagnosis of *Helicobacter pylori* infection: a review. *Helicobacter* 1997; 2: 111-117 (PMID: 9432337)
 41. Axon AT. Are all helicobacters equal? Mechanisms of gastroduodenal pathology and their clinical implications. *Gut* 1999; 45 Suppl 1: I1-I4 (PMID: 10457027)
 42. Blaser MJ. Role of *vacA* and the *cagA* locus of *Helicobacter pylori* in human disease. *Aliment Pharmacol Ther* 1996; 10 Suppl 1: 73-77 (PMID: 8730262)
 43. Parsonnet J, Friedman GD, Orentreich N, Vogelstein H. Risk for gastric cancer in people with *CagA* positive or *CagA* negative *Helicobacter pylori* infection. *Gut* 1997; 40: 297-301 (PMID: 9135515)
 44. Erzin Y, Altun S, Dobrucali A, Aslan M, Erdamar S, Dirican A, Tuncer M, Kocazeybek B. Analysis of serum antibody profile against *H. pylori* *VacA* and *CagA* antigens in Turkish patients with duodenal ulcer. *World J Gastroenterol* 2006; 12: 6869-6873 (PMID: 17106939)
 45. Sökücü S, Ozden AT, Süoğlu OD, Elkabes B, Demir F, Cevikbaş U, Gökçe S, Saner G. *CagA* positivity and its association with gastroduodenal disease in Turkish children undergoing endoscopic investigation. *J Gastroenterol* 2006; 41: 533-539 (PMID: 16868800 DOI: 10.1007/s00535-006-1788-z)
 46. Janulaityte-Günther D, Kupcinskis L, Pavidonis A, Valuckas K, Wadström T, Andersen LP. Combined serum IgG response to *Helicobacter pylori* *VacA* and *CagA* predicts gastric cancer. *FEMS Immunol Med Microbiol* 2007; 50: 220-225 (PMID: 17567283 DOI: 10.1111/j.1574-695X.2007.00268.x)
 47. Formichella L, Romberg L, Bolz C, Vieth M, Geppert M, Göttner G, Nölting C, Walter D, Schepp W, Schneider A, Ulm K, Wolf P, Busch DH, Soutschek E, Gerhard M. A novel line immunoassay based on recombinant virulence factors enables highly specific and sensitive serologic diagnosis of *Helicobacter pylori* infection. *Clin Vaccine Immunol* 2013; 20: 1703-1710 (PMID: 24006137 DOI: 10.1128/0144-5019.00433-13)
 48. Graham DY, Klein PD, Evans DJ, Evans DG, Alpert LC, Opekun AR, Boutton TW. *Campylobacter pylori* detected noninvasively by the ¹³C-urea breath test. *Lancet* 1987; 1: 1174-1177 (PMID: 2883491)
 49. Peura DA, Pambianco DJ, Dye KR, Lind C, Frierson HF, Garza-González E et al. Diagnosis and treatment of *H. pylori* infection 1448 February 14, 2014 [Volume 20] Issue 6 [WJG] [www.wjgnet.com Hoffman SR, Combs MJ, Guilfoyle E, Marshall BJ. Microdose ¹⁴C-urea breath test offers diagnosis of *Helicobacter pylori* in 10 minutes. *Am J Gastroenterol* 1996; 91: 233-238 (PMID: 8607486)
 50. Goddard AF, Logan RP. Review article: urea breath tests for detecting *Helicobacter pylori*. *Aliment Pharmacol Ther* 1997; 11: 641-649 (PMID: 9305471)
 51. Gisbert JP, Pajares JM. Review article: ¹³C-urea breath test in the diagnosis of *Helicobacter pylori* infection -- a critical review. *Aliment Pharmacol Ther* 2004; 20: 1001-1017 (PMID: 15569102 DOI: 10.1111/j.1365-2036.2004.02203.x)
 52. Capurso G, Carnuccio A, Lahner E, Panzuto F, Baccini F, Delle Fave G, Annibale B. Corpus-predominant gastritis as a risk factor for false-negative ¹³C-urea breath test results. *Aliment Pharmacol Ther* 2006; 24: 1453-1460 (PMID: 17032284 DOI: 10.1111/j.1365-2036.2006.03143.x)
 53. Shirin H, Levine A, Shevah O, Shabat-Sehayek V, Aeed H, Wardi J, Birkenfeld S, Eliakim R, Avni Y. Eradication of *Helicobacter pylori* can be accurately confirmed 14 days after termination of triple therapy using a high-dose citric acidbased ¹³C urea breath test. *Digestion* 2005; 71: 208-212 (PMID: 16024926 DOI: 10.1159/000087045)
 54. Leal YA, Flores LL, Fuentes-Pananá EM, Cedillo-Rivera R, Torres J. ¹³C-urea breath test for the diagnosis of *Helicobacter pylori* infection in children: a systematic review and meta-analysis. *Helicobacter* 2011; 16: 327-337 (PMID: 21762274 DOI: 10.1111/j.1523-5378.2011.00863.x)
 55. Malfertheiner P, Megraud F, O'Morain C, Bell D, Bianchi Porro G, Deltenre M, Forman D, Gasbarrini G, Jaup B, Misiewicz JJ, Pajares J, Quina M, Rauws E. Current European concepts in the management of *Helicobacter pylori* infection-the Maastricht Consensus Report. The European *Helicobacter Pylori* Study Group (EHPSG). *Eur J Gastroenterol Hepatol* 1997; 9: 1-2 (PMID: 9031888)
 56. Korkmaz H, Kesli R, Karabagli P, Terzi Y. Comparison of the diagnostic accuracy of five different stool antigen tests for the diagnosis of *Helicobacter pylori* infection. *Helicobacter* 2013; 18: 384-391 (PMID: 23551920 DOI: 10.1111/hel.12053)
 57. Gisbert JP, de la Morena F, Abaira V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: a systematic review and meta-analysis. *Am J Gastroenterol* 2006; 101: 1921-1930 (PMID: 16780557 DOI: 10.1111/j.1572-0241.2006.00668.x)
 58. Veijola L, Oksanen A, Löfgren T, Sipponen P, Karvonen AL, Rautelin H. Comparison of three stool antigen tests in confirming *Helicobacter pylori* eradication in adults. *Scand J Gastroenterol* 2005; 40: 395-401 (PMID: 16028433)
 59. Gisbert JP, Pajares JM. Stool antigen test for the diagnosis of *Helicobacter pylori* infection: a systematic re-

- view. *Helicobacter* 2004; 9: 347-368 (PMID: 15270750 DOI: 10.1111/j.1083-4389.2004.00235.x)
60. Choi J, Kim CH, Kim D, Chung SJ, Song JH, Kang JM, Yang JI, Park MJ, Kim YS, Yim JY, Lim SH, Kim JS, Jung HC, Song IS. Prospective evaluation of a new stool antigen test for the detection of *Helicobacter pylori*, in comparison with histology, rapid urease test, (13)C-urea breath test, and serology. *J Gastroenterol Hepatol* 2011; 26: 1053-1059 (PMID: 21362044 DOI: 10.1111/j.1440-1746.2011.06705.x)
 61. Pourakbari B, Mirsalehian A, Maleknejad P, Mamishi S, Azhdarkosh H, Daryani NE, Najafi M, Kazemi B, Paknejad M, Mahmoudi S, Bandehpour M, Ghazi M, Salavati A. Evaluation of a new antigen for diagnosis of *Helicobacter pylori* infection in stool of adult and children. *Helicobacter* 2011; 16: 42-46 (PMID: 21241411 DOI: 10.1111/j.1523-5378.2010.00813.x)
 62. Leal YA, Cedillo-Rivera R, Simón JA, Velázquez JR, Flores LL, Torres J. Utility of stool sample-based tests for the diagnosis of *Helicobacter pylori* infection in children. *J Pediatr Gastroenterol Nutr* 2011; 52: 718-728 (PMID: 21478757 DOI: 10.1097/MPG.0b013e3182077d33)
 63. Kato S, Ozawa K, Okuda M, Fujisawa T, Kagimoto S, Konno M, Maisawa S, Iinuma K. Accuracy of the stool antigen test for the diagnosis of childhood *Helicobacter pylori* infection: a multicenter Japanese study. *Am J Gastroenterol* 2003; 98: 296-300 (PMID: 12591044 DOI: 10.1111/j.1572-0241.2003.07263.x)
 64. Koletzko S, Konstantopoulos N, Bosman D, Feydt-Schmidt A, van der Ende A, Kalach N, Raymond J, Rüssmann H. Evaluation of a novel monoclonal enzyme immunoassay for detection of *Helicobacter pylori* antigen in stool from children. *Gut* 2003; 52: 804-806 (PMID: 12740334)
 65. Ni YH, Lin JT, Huang SF, Yang JC, Chang MH. Accurate diagnosis of *Helicobacter pylori* infection by stool antigen test and 6 other currently available tests in children. *J Pediatr* 2000; 136: 823-827 (PMID: 10839883)
 66. Guo YY, Zhang ST, Peng XX, Zhan SY. (A systematic review of diagnosis of *Helicobacter pylori* infection by *Helicobacter pylori* stool antigen test). *Zhonghua Yi Xue Zazhi* 2005; 85: 1564-1567 (PMID: 16179120)
 67. Sugimoto M, Yamaoka Y. Virulence factor genotypes of *Helicobacter pylori* affect cure rates of eradication therapy. *Arch Immunol Ther Exp (Warsz)* 2009; 57: 45-56 (PMID: 19219527 DOI: 10.1007/s00005-009-0007-z)
 68. 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: 10.1056/NEJMoa001999)
 69. Mégraud F. Current recommendations for *Helicobacter pylori* therapies in a world of evolving resistance. *Gut Microbes* 2013; 4: Epub ahead of print (PMID: 23929066)
 70. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Glupczynski Y. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; 62: 34-42 (PMID: 22580412 DOI: 10.1136/gutjnl-2012-302254)
 71. Su P, Li Y, Li H, Zhang J, Lin L, Wang Q, Guo F, Ji Z, Mao J, Tang W, Shi Z, Shao W, Mao J, Zhu X, Zhang X, Tong Y, Tu H, Jiang M, Wang Z, Jin F, Yang N, Zhang J. Antibiotic resistance of *Helicobacter pylori* isolated in the Southeast Coastal Region of China. *Helicobacter* 2013; 18: 274-279 (PMID: 23418857 DOI: 10.1111/hel.12046)
 72. Lee JW, Kim N, Kim JM, Nam RH, Chang H, Kim JY, Shin CM, Park YS, Lee DH, Jung HC. Prevalence of primary and secondary antimicrobial resistance of *Helicobacter pylori* in Korea from 2003 through 2012. *Helicobacter* 2013; 18: 206-214 (PMID: 23241101 DOI: 10.1111/hel.12031)
 73. De Francesco V, Margiotta M, Zullo A, Hassan C, Giorgio F, Burattini O, Stoppino G, Cea U, Pace A, Zotti M, Morini S, Panella C, Ierardi E. Prevalence of primary clarithromycin resistance in *Helicobacter pylori* strains over a 15 year period in Italy. *J Antimicrob Chemother* 2007; 59: 783-785 (PMID: 17329269 DOI: 10.1093/jac/dkm005)
 74. Megraud F. *Helicobacter pylori* and antibiotic resistance. *Gut* 2007; 56: 1502 (PMID: 17938430 DOI: 10.1136/gut.2007.132514)
 75. Ford AC, Moayyedi P. Should we step-up or step-down in the treatment of new-onset dyspepsia in primary care? *Pol Arch Med Wewn* 2009; 119: 391-396 (PMID: 19694221)
 76. Talley NJ. Dyspepsia: management guidelines for the millennium. *Gut* 2002; 50 Suppl 4: iv72-iv8; discussion iv79 (PMID: 11953354)
 77. 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 DOI: 10.1136/gutjnl-2012-302084)
 78. Moayyedi P, Axon AT. The usefulness of the likelihood ratio in the diagnosis of dyspepsia and gastroesophageal reflux disease. *Am J Gastroenterol* 1999; 94: 3122-3125 (PMID: 10566701 DOI: 10.1111/j.1572-0241.1999.01502.x)
 79. Moayyedi P, Soo S, Deeks J, Forman D, Mason J, Innes M, Delaney B. Systematic review and economic evaluation of *Helicobacter pylori* eradication treatment for non-ulcer dyspepsia. *Dyspepsia Review Group. BMJ* 2000; 321: 659-664 (PMID: 10987767)
 80. Laine L, Schoenfeld P, Fennerty MB. Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia. A metaanalysis of randomized, controlled trials. *Ann Intern Med* 2001; 134: 361-369 (PMID: 11242496)
 81. Malfertheiner P, Mégraud F, O'Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G. Current concepts in the management of *Helicobacter pylori* infection—the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 2002; 16: 167-180 (PMID:

- 11860399)
82. Loyd RA, McClellan DA. Update on the evaluation and management of functional dyspepsia. *Am Fam Physician* 2011; 83: 547-552 (PMID: 21391521)
 83. Furuta T, Sugimoto M, Shirai N, Matsushita F, Nakajima H, Kumagai J, Senoo K, Kodaira C, Nishino M, Yamade M, Ikuma M, Watanabe H, Umemura K, Ishizaki T, Hishida A. Effect of MDR1 C3435T polymorphism on cure rates of *Helicobacter pylori* infection by triple therapy with lansoprazole, amoxicillin and clarithromycin in relation to CYP 2C19 genotypes and 23S rRNA genotypes of *H. pylori*. *Aliment Pharmacol Ther* 2007; 26: 693-703 (PMID: 17697203 DOI: 10.1111/j.1365-2036.2007.03408.x)
 84. 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)
 85. Sachdeva A, Nagpal J. Meta-analysis: efficacy of bovine lactoferrin in *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2009; 29: 720-730 (PMID: 19183156 DOI: 10.1111/j.1365-2036.2009.03934.x)
 86. Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: the effects of *Saccharomyces boulardii* supplementation on *Helicobacter pylori* eradication rates and side effects during treatment. *Aliment Pharmacol Ther* 2010; 32: 1069-1079 (PMID: 21039671 DOI: 10.1111/j.1365-2036.2010.04457.x)
 87. Ali Habib HS, Murad HA, Amir EM, Halawa TF. Effect of sequential versus standard *Helicobacter pylori* eradication therapy on the associated iron deficiency anemia in children. *Indian J Pharmacol* 2013; 45: 470-473 (PMID: 24130381 DOI: 10.4103/0253-7613.117757)
 88. Stenström B, Mendis A, Marshall B. *Helicobacter pylori*—the latest in diagnosis and treatment. *Aust Fam Physician* 2008; 37: 608-612 (PMID: 18704207)
 89. McColl KE. Clinical practice. *Helicobacter pylori* infection. *N Engl J Med* 2010; 362: 1597-1604 (PMID: 20427808 DOI: 10.1056/NEJMc1001110)
 90. De Francesco V, Giorgio F, Hassan C, Manes G, Vannella L, Panella C, Ierardi E, Zullo A. Worldwide *H. pylori* antibiotic resistance: a systematic review. *J Gastrointest Liver Dis* 2010; 19: 409-414 (PMID: 21188333)
 91. Tay CY, Windsor HM, Thirriot F, Lu W, Conway C, Perkins TT, Marshall BJ. *Helicobacter pylori* eradication in Western Australia using novel quadruple therapy combinations. *Aliment Pharmacol Ther* 2012; 36: 1076-1083 (PMID: 23072648 DOI: 10.1111/apt.12089)
 92. McNicholl AG, Marin AC, Molina-Infante J, Castro M, Barrio J, Ducons J, Calvet X, de la Coba C, Montoro M, Bory F, Perez-Aisa A, Forné M, Gisbert JP. Randomised clinical trial comparing sequential and concomitant therapies for *Helicobacter pylori* eradication in routine clinical practice. *Gut* 2014; 63: 244-249 (PMID: 23665990 DOI: 10.1136/gutjnl-2013-304820)
 93. 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)
 94. Zullo A, Scaccianoce G, De Francesco V, Ruggiero V, D' Ambrosio P, Castorani L, Bonfrate L, Vannella L, Hassan C, Portincasa P. Concomitant, sequential, and hybrid therapy for *H. pylori* eradication: a pilot study. *Clin Res Hepatol Gastroenterol* 2013; 37: 647-650 (PMID: 23747131 DOI: 10.1016/j.clinre.2013.04.003)
 95. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. *Am J Gastroenterol* 2006; 101: 488-496 (PMID: 16542284 DOI: 10.1111/j.1572-0241.1998.455_tx)
 96. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther* 2006; 23: 35-44 (PMID: 16393278 DOI: 10.1111/j.1365-2036.2006.02737.x)
 97. Morgan DR, Torres J, Sexton R, Herrero R, Salazar-Martínez E, Greenberg ER, Bravo LE, Dominguez RL, Ferreccio C, Lazcano-Ponce EC, Meza-Montenegro MM, Peña EM, Peña R, Correa P, Martínez ME, Chey WD, Valdivieso M, Anderson GL, Goodman GE, Crowley JJ, Baker LH. Risk of recurrent *Helicobacter pylori* infection 1 year after initial eradication therapy in 7 Latin American communities. *JAMA* 2013; 309: 578-586 (PMID: 23403682 DOI: 10.1001/jama.2013.311)
 98. Malik R, Guleria K, Kaur I, Sikka M, Radhakrishnan G. Effect of *Helicobacter pylori* eradication therapy in iron deficiency anaemia of pregnancy - a pilot study. *Indian J Med Res* 2011; 134: 224-231 (PMID: 21911976)
 99. Wang ZH, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in *Helicobacter pylori* eradication therapy. *J Clin Gastroenterol* 2013; 47: 25-32 (PMID: 23090045 DOI: 10.1097/MCG.0b013e318266f6cf)
 100. Ahmad K, Fatemeh F, Mehri N, Maryam S. Probiotics for the treatment of pediatric *Helicobacter pylori* infection: a randomized double blind clinical trial. *Iran J Pediatr* 2013; 23: 79-84 (PMID: 23446685)