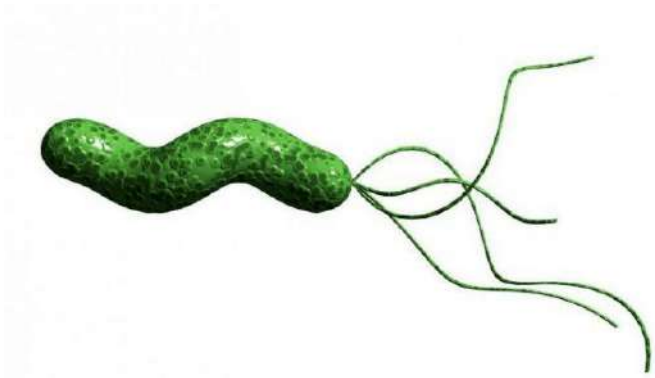
H. Pylori eradikasyonu: Son güncelleme

Prof. Dr. Mustafa Kaplan

EPİDEMİYOLOJİ

- Dünyada görülen en sık kronik enfeksiyon etkeni, yaklaşık %50
- Gelişmiş ülkelerde prevalans %10-50,
- Gelişmekte olan ülkelerde %80
- Yıllık insidans; gelişmiş ülkeler %1, gelişmekte olanlar %5-10
- Yaşa bağlı prevalans değişir, 0-5 yaş % 5



EPİDEMİYOLOJİ

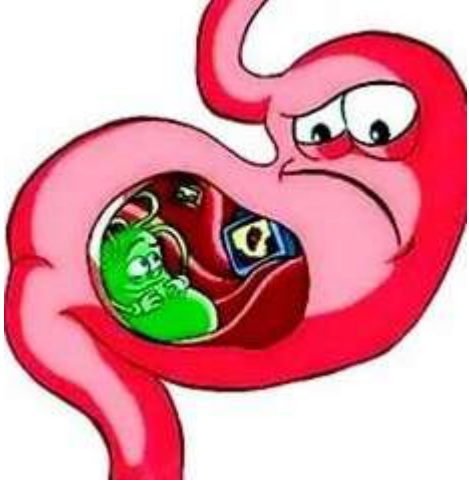
- Türkiye

  TURHEP

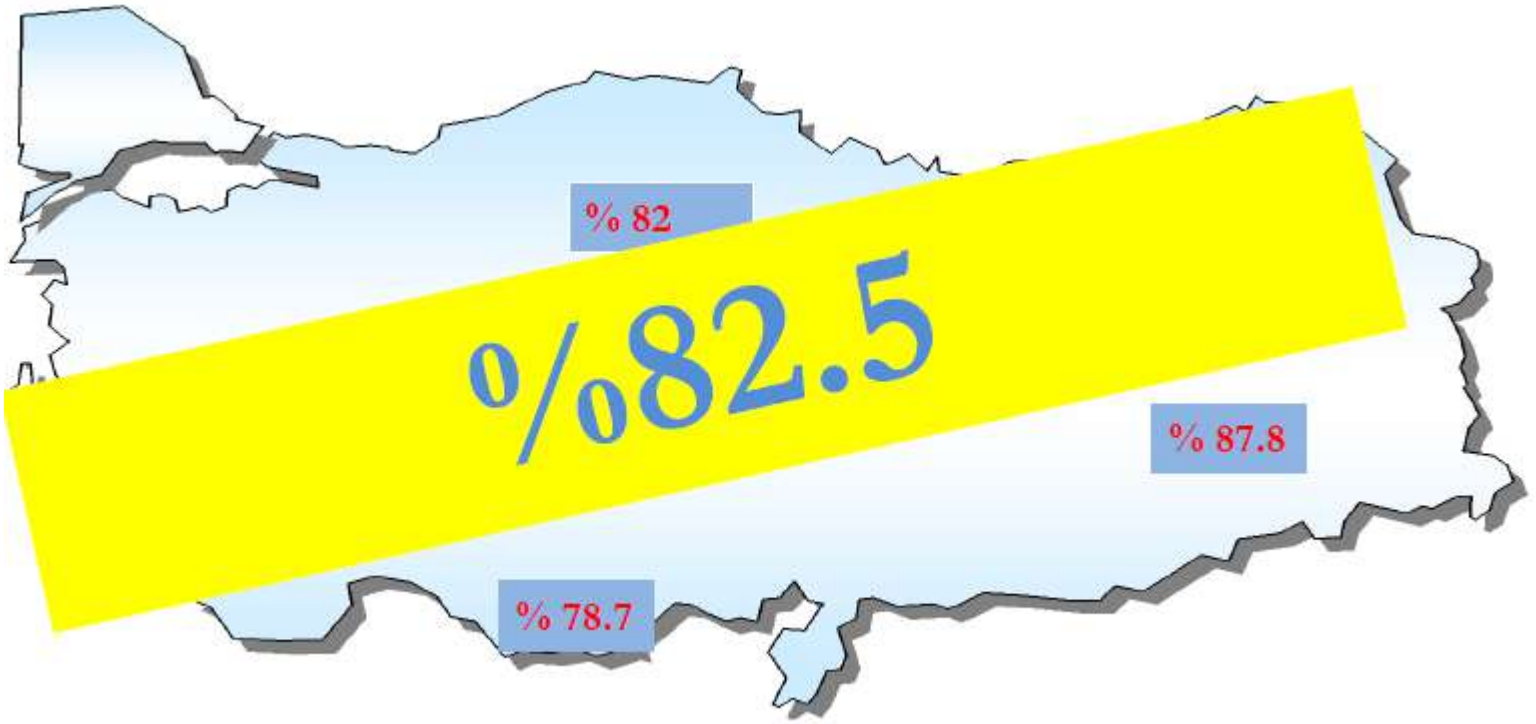
Socio-demographic factors	Hp positive		Hp negative			
	n	(%)*	n	(%)*	Total	P**
Sex						
Female	2075	(81.4)	457	(18.6)	2532	0.014
Male	1777	(83.9)	313	(16.1)	2090	
Age groups						
18–24	736	(79.6)	170	(20.4)	906	0.000
25–34	957	(86.3)	145	(13.7)	1102	
35–44	746	(84.2)	123	(15.8)	869	
45–54	599	(83.7)	108	(16.3)	707	
55–64	372	(78.9)	99	(21.1)	471	
65 +	442	(78.6)	125	(21.4)	567	
Region						
West	1027	(80.3)	247	(19.7)	1274	0.000
South	444	(78.7)	118	(21.3)		
Central	1089	(85.0)	192	(15.0)		
North	369	(82.3)	83	(17.8)		
East	923	(88.1)	130	(11.9)	1053	
Residence						
Urban	2411	(81.7)	509	(18.3)	2920	0.020
Rural	1441	(84.0)	261	(16.0)	1702	
Total	**3852**	**(82.5)**	**770**	**(17.5)**	**4622**	

%82,5

EPİDEMİYOLOJİ



- TURHEP



Helicobacter

Helicobacter ISSN 1523-5378
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REVIEW ARTICLE

Epidemiology of *Helicobacter pylori* Infection

Leonardo H. Eusebi, Rocco M. Zagari and Franco Bazzoli

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Western Europe				
The Netherlands [3]	Blood donors	1550	Serology	31.7
The Netherlands [4]	Pregnant women	6837	Serology	46
Portugal [5]	General population	2067	Serology	84.2
Eastern Europe				
Cyprus [35]	Patients with dyspepsia	103	PCR	39.8
Turkey [6]	General population	4622	UBT	82.5
America				
Canada [7]	Aboriginal population	203	Histology	37.9
Mexico [8]	Pregnant women	343	Serology	52.2
Asia				
Saudi Arabia [17]	Healthy individuals	456	Serology	28.3
Korea [10]	Routine health check-up	10796	Serology	54.4
India [12]	Patients with dyspepsia	2000	Histology RUT	58
India [13]	Patients with dyspepsia	530	Histology Urease test	62
China [11]	Healthy individuals	5417	UBT	63.4
Bhutan [15]	Volunteers	372	Histology RUT Culture Serology	73.4
Bhutan [16]	Patients with dyspepsia	244	Serology	86
Kazakhstan [14]	Asymptomatic and patients with dyspepsia	835	Serology	76.5
Africa				
Ethiopia [21]	Selected population	1388	Serology	65.7
Morocco [20]	Patients with dyspepsia	429	Histology RUT Culture	75.5
Nigeria [22]	Patients with dyspepsia	125	Serology Histology	93.6 80

UBT, urea breath test; RUT, rapid urease test.

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ORIGINAL ARTICLE

Observational Study

Prevalence of gastroesophageal reflux disease in a country with a high occurrence of *Helicobacter pylori*

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Revised: October 4, 2016

Bor S *et al*. GERD prevalence in a high *H. pylori* country

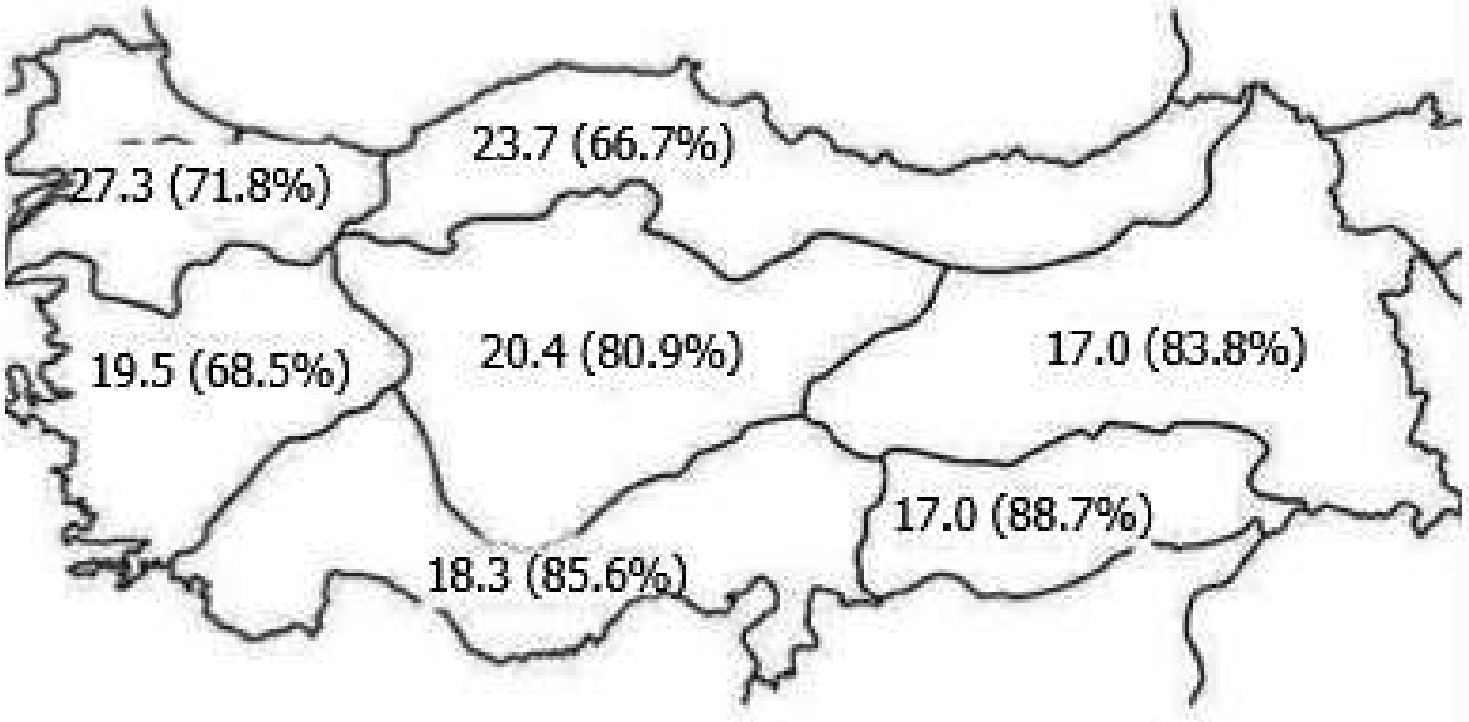

Figure 3 Prevalence of gastroesophageal reflux disease and *Helicobacter pylori* positivity (between parenthesis) according to geographicraphical areas.

***Hp* eradikasyonu Gastroözofageal Reflü Hastalığına neden olmaz. *Hp* eradikasyonu insanı Fonksiyonel Dispepsi, Peptik Ülser, MALToma, Mide Kanseri gelişiminden korur.**

Hp'nin 30. Yılı (1983-2013) *Helicobacter pylori* Eradikasyonunda Proton Pompa İnhibitörlerinin Yarattığı Mucize!!

Ali ÖZDEN

JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Prevalence of *H. pylori* in gastric biopsy specimen in the southeastern region of Turkey

Fulya Bayındır Bilman[1], Mehmet Özdemir[2], Birol Baysal[3], Muhammed Güzel Kurtoğlu[4]

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[4] *Department of Medical Microbiology, Konya Training and Research Hospital, Konya, Turkey*

Abstract

Introduction: *Helicobacter pylori* is a Gram-negative, microaerophilic bacterium that colonizes human gastric mucosa. Gastric ulcer, duodenal ulcer, chronic atrophic gastritis, mucosa-associated lymphoid tissue lymphoma, and stomach adenocarcinoma are associated with *H. pylori* as the etiological agent. Cytotoxin-associated gene A (*cagA*), which is one of the most important virulence factors of *H. pylori*, encodes a 120–145 kDa protein. The prevalence of *cagA* genes shows differences in *H. pylori* infections based on geographical area, and *cagA*-positive *H. pylori* strains play an important role in pathogenesis of gastric carcinoma.

Methodology: The aim of this study was to detect the prevalence of *cagA* and *vacA* genes in *H. pylori* isolates in adult patient groups in the southeastern region of Turkey. The presence of *H. pylori* was investigated in gastric biopsy specimens using the culture method, and polymerase chain reaction (PCR) analysis was performed to detect the presence of the *cagA* and *vacA* s1 genes.

Results: *H. pylori* was detected in 65% (84/129) of patients who had gastrointestinal complaints. The number of *vacA* s1 and *cagA* genes of isolates were 44 (74.5%) and 31 (52.5%), respectively.

Conclusions: *H. pylori* infection in southeastern region of Turkey with are comparable to those in developed countries. Patients with *cagA*- and *vacA*-positive *H. pylori* have a higher risk of severe inflammation and atrophy and should therefore be monitored for the development of gastric cancer.

Key words: *Helicobacter pylori*; *cagA*; *vacA* s1; polymerase chain reaction.

J Infect Dev Ctries 2016; 10(11):1177-1182. doi:10.3855/jidc.6690

(Received 05 February 2015 – Accepted 09 February 2016)

.: ORİJİNAL ARAŞTIRMA

Erzurum Yöresi Gastroskopi ve Patoloji Sonuçlarının Değerlendirilmesi

Evaluation of Gastroscopic and Pathologic Results Erzurum Region

Ahmet UYANIKOĞLU[a],Muharrem COŞKUN[b],Doğan Nasır BİNİCİ[c],Yunus İlyas KİBAR[c],Ahmet TAY[c],Yasin ÖZTÜRK[c]

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[b]Gastroenteroloji Kliniği,

[c]İç Hastalıkları Kliniği, Erzurum Bölge Eğitim ve Araştırma Hastanesi, Erzurum

Turkiye Klinikleri J Gastroenterohepatol 2011;18(2):70-4

Makale Dili: TR

ÖZET

Amaç: Erzurum yöresi endoskopi ve patoloji sonuçlarının değerlendirilmesidir. **Gereç ve Yöntemler:** Şubat 2010-Haziran 2010 tarihleri arasında, Erzurum Bölge Eğitim ve Araştırma Hastanesi Endoskopi Ünitesinde yapılan özofagogastroduodenoskopi (ÖGD) ve biyopsi sonuçları retrospektif değerlendirildi. Antrum biyopsileri güncellenmiş Sydney sınıflaması, maligniteler Dünya Sağlık Örgütü sınıflaması dikkate alınarak değerlendirildi. **Bulgular:** Toplam 1950 hastanın 924 (%47)\\ü erkek, yaş ortalaması 48,27±17,09 (dağılım 14-100) yıl idi ve hastaların 1395 (%71,5)\\inden biyopsi alınmıştı. En yaygın bulgular özofagus için özofajit 361 (%20), mide için 1109 (56,9) eritemli/antral gastrit, duodenum için duodenit 284 (%14,6) idi. Toplam 133 (%6,5) hastada üst gastrointestinal sistem kanseri saptandı. Kırk beş (%2,3) özofagus, 86 (%4,2) mide, 2 (%0,01) duodenum kanseri saptandı. Özofagusta en sık yassı epitel hücreli kanser, midede adenokanser vardı. Antrum biyopsilerinde Helicobacter pylori sıklığı, inflamatuar aktivite varlığı, atrofi, intestinal metaplazi sıklığı sırasıyla %71, %73, %21 ve %18 idi. **Sonuç:** Yöremizde endoskopik olarak saptanan üst gastrointestinal sistem kansek oranı %6,5 olup, özofagusta en sık yassı epitel hücreli kanser, midede adenokanser görülmektedir. H. pylori sıklığı %71'dir.

Anahtar Kelimeler: Endoskopi, sindirim sistemi; patoloji; gastrointestinal tümörler

Bölgemizde *Helicobacter pylori* Sıklığı

Sedat ÇİFTEL[1], Nihat OKÇU[1], Hakan DURSUN[1], Fatih ALBAYRAK[1], Serpil USTA[2]

Atatürk Üniversitesi, Tıp Fakültesi, [1]Gastroenteroloji Bilim Dalı, Erzurum

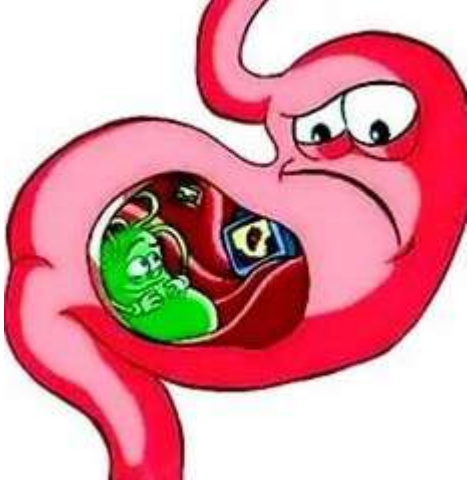
Bölge Eğitim ve Araştırma Hastanesi, [2]İç Hastalıkları Kliniği, Erzurum

Tablo 1. *Helicobacter pylori*'nin yaşa göre sıklığının ve pozitiflik derecesinin dağılımı.

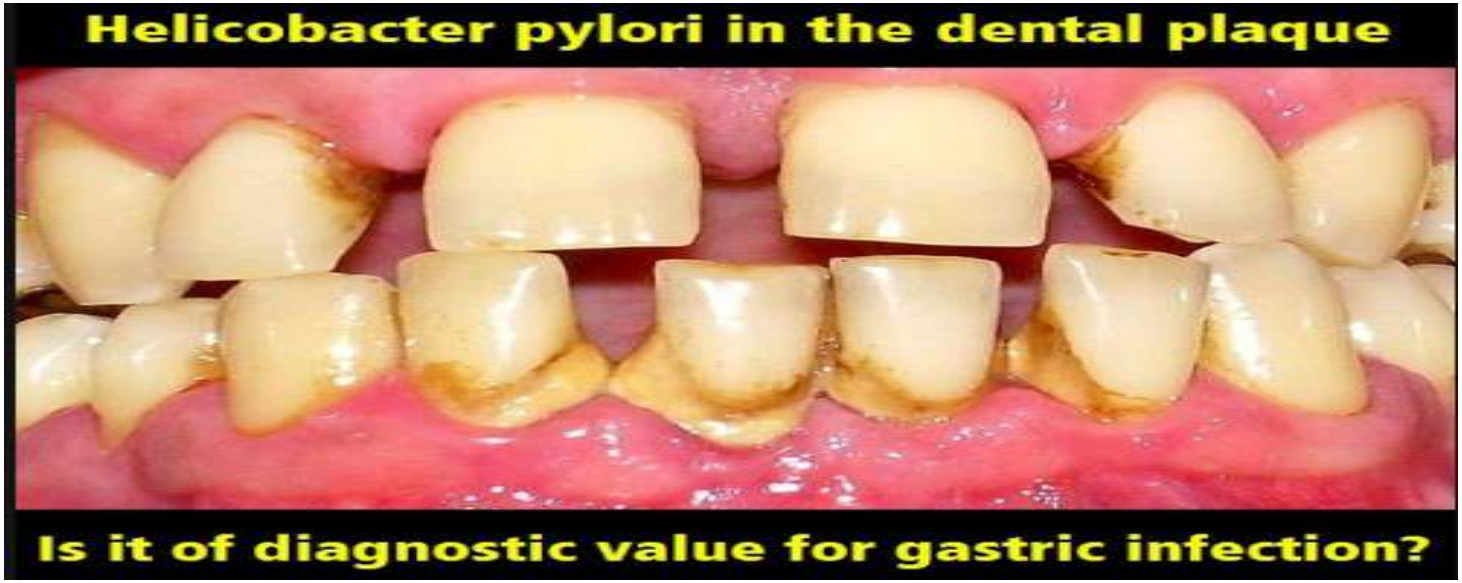
Yaş	E/K	*Hp* Sıklığı	Hafif *Hp* (+)	Şiddetli *Hp* (++)
20 yaş ↓	(41/21)	%56.2	%58.5	%41.5
21-40	(72/57)	%57.7	%59.0	%41.0
41-60	(69/40)	%59.2	%57.0	%43.0
60 yaş ↑	(40/37)	%57.3	%60.5	%39.5
Toplam	**(222/155)**	**%57.7**	**%58.7**	**%41.2**

E/K: Erkek Hasta/Kadın Hasta ***Hp:*** *Helicobacter pylori* p>0.05

EPİDEMİYOLOJİ



- Bulaş
  - Tek konak ve kaynak insan
  - Genellikle çocukluk döneminde aile içi bulaş ‘anneden bebeğe’
  - Tükürük ve dışkı ile direk temas veya bunlarla kirlenmiş gıda-su-medikal cihazlar
  - Diş taşlarındaki kolonizasyon, endojen enfeksiyon?



J Periodontol. 2006 Apr;77(4):692-8.

Are dental plaque, poor oral hygiene, and periodontal disease associated with Helicobacter pylori infection?

Anand PS[1], Nandakumar K, Shenoy KT.

⊕ **Author information**

Abstract

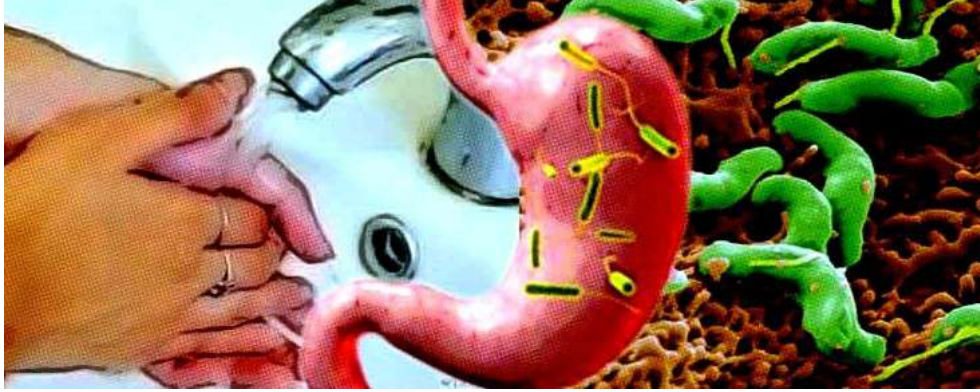
BACKGROUND: The microorganism Helicobacter pylori has been closely linked to chronic gastritis, peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma. Despite the current treatment regimens that lead to successful management of H. pylori-positive chronic gastritis, the reinfection rate is high. It has been suggested that one of the possible mechanisms of reinfection is the recolonization from dental plaque. The purpose of this study was to determine whether dental plaque, poor oral hygiene, and periodontal disease were risk factors for H. pylori infection.

METHODS: Among the 134 patients, 65 patients who had a positive H. pylori serology or positive rapid urease test or histologic evidence for the presence of H. pylori in antral biopsy specimens were categorized as cases. The remaining 69 patients who were negative for H. pylori serology, the rapid urease test, and histology were controls.

RESULTS: It was found that the association of periodontal disease and poor oral hygiene with H. pylori infection was not significant. There was a higher prevalence of H. pylori in the dental plaque of patients with gastric H. pylori infection than in controls, but both groups had a surprisingly high positive urease test for H. pylori in plaque (89% and 71%, respectively).

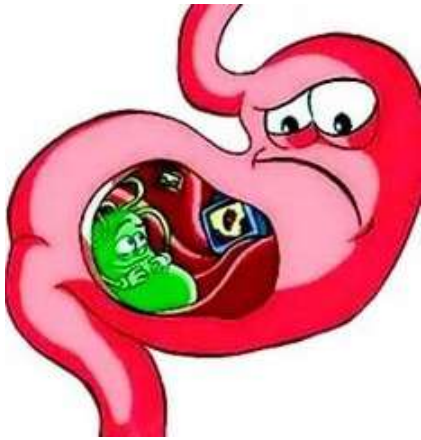
CONCLUSIONS: H. pylori in dental plaque is seldom eliminated by H. pylori-eradication therapy, and this may act as a source for future reinfection. Hence, eradication of H. pylori from the dental plaque should be made an important part of comprehensive management of H. pylori-associated gastric diseases.

EPİDEMİYOLOJİ

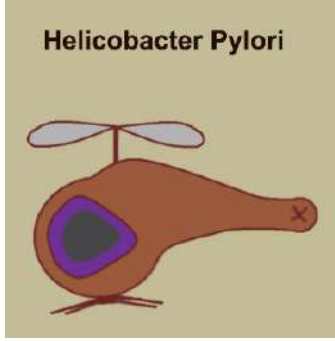


- Risk faktörleri
  - En önemli risk faktörü düşük sosyoekonomik durumu olan ailenin çocuğu olmak
  - Su ve yiyeceklerin temiz olmaması
  - Ailede başka çocukların olması
  - Anne veya babanın enfekte olması
  - Kalabalık aile veya ortamda yaşam
  - Enfekte cihaz veya mide içeriği ile temas

EPİDEMİYOLOJİ



- Helicobacter pylori enfeksiyonunun yetişkin popülasyondaki prevalansı ülkedeki sanitasyon sorunlarının iyileştirilmesiyle düşmez.
- Sanitasyon sorunlarının çözümüyle, sağlıklı yaşam koşullarının oluşmasıyla çocukluk çağı Hp prevalansı düşer.
- Yetişkinlerde prevalansın düşmesi toplum genelinde Hp pozitif olguların etkin eradikasyonuyla mümkündür.



EPİDEMİYOLOJİ

- Hp'ye yönelik bir tedaviden sonra yapılan bir değerlendirmede tedavinin bitiminden 4 hafta sonra yapılan tetkiklerde Hp'nin varlığı gösterilemez ise buna eradikasyon denmektedir.
- Bazıları bu sürenin 3-6 ay sonra yapılmasını önermektedir.
- Gerçek reenfeksiyon ise mutlak eradikasyondan sonra başka bir Hp suşu ile enfekte olmaktır.
- Yetişkinlerde gerçek reenfeksiyon nadirdir.
- Eradikasyon başarı oranı %80'in üzerinde ise 6 ayda nüks %1,7 olarak bildirilmiştir.

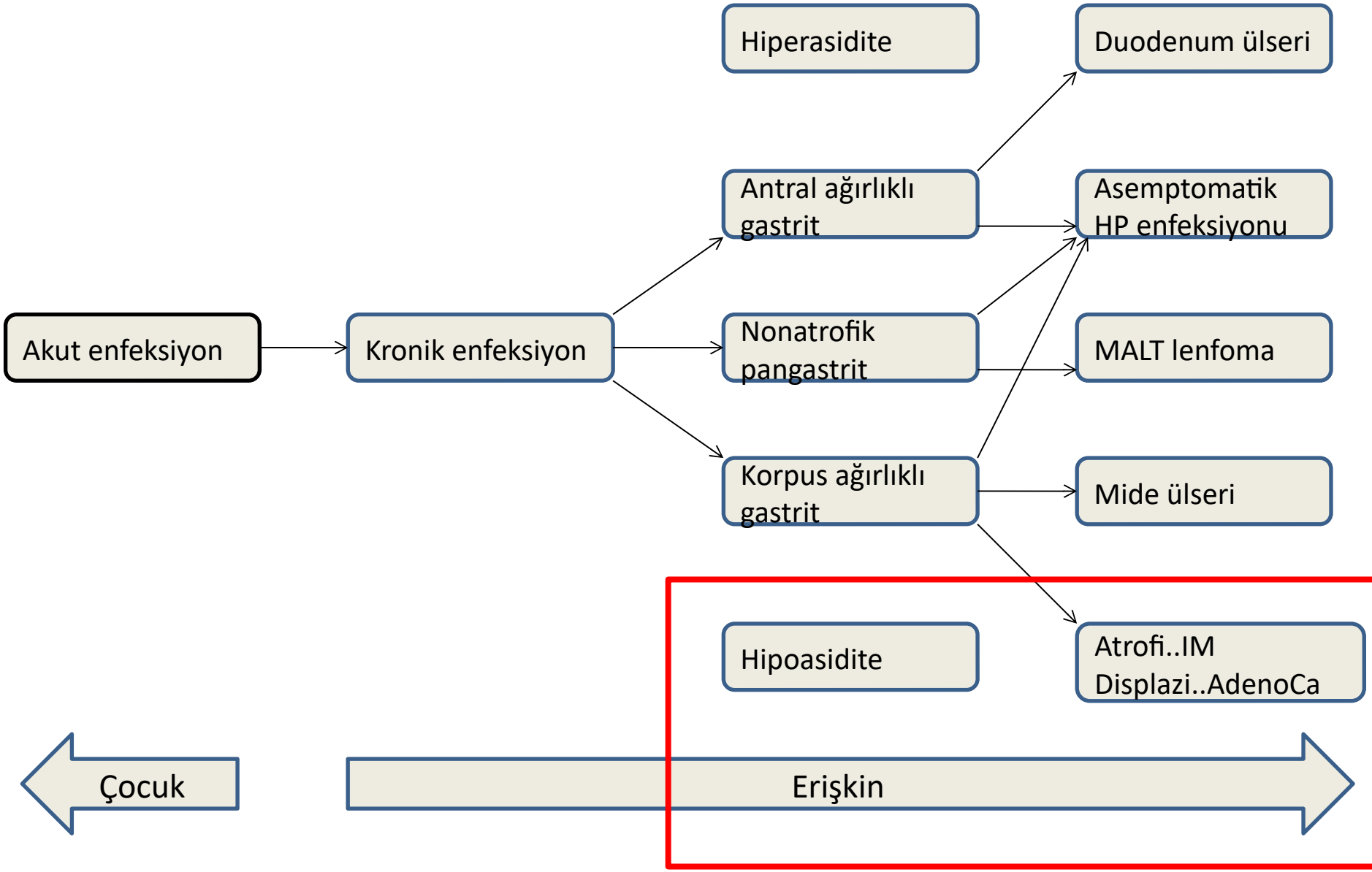
Helicobacter Pylori

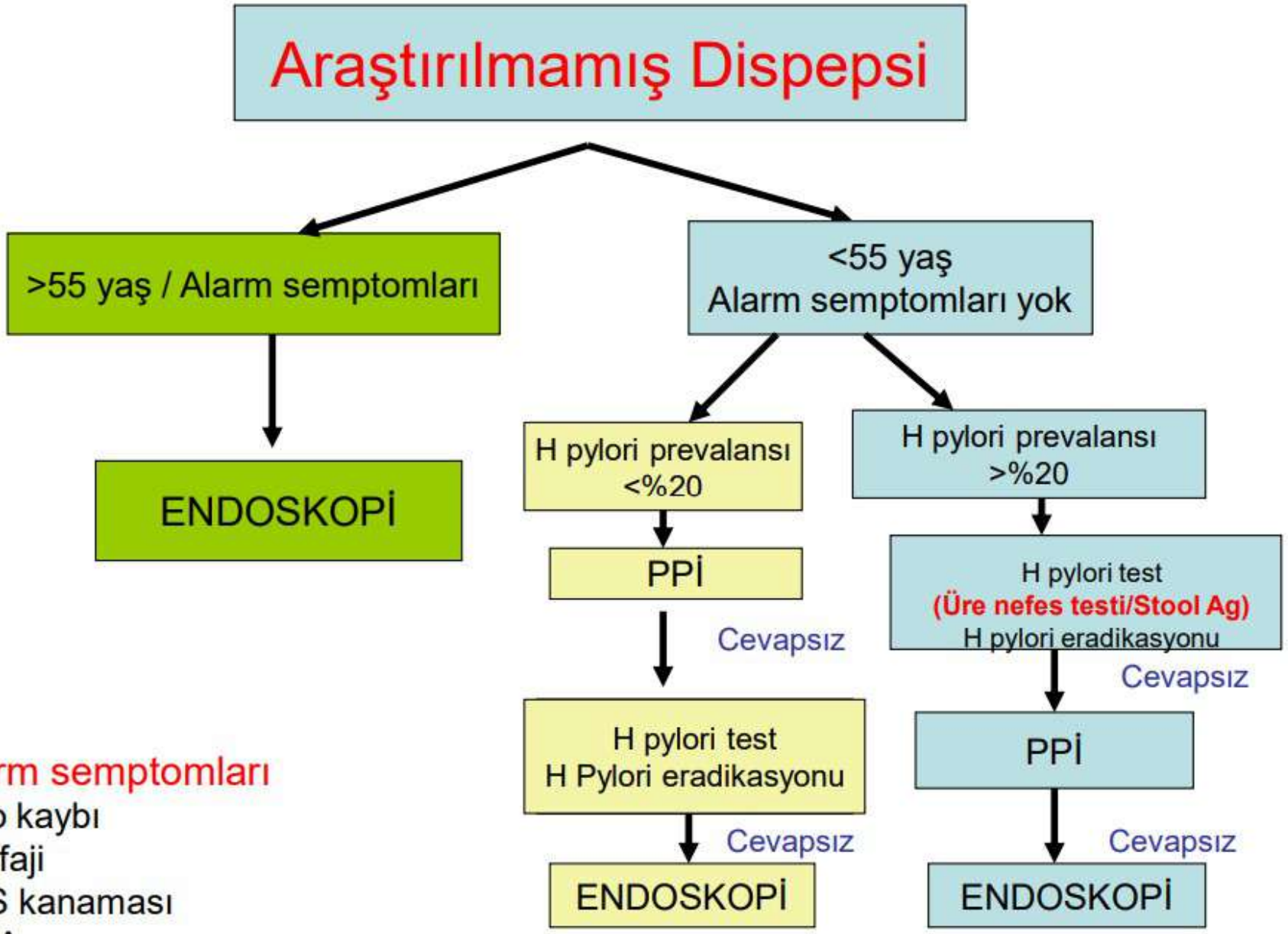
- İlişkili hastalıklar
  - Gastrit % 100
  - PÜ % 15-20 (DÜ'lilerin 95'inde GÜ'lilerin %75'inde +)
  - Mide Ca % 1-3
  - Mide lenfoması % 0,1
  - Fonksiyonel dispepsi

Helicobacter Pylori

- Muhtemel ilişkili
  - Koroner arter hastalığı
  - ITP
  - DEA
  - Reynoud fenomeni
  - Migren
  - Gelişme geriliği
  - Diabetes mellitus
  - Skleroderma
  - Pernisiyöz anemi
  - İdiopatik ürtiker
  - Tiroidit
  - Safra taşları
  - Gıda allerjisi

HP enfeksiyonunun doğal seyri

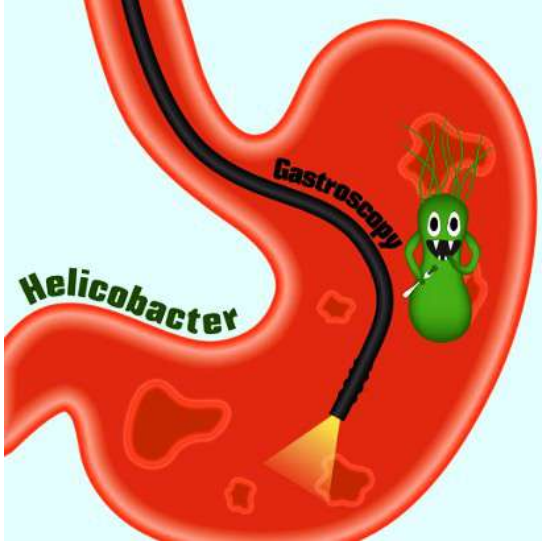




Alarm semptomları

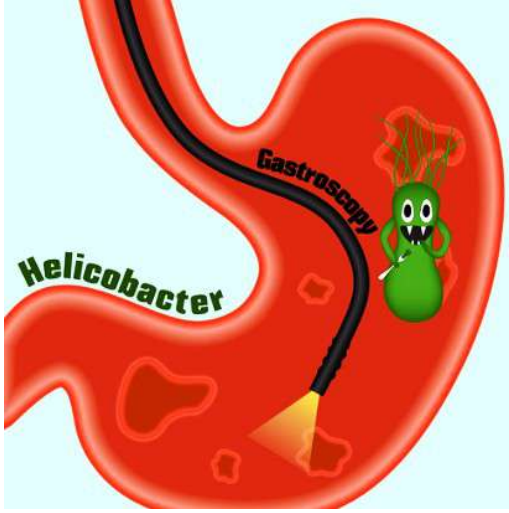
- Kilo kaybı
- Disfaji
- GİS kanaması
- DEA
- İntra abdominal kitle

TANI

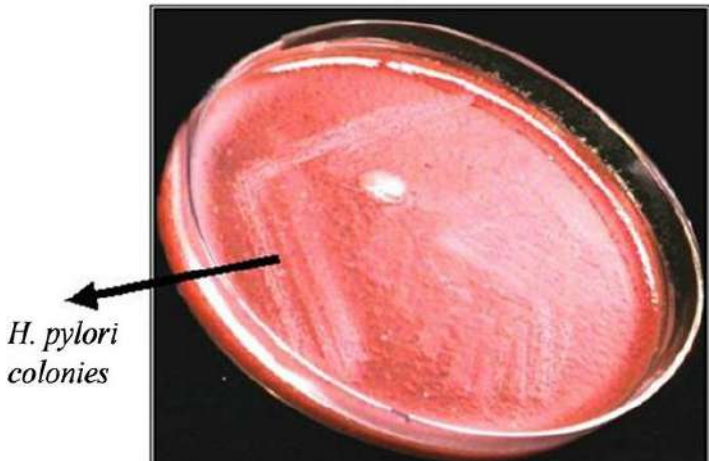


- Non invaziv testler
  - Seroloji; eradikasyon kontrolünde önerilmez
    - Duyarlılık %88-99, özgüllük %89-95
    - Aktif enfeksiyonu göstermez
    - Eradikasyon sonrası 6-12 ay antijenler pozitif
  - Üre nefes testi; ideal test
    - Duyarlılık %90-100, özgüllük %95-100
    - C13-14 işaretli üre (NH2-CO-NH2) $\longrightarrow$ 13-14 CO2 + NH3
    - C13-14 işaretli üre solüsyonu içilir, 30-60 dk sonra nefesten sintigrafik ölçüm
    - Mide operasyonunda solüsyon mideyi erken terk eder, yanlış negatiflik
    - Aklorhidride ise yanlış pozitif sonuç
  - Gaitada HP antijeni; ideal test, Duyarlılık, özgüllük %90-95

TANI



- **İnvaziv testler**
  - Hızlı üreaz testi..Clo test;
    - Duyarlılık %90-95, özgüllük %90-98
    - Endoskopik biyopsi materyali ile üreaz aktivitesi ölçümü
    - Avantajları
      - Tedavi öncesi (2 adet prepilorik antrum), sonrası (antrum, korpus) kullanılab
      - Sensitivite ve spesifite yüksek
      - Endoskopi sırasında HP ile ilişkili patolojilerde tanınır
    - Dezavantajları
      - İnvaziv, pahalı ve uygulama için hastane gerekli
      - Örnekleme hatası, antibiyotik ve PPI ile duyarlılık azalır



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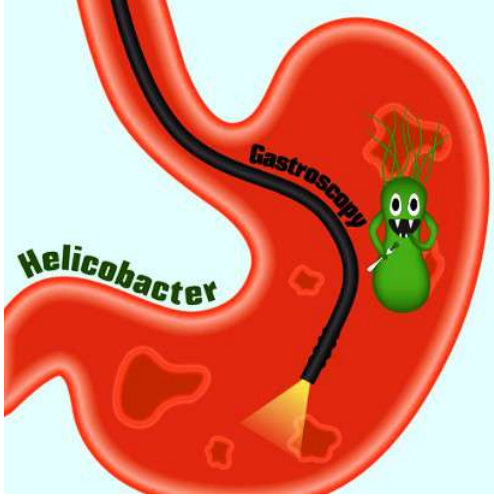
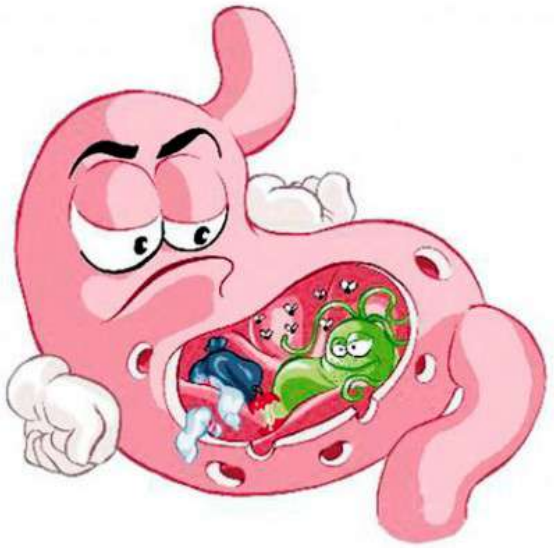


- İnvaziv testler
  - Histopatoloji; Gold Standart
    - Duyarlılık, özgüllük %90-99
    - En sık HE kullanılır ama gümüş boyamada duyarlılık daha fazla
    - Endoskopi sırasında HP ile ilişkili patolojilerde tanınır
  - Kültür;
    - HP tanısında en özgül yöntem ancak zor, uygun şartlarda ve hızlı taşıma, 3-6 günde sonuç
    - Tanıdan ziyade antibiyotik direncinde kullanılır
  - PCR, DNA tespiti çok duyarlı ama pahalı, rutinde kullanılmaz

TEDAVİ



Tablo 2. *Helicobacter pylori* tedavisi, kuvvetle tavsiye edilen endikasyonlar

Kuvvetle tavsiye edilen endikasyonlar	Bilimsel delil dereceleri
Duodenal veya gastrik ülser (aktif veya komplikasyon içermeyen)	1
MALT-lenfoma (midede)	2
Atrofik gastrit	2
Daha önce mide ameliyatı olanlar	3
Birinci derece akrabalarında mide kanseri öyküsü olanlar	3
Hasta bizzat kendisi *H. pylori* için tedavi arzu ediyorsa	4

Türkiye'de Helicobacter Pylori: Güncel Durum ve Tedavi Seçenekleri

- H. Pylori ile enfekte olan insanların midelerinden alınan doku örnekleri az veya çok kronik gastritisin varlığını ortaya koymaktadır.
- Kronik gastritisin seyrinde olguların;
- %8-10'unda ülser (mide-duodenum),
- %1-3'ünde mide kanseri (bazılarına göre % 0,5-3)
- %0,01-0,1'inde MALToma gelişti̇ği görülmektedir.
- Çoğu yaşam boyu asemptomatik kalmaktadır.

TEDAVİ

Tablo 3. *Helicobacter pylori* tedavisi, tavsiye edilen endikasyonlar

Tavsiye edilen endikasyonlar ve ilgili durumlar	Bilimsel delil dereceleri
Dispepsili hastalar	2
Gastroözefageal reflü hastalığı	3
Nonsteroid antiinflamatuvar ilaçlar	2-1
İdiyopatik trombositopeni	3-4
Açıklanamayan demir eksikliği anemisi	3-4
Diğer tartışmalı ekstragastrik (iskemik kalp hastalığı, serebrovasküler olaylar, kronik bronşit, astım, kronik obstrüktif akciğer hastalığı, kronik idiyopatik nötropeni, safra kesesinde kolesterol taşı oluşumu, inflamatuvar bağırsak hastalığı, kolorektal kanser, kolonun adenomatöz polibi, idiyopatik anterior üveit, blefarit, otitis media, idiyopatik ürtiker, çocuklarda otoimmün tiroid hastalığı, tekrarlayan aftöz stomatit, glossit, halitosis, lingual hiperplazi, plazma Gherelin dinamiklerini etkileyerek, nöroendokrin, nörotoksinleri ve dopaminerjik nöronları etkileyerek parkinsonizmi hızlandırma) endikasyonlar	??

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Effect of *Helicobacter pylori* infection on the first-line treatment outcomes in patients with immune thrombocytopenic purpura

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Abstract. – OBJECTIVE: ***Helicobacter pylori*** **(*H. pylori*) eradication therapy is known to increase the platelet count, but in immune thrombocytopenic purpura (ITP), the effect of *H. pylori* infection on the response to treatment is not clear. This study aims to determine whether the response to the first-line treatment is affected by the states of *H. pylori*-positivity and -negativity in ITP patients.**

PATIENTS AND METHODS: Adult newly diagnosed or chronic ITP patients who had not received eradication therapy for *H. pylori* infection were included. Characteristics of the patients, presence and severity of bleeding, initial platelet count, administered treatments, and treatment response rates were inspected.

RESULTS: Of 119 total patients, 66 (55.5%) were female, 32 (26.9%) were *H. pylori*-positive, 87 (73.1%) were *H. pylori*-negative. *H. pylori*-positive and *H. pylori*-negative groups were not significantly different in terms of age (p=0.127), gender (p=0.078), diagnosis status (p=0.094) and the distribution of bleeding symptoms (p=0.712). The most common treatment was standard-dose steroid in both groups (62.5% *vs.* 68.9%, p=0.524). Rates of complete response, partial response, no response were comparable for the two groups (respectively, 75% *vs.* 73.6%, and 18.8% *vs.* 19.5%, and 6.2% *vs.* 6.9%), and there was no significant difference between the groups (p=0.283).

CONCLUSIONS: It can be stated, according to the present study, that in ITP patients in whom treatment is indicated, the response to the first-line treatment without the administration of *H. pylori* eradication therapy is similar between *H. pylori*-positive and *H. pylori*-negative patients.

porary or permanent decrease in the platelet count that results from the effects of immune–mediated anti–platelet antibodies[1]. Its prevalence in adults is approximately 5–10/100.000 and it is more common among females in the adult age group[2]. It is usually associated with a chronic progression and an elevated risk of bleeding due to the severity of thrombocytopenia[3].

Thrombocytopenia may be induced by antibodies that are produced in response to pathogen antigens and cross-react with platelets in certain infections. These antibodies mainly occur in viral infections but also consist of bacterial infections. There is no mechanism that has been proposed to explain how *Helicobacter pylori* (*H. pylori*) could be involved in the pathogenesis of immune–mediated platelet destruction. However, the role of bacterial factors such as the cytotoxin–associated gene A (CagA) protein is currently being investigated[4]. Particularly, lipopolysaccharides in bacteria are reported to bind to the platelet membrane and trigger platelet phagocytosis similarly[5].

The relationship between *H. pylori* infection and ITP was first defined in 1998 by Gasbarrini et al[6] in a study where they reported a high platelet count in 8 of their 11 ITP patients. Since then, numerous studies on *H. pylori* eradication in ITP have been published. However, it is still controversial whether *H. pylori* eradication always increases the platelet count in patients diagnosed with ITP.

TEDAVİ

- Antibiyotikler
  - Amoksisilin (A) 2X1000 mg
  - Klaritromisin (K) 2X500 mg
  - Metranidazol (M) 3X500 mg
  - Tetrasiklin (T) 4X500 mg
  - Levofloksasilin (L) 1X500 mg
  - Tinidazol (Ti)
  - Doksisiklin (D)
  - Furazolidon (F)
  - Rifabutin (R)

- PPI'lar (2X1)
  - Omeprazol (O)
  - Lansaprazol (L)
  - Pantoprazol (P)
  - Esomeprazol (E)
  - Rabeprazol (R)
- Bizmut tuzları (4X1)
  - Ranitidin bizmut sitrat (Pylorid)
  - Kolloid bizmut sitrat (De-Nol)
  - Bizmut subsalisilat (Bizmopen)

TEDAVİ

- Antibiyotik duyarlılığında Avrupa İlaç Ajansı önerileri
  1. Genellikle duyarlı; <%10 direnç varlığı
  2. Ender olarak duyarlı; %10-50 direnç varlığı
  3. Genellikle dirençli; >%50 direnç varlığı
  - Klaritromisin için %20'nin altı ve üstü direnç varlığı direnç bölgelerini ayırmak için önemli
  - Düşük klaritromisin direnci olan bölgelerde birinci basamak tedavi hala klasik 3'lü tedavi

H. Pylori Direnç

- Klaritromisine yaklaşık → %40-50
- Levofloksasine → %41
- Metronidazole → %50-76
- Amoksisiline → %0,5-1,1

H. Pylori Direnç

- Temel neden antibiyotik direnci
- Metronidazol direnci
  - % 10-50 (gelişmiş ülkelerde)
  - % 80-90 (gelişmekte olan ülkelerde)
- Klaritromisin direnci …
  - ABD % 12
  - Almanya % 9.8
  - İtalya % 26
  - Türkiye % 40

İlk seçenek standart üçlü tedavi sonrası *Helicobacter pylori* eradikasyon oranlarındaki düşüş*

Ülke	Ref.	Yayın Yılı	Tedavi süresi	Hasta sayısı	Tedavi rejimi	Eradikasyon oranı (ITT)	Eradikasyon oranı (PP)
Güney Kore	Na et al[177]	2007	7 gün	3267	Standart PPI Cla 500 mg bid Amo 1 g bid	NA	84.3%
	Chung et al[178]	2012	10 gün	80	Lan 30 mg bid Cla 500 mg bid Amo 1 g bid	58.7%	67.6%
Japonya	Asaka et al[179]	2001	7 gün	96	Lan 30 mg bid Cla 200 mg bid Amo 750 mg bid	NA	90.7%
	Fujioka et al[180]	2012	7 gün	3162	Rab 10 mg bid Amo 750 mg bid Cla 200 mg bid	80.7%	NA
	Nishizawa et al[27]	2012	7 gün	55	Lan 30 mg bid Cla 400 mg bid Amo 750 mg bid	74.5%	80.4%
	Nishida et al[181]	2014	7 gün	134/134	Eso 20 mg bid Cla 400 mg bid Amo 750 mg bid Lan 30 mg bid	69.4%/73.9%	76.9%/79.8%

Tayvan	Sheu et al[182]	2000	7 gün veya 2 hafta	286	Ome 20 mg bid Amo 1 g bid Cla veya Met bid	NA	87.8%
	Chen et al[117]	2014	7 gün	73	Rab 20 mg bid Cla 500 mg bid Amo 1 g bid	57.5%	61.8%
Türkiye	Özçay et al[183]	2004	4 hafta: PPI 2 hafta: Cla, Amo	102	Ome veya Lan Cla 7.5 mg/kg bid Amo 20 mg/kg bid	NA	75.7%
	Kutluk et al[184]	2014	10 gün	74	Lan 1 mg/kg per day Cla 20 mg/kg per day Amo 50 mg/kg per day	52.7%	55.7%
İtalya	Catalano et al[185]	1999	10 gün	84	Ome 20 mg bid Cla 500 mg bid Amo 1 g bid	NA	94.0%
	Paoluzi et al[186]	2010	7 gün	90	Eso 20 mg bid Cla 500 mg bid Amo 1 g bid	66.0%	75.0%
Latin Amerika	Greenberg et al[106]	2011	14 gün	488	Lan 30 mg bid Cla 500 mg bid Amo 1 g bid	82.2%	87.1%

İlk seçenek ardışık tedavi sonrası *Helicobacter pylori* eradikasyon oranları*

Ülke	Ref.	Yayın Yılı	Tedavi süresi	Hasta sayısı	Tedavi rejimi	Eradikasyon oranı (ITT)	Eradikasyon oranı (PP)
Güney Kore	Lee et al[92]	2014	10 gün	111	1st 5 d: Eso + Amo 2nd 5 d: Eso + Cla + Met	72.1%	78.4%
	Lee et al[91]	2015	10 gün	100	1st 5 d: Rab + Amo 2nd 5 d: Rab + Cla + Met	79.0%	84.9%
Çin	Zhou et al[93]	2014	10 gün	140	1st 5 d: Eso + Amo 2nd 5 d: Eso + Cla + Tin	72.1%	76.5%
Katar	Ben Chaabane et al[94]	2015	14 gün	106	1st 7 d: Rab + Amo 2nd 7 d: Rab + Cla + Met	66.0%	76.0%
İtalya	Pontone et al[187]	2010	10 gün	84	1st 5 d: Lan + Amo 2nd 5 d: Lan + Cla + Met	83.3%	90.9%
İspanya	Molina-Infante et al[114]	2010	10 gün	115	1st 5 d: Ome + Amo 2nd 5 d: Ome + Cla + Met	76.5%	80.8%

ITT: Intention to treat; PP: Per protocol; Lan: Lansoprazole; Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; Ome: Omeprazole; Eso: Esomeprazole; Tin: Tinidazole; Rab: Rabeprazole.

*(Kim SY, et al. World J Gastrointest Pharmacol Ther 2015;6:183-98.)

İlk seçenek konkomitant (birlikte) tedavi sonrası *Helicobacter pylori* eradikasyon oranları*

Ülke	Ref.	Yayın Yılı	Tedavi süresi	Hasta sayısı	Tedavi rejimi	Eradikasyon oranı (ITT)	Eradikasyon oranı (PP)
Güney Kore	Lim et al[104]	2013	14 gün	78	Rab 20 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg bid	80.8%	81.3%
	Lee et al[100]	2015	7 gün	170	Rab 20 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg tid	79.4%	94.4%
Tayland	Kongchayanun et al[188]	2012	5 gün/10 gün	55/55	Rab 20 mg bid Amo 1 g bid Met 400 mg tid Cla 1 g qd	89.1%/96.4%	NA
Singapur	Ang et al[102]	2015	10 gün	153	PPI standart doz Amo 1 g bid Cla 500 mg bid Met 400 mg bid	81.7%	95.4%
İspanya	Molina-Infante et al[97]	2012	10 gün	209	PPI standart doz Amo 1 g bid Cla 500 mg bid Met 500 mg bid	87.0%	89.0%
	McNicholl et al[103]	2014	10 gün	168	Ome 20 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg bid	87.0%	91.0%
Latin Amerika	Greenberg et al[106]	2011	5 gün	489	Lan 30 mg bid Amo 1 g bid Cla 500 mg bid Met 500 mg bid	73.6%	NA

ITT: Intention to treat; PP: Per protocol; NA: Not available; Lan: Lansoprazole; Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; PPI: Proton pump inhibitor; Rab: Rabeprazole; Ome: Omeprazole.

*Kim SY, et al. World J Gastrointest Pharmacol Ther 2015;6:182-98.)

İlk seçenek, levofloksasin içeren tedavi sonrası *Helicobacter pylori* eradikasyon oranları*

Ülke	Ref.	Yayın Yılı	Tedavi süresi	Hasta sayısı	Tedavi rejimi	Eradikasyon oranı (ITT)	Eradikasyon oranı (PP)
Güney Kore	Choi et al[89]	2011	7 gün	98	Ome 20 mg bid Lev 200 mg bid Amo 1 g bid	65.3%	73.6%
Çin	Liao et al[22]	2013	14 gün	81	Lan 30 mg bid Lev 500 mg qd Amo 1 g bid	82.7%	85.9%
Tayvan	Liou et al[90]	2010	7 gün	217	Lan 30 mg bid Lev 750 mg qd Amo 1 g bid	74.2%	80.1%
	Chen et al[87]	2014	7 gün	73	Rab 20 mg bid Lev 500 mg bid Amo 1 g bid	78.1%	80.9%
İspanya	Molina-Infante et al[14]	2010	10 gün	115	Ome 20 mg bid Lev 500 mg bid Amo 1 g bid	80.8%	82.6%

ITT: Intention to treat; PP: Per protocol; Lan: Lansoprazole; Lev: Levofloxacin; Amo: Amoxicillin; Rab: Rabeprazole; Eso: Esomeprazole; Cla: Clarithromycin; Ome: Omeparzole.

*(Kim SY, et al. World J Gastrointest Pharmacol Ther 2015;6:183-98.)

Helicobacter pylori eradikasyon oranının kabul edilebilirliğinin değerlendirilmesi

Derece	Tedaviye Alınan Olgularda Kür Oranı	Değerlendirme
A	≥95	Mükemmel
B	90-94	İyi
C	85-89	Kabul edilebilir
D	81-84	Kötü (Poor)
F	≤80	Kabul edilemez

TEDAVİ

- Yüksek klaritromisin direnci
  - Birinci basamak tedavi
    - Bizmutlu 4'lü tedavi
    - Bu uygulanamıyorsa sequential veya bizmutsuz dörtlü tedavi
    - Tetrasiklin direnci nadir, metranidazol direnci yaygın ama tedavi süresini uzatmakla aşılabilir
  - İkinci basamak tedavi
    - Levofloksasinli 3'lü tedavi, artan levofloksasin direncine dikkat
  - Üçüncü basamak tedavi/kurtarma tedavileri
    - Antimikrobiyal duyarlılığa göre tedavi
- Penisilin allerjisi; bizmutlu dörtlü tedavi

TEDAVİ

- Tedavi süresi en az 14 gün olmalıdır
- PPI'lar yemekten yarım saat önce, diğer tüm ilaçlar yemek sonrası alınmalı
- Bizmut tuzları, tetrasiklin ve metranidazol midede ki pH değişikliklerinden etkilenmez
- Amoksisilin ve klaritromisin mide pH'dan etkilenir

TEDAVİ

Bizmutlu dörtlü tedavi sonuçları (Türkiye)

Rejim	Süre(gün)	Olgu	Eradikasyon(%)	
PPİ+B+A+K	14	97	90	*Ergül B. 30. UGH 2013*
PPİ+B+M+T	14	54	96.4	*Etik DE 30. UGH 2013*
	14	31	77	*Güliter S. Hebipa 2013*

TEDAVİ

Ardışık tedavi (Türkiye)

Rejim	Olgu	Eradikasyon(%)
7 gün PPİ + A	63	39
+		*Sezgin O. 23. UGH 2006*
7 gün PPİ + M + T		
	136	80
		Uygun A, Clinical Therapeutics 2008
	56	82
		Çetinkaya ZA. Helicobacter 2010

TEDAVİ

Ardışık tedavi (Türkiye)

Rejim	Olgu	Eradikasyon(%)
5 gün PPİ + A + 12 gün PPİ+B+M+T	31	88
		Gülter S . 30. UGH 2013
5 gün PPİ+ A + 7 gün PPİ + L + M	92	95
		Ozdil K. Hepatogastroenterology 2011
	73	82
		Calhan T. Helicobacter 2013

TEDAVİ

Türkiye'de concomitant tedavinin sonuçları

Rejim	Süre(gün)	Olgu	Eradikasyon(%)
PPİ+A+K+M	14	84	75
		Toros AB. Helicobacter 2011	
PPİ+B+T+L	10	75	90
		Calhan T. Helicobacter 2013	

TEDAVİ

Hybrid tedavi(Türkiye)

Rejim	Olgu	Eradikasyon(%)
5 gün PPİ + A + 9 gün PPİ+A+T+M	56	83

Çetinkaya ZA. Helicobacter 2010

TEDAVİ

Levofloxacin-temelli tedavi (Türkiye)

Rejim	Süre	Olgu	Eradikasyon(%)
PPİ+L +A	10	54	84
			Etik DÖ. 30. UGH 2013
	14	40	72
			Erçin CN. Turk J Gastroenterol. 2010
	7	52	61
			Bal K. 23. UGH 2006
	14	25	56
			Ünler GK. 23.UGH 2006

Helicobacter pylori eradikasyonunda ardışık 5+5 (10) günlük ve ardışık 7+7 (14) günlük tedavilerin karşılaştırılması

Comparison of 10 and 14 days sequential therapy for the eradication of *helicobacter pylori* (Comparison for eradication of *helicobacter pylori*)

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Giriş ve Amaç: *1. basamak Helicobacter pylori tedavisinde klasik 3'lü tedavi (amoksisilin+klaritromisin+proton pompa inhibitörü) ile eradikasyon oranları %50'lerin altına düşmüştür. Bu randomize, prospektif çalışmada gastroskopisinde peptik ülser (gastrik ülser ve/veya duodenal ülser) saptanan, histopatolojik olarak Helicobacter pylori pozitif olan hastalarda 5+5 (10) günlük ve 7+7 (14) günlük ardışık tedavi sonuçlarının karşılaştırılması amaçlanmıştır.* ***Gereç ve Yöntem:*** *Mart 2014-Ağustos 2015 tarihleri arasında gastroskopide peptik ülser saptanan, histopatoloji, üre-nefes testi veya gaitada Helicobacter pylori antijeni sonuçlarından en az ikisinde pozitiflik tespit edilen ve daha önce eradikasyon tedavisi almamış 66 hasta ardışık olarak 2 gruba randomize edilerek çalışmaya alındı. Grup 1 hastalara (n: 33) 5 gün (amoksisilin 1 gr+esomeprazol 40 mg 2x1) ardından 5 gün (klaritromisin 500 mg+metronidazol 500 mg+esomeprazol 40 mg 2x1) verildi. Grup 2 hastalara (n: 33) 7 gün (amoksisilin 1 gr+esomeprazol 40 mg 2x1) ardından 7 gün (klaritromisin 500 mg+metronidazol 500 mg+esomeprazol 40 mg 2x1) verildi. Her iki grupta esomeprazol 40 mg (1x1) 12 haftaya tamamlandı. 15 gün ilaçsız dönem sonrası üre-nefes testi ve gaitada Helicobacter pylori antijen testi ile eradikasyon kontrolü yapıldı.* ***Bulgular:*** *Grup 1 hastalarının 10'u (%30.3) kadın, yaş ortalaması 38±13.1 yaş, grup 2 hastalarının 12'si kadın (%34.4), yaş ortalaması 39±15.6 yaş idi. Tedavi sonrası üre-nefes testi ve gaitada Helicobacter pylori antijen testi ile yapılan değerlendirmede grup 1'de eradikasyon oranı %70, grup 2'de %72.7, toplamda %71.2 saptandı. İki grup arasında istatistiksel anlamlı farklılık yoktu.* ***Sonuç:*** *Ardışık 5+5 (10) günlük ve 7+7 (14) günlük tedavi sonucunda benzer şekilde yüzde yetmiş civarında eradikasyon sağlanmıştır. Çok ideal olmamakla birlikte bu eradikasyon oranı 5+5 (10) günlük ardışık tedavinin 1. basamak için alternatif olabileceğini göstermiştir.*

Background and Aims: *The eradication rate of Helicobacter pylori using standard triple therapy (amoxicillin+clarithromycin+proton pump inhibitor) as the first-line therapy has fallen below 50%. This prospective, randomized study was conducted to compare the 5+5 (10)-day and 7+7 (14)-day sequential treatment results in patients with peptic ulcer (gastric ulcer and/or duodenal ulcer) who were identified as histologically positive for Helicobacter pylori infection by gastroscopy.* ***Materials and Methods:*** *This study included 66 patients who had peptic ulcer diagnosed through gastroscopy, had at least two histopatholgically positive results, underwent urea breath test, had positive stool test for Helicobacter pylori antigen, and did not receive eradication therapy before. These patients were randomly divided into two groups and enrolled into the study between March 2014 and August 2015. Group 1 patients (n=33) were administered amoxicillin 1 g+esomeprazole 40 mg 2x1 for the first 5 days, followed by clarithromycin 500 mg+metronidazole 500 mg+esomeprazole 40 mg 2x1 for the next 5 days. Group 2 patients (n=33) were administered amoxicillin 1 g+esomeprazole 40 mg 2x1 for the first 7 days, followed by clarithromycin 500 mg+metronidazole 500 mg+esomeprazole 40 mg 2x1 for the next 7 days. Esomeprazole 40 mg (1x1) treatment was completed during 12 weeks in both groups. After a drug-free period of 15 days, the eradication rate was analyzed by urea breath test and Helicobacter pylori antigen stool test.* ***Results:*** *Ten patients in Group 1 (30.3%) were females, with a mean age of 38.0±13.1 years. Twelve patients in Group 2 (34.4%) were females, with a mean age of 39.0±15.6 years. After treatment, the urea breath test and Helicobacter pylori antigen stool test revealed an eradication rate of 70% in Group 1 and 72.7% in Group 2, with an overall eradication rate of 71.2% in all patients. No significant difference was observed between the two groups.* ***Conclusion:*** *At the end of the con-*

Birinci tercih *Helikobakter pilori* eradikasyon tedavileri alarm mı veriyor?

Are first-line *Helicobacter pylori* eradication therapies alarming?

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Amaç: *Helikobakter pilori* pozitif nonülser dispepsili hastalarda birinci tercih dört farklı eradikasyon tedavi protokolünün etkinliğinin değerlendirilmesi **Gereç ve Yöntem :** Gastroenteroloji polikliniğinde endoskopi ile *Helikobakter pilori* (+) nonülser dispepsi tanısı konan, daha önce eradikasyon tedavisi almamış hastaların dosya bilgileri retrospektif olarak incelendi. 14 günlük eradikasyon tedavisi verilen ve tedavinin bitiminden 4-6 hafta sonra ^{14}C üre nefes testi kontrolü yapılan 248 hastanın dosya bilgisi kaydedildi. Birinci tercih eradikasyon tedavi protokolleri dört gruba ayrıldı. Bunlar; Grup LAK: Lansoprazol 2x30 mg, amoksisilin 2x1000 mg, klaritromisin 2x500 mg Grup LAKB: Lansoprazol 2x30 mg, amoksisilin 2x1000 mg, klaritromisin 2x500 mg, bizmuth subsitrat 4x300 mg Grup PLA: Proton pompa inhibitörü (standart doz) 2x1, levofloksasin 1x500 mg, amoksisilin 2x1000 mg Grup PBTM: Proton pompa inhibitörü (standart doz) 2x1, bizmuth subsitrat 4x300 mg, tetrasiklin 4x500 mg, metronidazol 3x500 mg **Bulgular:** Grup LAK'da hasta sayısı: 114 ve eradikasyon oranı: %52.6, Grup LAKB'de hasta sayısı: 62 ve eradikasyon oranı: %59.7, Grup PLA'da hasta sayısı: 43 ve eradikasyon oranı: %60.5, Grup PBTM'de hasta sayısı: 29 ve eradikasyon oranı: %72.4 bulundu. Gruplar arasında eradikasyon başarısı açısından istatistiksel olarak anlamlı fark bulunmadı (p=0,261). **Sonuç:** Antibiyotiklere karşı *Helikobakter pilori* direnci ciddi bir problem olarak karşınıza çıkmaktadır. *Helikobakter pilori* tedavilerinin tekrar gözden geçirilmesi ve bu alanda yeni araştırmalara ihtiyaç vardır.

Background and Aims: We aimed to assess the efficacy of four different eradication therapies (first-line) in non-ulcer dyspeptic patients in a gastroenterology polyclinic. **Materials and Methods:** The file information of 248 patients was examined retrospectively. These patients had been diagnosed as non-ulcer dyspepsia via endoscopy. They tested positive for *Helicobacter pylori* and received eradication therapy for two weeks. Subsequently, they were monitored using the C14 urea breath test after 4-6 weeks. Four first-line eradication therapy regimes were used as follows: Group LAC (n: 114): Lansoprazole 2x30 mg, amoxicillin 2x1000 mg, clarithromycin 2x500 mg; Group LACB (n: 62): Lansoprazole 2x30 mg, amoxicillin 2x1000 mg, clarithromycin 2x500 mg, bismuth subcitrate 4x300 mg; Group PLA (n: 43): proton pump inhibitor (PPI) (standard dose) 2x1, levofloxacin 1x500 mg, amoxicillin 2x1000 mg; Group PBTM (n: 29): PPI (standard dose) 2x1, bismuth subcitrate 4x300 mg, tetracycline 4x500 mg, metronidazole 3?500 mg. **Results:** The eradication rates were as follows: Group LAC 52.6%, Group LACB 59.7%, Group PLA 60.5%, and Group PBTM 72.4%. The difference in eradication rates between groups was not statistically significant (p=0.261). **Conclusions:** The resistance of *H. pylori* to antibiotics is a significant problem. Current *H. pylori* therapies should be revised and new studies should be conducted.

Sayın Editör

Son sayıda yayınlanan Harran Üniversitesi'nden Ahmet UYANIKOĞLU ve arkadaşlarının yaptığı "*Helikobakter pilori* eradikasyonunda klasik 3'lü tedavi Doğu Anadolu bölgesinde halen etkilidir" adlı çalışmayı okuduk. Yazıyla ilgili eleştirilerimizi belirtmek isteriz.

Helikobakter pilori (Hp) eradikasyonu özellikle ülkemiz gibi yoğun ve gereksiz antibiyotik kullanımına bağlı ilaç direncinin yüksek olduğu ülkelerde önem arz etmektedir. Klasik tedavi olarak adlandırılan amoksisilin+klaritromisin+proton pompa inhibitörü (PPI) eradikasyonlar oranları ilk dönemlerde elde edilen yüksek oranlar son dönemlerde belirgin düşmüştür (%40-60) (1-4).

Yayınlanan çalışmada %97 olarak beyan edilen eradikasyon oranları dikkat çekicidir. Bununla birlikte çalışmanın metodu incelendiğinde eradikasyon verilen hastalara devamında 2 ay boyunca PPI devam edilmiş. Eradikasyon kontrolü için PPI ve antibiyotik verilmeden geçmesi gereken en az 2 hafta süre dikkate alınmadan gaytada HpSA bakılmıştır. Bu nokta çalışmanın güvenilirliğini belirgin oranda düşürmektedir. Literatür ve tedavi kılavuzları gözden geçirildiğinde *Hp* eradikasyon kontrolü yapabilmek için hastanın en az 1-2 hafta PPI, 3-4 hafta antibiyotik almaması gerektiği aşikardır (5-8). Bu şekilde yanlış bir metodla yapılan çalışmanın sonuçları ülkemiz "Helikobakter Çalışma Grubu"nca da ilk basamak olarak tercih edilmemesi gerektiği şeklinde belirtilen klasik 3'lü tedaviye bilimsel bir köken sağlanmadan tekrar kullanılabileceği şeklinde bir intiba oluşturabilir.

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Mesut SEZİKLİ, Züleyha AKKAN ÇETİNKAYA

Helikobakter Pylori Birinci Basamak Tedavisi Alan Hastalarda Üç Farklı Tedavi Rejiminin Etkinliğinin Değerlendirilmesi

Evaluation of the Effectiveness of Three Different Treatment Regimens in Patients Receiving Helicobacter Pylori First-Line Therapy

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ÖZ.

Amaç: Bu çalışmadaki amacımız en sık kullanılan Helikobakter pylori (Hp) tedavi rejimlerinin HP eradikasyon başarı oranlarını saptamaktır.

Materyal ve Metod: 2016 – 2020 yılları arasında üst gastrointestinal sistem endoskopisi sırasında Helikobakter pylori pozitif saptanan ve eradikasyon tedavisi sonrası kontrol endoskopik biyopsi alınan hastalar geriye dönük olarak değerlendirildi. Hastalar tedavi rejimlerine göre 3 gruba ayrıldı; lansoprazol 30 mg 2x1, klaritromisin 500 mg 2x1, amoksisilin 1000 mg 2x1 14 gün alanlar (grup 1, n=20), lansoprazol 30 mg 2x1, bizmut subsalisilat 262 mg 4x1, klaritromisin 500 mg 2x1, amoksisilin 1000 mg 2x1 14 gün alanlar (grup 2, n = 23) ve lansoprazol 30 mg 2x1, bizmut subsalisilat 262 mg 4x1, metronidazol 500 mg 3x1, tetrasiklin 500 mg 4x1 14 gün alanlar (grup 3, n = 17). Bu üç grubun tedavi başarıları değerlendirildi.

Bulgular: Çalışmaya, ortalama yaşı 42.8±15.17 olan 60 hasta dahil edildi. Grup 1,2 ve 3'ün yaş ortalamaları sırasıyla 40.05±15.33, 42.86±15.90 ve 46.23±14.14 olup gruplar arasında istatiksel olarak anlamlı farklılık yoktu. Çalışmaya alınan hastaların %57.6'sında (34/60) eradikasyon tedavisi sonrası Hp eradikasyonu sağlandı. Grup 1, 2 ve 3'teki HP eradikasyon oranları sırasıyla %50, %52.2 ve %66.7 idi. Gruplar arasında başarı oranları açısından istatiksel olarak anlamlı farklılık yoktu.

Sonuç: Bu çalışmada, yüksek antibiyotik direnci ve hedeflenen eradikasyon oranlarından daha düşük eradikasyon oranları nedeniyle klasik üçlü tedavi, bizmut eklenmiş klasik üçlü tedavi ve bizmutlu dörtlü tedavinin Türkiye'de kullanılmasının uygun olmayabileceği sonucuna vardık. Helikobakter pylori tedavisinde yeni tedavi rejimlerinin geliştirilmesi gerekmektedir.

Anahtar kelimeler: Helikobakter pylori, Eradikasyon, Üçlü tedavi, Dörtlü tedavi

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Hangi Antibiyotik Kullanılmalı?

- Antibiyotikler kombine edilirken
  - **Kinolonlar, nitroimidazoller ve rifampisin** aynı grupta olmamalı
    - Bakteri RNA/DNA sını etkileyerek etkili olurlar
  - **Tetrasiklinler ve makrolidler** aynı grupta olmamalı
    - Bakteri ribozom fonksiyonunu bozarak etkili olurlar
  - **Tetrasiklin, penisilin** ile kombine edilmemeli
    - Penisilinin antibakteryel etkisini antagonize eder

Helicobacter

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Efficacy of Two Levofloxacin-Containing Second-Line Therapies for *Helicobacter pylori*: A Pilot Study

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Keywords

H. pylori eradication, *H. pylori* re-treatment, levofloxacin, second-line therapy.

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Abstract

Background: An ideal second-line therapeutic regimen for the treatment of patients who do not respond to standard triple therapy is currently being investigated. In this study, we aimed to investigate the efficacy of two levofloxacin-containing second-line therapies for *Helicobacter pylori* (*H. pylori*).

Materials and Methods: One hundred and forty eight consecutive *H. pylori* -positive patients who did not respond to the standard triple therapy (77 female, 71 male) were enrolled in the study. The patients were randomized consecutively to two-second-line therapy groups; 73 to the levofloxacin-containing sequential (LCS) and 75 to the levofloxacin-containing quadruple (LCQ) therapy group. The LCS therapy group received pantoprazole 40 mg and amoxicillin 1,000 mg twice daily for 5 days followed by pantoprazole 40 mg twice daily and metronidazole 500 mg three times daily and levofloxacin 500 mg one time daily for 7 days. The LCQ therapy group received pantoprazole 40 mg twice daily, tetracycline 500 mg four times daily, bismuth subcitrate 300 mg four times daily and levofloxacin 500 mg one time daily for 10 days. *H. pylori* eradication was confirmed by stool antigen testing at least 6 weeks after cessation of therapy. Side-effects and compliance were assessed by a questionnaire.

Results: Intention-to-treat cure rates were: 82.2% (95%CI; 73–91) and 90.6% (95%CI; 79–95) in the LCS and LCQ therapy, respectively. Per protocol cure rates were: 85.7% (95%CI; 75–92) and 93.1% (95%CI; 85–98) in the LCS and LCQ therapy, respectively. No statistically significant difference was found between two groups ($p = .1$). No differences in compliance or adverse effects were demonstrated between two groups.

Conclusions: This prospective trial demonstrates that both levofloxacin-containing sequential therapy and levofloxacin-containing quadruple therapy regimens have higher *H. pylori* eradication rates and are well tolerated. The levofloxacin-containing quadruple therapy is likely the best treatment option for a second-line therapy, at least in the Turkish population.

Pantoprazol 40 mg 2x1
Amoksisilin 1 gr 2x1
5 gün
%85,7

Pantoprazol 40 mg 2x1
Metronidazol 500 mg 3x1
Levofloksasin 500 mg 1x1
7 gün

%93,1

Pantoprazol 40 mg 2x1
Bizmut subsitrat 300 mg 4x1
Levofloksasin 500 mg 1x1
Tetrasiklin 500 mg 4x1
10 gün

Ardışık tedavi...

- Ardışık tedavi
  - 14 gün PPI
    - İlk 7 gün PPI + Amoksisilin
    - İkinci 7 gün PPI + Metronidazol + Tetrasiklin
- İtalya da klaritromisine dirençli hastalarda
  - *Eradikasyon oranı % 90*
- Türkiye'de
  - *Eradikasyon oranı % 88*

Levofloksasin…

- 10 gün süre ile 300 hastada (Gisbert, 2008)
  - *Eradikasyon oranı % 77*
  - *Penisiline allerjisi olanlarda ikinci tercih olarak*
  - *Yan etki: tenosinovit !*

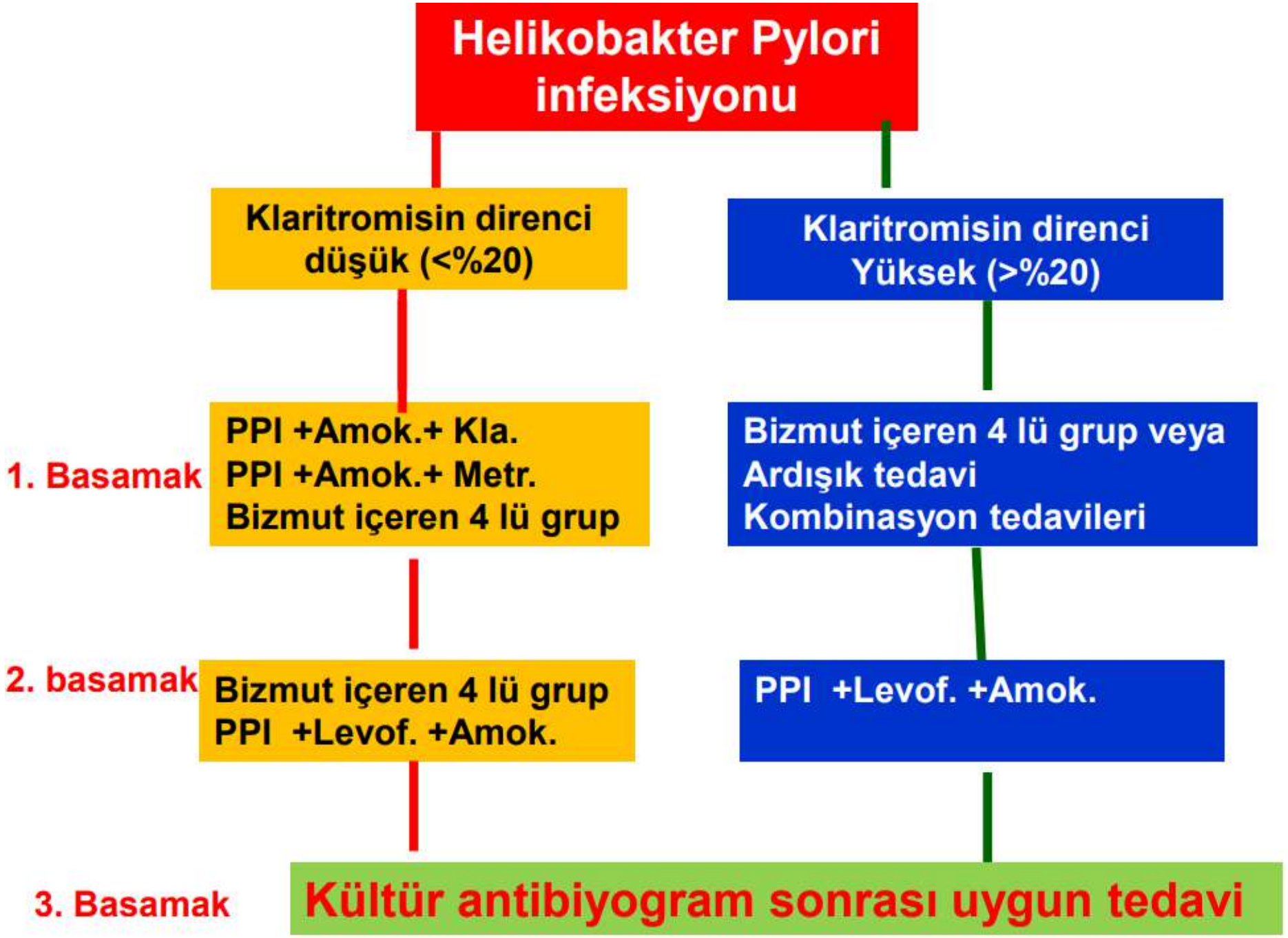
- Levofloksasinli ardışık tedavi (Aydın, 2009)
  - *7 gün Rabeprazol + Amoksisilin*
  - *7 gün Rabeprazol + Levofloksasin + Metronidazol*
  - *Eradikasyon oranı % 80*

Ampirik üçüncü tercih tedavi…

- Hp kültürü
  - zor
  - zahmetli
- Miehlke 2003
  - 14 gün süreyle
  - Omeprazol 4 x 40 mg + Amoksisilin 4 x 750 mg
  - Eradikasyon oranı *% 76*
- Gisbert 2006
  - Levofloksasinli tedaviler
  - Eradikasyon oranı *% 66*
- Rifabutin bazlı tedaviler

Rifabutin bazlı tedaviler …

- Rifampisin türevi
- Antibakteryel aktivitesi mide asidinden etkilenmez
- Rifabutine dirençli Hp suşu izole edilmemiş
- İki kez başarısız tedavi almış hastalarda…
  - *14 gün süreyle*
  - *PPI + Amoksisilin + Rifabutin*
  - *Eradikasyon oranı % 79*
- Yan etkiler …
  - *Ciddi nötropeni, trombositopeni*
- *Tüberküloz ilacı olarak korunmalı …*


Helikobakter Pylori infeksiyonu
Klaritromisin direnci düşük (<%20)
Klaritromisin direnci Yüksek (>%20)
1. Basamak
PPI +Amok.+ Kla.
PPI +Amok.+ Metr.
Bizmut içeren 4 lü grup
Bizmut içeren 4 lü grup veya Ardışık tedavi Kombinasyon tedavileri
2. basamak
Bizmut içeren 4 lü grup
PPI +Levof. +Amok.
PPI +Levof. +Amok.
3. Basamak
Kültür antibiyogram sonrası uygun tedavi

	Tedavi tipi	Kullanılan ilaçlar ve doz	Süre (gün)
1. Basamak	Standart üçlü tedavi	PPI (2x1)+Amok. (2x1 gr)+ Kla. (2x500 mg)	7-14
	Ardışık tedavi	5 gün PPI (2x1)+Amok. (2x1 gr) 5 gün PPI (2x1) +Kla. (2x500 mg)+ Metr.(2x500mg)	10
	Kombinasyon tedavileri	PPI (2x1)+Amok. (2x1 gr)+ Kla. (2x500 mg)+ Metr.(2x500mg)	10
	Hibrid tedavi	7 gün) PPI (2x1+Amok. (2x1 gr) 7 gün PPI (2x1)+Amok. (2x1 gr) +Kla. (2x500 mg)+ Metr.(2x500mg)	14
	Bizmut içeren grup	PPI (2x1)+ Bizmut (4x1) +tetrasiklin (4x1)+ Metr.(4x250)	10-14
2. Basamak	Bizmut içeren grup	PPI (2x1)+ Bizmut (4x1)+ tetrasiklin (4x1)+ Metr.(4x250)	10-14
	Levofloksasin içeren grup	PPI (2x1) +Levofloksasin (4x500) +Amok. (2x1 gr)	10
3. Basamak	Kültür sonrası	PPI (2x1)+ Bizmut (4x1)+ duyarlılığı yapılmış 2 antibiyotik	10
	Levofloksasin içeren 4'lü grup	PPI (2x1) +Bizmut (4x1)+Levofloksasin (4x500) +Amok. (2x1 gr)	10
	Rifabutin-içeren 3 lü tedavi	PPI (2x1)+Amok. (2x1 gr)+ rifabutin (150 mg 2x1)	14
	Furazolidonetem elli 4lü tedavi	PPI (2x1)+ tripotassium dicitratobismuthate (240 mg 2x1)+ furazolidone (200 mg, 2x1) + tetracycline (1 g, b.i.d.)	

1. Basamak tedaviye yanıtlar

Tedavi tipi	Kullanılan ilaçlar ve doz	Süre (gün)	Yanıt (%)
Standart üçlü tedavi	PPI (2x1)+Amok. (2x1 gr)+ Kla. (2x500 mg)	7-14	88/70
Ardışık tedavi	5 gün PPI (2x1)+Amok. (2x1 gr) 5 gün PPI (2x1) +Kla. (2x500 mg)+ Metr.(2x500mg)	10	90-94
Kombinasyon tedavileri	PPI (2x1)+Amok. (2x1 gr)+ Kla. (2x500 mg)+ Metr.(2x500mg)	10	93
Hibrid tedavi	7 gün) PPI (2x1+Amok. (2x1 gr) 7 gün PPI (2x1)+Amok. (2x1 gr) +Kla. (2x500 mg)+ Metr.(2x500mg)	14	99
Bizmut içeren grup	PPI (2x1)+ Bizmut (4x1) +tetrasiklin (4x1)+ Metr.(4x250)	10-14	90

Ülkemizde durum ne?

Tedavi tipi	Kullanılan ilaçlar ve doz	Yıl	Yanıt (%)
Üçlü tedavi	PPI (2x1)+Amok. (2x1 gr)+ Kla. (2x500 mg) Bizmut+ Amok. (2x1 gr)+ Kla. (2x500 mg Bizmut (4x1) +tetrasiklin (4x1)+ Metr.(4x250)	1995 2003 2002	100 55-70 46-87 92.3
Ardışık tedavi	5 gün PPI (2x1)+Amok. (2x1 gr) 5 gün PPI (2x1) +Kla. (2x500 mg)+ Metr.(2x500mg) 7 gün PPI (2x1)+Amok. (2x1 gr)+ Bizmut (4x1) 7gün PPI (2x1) + Bizmut (4x1) +Kla. (2x500 mg)+ Metr.(2x500mg)	14	75-80* 87
Kombinasyon tedavileri	PPI (2x1)+Amok. (2x1 gr)+ Kla. (2x500 mg)+ Metr.(2x500mg)	14	66.6
Hibrid tedavi	7 gün) PPI (2x1+Amok. (2x1 gr) 7 gün PPI (2x1)+Amok. (2x1 gr) +Kla. (2x500 mg)+ Metr.(2x500mg)	14	99
Bizmut içeren grup	PPI (2x1)+ Bizmut (4x1) +tetrasiklin (4x1)+ Metr.(4x250)	14	81

Birinci basamak *Helicobacter pylori* eradikasyon tedavisinde levofloksasin içeren hibrid tedavi protokolünün etkinlik ve güvenilirliğinin değerlendirilmesi

Evaluating the efficacy and safety of levofloxacin containing hybrid treatment protocol in the first-line therapy of *Helicobacter pylori* eradication

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Gaziosmanpaşa Üniversitesi Tıp Fakültesi, [4]Gastroenteroloji Bilim Dalı, Tokat

7 + 7

Rabeprazol 2x20 mg
Amoksisilin 1gr 2x1

Rabeprazol 2x20 mg
Amoksisilin 1 gr 2x1
Metronidazol 500 mg 3x1
Levofloksasin 500 mg 1x1

%79,3

Giriş ve Amaç: *Birinci basamak Helicobacter pylori eradikasyon tedavisinde levofloksasinli hibrid tedavi protokolünün eradikasyon başarısını ve tolere edilebirliğini değerlendirmeyi amaçladık.* ***Gereç ve Yöntem:*** *Bu çalışma retrospektif olarak dizayn edildi. Çalışmaya endoskopik biyopsi ile histopatolojik olarak Helicobacter pylori enfeksiyonu tanısı almış ve birinci basamak tedavi rejimi olarak 14 günlük levofloksasinli hibrid tedavi protokolü (birinci hafta; rabeprazol 2x20 mg + amoksisilin 2x1 gr, ikinci hafta; rabeprazol 2x20 mg + amoksisilin 2x1 gr + metronidazol 3x500 mg + levofloksasin 1x500 mg) verilmiş olan ve tedavi süresini tamamladıktan 6 hafta sonrasında Helicobacter pylori dışkı antijen testi ile eradikasyon kontrolü yapılmış olan hastalar dahil edildi. Levofloksasinli hibrid tedavi protokolü verildiği halde sonuç değerlendirmesine katılmayan hastaların verileri de ayrıca kaydedildi. Hastane kayıtlarından hastalara ait reçete bilgileri, laboratuvar testleri, endoskopik ve patolojik bulguları elde edildi. Hastaların tedaviye uyum durumu, tedavi alırken yaşadıkları ilaç yan etkileri hastalarla yapılan telefon görüşmesi sonucunda kaydedildi.* ***Bulgular:*** *Çalışmaya dahil edilme kriterlerine uyan 92 hasta PP (per protocol) grubu olarak, tedavi başlanmış olan toplam 130 hasta ise ITT (intention to treat) grubu olarak tanımlandı. Eradikasyon başarısı ITT grubunda %56.2 (%95 CI:%48.4-%64), PP grubunda %79.3 (%95 CI:%71.5-%87.6) olarak hesaplandı. Hastaların %6.9'unun yan etki nedeniyle tedaviyi bıraktığı belirlendi.* ***Sonuç:*** *Levofloksasinli hibrid tedavi protokolü güvenli bir tedavi olmasına karşın sağladığı eradikasyon başarısı ve maliyet etkinlik analizi açısından uygun bir tedavi değildir.*

Anahtar kelimeler: *Helicobacter pylori eradikasyonu, levofloksasin, hibrid tedavi*

Background and Aims: *We aimed to evaluate the efficacy and tolerability of levofloxacin containing hybrid treatment protocol in the first-line therapy of Helicobacter pylori eradication.* ***Material and Methods:*** *This retrospective study included patients who were diagnosed with Helicobacter pylori infection histopathologically by endoscopic biopsy and underwent a 14-day levofloxacin containing hybrid treatment protocol (first week, rabeprazole 2x20 mg + amoxicillin 2x1 g; second week, rabeprazole 2x20 mg + amoxicillin 2x1 g + metronidazole 3x500 mg + levofloxacin 1x500 mg) as a first-line treatment regimen and controlled for Helicobacter pylori eradication using Helicobacter pylori stool test 6 weeks later from the end of the treatment. Data were also recorded for patients who did not come for eradication control while they were taking the levofloxacin containing hybrid treatment protocol. Patients' details regarding their prescriptions, laboratory tests, and endoscopic and pathologic findings were obtained from hospital records. Patients' treatment compliance and the side effects related to the treatment, which they experienced while taking the medication, were recorded through telephone interviews.* ***Results:*** *A total of 92 patients who fulfilled the inclusion criteria of the study were defined as the per protocol group, and a total of 130 patients who took the treatment were defined as the intention to treatment group. Eradication rates were calculated to be 56.2% (95% CI: 48.4%-64%) for the intention to treatment group and 79.3% for the per protocol group (95% CI: 71.5%-87.6%). It was observed that 6.9% of patients discontinued the treatment because of side effects.* ***Conclusion:*** *Although levofloxacin containing hybrid treatment protocol is a safe treatment, it is not suitable in terms of eradication success and cost-effectiveness analysis.*

Türkiye'de HP Eradikasyonunda PPI Kullanımı Nasıl Olmalı?

CYP2C19 polimorfizmi nedeniyle fenotip olarak üç ayrı grup oluşmaktadır.

1) RM (Rapide extensive metabolizer-hızlı tip)

2) IM (Intermediate metabolizer-orta)

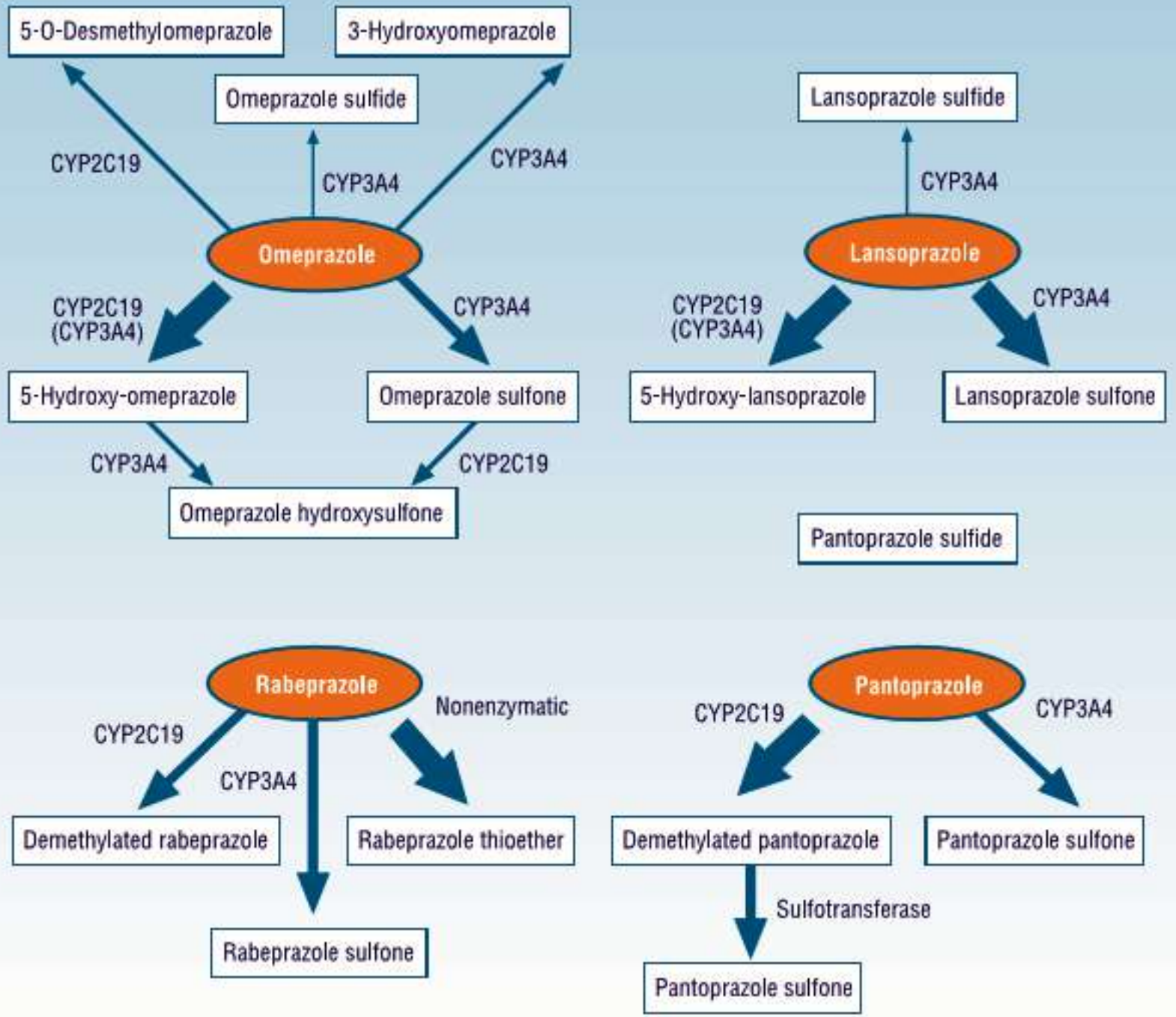
3) PM (Poor metabolizer-Yavaş, kötü)

Genotipik olarak ta üç grup olarak ele alınır.

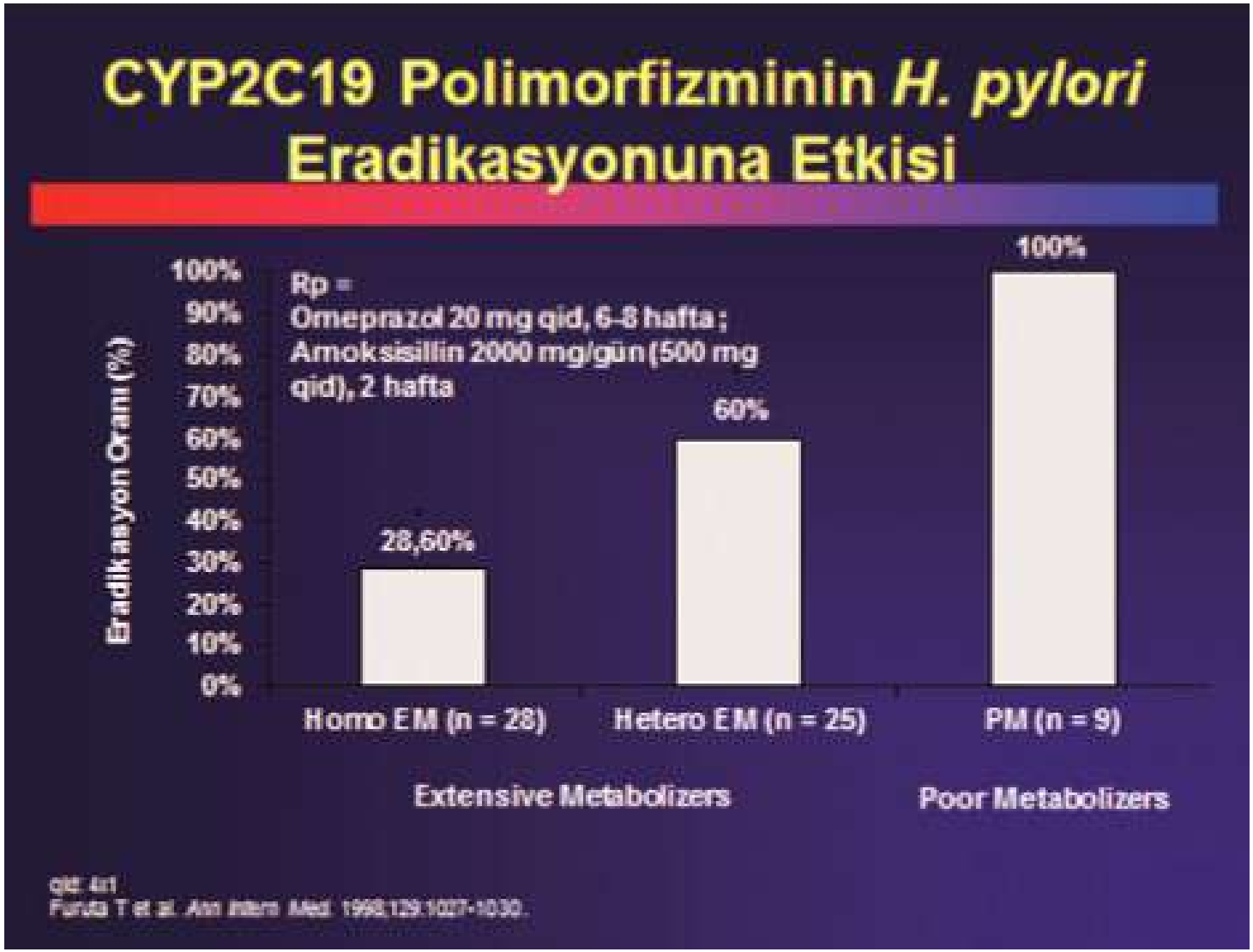
1) Homozygous extensive metabolizer (homEM)

2) Heterozygous extensive metabolizer (hetEM)

3) Poor metabolizer (PM)


5-O-Desmethylomeprazole
3-Hydroxyomeprazole
Omeprazole sulfide
CYP2C19
CYP3A4
CYP3A4
Omeprazole
CYP2C19 (CYP3A4)
CYP3A4
5-Hydroxy-omeprazole
Omeprazole sulfone
CYP3A4
CYP2C19
Omeprazole hydroxysulfone
Lansoprazole sulfide
CYP3A4
Lansoprazole
CYP2C19 (CYP3A4)
CYP3A4
5-Hydroxy-lansoprazole
Lansoprazole sulfone
Pantoprazole sulfide
Rabeprazole
Nonenzymatic
CYP2C19
CYP3A4
Demethylated rabeprazole
Rabeprazole thioether
Rabeprazole sulfone
Pantoprazole
CYP2C19
CYP3A4
Demethylated pantoprazole
Pantoprazole sulfone
Sulfotransferase
Pantoprazole sulfone

PPI'lı üçlü tedavilerde CYP2C19 polimorfizminin Hp eradikasyonu üzerine %20-25 oranında etkili olduğu görülmektedir.



PPI'lı üçlü tedavilerde CYP2C19 polimorfizminin Hp eradikasyonu üzerine %20-25 oranında etkili olduğu görülmektedir.

CYP2C19 Genotip Polimorfizminin İntragastrik pH'a Etkisi

	24 saatlik ortalama intragastrik pH		
PPI	**PM**	**hetEM**	**homEM**
Omeprazol (20 mg 7/8 gün)	5.7-6.6	4.4-5.5	3.1-4.1
Lansoprazol (30 mg 8 gün)	5.4-6.2	3.5-5.0	3.1-4.5
Rabeprazol (20 mg 8 gün)	5.8-6.0	4.6-5.0	3.8-4.8

PPI: Proton pump inhibitor, PM: poor metabolizers, hetEM: heterozygous extensive metabolizers, homEM: homozygous extensive metabolizers

Türkiye'de HP Eradikasyonunda PPI Kullanımı Nasıl Olmalı?

Farklı CYP2C19 genotiplerde *Hp* eradikasyon oranı

Tedavi	% Eradikasyon Oranı homEM	hetEM	PM
Dual tedavi PPI + Amok.	%50	%64	%97
Triple tedavi PPI + Amok. + Klar.	%76	%89	%90
Quadruple tedavi PPI + Amok. + Met.+Klar.	%80	%98	%100

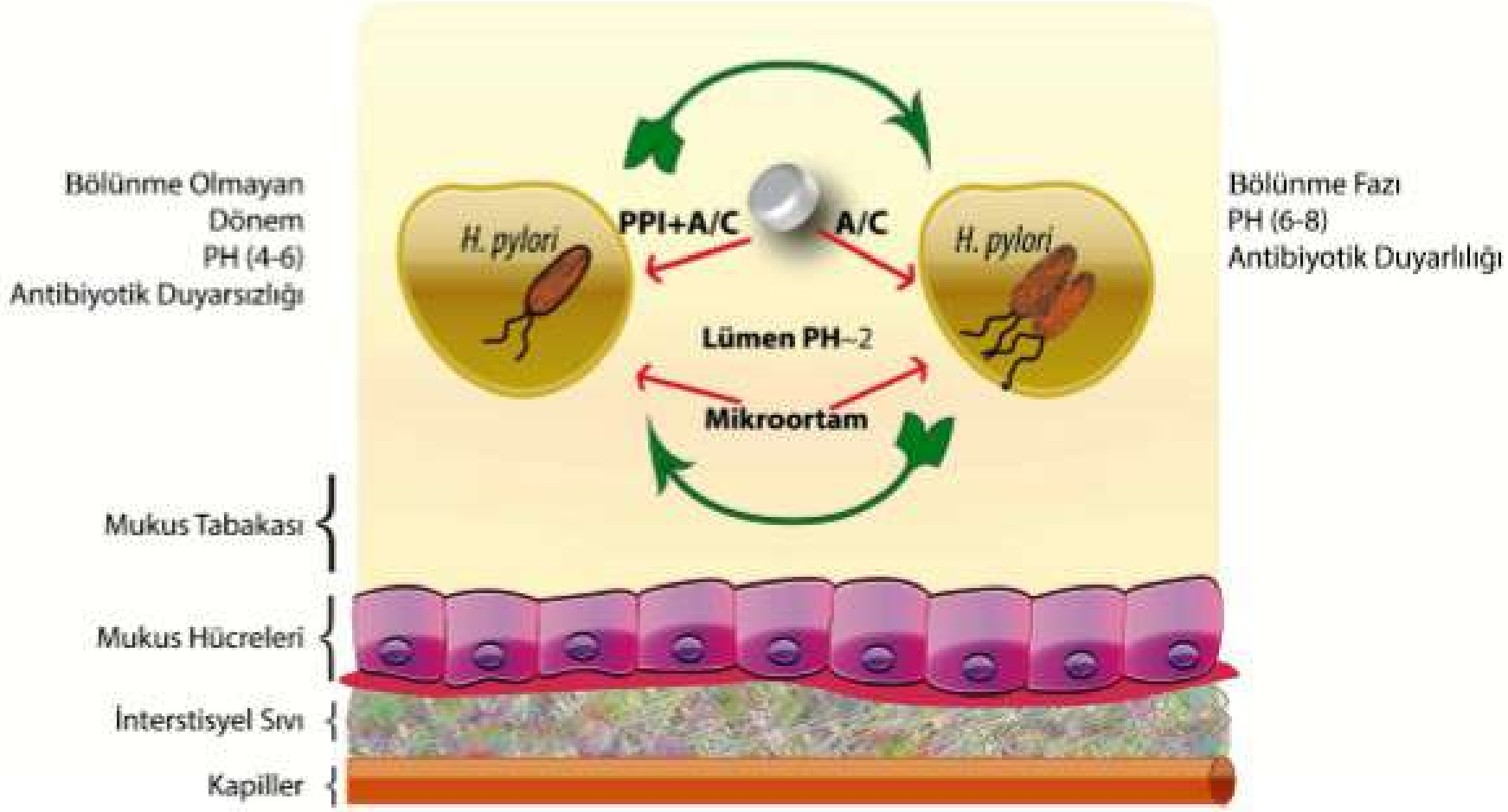
Amok: Amoksisilin, Klar: Klaritromisin, Met: Metronidazol (Klotz U. Int J Clin Pharmacol Ther 2006;44:297-302.)

Türkiye'de Helicobacter Pylori: Güncel Durum ve Tedavi Seçenekleri

Helicobacter pylori enfeksiyonunun yaklaşık eradikasyon oranı
[yalnız antibiyotiklerle ya da H_2RA (H_2 reseptör antagonistleri) veya PPI (Proton Pompa İnhibitörü) ilave edilmesiyle]

Antibiyotikler	Eradikasyon-Kür (%) Yalnız	+H_2RA	+PPI
Amoksisilin	20	35	60
Klaritromisin	40	55	70
Amoksisilin + Nitroimidazol	60	70	80
Klaritromisin +Nitroimidazol	60	80	90
Bizmut üçlü tedavi (Bizmut + İki antibiyotik)	80	90	95

Türkiye'de Helicobacter Pylori: Güncel Durum ve Tedavi Seçenekleri



Türkiye'de CYP2C19 polimorfizmi üzerine yapılan çalışmalarda

"Poor" yavaş metabolize edenlerin oranı %1-5,

"homozygous extensive" metabolize edenlerin oranı ise %75-84

Farklı etnik gruplarda CYP2C19 genotip dağılımı (%

	EM	İM	PM
Çin	26,4	49,6	24
Japonya	36,5	45,8	17,7
Tayland	37,2	47,1	15,7
Vietnam	40	40	20
Batı Ülkeleri	72,6	25,3	2,1

EM: Extensive metabolizer. IM: Intermediate metabolizer. PM: Poor metabolizer.

1) **Bizmutlu Dörtlü Tedavi (2 Hafta)**

- Bizmut tuzu 500 mg 3x1/gün
- Tetrasiklin 500 mg 3x1/gün
- Metronidazol 500 mg 3x1/gün
- PPI 3x1/gün

2) **Ardışık Tedavi**

PPI 2x1 + Amoksisilin 1 g 2x1/5 gün

Sonra PPI 2x1 + Klaritromisin 500 mg 2x1 + Metronidazol 500 mg 2x1/5 gün

(Liou JM; Eradikasyon %87)

Ardışık tedaviyi 7+7 gün olarak uygulayan araştırmacılar da vardır. Eradikasyon oranını da %90,7 olarak bildirmişlerdir (Liou JM).

3) **Bizmutsuz Dörtlü Tedavi (14 Gün)**

- PPI 2x1
- Klaritromisin 500 mg 2x1
- Amoksisilin 1 g 2x1
- Metronidazol 500 mg 2x1

4) **Yüksek doz (PPI) ikili tedavi (iki hafta) PPI 4x1+ Amoksisilin 500 mg 4x1**

PPI'ların da belli aralıklarda -en uygunu 4x1 şeklinde- verilmesi yerinde olur.

Bu yaklaşım gece asiditesini de kontrolde kolaylık sağlayacaktır.

Böylece "Nocturnal acid breakthrough" da önlenecektir.

Helicobacter pylori eradikasyonu için önerilen tedaviler

Tedavi	İlaç Doz/Gün	Süre
Üçlü Tedavi	PPI 2x1 Amoksisilin I g 2x1 Klaritromisin 500 mg 2x1	14 gün
Bizmutlu Dörtlü Tedavi	PPI 2x1 Kolloidal Bizmut Subsitrat 200 mg 4x1 Metronidazol 500 mg 3xl Tetrasiklin 500 mg 3xl	14 gün
Bizmutsuz Dörtlü Tedavi	PPI 2x1 Amoksisilin 1 g 2x1 Metronidazol 500 mg 3xl Tetrasiklin 500 mg 3x	10-14 gün
Ardışık Tedavi	PPI 2x1 + Amoksisilin 1 g 2x1/5 gün Sonra PPI 2x1+ Klaritromisin 500 mg 2x1+ Tinidazol 500 mg 2x1/5 gün	10 gün
Levofloksasinli Üçlü Tedavi	PPI 2x1 + Amoksisilin 1 g 2x1 + Levofloksasin 1 g 2x1	10 gün
Rifabutinli Üçlü Tedavi	PPI 2x1+ Amoksisilin 1 g 2x1 + Rifabutin 150 mg 2x1	10 gün

European Review for Medical and Pharmacological Sciences 2016; 20: 1795-1797

Can *Helicobacter pylori* be eradicated with high-dose proton pump inhibitor in extensive metabolizers with the CYP2C19 genotypic polymorphism?

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[2]Department of Genetics, Institute for Experimental Medicine, Istanbul University, Istanbul, Turkey
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Abstract. – Proton pump inhibitors (PPI) metabolism and pharmacokinetics are regulated by cytochrome P450 enzymes in the liver. Cytochrome P450 2C19 (CYP2C19) polymorphism plays an import role in the metabolism of PPIs. The three possible genotypes for CYP2C19 each has a distinct effect on the pharmacodynamics of PPIs. Homozygote extensive metabolizers (HomEM) are the most frequent genotype and have two wild-types (non-mutant) (*1/*1) alleles. HomEM is associated with increased enzyme activity, which increases the rate of PPI metabolism. Intragastric pH, which is required for eradication, is lowest in HomEM. In HomEMs, an insufficient increase in intragastric pH results in decreased anti-*Helicobacter pylori* (HP) efficacy of the antibiotics and, therefore, lower eradica-

Introduction

The CYP2C19 genotypic polymorphism significantly affects the success of *Helicobacter pylori* (HP) eradication treatment[1]. All current treatment options for the eradication of *H. pylori* infection involve the combination of a proton pump inhibitor (PPI) and antibiotics[2]. PPIs are indispensable in the eradication of *H. pylori* infection, and the rationale for their use involves a number of potential mechanisms. PPI components with antisecretory properties increase gastric pH, therefore stabilizing acid-labile antibiotics in the stomach, and increase gastric luminal antibiotic concentrations[3-5].

Table I. Eradication rates with different proton pump inhibitors (PPIs) in extensive metabolizers according to the CYP2C19 genotypic polymorphism.

First-line therapy for extensive metabolizers according to the CYP2C19 genotypic polymorphism	
Eradication rate	64.7% (101/156)
Eradication rate of the amoxicillin-clarithromycin- rabeprazole group	60 % (45/75)
Eradication rate of the amoxicillin-clarithromycin-pantoprazole group	69.1% (56/81)

Table II. Eradication rates with high-dose proton pump inhibitors (PPIs) in extensive metabolizers according to the CYP2C19 genotypic polymorphism (patients who failed the first-line treatment).

Second therapy with high dose PPI in extensive metabolizers according to the CYP2C19 genotypic polymorphism	
Eradication rate	80% (20/25)
Amoxicillin–clarithromycin-high dose rabeprazole	83.3% (10/12)
Amoxicillin–clarithromycin-high dose pantoprazole	76.9% (10/13)

Sa1915

Effect of Genotypic Differences in CYP2C19 and on Cure Rates for *Helicobacter pylori* Infection by Triple Therapy With Different Proton Pump Inhibitors

Kadir Demir, Asli Ormeci, Zeliha Emrence, Suut Gokturk, Bulent Baran, Ozlem Mutluay Soyer, Filiz Akyuz, Cetin Karaca, Fatih Besisik, Sabahattin Kaymakoglu, Duran Ustek

Introduction and Aim: In *H. pylori* eradication, we aimed at investigating whether the rabeprazole and pantoprazole based eradication treatments were affected by the genotypic polymorphism in patients taking the same antibiotics for the same time period. Materyal and Method: 200 patients found to have H.pylori infection following the rapid urease test in at least one of the endoscopic antrum and corpus biopsies carried out with a functional dyspepsia diagnosis were included in the study. While all the patients were given clarithromycin 2x500 mg and amoxicillin 2x1 g, as PPI rabeprazole 2x20 mg was given to one group and to the other pantoprazole in doses of 2x 40 mg. The genotypes of cytochrome P450 2C19 were classified into the three groups, as rapid extensive metabolizer, intermediate metabolizer and poor metabolizer. The CYP2C19 genotype of all patients, the effectiveness of the treatment regimen, the effect of the genotypic polymorphism on the treatment were assessed. The success of the treatment was assessed with stool antigen test after 12 weeks of the completion of the treatment. Results: The mean age of the patients was 40±13 (18-72) years, 41% of whom were male. 48% of the patients received a treatment with rabeprazole and 52% with pantoprazole. In our patient population, the frequencies of rapid extensive metabolizer, intermediate metabolizer and poor metabolizer were 78%, 19.5% and 2.5%, respectively. The eradication rate was 68.5% in all group, 64.7% for rapid extensive metabolizer, 79.4% for intermediate metabolizer, 100% poor metabolizer. In intermediate and poor metabolizer, are considered as a single group the success rate is 81%; on the other hand rapid metabolizing group's success rate is %64.7. When both groups are compared, the success of eradication in those intermediate and poor metabolizer was found to be high and statistically significant ($p<0.05$). In rapid extensive metabolizer, the use of a different PPI was found to have no effect on the success rate of the eradication ($p>0.05$). In patients metabolizing poor and intermediate group the different treatment regimens were also found to have no effect on the success of the treatment ($p> 0.05$). Discussion: The genotypic polymorphism is effective on the rate of eradication. In rapid extensive metabolizer, the use of a different PPI was found to have no effect on the success rate of the eradication.

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Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report

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ABSTRACT
Important progress has been made in the management of *Helicobacter pylori* infection and in this fifth edition of the Maastricht Consensus Report, key aspects related to the clinical role of *H. pylori* were re-evaluated in 2015. In the Maastricht V/Florence Consensus Conference, 43 experts from 24 countries examined new data related to *H. pylori* in five subdivided workshops: (1) Indications/Associations, (2) Diagnosis, (3) Treatment, (4) Prevention/Public Health, (5) *H. pylori* and the Gastric Microbiota. The results of the individual workshops were presented to a final consensus voting that included all participants. Recommendations are provided on the basis of the best available evidence and relevance to the management of *H. pylori* infection in the various clinical scenarios.

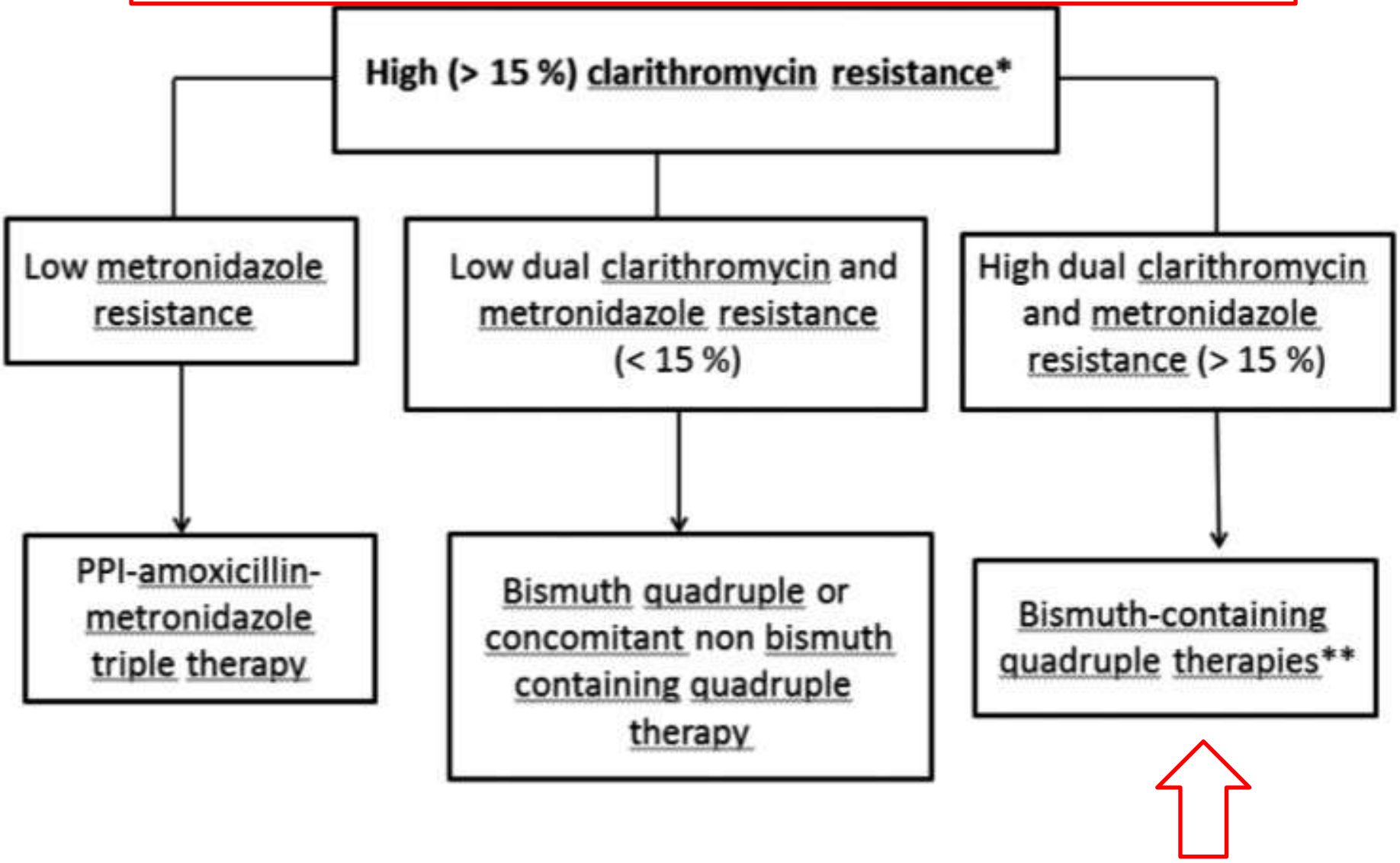
complexity of gastric functions in health and disease has recently addressed this issue.[3]

The aim of this report is to serve as a state-of-the-art guide for the management of *H. pylori* infection and related clinical manifestations and also as an inspiration for new clinical research in the area.

In the Maastricht V/Florence Consensus Report 43 experts from 24 countries convened for 2 days for a face-to-face meeting after having been actively involved in a previously started Delphi process as described below.

The working groups were set up according to the following topics:
Working group 1: Indications/Associations
Working group 2: Diagnosis
Working group 3: Treatment
Working group 4: Prevention/Public Health

Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report



WORKING GROUP 3: TREATMENT

- **Statement 7:** Currently, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred non-bismuth quadruple therapy, as it has shown to be the most effective to overcome antibiotic resistance.
- Statement 8: The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is **14 days**, unless 10 day therapies are proven effective locally.

WORKING GROUP 3: TREATMENT

- **Statement 9:** In areas of low clarithromycin resistance, triple therapy is recommended as first-line empirical treatment. Bismuth-containing quadruple therapy is an alternative.
- **Statement 10:** The use of high dose PPI twice daily increases the efficacy of triple therapy. Esomeprazole and rabeprazole may be preferred in Europe and North America where the prevalence of PPI extensive metabolisers is high.

Turk J Gastroenterol *2016; 27: 408-14*

Comparison of the effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on intragastric pH in extensive metabolizer patients with gastroesophageal reflux disease

ESOPHAGUS

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ABSTRACT

Background/Aims: Studies on the therapeutic efficacy of proton pump inhibitors (PPIs) in patients with gastroesophageal reflux disease (GERD) have been recently published. In most of these studies, comparison of only two PPIs have been made. There are few studies on the comparison of four or more PPIs. We aimed to compare the acid inhibitory effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on days 1 and 5 of treatment in patients with GERD, who were extensive metabolizers in regard to the CYP2C19 genotype.

Materials and Methods: *Helicobacter pylori*-negative with typical symptoms of GERD patients were randomly divided into four treatment groups. Efficacy analysis on days 1 and 5 were performed on the four groups which comprised 10 (esomeprazole), 11 (rabeprazole), 10 (lansoprazole), and 10 (pantoprazole) patients.

Results: On day 1 of PPI treatment, the mean percentage of time with intragastric pH>4 were 54%, 58%, 60%, and 35% for the groups, respectively, and on day 5, these values were 67%, 60%, 68%, and 59%, respectively. Esomeprazole, rabeprazole, and lansoprazole were found to be superior to pantoprazole on the first day of treatment.

Conclusion: Pantoprazole is a less potent proton pump inhibitor than the other PPIs tested on the first day of treatment. When the time needed to raise the intragatric pH to over 4 was evaluated, esomeprazole was found to have the most rapid action, followed by lansoprazole and rabeprazole.

Keywords: Extensive metabolizer, GERD, PPI, intragastric pH, CYP2C19

WORKING GROUP 3: TREATMENT

- **Statement 11:** The treatment duration of PPI-clarithromycin based triple therapy should be extended to 14 days, unless shorter therapies are proven effective locally.
- **Statement 12:** After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing triple or quadruple therapy may be recommended. In cases of high quinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option.

WORKING GROUP 3: TREATMENT

- **Statement 13:** After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended as a second-line treatment.
- **Statement 14:** After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended.

WORKING GROUP 3: TREATMENT

- **Statement 15:** After failure of second-line treatment, culture with susceptibility testing or molecular determination of genotype resistance is recommended in order to guide treatment.
- **Statement 16:** After failure of the first-line treatment (clarithromycin based) and second-line treatment (with bismuth-containing quadruple regimen), it is recommended to use the fluoroquinolone-containing regimen.
- In regions with a known high fluoroquinolones resistance, a combination of bismuth with different antibiotics or a rifabutin-containing rescue therapy should be considered.

Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report

Peter Malfertheiner ,[1,2] Francis Megraud ,[3] Theodore Rokkas ,[4,5] Javier P Gisbert ,[6,7] Jyh-Ming Liou ,[8] Christian Schulz ,[1,9] Antonio Gasbarrini,[10] Richard H Hunt,[11,12] Marcis Leja ,[13,14] Colm O'Morain,[15] Massimo Rugge ,[16,17] Sebastian Suerbaum,[9,18] Herbert Tilg ,[19] Kentaro Sugano ,[20] Emad M El-Omar ,[21] On behalf of the European Helicobacter and Microbiota Study group

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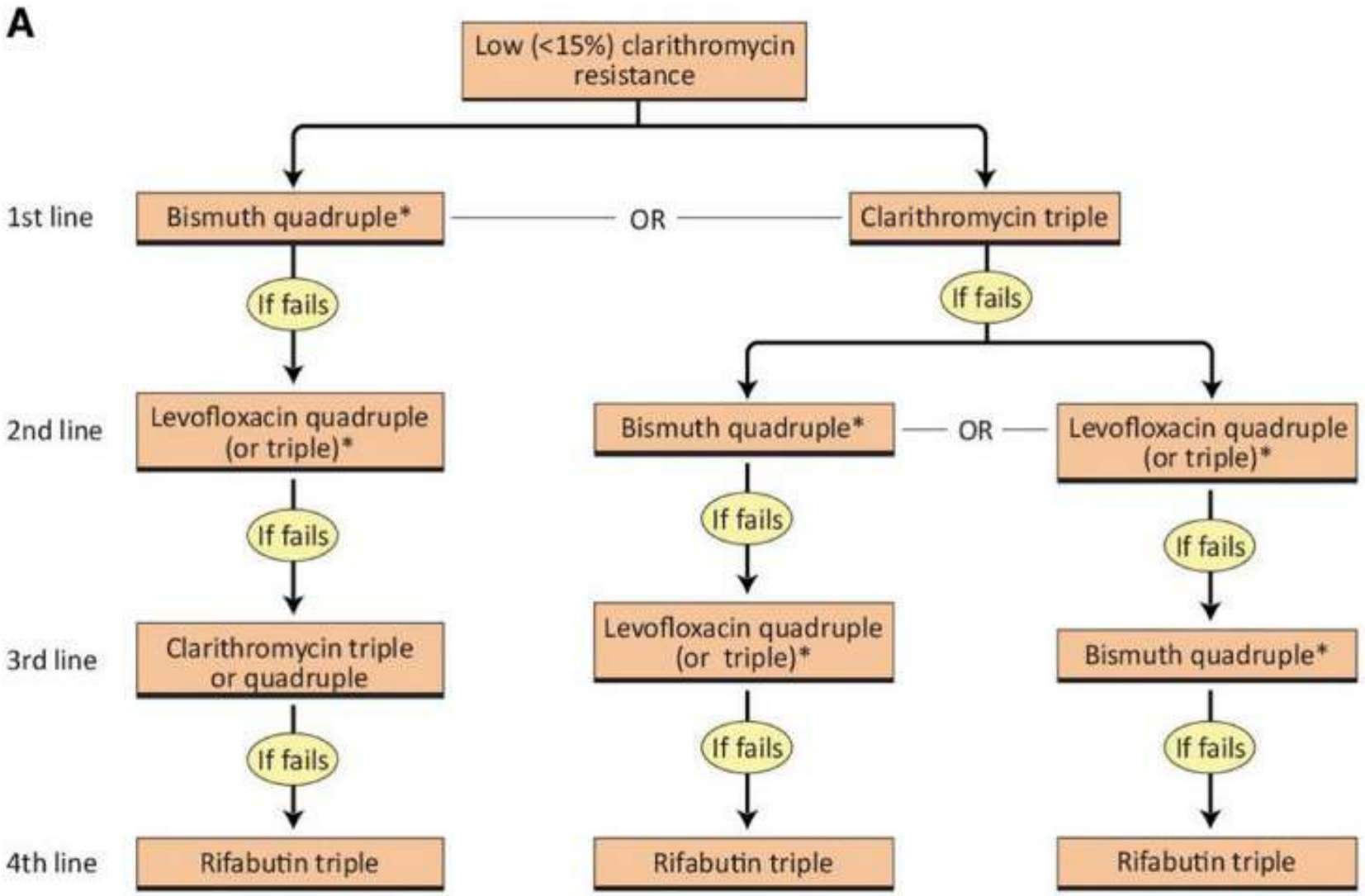
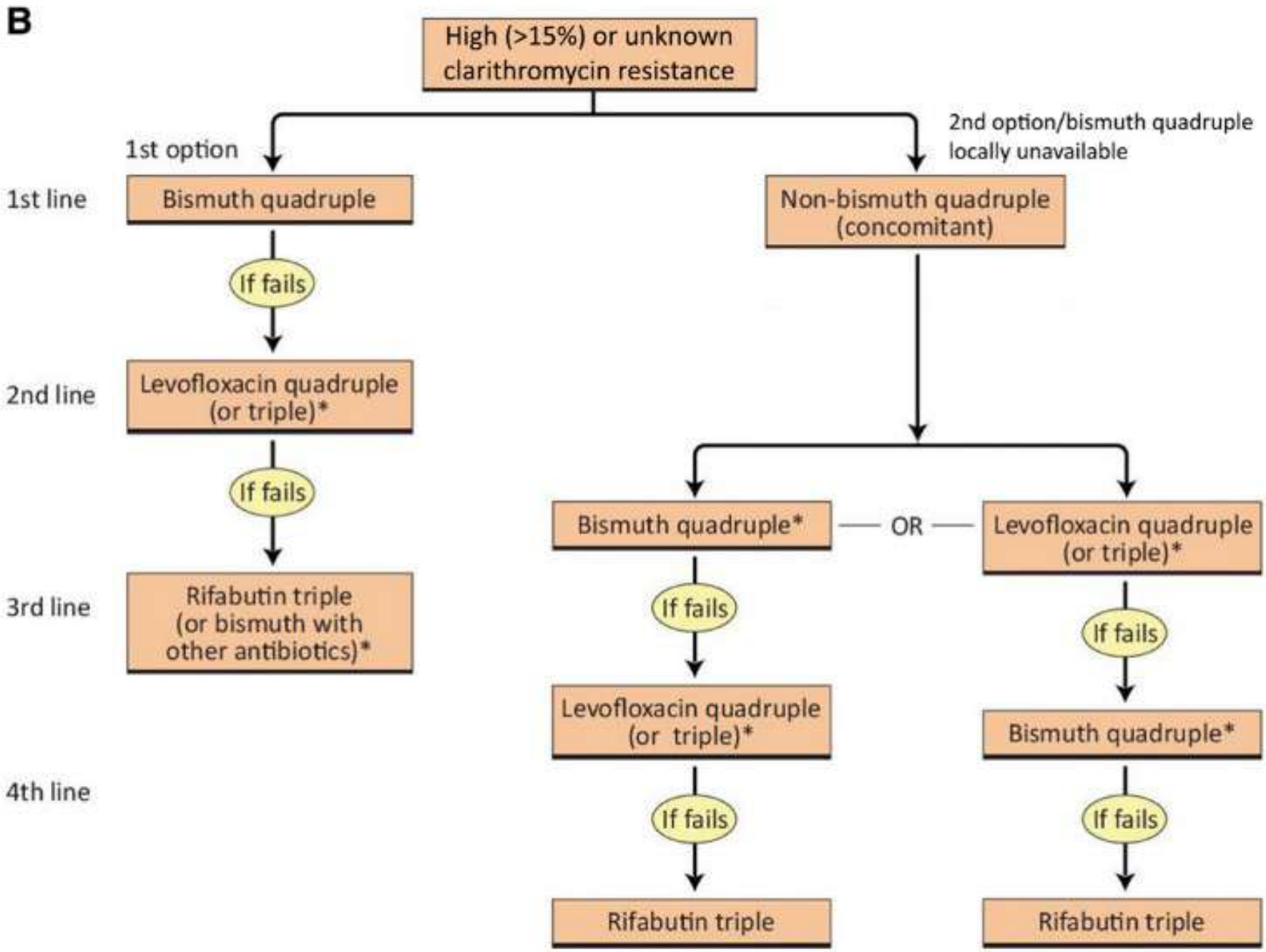
ABSTRACT

Helicobacter pylori Infection is formally recognised as an infectious disease, an entity that is now included in the International Classification of Diseases 11th Revision. This in principle leads to the recommendation that all infected patients should receive treatment. In the context of the wide clinical spectrum associated with *Helicobacter pylori* gastritis, specific issues persist and require regular updates for optimised management. The identification of distinct clinical scenarios, proper testing and adoption of effective strategies for prevention of gastric cancer and other complications are addressed. *H. pylori* treatment is challenged by the continuously rising antibiotic resistance and demands for susceptibility testing with consideration of novel molecular technologies and careful selection of first line and rescue therapies. The role of *H. pylori* and antibiotic therapies and their impact on the gut microbiota are also *H. pylori* detection and antibiotic susceptibility with support for the role of antibiotic stewardship. The most effective empirical regimens are revised if individual antibiotic resistance is not available.

A recent important evolution has taken place as a consequence of the Kyoto consensus report on gastritis[2] with the designation of *H. pylori* gastritis as an infectious disease. *H. pylori* gastritis as an infectious disease is now included as a nosological entity in itself in the new International Classification of Disease 11th Revision (ICD 11), which implies treatment of all *H. pylori*-infected patients. This represents a paradigm shift, as the indication for treatment is no longer reserved for patients with clinical manifestations of infection. Nevertheless, the clinical scenarios of *H. pylori* gastritis-related diseases remain diverse with specific aspects that require critical re-examination.


A
Low (<15%) clarithromycin resistance
1st line
Bismuth quadruple*
OR
Clarithromycin triple
If fails
If fails
2nd line
Levofloxacin quadruple (or triple)*
Bismuth quadruple*
OR
Levofloxacin quadruple (or triple)*
If fails
If fails
If fails
3rd line
Clarithromycin triple or quadruple
Levofloxacin quadruple (or triple)*
Bismuth quadruple*
If fails
If fails
If fails
4th line
Rifabutin triple
Rifabutin triple
Rifabutin triple


B
High (>15%) or unknown clarithromycin resistance
1st option
2nd option/bismuth quadruple locally unavailable
1st line
Bismuth quadruple
Non-bismuth quadruple (concomitant)
If fails
2nd line
Levofloxacin quadruple (or triple)*
If fails
3rd line
Rifabutin triple (or bismuth with other antibiotics)*
Bismuth quadruple*
OR
Levofloxacin quadruple (or triple)*
If fails
If fails
Levofloxacin quadruple (or triple)*
Bismuth quadruple*
4th line
If fails
If fails
Rifabutin triple
Rifabutin triple

Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report

Guidelines

Table 1 Statements, Level of evidence, Strenght of recommendation

	Grading	Agreement	
WG1: Indications/Associations			
Statement 1	A1	100.00%	H. pylori infection always causes gastritis, irrespective of symptoms or complications.
Statement 2	A1	94.00%	H. pylori is a gastric pathogen. H. pylori gastritis is an infectious disease.
Statement 3	A1	94.00%	Test-and-treat is an appropriate strategy for uninvestigated dyspepsia.
Statement 4	A1	92.00%	Endoscopy is not necessary in the initial investigation of dyspepsia in low H. pylori prevalence areas.
Statement 5	A1	100.00%	H. pylori gastritis is associated with increased, decreased or no overall change in acid secretion in the stomach.
Statement 6	A1	100.00%	Overall, H. pylori eradication is superior to placebo or acid suppressive therapy for long-term relief of dyspepsia, but the magnitude of the benefit is small.
Statement 7	B1	100.00%	H. pylori gastritis has to be excluded before a reliable diagnosis of functional dyspepsia can be made.
Statement 8	A1	100.00%	The use of either aspirin or NSAIDs increases the risk of peptic ulcer disease and its complications in H. pylori infected subjects.
Statement 9	A1	100.00%	H. pylori testing and treatment are advisable for high-risk patients who are already on long-term aspirin. H. pylori testing and treatment are advisable for naïve patients starting long-term NSAID therapy. Those at high-risk may need additional PPI therapy.
Statement 10	A1	91.00%	There is no evidence to suggest that anticoagulants (coumarins, direct oral and vitamin K antagonists) increase the risk of bleeding in patients with H. pylori infection.
Statement 11	A1	94.00%	Long-term treatment with PPIs alters the topography of H. pylori gastritis.
Statement 12	A1	97.00%	H. pylori eradication improves gastritis in long- term PPI users.
Statement 13	A1	97.00%	H. pylori eradication is recommended for patients with unexplained iron deficiency anaemia (IDA), idiopathic thrombocytopenic purpura (ITP) and Vitamin B12 deficiency.
Statement 14	A1	100.00%	H. pylori eradication is the first-line treatment for localised low grade gastric MALT lymphoma. H. pylori eradication therapy is also recommended for cases without evidence of H. pylori infection and may provide benefit even for more advanced staged disease
Statement 15	D2	90.00%	H. pylori has been positively and negatively associated with some extra-gastroduodenal disorders. However, the causality of these associations has not been definitively proven.
Statement 16	A1	86.00%	The COVID-19 pandemic has negatively impacted the management of H. pylori-related diseases.

Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report

WG 2 Diagnostics			
Statement 1	A1	97.00%	In young dyspeptic patients (age below 50) with no specific risk and no alarm symptoms, non-invasive testing for H. pylori infection is recommended.
Statement 2	B1	94.00%	In dyspeptic patients older than 50 years, upper GI endoscopy is required. Functional serology may be considered as complementary diagnostic tool.
Statement 3	A2	100.00%	When endoscopy is indicated it should: i) apply the best available technologies; ii) include biopsy sampling. Biopsy samples, as obtained in accordance with validated protocols, should result in both aetiological diagnosis and gastritis staging. Any focal lesions should be additionally sampled.
Statement 4	A1	87.00%	UBT remains an important tool for H. pylori diagnosis before and after eradication therapy. Citric acid is an essential component of the protocol.
Statement 5	A1	96.00%	Monoclonal stool antigen test, if properly validated, is an appropriate test before and after H. pylori treatment
Statement 6	A1	98.00%	Gastric functional serology (pepsinogens I-II and gastrin levels), anti-H. pylori antibodies, anti-intrinsic factor and anti-parietal cell auto-antibodies may provide clinically valuable information on the likelihood of gastric mucosal atrophy, including its aetiology.
Statement 7	A1	100.00%	Molecular methods (in particular, real time-PCR, whole genome sequencing and digital PCR) allow detection of H. pylori mutations associated with resistance to clarithromycin, levofloxacin, tetracycline and rifampicin.
Statement 8	B2	100.00%	Gastric biopsies recovered from rapid urease tests (RUT) can be reused for molecular testing by PCR.
Statement 9	A1	91.00%	Clarithromycin susceptibility testing, if available through molecular techniques or culture, is recommended before prescribing any clarithromycin containing therapy.
Statement 10	A1	96.00%	In the short-term post-eradication (4–6 weeks) follow-up, no antibiotics or bismuth should be used to permit optimum testing for H. pylori. Proton pump inhibitors should be stopped 14 days before testing
Statement 11	A1	91.00%	Tests for serum IgG antibodies against H. pylori can serve as a screening test in specific clinical situations.
Statement 12	A1	100.00%	Gastric mucosal atrophy is defined as "loss of native glands." Atrophy is the major determinant of non-hereditary gastric cancer risk assessed by endoscopy and histology, and it may be complementarily assessed by gastric serology.
Statement 13	A1	97.00%	The histological assessment of atrophy should result in a conclusive gastritis staging (OLGA/OLGIM), which consistently ranks the patient-specific cancer risk. Histological staging makes IM subtyping clinically redundant.
Statement 14	B2	91.00%	In H. pylori-negative gastritis (primary or after eradication), clinically suspected autoimmune gastritis (AIG) requires testing for gastrin, pepsinogens ratio, and auto-antibodies to intrinsic factor and parietal cells. Clinical factors and functional serology may provide the rationale for any further need for endoscopy/biopsy assessment.
Statement 15	B2	97.00%	Currently, no large-scale trials have provided evidence that molecular biomarkers can reliably predict the risk of non-hereditary (ie, non-syndromic) gastric cancer.
Statement 16	B1	100.00%	In H. pylori-eradicated patients, low-stage gastritis as properly assessed by endoscopy/histology, only requires clinical follow-up.
Statement 17	B1	100.00%	After successful H. pylori eradication, patients with high-stage (III-IV) gastritis and/or extensive endoscopic atrophy are still at risk for gastric cancer. The timing of the endoscopic/biopsy surveillance is based on the gastritis stage as assessed at the last check-up.
Statement 18	A1	100.00%	Low- and high-grade intra-epithelial neoplasia requires: i) confirmatory histological assessment, ii) gastric mapping by high resolution endoscopy and iii) targeted EMR or SBD, particularly for high grade, in tertiary endoscopy centres. Ablation does not abolish metachronous cancer risk. H. pylori eradication and post-ablation surveillance are both mandatory.

Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report

WG3 Treatment			
Statement 1	D2	91.00%	It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment, in respect to antibiotic stewardship. However, the generalised use of such a susceptibility-guided strategy in routine clinical practice remains to be established.
Statement 2	B1	92.00%	If individual susceptibility testing is not available, the first line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance is bismuth quadruple therapy. If this is not available, non-bismuth concomitant quadruple therapy may be considered.
Statement 3	D2	85.00%	The treatment duration of bismuth quadruple therapy should be 14 days, unless 10- days effective therapies are available.
Statement 4	B1	94.00%	In choosing a non-bismuth quadruple therapy, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred choice given its proven reproducible effectiveness and less complexity compared with sequential and hybrid therapies.
Statement 5	D2	100.00%	The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days.
Statement 6	B1	94.00%	In areas of low clarithromycin resistance, bismuth quadruple therapy or clarithromycin-containing triple therapy may be recommended as first-line empirical treatment, if proven effective locally.
Statement 7	B1	100.00%	The recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days.
Statement 8	C2	97.00%	The use of high dose PPI twice daily increases the efficacy of triple therapy. It remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies.
Statement 9	B2	100.00%	Potassium-Competitive Acid Blockers (P-CAB) - antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections.
Statement 10	D2	94.00%	Empiric second line and rescue therapies should be guided by local resistance patterns assessed by susceptibility testing and eradication rates in order to optimise treatment success.
Statement 11	C2	83.00%	After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option.
Statement 12	C2	84.00%	After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment.
Statement 13	C2	87.00%	After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing quadruple (or triple) therapy is recommended. PPI-amoxicillin high- dose dual therapy might also be considered.
Statement 14	B2	86.00%	After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies and second line with bismuth quadruple therapy, it is recommended to use a fluoroquinolone-containing regimen. In regions with a known high fluoroquinolone resistance, a bismuth quadruple therapy with different antibiotics, rifabutin-containing rescue therapy, or a high dose PPI-amoxicillin dual therapy, should be considered.
Statement 15	B2	84.00%	After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the bismuth-based quadruple therapy. If bismuth is not available, high-dose PPI-amoxicillin dual or a rifabutin-containing regimen could be considered.
Statement 16	C2	90.00%	After failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use a clarithromycin-based triple or quadruple therapy only if from an area of low (<15%) clarithromycin resistance. Otherwise, a high-dose PPI-amoxicillin dual therapy, a rifabutin- containing regimen or a combination of bismuth with different antibiotics should be used.
Statement 17	C2	85.00%	In patients with proven penicillin allergy, for a first-line treatment, bismuth quadruple therapy (PPI-bismuth-tetracycline-metronidazole) should be recommended. As second line therapy, bismuth quadruple therapy (if not previously prescribed) and fluoroquinolone-containing regimen may represent empirical second-line rescue options.

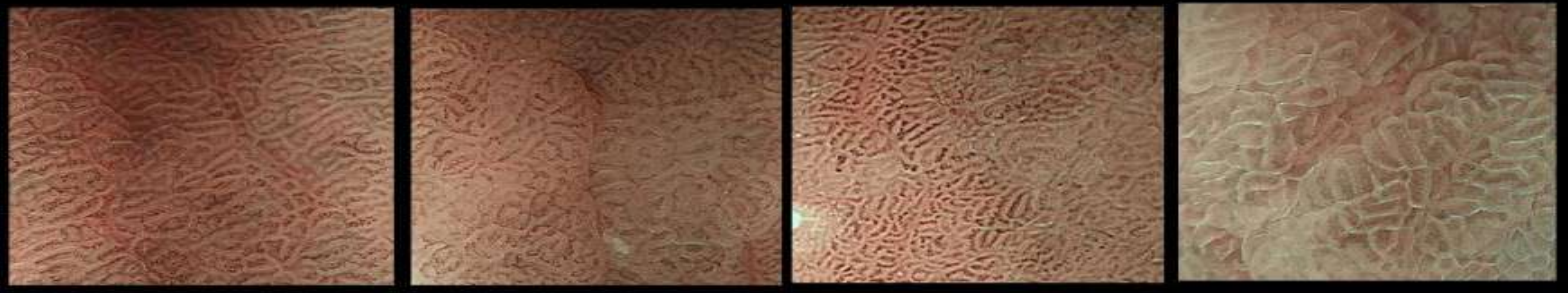
Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report

WG 4 Gastric cancer & prevention			
Statement 1	A1	100.00%	H. pylori infection is the primary aetiological factor for gastric adenocarcinoma including proximal gastric cancer (PGC)
Statement 2	A1	94.00%	H. pylori infection plays an aetiological role in a subset of adenocarcinoma of the Gastro-oesophageal Junction zone.
Statement 3	A1	100.00%	The influence of environmental factors is subordinate to the effect of H. pylori infection.

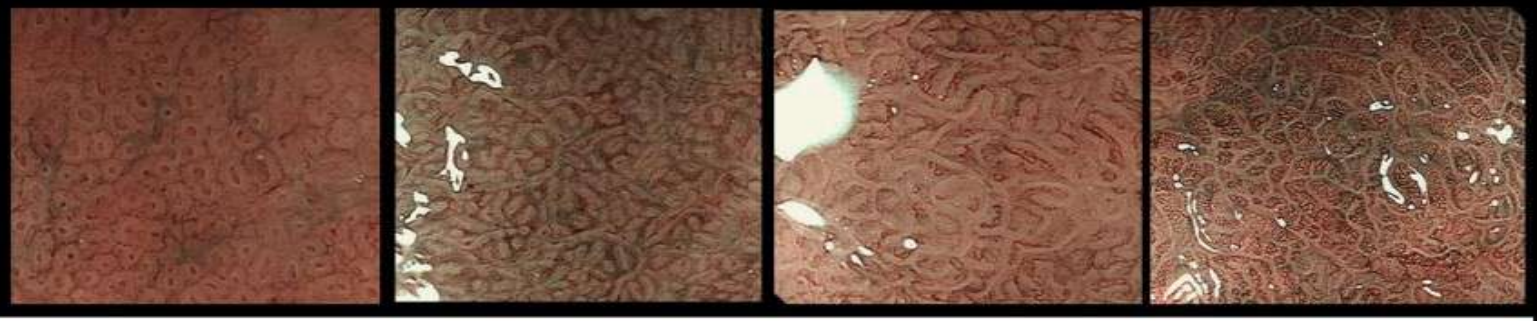
		Corpus			
	Atrophy score	No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum	No atrophy (score 0) (*including incisura angularis*)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score 1) (*including incisura angularis*)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2) (*including incisura angularis*)	Stage II	Stage II	Stage III	Stage IV
	Severe atrophy (score 3) (*including incisura angularis*)	Stage III	Stage III	Stage IV	Stage IV

Statement 15	B1	95.00%	Population-based H. pylori test-and-treat programmes for gastric cancer prevention require caution in the selection of antibiotics to minimise development of antimicrobial resistance.
Statement 16	B2	84.00%	Broad use of H. pylori eradication therapies for the purpose of gastric cancer prevention does not lead to an increase in other severe pathologies
Statement 17	A1	94.00%	Population-based H. pylori test-and-treat strategy provides additional benefits by preventing other gastroduodenal pathologies.
Statement 18	C2	81.00%	Screening modalities for gastric cancer prevention (noninvasive or endoscopic) combined with colorectal cancer screening is an opportunity
Statement 19	A1	97.00%	A population-based H. pylori test and treat programme is cost-effective in populations with intermediate or high incidence of gastric cancer.
Statement 20	B1	97.00%	Follow-up at regular intervals, and by use of endoscopic biopsy protocols, is mandatory in patients with severe atrophic gastritis (OLGA 3/4).

Score	0	1	2	3
LBC or WOS	Absent	< 1/3	≥ 1/3 and < 1/2	≥ 1/2



Score	0	1	2	3
Mucosal pattern	Round pit	Oval or slit-like pit	Tubular or granular	Tubular or granular
LBC or WOS			(-)	(+)



Antrum: IM score \ Corpus: Atrophy score	No atrophy (score 0)	Mild atrophy (score 1)	Moderate Atrophy (score 2)	Severe atrophy (score 3)
No IM (score 0)	STAGE 0	STAGE I	STAGE II	STAGE II
Mild IM (score 1)	STAGE I	STAGE I	STAGE II	STAGE III
Moderate IM (score 2)	STAGE II	STAGE II	STAGE III	STAGE IV
Severe IM (score 3)	STAGE III	STAGE III	STAGE IV	STAGE IV

Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report

Table 1 Continued

	Grading	Agreement	
Statement 21	A1	100.00%	Eradication of H. pylori is mandatory to reduce the risk of metachronous gastric cancer after curative endoscopic resection or gastric subtotal resection of early gastric cancer.
Statement 22	C2	100.00%	Medical and special dietary chemoprevention cannot in general be recommended in patients with severe gastric atrophy or intestinal metaplasia (OLGA3/4) after H. pylori eradication.
Statement 23	D1	94.00%	Population-based H. pylori test-and-treat programmes should be targeted to special requirements at the regional level (ie, selection of screening tool, use of eradication regimen, surveillance)
Statement 24	B1	94.00%	Population-based H. pylori test-and-treat programmes should be integrated into healthcare priorities, especially in regions with intermediate to high gastric cancer incidence.
Statement 25	D2	100.00%	The use of genetic and epigenetic markers for gastric cancer risk assessment and gastric cancer progression in clinical management requires further validation.
Statement 26	A1	100.00%	Image-enhanced endoscopy (IEE) should be used in the endoscopy-based screening for dysplasia and early gastric cancer.
Statement 27	C1	100.00%	There is still demand for a prophylactic and/or therapeutic vaccine.
WG 5 Helicobacter pylori and the Gut Microbiota			
Statement 1	B2	100.00%	Early life antibiotic exposure has a long-lasting effect on the intestinal microbiota.
Statement 2	A1	94.00%	The human stomach is colonised by other bacteria beyond H. pylori, the so-called gastric microbiome.
Statement 3	B2	91.00%	Gastric bacteria other than H. pylori may also affect H. pylori related changes.
Statement 4	C2	91.00%	Non-H. pylori Helicobacter species can cause human gastric disease.
Statement 5	B2	89.00%	H. pylori eradication therapy has the potential to select resistant strains of gut microbiota.
Statement 6	A2	89.00%	Certain probiotics have been shown to be effective in reducing GI side effects caused by H. pylori eradication therapies.
Statement 7	B2	80.00%	Certain probiotics may have a beneficial effect on H. pylori eradication therapy through reduction of antibiotic related side effects.
Statement 8	B2	97.00%	Antibiotic treatment for other reasons might select resistant H. pylori strains.
Statement 9	A2	86.00%	The oral cavity may contribute to the gastric microbiota composition.

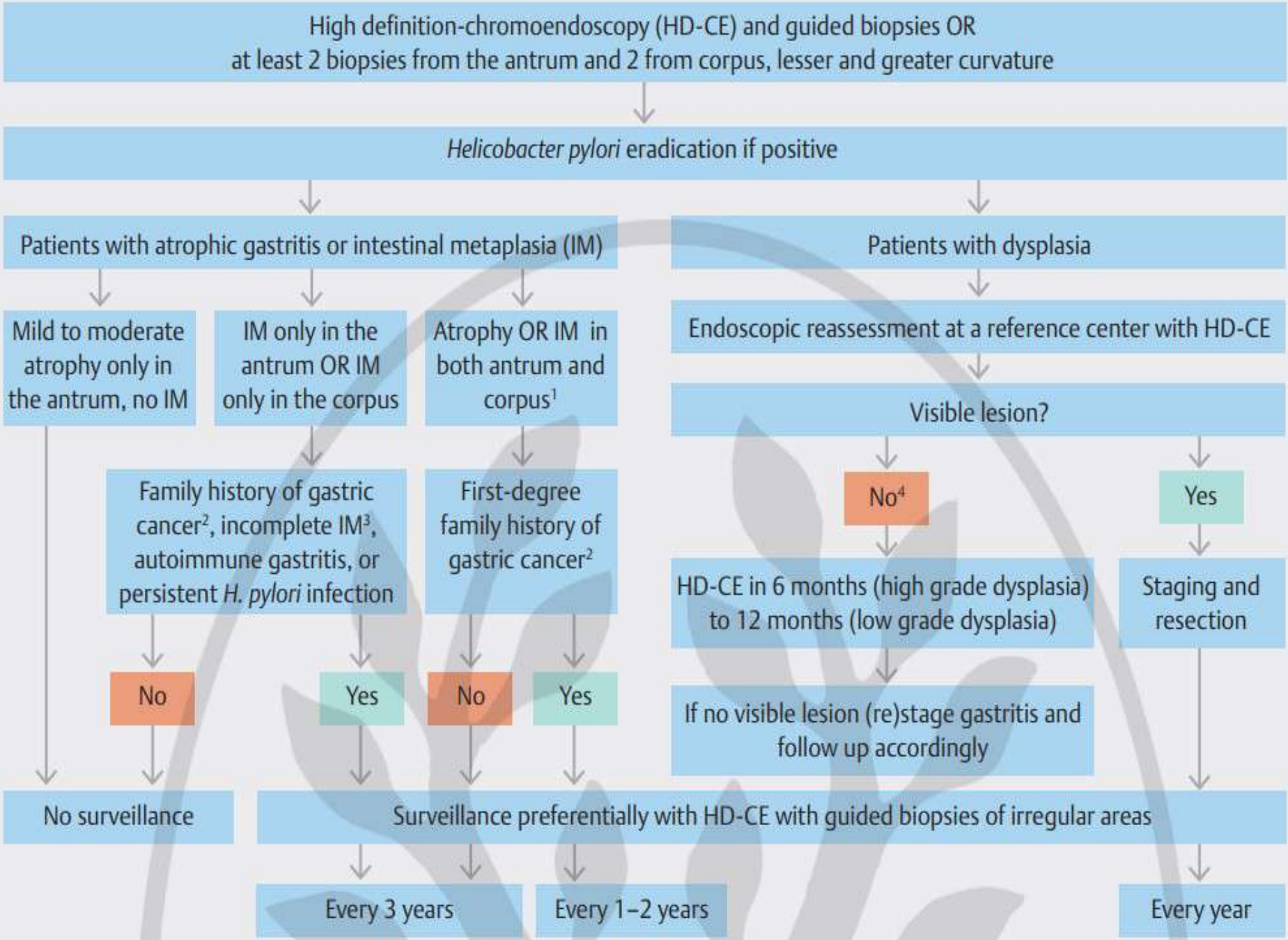
Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report

***Statement 2*: *H. pylori* infection plays an aetiological role in a subset of adenocarcinoma of the Gastro-oesophageal Junction (GOJ) zone (GOJZ).**

Agreement 94% **Grade A1**

GOJ cancer, which was classified as a separate entity in the IARC classification,[310] is included into oesophageal cancer in the new edition.[306] It should be noted that neither 'gastric cancer in the cardia' nor 'cardia gastric cancer (CGC)' is recommended as a categorical naming in this classification, because the presence of genuine cardiac mucosa has been questioned or, if present, is limited to a very narrow area mostly within 5 mm from the GOJ. Thus, conventional CGC is now either classified as GOJ cancer or PGC depending on the location of the tumour in relation to GOJ, namely those classified as Siewert type II as GOJ cancer and those of type III as PGC. *H. pylori* is the key risk factor also in PGC.[308] This fits in the new concept of GOJZ cancer which addresses the adenocarcinoma occurring 1 cm proximal to and 1 cm distal to GOJ which clarifies the pathogenetic mechanisms for cancer occurring at the GOJZ.[311]

A number of studies have strongly indicated that there are at least two major aetiological factors for GOJ adenocarcinoma, one from inflammation caused by gastroduodenal reflux and the other from inflammation of junctional gastric mucosa including cardiac-type mucosa mainly by *H. pylori* infection.[307 312–314]


High definition-chromoendoscopy (HD-CE) and guided biopsies OR at least 2 biopsies from the antrum and 2 from corpus, lesser and greater curvature
Helicobacter pylori eradication if positive
Patients with atrophic gastritis or intestinal metaplasia (IM)
Patients with dysplasia
Mild to moderate atrophy only in the antrum, no IM
IM only in the antrum OR IM only in the corpus
Atrophy OR IM in both antrum and corpus[1]
Endoscopic reassessment at a reference center with HD-CE
Visible lesion?
Family history of gastric cancer[2], incomplete IM[3], autoimmune gastritis, or persistent *H. pylori* infection
First-degree family history of gastric cancer[2]
No[4]
Yes
HD-CE in 6 months (high grade dysplasia) to 12 months (low grade dysplasia)
Staging and resection
No
Yes
No
Yes
If no visible lesion (re)stage gastritis and follow up accordingly
No surveillance
Surveillance preferentially with HD-CE with guided biopsies of irregular areas
Every 3 years
Every 1–2 years
Every year

Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report

***Statement 2*: *H. pylori* is a gastric pathogen. *H. pylori* gastritis is an infectious disease.**

Agreement 94% **Grade A1**

In the absence of *H. pylori* the gastric mucosa does not demonstrate signs of chronic active inflammation, neutrophils are absent and infiltration with mononuclear cells is minor.[8–10] Therefore, an agent causing such changes in the gastric mucosa cannot be considered part of the normal microbiota and the fact that *H. pylori* has coinhabited mankind for millennia does not preclude its pathogenicity of today.[11] Koch's postulate for pathogenicity has been documented since the early days of *H. pylori* discovery.[12] Eradication therapy restores normal gastric mucosa or halts progression to mucosal lesions[13] and can reduce symptoms, minimise complications of the infection and reduce gastric cancer risk. Eradication of *H. pylori* is recommended even in the absence of symptoms.[1 2 6] There is an entity of *H. pylori*-negative gastritis with characteristics similar to *H. pylori* gastrit but its pathological relevance remains unclear.[14]

Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report

***Statement 18*: Screening modalities for gastric cancer prevention (noninvasive or endoscopic) combined with colorectal cancer screening is an opportunity**

Agreement 81% **Grade C2**

In several Western countries colorectal cancer programmes start at the age of 50. At that time, approximately 10% H. *pylori*-infected patients may already have gastric preneoplastic lesions (atrophy, IM). The prevalence of advanced preneoplastic lesions in Europe in the older age group is up to 19%.[396–399] To reduce costs and to increase the compliance, a screen and treat approach for *H. pylori* infection could be combined with colorectal cancer screening in countries with intermediate and high gastric cancer risk. The best option for non-invasive assessment of preneoplastic changes in gastric mucosa is serological screening with the determination of serum pepsinogen I and II (sPG-I and sPG-II), including the calculation of the sPG-I/II ratio, in combination with the analysis of anti-*H. pylori* antibodies. A systematic review that enrolled 20 studies calculated a pooled sensitivity of 74.7% and specificity of 95.6%, respectively, to detect atrophic gastritis by these means.[400] Eradication therapy should be offered to all *H. pylori* positive patients[2] combined with upper GI endoscopy for all patients with positive serologic biopsy (pepsinogen I/II<3 and/or pepsinogen I<30 µg/L). Regular endoscopic surveillance should be offered to those with OLGA/OLGIM II-IV stage as recommended by MAPPS II guidelines.[89]

Gastroenterology 2016;151:51–69

CONSENSUS STATEMENT

The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults

Carlo A. Fallone,[1] Naoki Chiba,[2,3] Sander Veldhuyzen van Zanten,[4] Lori Fischbach,[5] Javier P. Gisbert,[6] Richard H. Hunt,[3,7] Nicola L. Jones,[8] Craig Render,[9] Grigorios I. Leontiadis,[3,7] Paul Moayyedi,[3,7] and John K. Marshall[3,7]

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Table 1. Recommendations for Regimens Used for the Eradication of *H pylori*

Recommendation	Regimen	Definition (see dose table)
First line		
Recommended option	Bismuth quadruple (PBMT)	PPI + bismuth + metronidazole[a] + tetracycline
Recommended option	Concomitant nonbismuth quadruple (PAMC)	PPI + amoxicillin + metronidazole[a] + clarithromycin
Restricted option[b]	PPI triple (PAC, PMC, or PAM)	PPI + amoxicillin + clarithromycin PPI + metronidazole[a] + clarithromycin PPI + amoxicillin + metronidazole[a]
Not recommended	Levofloxacin triple (PAL)	PPI + amoxicillin + levofloxacin
Not recommended	Sequential nonbismuth quadruple (PA followed by PMC)	PPI + amoxicillin followed by PPI + metronidazole[a] + clarithromycin
Prior treatment failure		
Recommended option	Bismuth quadruple (PBMT)	PPI + bismuth + metronidazole[a] + tetracycline
Recommended option	Levofloxacin-containing therapy (usually PAL)	PPI + amoxicillin + levofloxacin[c]
Restricted option[d]	Rifabutin-containing therapy (usually PAR)	PPI + amoxicillin + rifabutin
Not recommended	Sequential nonbismuth quadruple therapy (PA followed by PMC)	PPI + amoxicillin followed by PPI + metronidazole[a] + clarithromycin
Undetermined	Concomitant nonbismuth quadruple therapy (PAMC)	PPI + amoxicillin + metronidazole[a] + clarithromycin

[a] Tinidazole may be substituted for metronidazole.
[b] Restricted to areas with known low clarithromycin resistance (<15%) or proven high local eradication rates (>85%) (see statement 5).
[c] There is some evidence that adding bismuth to this combination may improve outcomes.
[d] Restricted to cases in which at least 3 recommended options have failed (see statement 13).

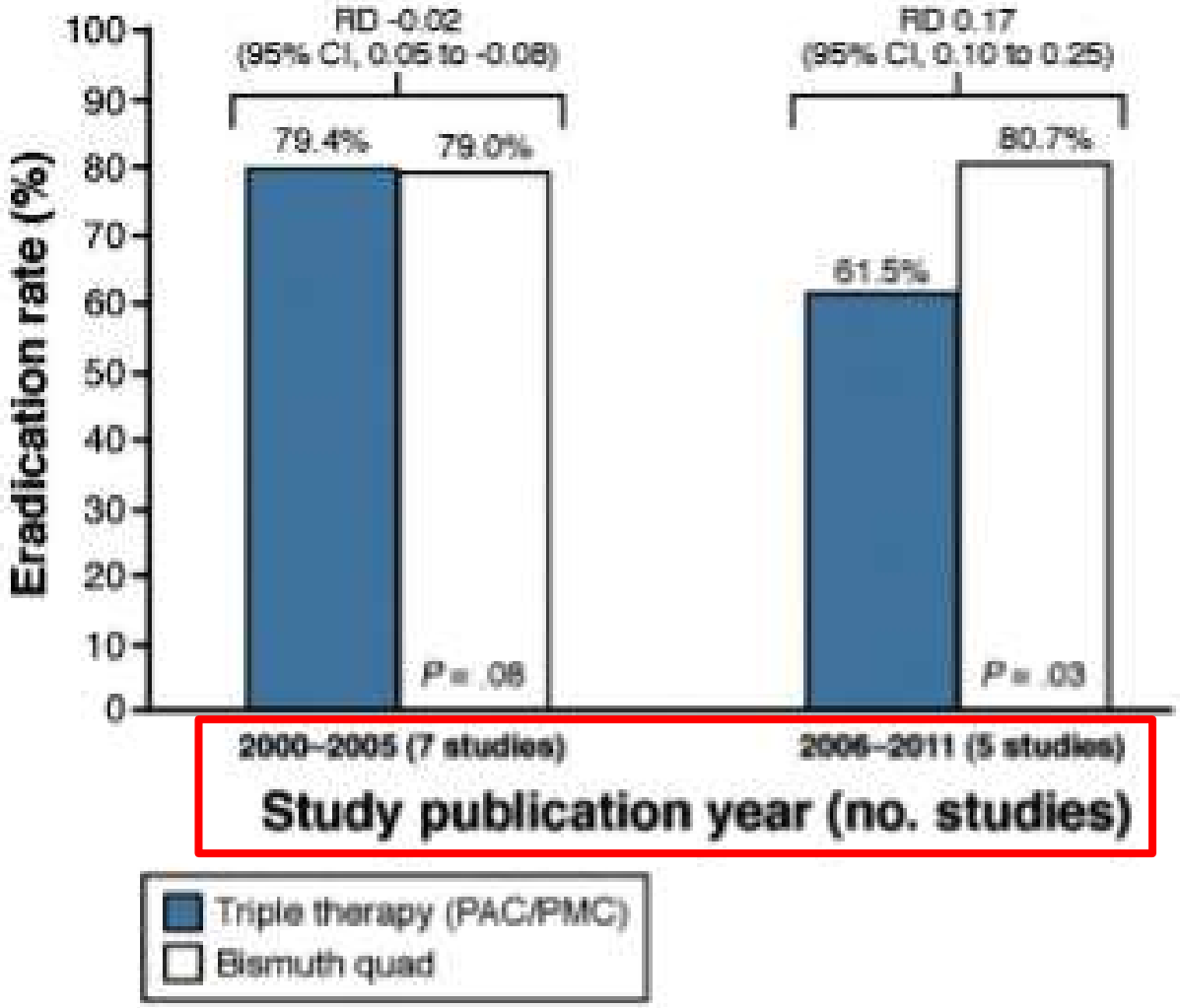


Figure 1. Pooled successful eradication (ITT) in subgroup analysis according to year of study publication. Based on data from a meta-analysis by Venerito et al.[22] RDs are shown as proportions rather than percentages.

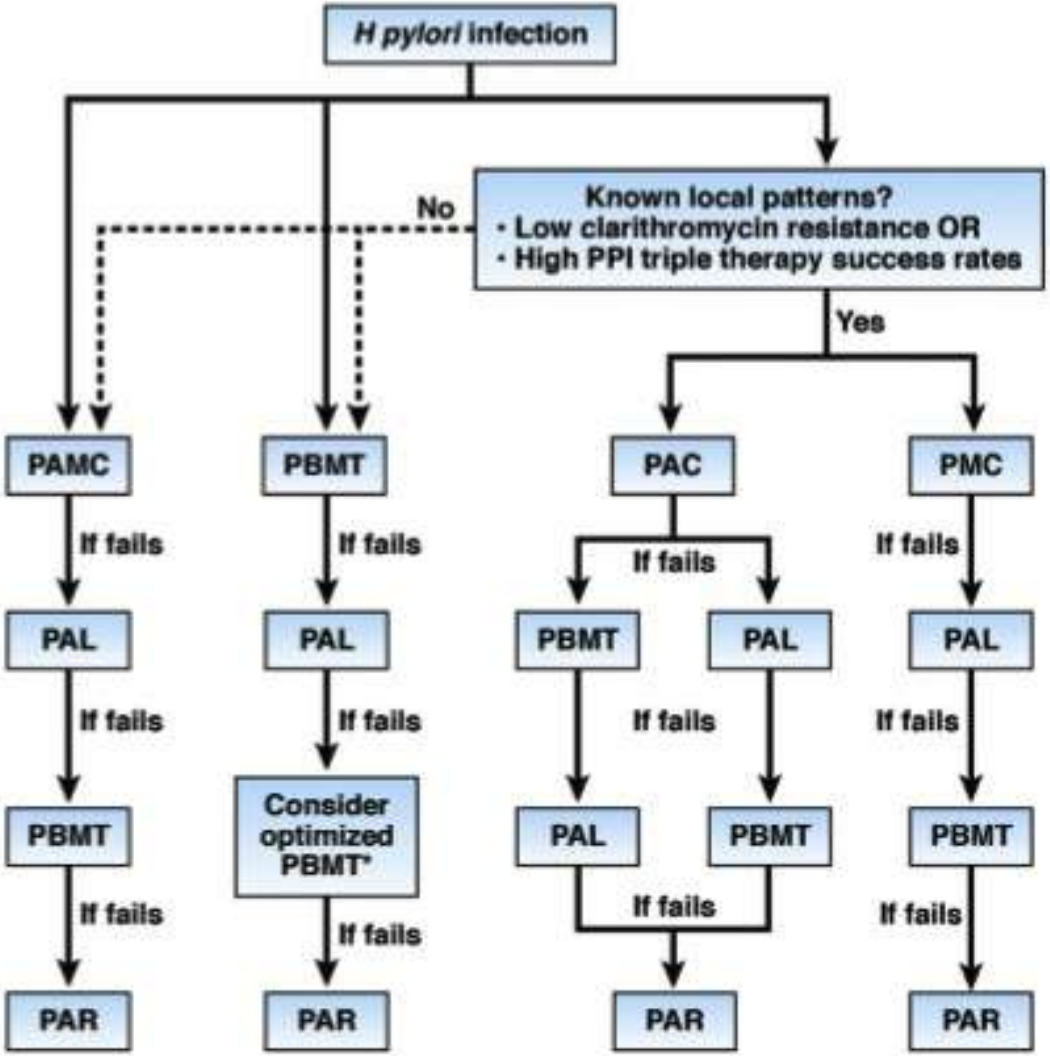


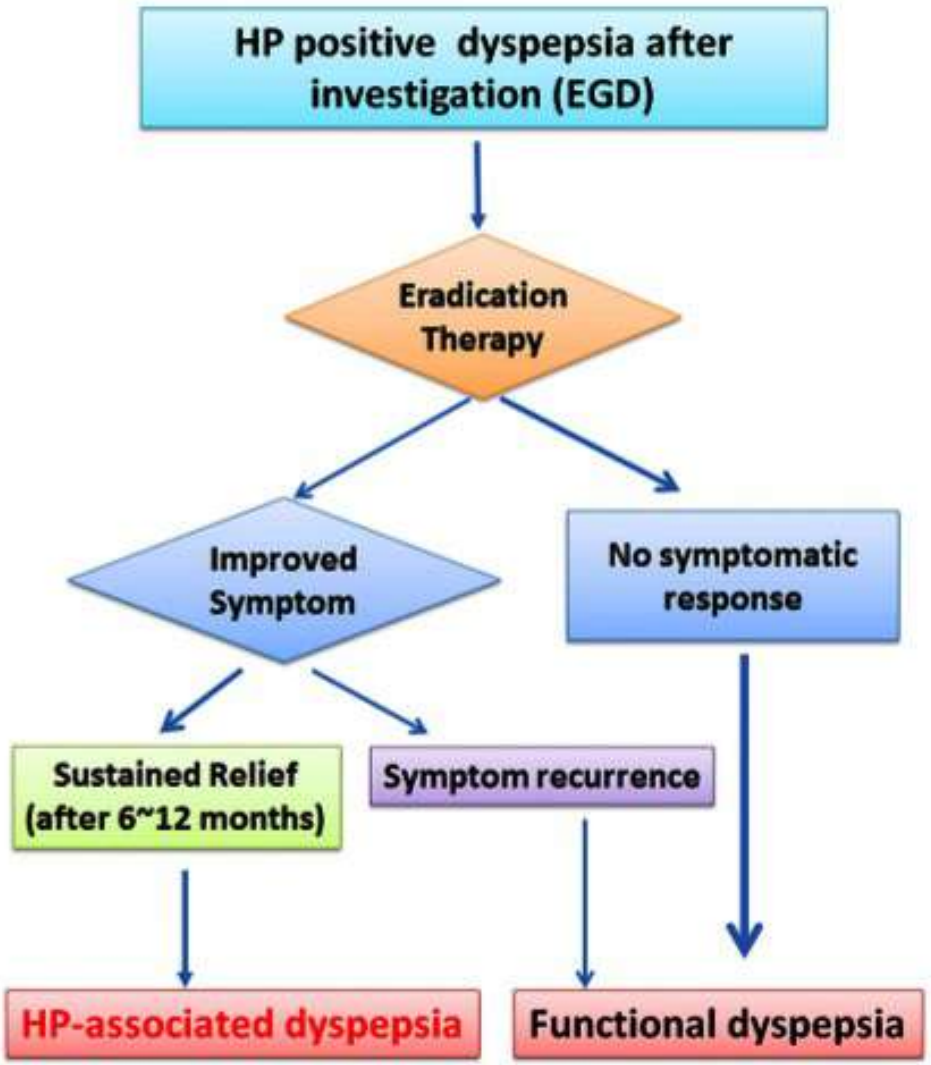
Figure 3. Algorithm for eradication therapies for first-line and rescue treatments. *Some members of the consensus group advocated against the repeat use of PBMT, whereas others suggested it may be useful to reserve rifabutin for fourth-line use (see statement 8). Optimized refers to using a higher dose of PPI or metronidazole. See Tables 1 and 2 for more details on regimens and dosing.

Gut Online First, published on July 23, 2015 as 10.1136/gutjnl-2015-309252

OPEN ACCESS

Kyoto global consensus report on *Helicobacter pylori* gastritis

Kentaro Sugano,[1] Jan Tack,[2] Ernst J Kuipers,[3] David Y Graham,[4] Emad M El-Omar,[5] Soichiro Miura,[6] Ken Haruma,[7] Masahiro Asaka,[8] Naomi Uemura,[9] Peter Malfertheiner,[10] on behalf of faculty members of Kyoto Global Consensus Conference



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Section 4 Management of gastritis

CQ17. Should all *H. pylori*-positive individuals receive eradication therapy?

Statement 17

H. pylori infected individuals should be offered eradication therapy, unless there are competing considerations.

Grade of recommendation strong

Evidence level: high

Consensus level: 100%

Türkiye'de Helicobacter Pylori: Güncel Durum ve Tedavi Seçenekleri

- Son 10 yılda Metronidazol'e ve Klaritromisin'e karşı Hp 'nin direnç kazanması nedeniyle üçlü tedavide başarı oranı %80'lerin altına (%50-79) düşmüştür.
- Bu nedenle üçlü tedavinin; Klaritromisin direncinin %15-20'nin, Metronidazol direncinin de %40'ın altında olduğu toplumlarda ilk seçenek olarak kullanılması önerilirken,
- Direncin yüksek olduğu toplumlarda ise;
- Bizmut + PPI + iki antibiyotik,
- Bizmut temini mümkün değilse;
- PPI + üç antibiyotik içeren dörtlü tedaviler önerilmiştir.

H.PYLORİ İNFEKSİYONUNDA TEDAVİ (FİRST-LİNE TREATMENTS)

-Standart Üçlü Tedavi

PPI standart doz bid
Klaritromisin 500 mg bid
Amoksisilin 1 g bid
} 7 -14 gün, önerimiz 14 gün

-Bizmutlu Dörtlü Tedavi

PPI standart doz bid
Bizmut standart doz qid
Tetrasiklin 500 mg qid
Metronidazol 250 mg qid
} 10-14 gün

-Hibrid Tedavi

İlk yedigün;

PPI standart doz bid

Amoksisilin 1 g bid

İkinci yedigün;

PPI standart doz bid

Amoksisilin 1 g bid

Klaritromisin 500 mg bid

Metronidazol 500 mg bid

(bid=2x1, qid=4x1, qd=1x1, tid=3x1)

-Ardışık Tedavi

İlk 5 gün;

PPI standart doz bid

Amoksisilin 1 g bid

İkinci 5 gün;

PPI standart doz bid

Klaritromisin 500 mg bid

Metronidazol 500 mg bid

-Bizmutsuz Dörtlü Tedavi

PPI standart doz bid
Klaritromisin 500 mg bid
Amoksisilin 1 g bid
Metronidazol 500 mg bid
} 7-10 gün

-Levofloksasin'li Üçlü Tedavi

PPI standart doz bid
Levofloksasin 500 mg qid
Amoksisilin 1 g bid
} 10 gün

H.PYLORİ İNFEKSİYONUNDA TEDAVİ (SECOND-LİNE TREATMENTS)

- Levofloksasin'li Üçlü Tedavi

PPI standart doz bid
Levofloksasin 500 mg bid } 10 gün
Amoksisilin 1 g bid

-Bizmutlu Dörtlü Tedavi

PPI standart doz bid
Bizmut standart qid
Tetrasiklin 500 mg qid } 14 gün
Metronidazol 500 mg tid

-Levofloksasin'li Ardışık Tedavi

İlk beş gün;
PPI standart doz bid
Amoksisilin 1 g bid
İkinci beş gün;
PPI standart doz bid
Levofloksasin 250 mg bid
Amoksisilin 1 g bid

-Furazolidon'lu Dörtlü Tedavi

PPI standart doz bid
Tripotasyum dicitrato bismuthat 240 mg bid } 7 gün
Furazolidon 200 mg bid
Tetrasiklin 1 g bid

Second-line “Rescue therapy”

?

– Ardışık Tedavi ise; (5+5 → 7+7)
  - PPI dozu → 4 x 1
  - Amoksisilin 500 mg 4 x 1

  - PPI dozu → 4x1
  - Bizmut standart 300 mg (4x1)
  - Tetracycline 500 mg x 4
  - Metronidazole yüksek dozlarda (örn. 500 mg x 3)

H.PYLORİ İNFEKSİYONUNDA TEDAVİ (THİRD-LİNE TREATMENTS)

-Dörtlü tedavi;

PPI standart doz bid
Bizmut subsitrat 300 mg qid
Amoksisilin 500 mg qid
Levofloksasin 500 mg qid
} 14 gün

-Rifabutin'li üçlü tedavi;

PPI standart doz bid
Rifabutin 150 mg bid
Amoksisilin 1 g bid
} 14 gün

Türkiye'de H.Pylori eradikasyonunda ilk seçenek tedavi olarak önerilerimiz:

1) Bizmutlu dörtlü tedavi (PPI + Bizmut + İkili antibiyotik)
2) Bizmutsuz dörtlü tedavi (PPI + Üç antibiyotik)
3) Yüksek doz PPI (4X1) + Amoksisilin 500 mg (4x1)
   Klaritromisin 500 mg (2x1) + Metranidazol 500 mg (3x1)

Bizmut tuzları

- H. Pylori'ye karşı bakterisidal etki gösterir.
- Tek başına kullanıldığı zaman eradikasyon oranı %10-27,
- Üreaz, fosfolipaz ve proteolitik aktiviteyi inhibe ederler,
- Dili ve gaytayı geçici olarak siyaha boyarlar,
- Mukozal bikarbonat ve prostaglandin sekresyonunu arttırır.
- Uzun süre kullanıldığı zaman nörotoksisite ,
- KBY'de dikkatli kullanım önerilmektedir.

Bizmut tuzları

Gastroenterolojide kullanılan bizmut tuzları

Bizmut Bileşiği	Endikasyon
Bizmut subnitrat	İrritabl barsak sendromu, mide hastalıkları, kabızlık
Bizmut subgallat	Gaita'yı şekillendirmek, kokusunu gidermek için, ileostomide
Bizmut fosfat	Değişik gastrointestinal hastalıklar
Aluminat	
Subkarbonat	
Bizmut subsalisilat	Turist diyaresi (Prevantif), dispepsi, *Hp*
Kolloidal bizmut subsitrat	Peptik ülser hastalığı, fonksiyonel dispepsi, *Hp*
Ranitidin bizmut sitrat	Peptik ülser hastalığı, dispepsi, *Hp*

Bizmut tuzlarının bakterisidial etki mekanizmaları

- Bakteri duvarı ve periplazmik alanda kompleks oluşturması
- *Hp* enzimleri (üreaz, katalaz, lipaz, fosfolipaz) inhibe etmesi
- ATP sentezini inhibe etmesi
- *Hp*'nin epitele yapışmasına mani olması

H. Pylori eradikasyonunda başarısızlığa neden olan faktörler:

1) H. Pylori'nin antibiyotiklere karşı direnç kazanımı
2) CYP2C19 genetik polimorfizmi
3) Tedavi süresinin uygun olmaması
4) İlaçların düzenli kullanılmaması
5) Tedavi protokolünün iyi hazırlanmaması
6) H. Pylori eradikasyon tedavisindeki başarının değerlendirilmesinde yapılan hatalar (Pseudo-eradikasyon)

H.Pylori eradikasyon tedavisinin başarılı olup olmadığı kontrol edilmesi gereken durumlar:

1) Peptik Ülser olguları,
2) Geçirilmiş GİS kanaması ve perforasyon hikayesi olan olgular,
3) MALT'oma,
4) Mide Ca nedeniyle mide ameliyatı olanlar,
5) Birinci derece yakınlarında mide kanseri olanlar,
6) Preneoplastik lezyon saptanan olgular.

H. Pylori'de yeni tedavi yaklaşımları:

- Lipozomal Linoleik Asit (Lipo LLA)
- Sentetik antimikrobiyal peptid Pexiganan
- Probiyotikler
- Phytomedicine (Kekik yağı, tarçın, karanfil yağı)
- N-Asetil sistein, capsaicin, red ginseng
- Yeşil çay, Kırmızı şarap
- Fotodinamik tedavi
- Aşı (Üreaz'a karşı preventif aşı → Etkinlik %71,8) (Çin)
- Baskılanmış T hücre yanıtının yeniden immünizasyon ile ortaya çıkarılması (Almanya)


Bittin Sen!

Helicobacter pylori'nin Ülser,

Kronik İnflamasyonu ve Karamaya Usulü Elde Edilen Kefir ile Tedavisi

Oxidative Stress in *Helicobacter pylori* Infection: Does Supplementation with Vitamins C and E Increase the Eradication Rate?

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Issue

Helicobacter

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Abstract

Aim: This study aims to assess the antioxidant property of vitamins E and C in *Helicobacter pylori* infection, and to determine if adding them to standard triple therapy plus bismuth subcitrate increases the *H. pylori* eradication rate.

Methods: This study included 160 patients infected with *H. pylori*, who were randomized into one of two groups. Patients in group A (n = 80) received lansoprazole (30 mg, b.i.d.), amoxicillin (1000 mg, b.i.d.), clarithromycin (500 mg, b.i.d.), and bismuth subcitrate (300 mg, q.i.d.) for 14 days, while patients in group B (n = 80) received vitamin C (500 mg, b.i.d.) and vitamin E (200 IU, b.i.d.) for 30 days, in addition to lansoprazole (30 mg, b.i.d.), amoxicillin (1000 mg, b.i.d.), clarithromycin (500 mg, b.i.d.), and bismuth subcitrate (300 mg, q.i.d.) for 14 days. Total antioxidant capacity (TAC) was evaluated with a Randox kit. Success rate was calculated using both intention-to-treat (ITT) and per-protocol (PP) analyses.

Results: One hundred and sixty patients were analyzed using ITT analysis. One hundred and fifty-three patients completed the study. In group A, *H. pylori* eradication was achieved in 48 (60%) of the 80 patients included in the ITT analysis, and in 48 (64%) of the 75 patients included in the PP analysis. In group B, *H. pylori* eradication was achieved in 73 (91.25%) of the 80 included in the ITT analysis and in 73 (93.5%) of the 78 patients included in the PP analysis. The eradication rate was significantly higher in group B than in group A ($p < .005$). TAC was at the lower limit of normal in both groups and the difference between them was not statistically significant ($p > .05$).

Conclusion: In group B, *H. pylori* eradication rate was 91.25%, which is higher than the ideal 80% eradication rate. The results of the present study show that adding the prescribed doses of vitamins E and C to antimicrobial therapy is effective in eradicating *H. pylori* infection

Turk J Gastroenterol *2015; 26: 456-60*

Influence of vitamin C and E supplementation on the eradication rates of triple and quadruple eradication regimens for *Helicobacter pylori* infection

STOMACH

Hakan Demirci[1], Sevil Uygun İlikhan[2], Kadir Öztürk[1], Yücel Üstündağ[3], Ömer Kurt[1], Muammer Bilici[2], Furuzan Köktürk[4], Ahmet Uygun[1]

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ABSTRACT

Background/Aims: In our study, we aimed to assess the effect of vitamin E and C supplementation to triple and quadruple *Helicobacter pylori* eradication regimens.

Materials and Methods: Four hundred patients with *H. pylori* infection were classified into four groups. Patients in group A (n=100) received amoxicillin, clarithromycin, and lansoprazole for 2 weeks. In group B, patients (n=100) received vitamins C and E for a month, in addition to amoxicillin, clarithromycin, and lansoprazole for 2 weeks. Patients in group C (n=100) received amoxicillin, clarithromycin, lansoprazole, and bismuth subcitrate for 2 weeks, whereas those in group D (n=100) received vitamins C and E for a month, in addition to amoxicillin, clarithromycin, lansoprazole, and bismuth subcitrate for 2 weeks. *H. pylori* eradication was assessed with the C14 urea breath test 2 months after the end of the therapy. The eradication rate was assessed using per-protocol (PP) and intention-to-treat (ITT) analyses.

Results: Three hundred forty-eight patients finished the study. The eradication of *H. pylori* was achieved in 63 of 84 patients (75%) by PP and 63 of 100 (63%) by ITT analysis in group A, 60 of 84 (71.4%) by PP and 60 of 100 (60%) by ITT analysis in group B, 72 of 89 (80.9 %) by PP and 72 of 100 (72%) by ITT analysis in group C, and 76 of 91 (83.5%) by PP and 76 of 100 (76%) by ITT analysis in group D. There was no remarkable change between groups A and B ($p>0.05$). Similar results were also found between groups D and C ($p>0.05$).

Conclusion: This study revealed that supplementing vitamins C and E to either the triple or quadruple therapies did not provide an additional advantage for achieving significantly higher eradication rates for *H. pylori*.

Keywords: *Helicobacter pylori*, eradication rate, bismuth subcitrate, vitamins E and C

Use of probiotics as an adjuvant to sequential *H. pylori* eradication therapy: impact on eradication rates, treatment resistance, treatment-related side effects, and patient compliance

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ABSTRACT

Background/Aims: To evaluate the effect of probiotics administered as an adjuvant to sequential *Helicobacter pylori* (*H. pylori*) eradication therapy on treatment outcome and patient compliance.

Materials and Methods: In total, 159 patients with *H. pylori* infection receiving sequential *H. pylori* eradication therapy were included in this randomized placebo-controlled study. Starting from day 0 of sequential eradication therapy (ERA), patients in the ERA+probiotic group [n=53, mean (SD) age: 47.7 (14.0) years, 54.7% were females] also received a probiotic supplement with *Bifidobacterium animalis subsp. lactis B94* (1 capsule/day), patients in the ERA+placebo group [n=52, mean (SD) age: 46.4 (13.4) years, 51.9% were males] received placebo treatment (1 capsule/day), and patients in the ERA-only group [n=54, mean (SD) age: 46.3 (11.9) years, 55.6% were females] received no additional treatments. Eradication rates, patient compliance, and side effects of eradication therapy were recorded in each treatment group.

Results: Significantly higher eradication rates were noted in the ERA+probiotic group (86.8% vs. 70.8%, p=0.025) than in the combined ERA (ERA-only and ERA-placebo) group. Non-compliance with anti-*H. pylori* treatment was noted in 24 (15.1%) of 159 patients. Lower rates of first week treatment non-compliance due to diarrhea (1.88% vs. 12.26%, p=0.036) were noted in the ERA+probiotic group than in the combined ERA (ERA-only and ERA-placebo) group. Treatment resistance (p: 0.389) was similar between the groups, indicating pure antibiotic resistance without any compliance problems. The number needed to treat for an additional beneficial outcome (NNTB) was 6.2 (CI 95%, 3.5 to 28.9) for probiotic use.

Conclusion: In conclusion, adjuvant administration of probiotic (*B. animalis subsp. lactis*) in 2-week sequential *H. pylori* eradication therapy is associated with a higher *H. pylori* eradication rate, lower first week diarrhea-related treatment discontinuation rates, less common self-reported side effects, and higher treatment compliance.

Keywords: *H. pylori*, eradication, sequential therapy, probiotics, side effects, patient compliance

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REVIEW GASTROENTEROLOGY

Helicobacter pylori treatment in Turkey: Current status and rational treatment options

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ABSTRACT

According to the TURHEP study, the prevalence of *Helicobacter pylori* in Turkey is 82.5%. After FDA approval in 1995, many countries have used standard triple therapy (proton pump inhibitor 40 mg b.i.d clarithromycin 500 mg b.i.d and amoxicillin 1 gr b.i.d) for *Helicobacter pylori* treatment. In the beginning, eradication rates were above 90% in many countries; however, current studies have demonstrated a prominent decrease in successful treatment rates, even down to 60%. This unfavorable reduction stimulated searches for new treatment protocols. Treatment protocols differ according to country, prevalence, cost-effectiveness, antibiotic resistance, CYP2C19 polymorphism and eradication rates. Thus, each country/region needs to revise its own therapeutic results and the efficacy of various eradication regimens in the treatment of *Helicobacter pylori*. This report aims to review the current status of *Helicobacter pylori* treatment in Turkey and to provide recommendations for rational therapeutic considerations for the eradication of the bacterium.

Keywords: Eradication; Helicobacter pylori; proton pump inhibitors; Turkey.

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TABLE 4. Recommendations of classical treatment protocols in case of high clarithromycin resistant patients

First-line treatment	Quadruple treatment containing bismuth* If not possible, sequential or quadruple (without bismuth) therapy
Second-line treatment	Levofloxacin triple therapy (attention to increasing levofloxacin resistance)
Third-line treatment/ rescue treatments	Treatment according to antimicrobial susceptibility and culture results
Penicillin allergy	Bismuth quadruple therapy

*Tetracycline resistance is rare, metranidazole resistance is widespread but can be overcome by prolonging the treatment duration.

TABLE 5. New and experimental approaches for the treatment of HP

Liposomal Linoleic Acid (Lipo LLA)
Synthetic antimicrobial peptide; Pexiganan
Probiotics
Phytomedicine (thyme oil, cinnamon, clove oil)
N-Acetyl cysteine, capsaicin, red ginseng
Green tea, red wine
Photodynamic therapy
Vaccination (preventive vaccination against urease → efficacy 71.8%) (China)
Re-immunization of suppressed T cell response (Germany)

TABLE 6. Hp eradication rates in different CYP2C19 genotypes

Treatment	Eradication rate		
	Fast metabolizing (%)	Moderate metabolizing (%)	Slow metabolizing (%)
Dual therapy; PPI + Amoxicillin	50	64	97
Triple therapy; PPI + Amoxicillin + Clarithromycin	76	89	90
Quadruple therapy; PPI + Amoxicillin + Clarithromycin + Metronidazole	80	98	100

TABLE 1. Indications for *H. Pylori* treatment

Conditions requiring treatment:

1. Duodenal or gastric ulcer (without activity or complication)
2. MALT-lymphoma (gastric)
3. Atrophic gastritis
4. Story of previous gastric surgery
5. Gastric cancer in first-degree relatives
6. If the patient him/herself wants Hp eradication therapy

Conditions where treatment can be recommended:

1. Dyspepsia patients
2. Gastroesophageal reflux disease patients
3. NSAID users
4. Idiopathic thrombocytopenia
5. Unexplained anemia of iron deficiency
6. Other controversial extragastric conditions (such as IHD, DM)

TABLE 2. Drugs which are used in Hp treatment

Antibiotics
Amoxicillin (A) 2X1000 mg
Clarithromycin (K) 2X500 mg
Metranidazole (M) 3X500 mg
Tetracycline (T) 4X500 mg
Levofloxacin (L) 1X500 mg
Tinidazole (Ti)
Doxycycline (D)
Furazolidone (F)
Rifabutin (R)
PPIs
Omeprazole (O)
Lansaprazole (L)
Pantoprazole (P)
Esomeprazole (E)
Rabeprazole (R)
Bismuth salts (4X1)
Ranitidine bismuth citrate
Colloid bismuth citrate
Bismuth subsalicylate

PPIs: Proton pump inhibitors.

TABLE 3. European Medicines Agency recommendation for antibiotic sensitivity and Hp resistance rates (%)

European Medicines Agency recommendation for antibiotic sensitivity:

Generally sensitive	<10
Rarely sensitive	10–50
Usually resistant	>50

Clarithromycin is important for areas with the resistance of less than 20%; primary treatment can still be applied as a classical 3-drug therapy.

Resistance rates in Hp treatment:

Clarithromycin	Approximately 40–50
Levofloxacin	41
Metronidazole	50–76
Amoxycillin	0.5–1.1

TABLE 7. Recommendations for HP eradication

1) Bismuth quadruple therapy (PPI + Bismuth + Two antibiotics)*
2) Bismuth-out quadruple therapy (PPI + Three antibiotics)
3) High dose PPI (4X1) + Amoxicillin 500 mg (4x1) + Tetracycline 500 mg (3 x 1) + Metronidazole 500 mg (3 x 1)

First-line therapy:	**Bismuth containing quadruple therapy** Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Colloidal bismuth subcitrate 300 mg tb 4x1 Tetracycline 500 mg tb 4x1 Metronidazole 500 mg tb 3x1	**OR Sequential treatment without bismuth** 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1, 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Tetracycline 500 mg tb 4x1 Metronidazole 500 mg tb 3x1
Second-line therapy:	**Concomitant (without bismuth) quadruple therapy:** Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Metronidazole 500 mg tb 3x1 Clarithromycin 500 mg tb 2x1	**OR Hybrid therapy:** 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Clarithromycin 500 mg tb 2x1 Metronidazole 500 mg tb 3x1
Third-line therapy	**Levofloxacin Bismuth containing quadruple therapy:** Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Colloidal bismuth subcitrate 300 mg tb 4x1 Amoxicillin 750 mg tb 3x1 Levofloxacin 500 mg tb 2x1	**OR Sequential treatment with levofloxacin:** 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Levofloxacin 500 mg tb 2x1
Fourth-line therapy	**Culture + Treatment should be arranged according to antibiogram result**	**OR 14 days;** Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Rifabutin 150 mg tb 2x1 **OR 7 days;** Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Colloidal bismuth subcitrate 300 mg tb 4x1 Tetracycline 500 mg tb 4x1 Furazolidone 200 mg tb 2x1

Modified quadruple therapy or bismuth-containing quadruple therapy in the first-line treatment of *Helicobacter pylori* in Turkey

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ABSTRACT

Aim: *Helicobacter pylori (H. pylori)* eradication is still an important issue in countries with high antibiotic resistance. This study aimed to compare the efficacy and safety of two bismuth-containing treatment modalities in *H. pylori* treatment in Turkey.

Material and methods: subjects with *H. pylori* infection who were treated with either bismuth-containing quadruple therapy (pantoprazole 40 mg bid, tetracycline 500 mg qid, metronidazole 500 mg tid, bismuth subcitrate 262 mg qid daily) (BQT group) or modified quadruple therapy (pantoprazole 40 mg bid, amoxicillin 1g bid, metronidazole 500 mg tid, bismuth subcitrate 262 mg qid daily) (MBQT group) for 14 days were compared, retrospectively. The eradication success rate, adverse events related to the medications and compliance were investigated.

Results: a total of 128 patients in the BQT group and 102 patients in the MBQT group completed the treatment. The overall rate of adverse events was significantly higher in the BQT group compared with the MBQT group (39.4 % *vs* 18.6; p: 0.001). Among the adverse events, nausea-vomiting and abdominal discomfort was significantly more frequent in the BQT group than in the MBQT group (p: 0.001). The adverse events were mild-moderate in both groups and life threatening adverse events were not present in any of the patients.

Conclusion: although both regimens were highly effective and safe in *H. pylori* eradication, both intention-to-treat (ITT) and per-protocol (PP) eradication rates were higher and adverse events were lower in the modified quadruple therapy group. Modified quadruple therapy should be kept in mind for the first-line treatment of *H. pylori* in regions with high clarithromycin and metronidazole resistance.

Keywords: *H. pylori*. Quadruple therapy. First-line treatment.

INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacterium. More than 50 % of the world population is affected by this pathogen, which causes a public health problem worldwide. The International Agency for Research on Cancer classified *H. pylori* as a carcinogen because it is associated with peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma (1,2). Due to the increased prevalence of antimicrobial resistance of *H. pylori,* eradication success rates with standard treatment regimens have fallen worldwide (3-5).

In the Maastricht V Consensus Conference report, bismuth-containing quadruple treatments are suggested as the best alternative first-line treatment in populations with dual clarithromycin and metronidazole resistance higher than 15 % (6). In recent studies, bismuth add-on regimens were defined as the most effective in the first line treatment of *H. pylori* infection (7).

Helicobacter

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The Modified Sequential Treatment Regimen Containing Levofloxacin for *Helicobacter pylori* Eradication in Turkey

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Keywords
Helicobacter pylori, sequential, levofloxacin, eradication.

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Abstract

Background: Eradication rates of *Helicobacter pylori* have declined to unacceptable levels in recent years. New and effective treatment options are warranted both as a first and second line treatment.

Aim: To test an effectiveness of modified sequential therapy with levofloxacin for *H. pylori* eradication in Turkey.

Material and Methods: *Helicobacter pylori* infected dyspeptic patients were included to the study. Subjects were treated with modified sequential therapy consisting of rabeprazole 20 mg b.i.d. and amoxicillin 1 g b.i.d., for 7 days followed by rabeprazole 20 mg b.i.d, levofloxacin 500 mg q.d. and metronidazole 500 mg b.i.d for the remaining 7 days.

Results: Sixty-three treatment naive patients and 37 previous treatment failures were enrolled to the study (59 F, 41 M, age: 21–80 years). There was five drop out. *Helicobacter pylori* eradication was achieved in 80 patients, intention-to-treat (ITT): 80% (95% CI: 71–87%) and per-protocol (PP): 84.2% (95% CI: 75–91%), totally. In treatment naive patients ITT and PP eradication rates were 82.5% (95% CI: 71–91%), and 86.7% (95% CI: 75–94%), respectively. As a second line treatment eradication was successful in ITT 75.7%.(95% CI: 59–88%), and PP 80% (95% CI: 63–92%).Mild side effects were reported by 8 patients (8.4%).

Conclusions: Sequential therapy using ''rabeprazole and amoxicillin 7 days followed by rabeprazole, metronidazole and levofloxacin for 7 days'' is a new regimen with acceptable eradication rates in naïve patients in Turkey. Further modifications in the dose or duration of this new sequential therapy might increase its effectiveness as both first and second line treatment.

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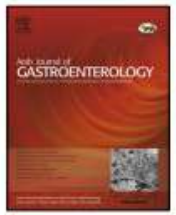

Original article

Therapeutic success with bismuth-containing sequential and quadruple regimens in *Helicobacter pylori* eradication

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ABSTRACT

Background and study aims: The success rate of *Helicobacter pylori* (*H. pylori*) eradication with the classical triple therapy is gradually declining. In this study, we aimed to compare and assess the efficacies of six different eradication regimens including sequential protocols.

Patients and methods: Endoscopically confirmed nonulcer dyspepsia patients were enrolled. *H. pylori* presence was determined either histologically or by a rapid urease test. Treatment-naive patients were randomly assigned to an either one of three 10-day (OAC, OTMB, and OACB) or one of three sequential protocols (OA + OCM, OA + OCMB, and OA + OMDB) (O = omeprazole, A = amoxicillin, C = clarithromycin, T = tetracycline, M = metronidazole, B = bismuth, D = doxycycline). The eradication was assessed 6–8 weeks after the completion of the treatment by a ^{14}C-urea breath test.

Results: In total, 301 patients were included. Fifty-two percent of the participants (n = 157) were female, and the mean age was 44.9 years (range = 18–70). The intention to treat (ITT) and per protocol (PP) eradication rate for each regimen is as follows: OAC (ITT = 61.2%, PP = 75%), OTMB (83.3%, 87%), OACB (76.5%, 79.6%), OA + OCM (72.3%, 73.9%), OA + OCMB (82.7%, 89.6%), and OA + OMDB (59.3%, 65.3%). Smoking significantly affected the eradication rate ($P = 0.04$).

Conclusion: In this study, OTMB and OA + OCMB were significantly superior to the triple therapy and succeeded to reach the eradication rate proposed by the Maastricht consensus (over 80%). These two bismuth-containing regimens could be considered for first-line therapy in the regions with high clarithromycin resistance.

Can the treatment duration be shortened in bismuth-containing therapies for Helicobacter pylori eradication?

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ABSTRACT

Background/Aims: The duration of Helicobacter pylori (H. pylori) eradication therapy as a range (e.g., 10–14 days) is an ignored problem. There is no any particular treatment duration described in current guidelines, and the conditions for when to use 10-day therapy vs. 14-day therapy have not been elucidated. The aim of this study is to determine an effective and reliable H. pylori treatment duration in clinical practice. There were four different treatment modalities administered to groups, and success rates were compared.

Materials and Methods: Patients were eligible to participate in the study if they had a biopsy-proven H. pylori infection. Each patient was randomly assigned to one of the four treatment groups according to a predetermined sequence: 14-day or 10-day bismuth-containing quadruple therapy (BQT) groups and 14-day or 10-day moxifloxacin-bismuth-combined treatment (MBCT) groups.

Results: A total of 216 patients (54 per group) were enrolled. Two-hundred six patients (95.3%) completed therapy. There was no significant difference in the eradication rates between those patients who received 10- and 14-days BQT regimens (p=0.67). The 14-BQT protocol had the highest eradication rate, the MBCT regimes had the highest compliance, and the 10-MBCT protocol had the poorest results for H. pylori eradication. The posttreatment questionnaire on adverse effects identified nausea/vomiting as the most common side effect (35.7%).

Conclusion: Overall, the results of our study suggest that shortening the BQT protocol duration to 10 days does not weaken the H. pylori eradication rate. Moreover, quinolone-containing therapies with the lowest eradication rate among the groups should not be offered as a salvage treatment in case of the BQT failure.

Keywords: Eradication rate, Helicobacter pylori, treatment duration

Standard triple therapy in Helicobacter pylori *eradication in Turkey: Systematic evaluation and meta-analysis of 10-year studies*

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ABSTRACT

Background/Aims: This study aims at evaluating the mean eradication rate by a systematic compilation of the studies which involved the standard triple therapy (STT) in first-line Helicobacter pylori (Hp) eradication in Turkey over a period of 10 years between 2004 and 2013 using the meta-analysis method.

Materials and Methods: The systematic compilation and meta-analysis were carried out according to the PRISMA standards defined in the Cochrane handbook. The results of full-text studies published in national and international journals in English and Turkish languages on Turkish population in a period of 10 years, from 2004 to 2013, are included in this study. The studies include open-label trials, controlled trials, treatment arms, and case series that included a triple therapy regimen consisting of standard doses of a proton pump inhibitor (PPI; omeprazole 20 mg BID, lansoprazole 30 mg BID, pantoprazole 40 mg BID, esomeprazole 40 mg BID, or rabeprazole 20 mg BID) along with clarithromycin 500 mg BID and amoxicillin 1 g BID for 7-14 days. They were scanned electronically via the search engines Google Scholar, PubMed, and the Turkish Medicine Index using specific keywords. The related keywords used were Turkey, Helicobacter pylori, infection, standard triple treatment, first-line therapy, eradication, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, clarithromycin, and amoxicillin. Studies carried out with adults were included in the evaluation. The publication year of the studies and the included number of patients, their age, gender, treatment duration (7, 10, and 14 days), and PPIs used were evaluated by two separate gastroenterologists and biostatisticians. Studies that used at least one reliable method (histology, urea breath test (UBT), or Helicobacter pylori stool antigen (HpSA) test) four weeks after completing the treatment for the control of Hp eradication were included. Only naive patients were accepted, and patients who had previously received eradication treatment were excluded. The effectiveness of the Hp eradication was analyzed using an intention-to-treat (ITT) or per-protocol (PP) analysis.

Results: The STT regime of 45 studies complying with the inclusion criteria was evaluated. A total of 3715 patients were included in the study. Of the 3010 patients whose gender information was available, 55% were women and 45% were men; the weighted age average given explicitly in the studies was 42.14±0.67. The treatment lasted for 14 days in 42 studies, for 7 days in six studies, and for 10 days in 1 study. The eradication rates evaluated according to the ITT and PP analyses were 60% (95% CI: 56%-63%) and 57% (95% CI: 51%-62%), respectively. The rates for 7 days of treatment were 57% (95% CI: 46%-68%) and 60% (95% CI: 51%-67%) and for 14 days of treatment were 60% (95% CI: 56%-63%) and 56% (95% CI: 50%-62%), respectively. The ITT eradication rate of the only 10-day study was 78% (95% CI: 66%-86%). In the meta-regression analysis, the treatment duration, PPI, age, and gender ratio (women/men) used for the ITT analysis had no effect. The gender ratio and age were not considered in this analysis because they were not clearly stated in studies using the PP analysis. The duration of treatment and the PPI used had no effect.

Conclusion: A systematic meta-analysis of studies conducted during the period 2004-2013 in Turkey revealed that the rate of first-line Hp eradication using STT was unacceptably low, and the duration of treatment and PPI used made no difference.

Keywords: Turkey, Helicobacter pylori, infection, first-line therapy, standard triple treatment, eradication

Comparison of Sequential, Hybrid, and Quadruple Therapy Protocols in *Helicobacter pylori* Eradication: A Single-Center Study

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ABSTRACT

Objective: Many treatment protocols are used in *Helicobacter pylori* eradication treatment within the framework of factors such as antibiotic resistance, drug side effects, patient compliance, and regional differences.

Materials and Methods: *H. pylori* was diagnosed with upper gastrointestinal system endoscopic biopsy in the Internal Diseases Gastroenterology Endoscopy Unit of Atatürk University Medical Faculty Hospital; a total of 229 patients over the age of 18 were evaluated prospectively by dividing them into 3 groups and applying 3 different *H. pylori* eradication treatment protocols.

Results: A total of 229 patients who completed the treatment were included in the study. *H. pylori* eradication was achieved in 186 patients and not achieved in 43 patients. The *H. pylori* eradication success of our study was found to be 81.2%. Among the 84 patients in group 1, while *H. pylori* eradication was achieved in 67 of them, it was not achieved in 17 patients. The eradication success of quadruple treatment with bismuth was 79.8%. Also, among the 68 patients in group 2, while *H. pylori* eradication was achieved in 55 patients, it was not achieved in 13. The eradication success of the 14-day hybrid treatment was 80.9%. Among the 77 patients in group 3, while *H. pylori* eradication was achieved in 64 patients, it was not achieved in 13. The eradication success of the 10-day sequential treatment was 83.1%.

Conclusion: It is necessary to conduct studies to find the most successful eradication regimen in primary care treatment of *H. pylori* in our country, to determine the regional antibiotic resistance rates, to individualize the proton pump inhibitor treatment due to metabolism and resistance differences, to examine the factors that stop from achieving the desired eradication success, and especially to avoid unnecessary antibiotic use.

Keywords: *Helicobacter pylori* eradication, hybrid and quadruple therapy protocols

Digestive Diseases and Sciences
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ORIGINAL ARTICLE

Cost-Effectiveness of Empirical Bismuth-Based Quadruple Therapy and Tailored Therapy After Clarithromycin Resistance Tests for *Helicobacter pylori* Eradication

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Abstract

Background The eradication rate of clarithromycin-based standard triple therapy (STT) for Helicobacter pylori infection has decreased due to clarithromycin resistance (CR). We evaluated the cost-effectiveness of tailored therapy according to CR test results, and compared the results of STT with those of empirical bismuth quadruple therapy (BQT).

Methods The prospectively collected data of 490 *H. pylori*-positive patients with chronic gastritis or peptic ulcer disease were retrospectively analyzed. Among them, 292 patients underwent CR testing using dual-priming oligonucleotide-based polymerase chain reaction. The tailored group ($n=282$) consisted of patients treated with STT for 7 days and BQT for 10 days as per their CR test results. The remaining patients were assigned to the empirical group ($n=198$) and received BQT for 10 days without a CR test. The eradication rate, adverse events and medical costs associated with *H. pylori* eradication therapy were investigated.

Results In the tested patients (tailored group), the CR-positive rate was 32.2% ($n=94/292$). The eradication rate according to an intention-to-treat analysis was 87.7% in the tailored group and 91.8% in the empirical group ($P=0.124$); the respective rates were 94.4% and 97.9% by per-protocol analysis ($P=0.010$). The frequency of adverse events was lower in the empirical group than the tailored group (35.1% vs. 52.7%, $P<0.001$). Total per capita medical costs were $406.50 and $503.50, respectively.

Conclusions Ten-day empirical BQT was more effective, safer, and less expensive than tailored therapy based on a CR test for *H. pylori* eradication.

Keywords *Helicobacter pylori* · Clarithromycin · Bismuth · Cost-effectiveness · Resistance · Eradication

diseases

MDPI

Review

Overview of *Helicobacter pylori* Infection: Clinical Features, Treatment, and Nutritional Aspects

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Abstract: *Helicobacter pylori* (*H. pylori*) is a 0.5–1 µm wide, 2–4 µm long, short helical, S-shaped Gram-negative microorganism. It is mostly found in the pyloric region of the stomach and causes chronic gastric infection. It is estimated that these bacteria infect more than half of the world's population. The mode of transmission and infection of *H. pylori* is still not known exactly, but the faecal–oral and oral–oral routes via water or food consumption are thought to be a very common cause. In the last three decades, research interest has increased regarding the pathogenicity, microbial activity, genetic predisposition, and clinical treatments to understand the severity of gastric atrophy and gastric cancer caused by *H. pylori*. Studies have suggested a relationship between *H. pylori* infection and malabsorption of essential micronutrients, and noted that *H. pylori* infection may affect the prevalence of malnutrition in some risk groups. On the other hand, dietary factors may play a considerably important role in *H. pylori* infection, and it has been reported that an adequate and balanced diet, especially high fruit and vegetable consumption and low processed salty food consumption, has a protective effect against the outcomes of *H. pylori* infection. The present review provides an overview of all aspects of *H. pylori* infection, such as clinical features, treatment, and nutrition.

Keywords: *H. pylori*; nutrition; infection; diet; clinical treatment

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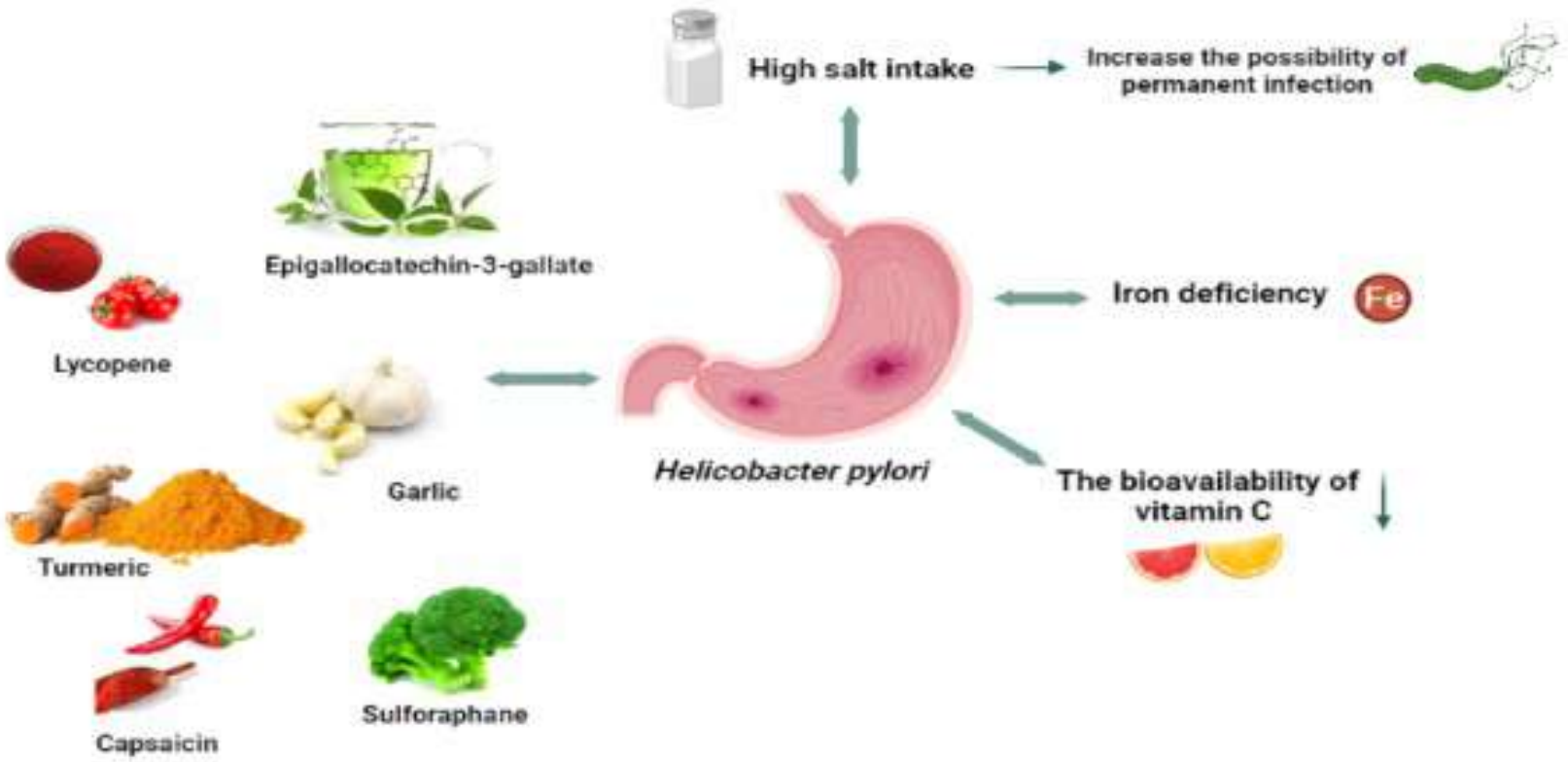
High salt intake
Increase the possibility of permanent infection
Epigallocatechin-3-gallate
Lycopene
Iron deficiency
Fe
Garlic
Helicobacter pylori
The bioavailability of vitamin C
Turmeric
Sulforaphane
Capsaicin

INTERNATIONAL DENTAL JOURNAL 71 (2021) 188–196

Concise Review

Periodontal Treatment Is Associated With Improvement in Gastric *Helicobacter pylori* Eradication: An Updated Meta-analysis of Clinical Trials

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ABSTRACT

Objectives: The efficacy of conventional systemic antibiotic therapy for eradication of *Helicobacter pylori* has been seriously challenged by antibiotic resistance. Identification of alternative therapeutic strategies might help to overcome this limitation. The aim of this study was to update previous meta-analyses that investigated the effect of periodontal treatment on gastric *H. pylori* eradication.

Methods: A systematic electronic search of the literature was conducted to identify all published clinical trials that compared the effect of adjunct periodontal treatment on conventional systemic *H. pylori* eradication therapy.

Results: The updated analysis (consisting of 541 participants representing six studies) demonstrated that, compared with conventional systemic eradication therapy alone, the addition of periodontal treatment resulted in improvements in gastric *H. pylori* eradication rates with OR 4.11 (P = 0.01). Moreover, not to lose any data, the previously presented Chinese results that could not be assessed by any available mechanism deduced from previously published meta-analysis and with other records were re-analysed. Similarly, the second meta-analysis adding up to a final cluster of 10 studies (909 participants) gives further credence to periodontal treatment as a useful concomitant therapy in the *H. pylori* eradication therapy (odds ratio [OR] = 2.65; P = 0.0002). Finally, the meta-analysis of four trials consisting of 177 cases and 161 controls showed that periodontal treatment also improved non-recurrence rates of gastric *H. pylori* infection, with an OR of 5.36 (P-value = 0.0002).

Conclusion: Although the inclusion of five additional clinical trials in this updated meta-analysis has not changed the result of the previous review, the current meta-analysis is superior for having removed one study involving the use of chlorhexidine, which did not meet appropriate criteria for inclusion. Our results strengthen the value of periodontal treatment as an adjunctive remedy. Consistency of these results suggests that the incorporation of professional periodontal treatment with systemic eradication therapy may be a wise strategy, enhancing the efficacy of *H. pylori* eradication therapy. Systematic review registration: in PROSPERO ID number: CRD42019119347.

frontiers in Oncology

ORIGINAL RESEARCH
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Hp-Positive Chinese Patients Should Undergo Colonoscopy Earlier and More Frequently: The Result of a Cross-Sectional Study Based on 13,037 Cases of Gastrointestinal Endoscopy

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Background: In China, the prevalence and mortality of colorectal cancer (CRC) have always been high, and more than 95% of CRC cases have evolved from colorectal polyps (CPs), especially adenoma. Early detection and treatment of CPs through colonoscopy is essential to reduce the incidence of CRC. Helicobacter pylori (Hp) is regarded as a risk factor for gastritis and gastric cancer and may also be a risk factor for CPs and CRC. However, few studies based on vast clinical cases exist in China to clarify whether Hp is a risk factor for CPs and CRC, and whether Hp-positive patients need to undergo colonoscopy checks earlier. This article attempts to make up for that deficiency.

Method: This cross-sectional study was conducted based on 13,037 patients without a treatment history of Hp who underwent their first gastroscopy and colonoscopy simultaneously at The First Affiliated Hospital of Zhejiang Chinese Medical University from January 2018 to December 2019. Pearson χ^2 test and logistic regression were used to determine whether Hp is a risk factor for CPs and CRC. Multifactor analysis of variance was used to define the impact of Hp on CPs prevalence with different ages, sexes.

Results: For Chinese individuals, Hp is a risk factor for CPs and CRC. The odds ratio (OR) value are 1.228 (95% CI, 1.130 to 1.336) and 1.862 (95% CI 1.240-2.796), respectively. Hp-positive patients have a higher probability of multiple or large intestinal polyps. However, Hp infection does not increase the incidence of adenomas, nor does it affect the pathological type of adenomas. The OR of Hp on the risk of CPs was 1.432 (95%CI 1.275-1.608) for males but increased to 1.937 (95%CI 1.334-2.815) for those aged 35 to 40. For females, the results were similar.

Conclusions: For the Chinese, Hp is a risk factor for CPs and CRC (OR>1); the infection of Hp increased CPs risk in Chinese of all ages, especially aged 35-40, suggesting that Hp-positive patients should undergo colonoscopy frequently.

Keywords: colorectal polyps, colorectal cancer, adenoma, cross-sectional study, age, Chinese

Tartışma:

- 13.037 vakada Hp enfeksiyon oranı %25,2 idi. Kadınlarda oranı %23,6 erkeklerde Hp enfeksiyon oranını %26,7 idi.
- Kadınlarda biraz daha yüksek
- Ancak çalışmada Hp pozitiflik derecesinin kolorektal polip ve malignite riskini orantılı olarak arttırmadığını göstermektedir. Ancak pozitifliğin maligniteyi tetiklediğini düşünmekteyiz.
- Positive Hp rapidly activates the cyclooxygenase 2 (COX-2) and increases the expression of P53, thus increasing the incidence of CPs and CRC.

SONUÇ:

(1) Hp pozitifliği, CP'ler ve CRC insidansını artıracaktır. Ancak Hp enfeksiyonunun derecesi insidansı etkilememektedir.

(2) Hp-pozitif hastalar çoklu polip geliştirmeye yatkındır.

(n ≥ 2) ve daha büyük polipler (çap > 10 mm).

(3) Hp pozitifliği, adenomlarda P53 ekspresyonu üzerinde bir etkiye sahiptir. Adenomların oluşumunu ve patolojik olarak morfolojisi CRC'lere dönüşümünü arttırmaktadır, ancak adenomların oluşumu üzerinde etkisi yoktur.

(4) 35-40 yaş arası Hp-pozitif Çinli hastalarda CP prevalansı diğer yaş gruplarına göre anlamlı olarak yüksektir, Hp ile 35-40 yaş arası Çinli bireylerin HP Pozitif olanlar düzenli olarak kolonoskopi yaptırmalıdır.

Helicobacter pylori
Original research

Helicobacter pylori promotes colorectal carcinogenesis by deregulating intestinal immunity and inducing a mucus-degrading microbiota signature

Anna Ralser [1], Alisa Dietl [1], Sebastian Jarosch [1, 2], Veronika Engelsberger [1], Andreas Wanisch [1], Klaus Peter Janssen [3], Moritz Middelhoff [4], Michael Vieth [5], Michael Quante [4, 6], Dirk Haller [7, 8], Dirk H Busch [1, 9], Li Deng [10, 11], Raquel Mejías-Luque [1, 9], Markus Gerhard [1, 9]

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Abstract

Objective *Helicobacter pylori* infection is the most prevalent bacterial infection worldwide. Besides being the most important risk factor for gastric cancer development, epidemiological data show that infected individuals harbour a nearly twofold increased risk to develop colorectal cancer (CRC). However, a direct causal and functional connection between *H. pylori* infection and colon cancer is lacking.

Design We infected two *Apc*-mutant mouse models and C57BL/6 mice with *H. pylori* and conducted a comprehensive analysis of *H. pylori*-induced changes in intestinal immune responses and epithelial signatures via flow cytometry, chip cytometry, immunohistochemistry and single cell RNA sequencing. Microbial signatures were characterised and evaluated in germ-free mice and via stool transfer experiments.

Results *H. pylori* infection accelerated tumour development in *Apc*-mutant mice. We identified a unique *H. pylori*-driven immune alteration signature characterised by a reduction in regulatory T cells and pro-inflammatory T cells. Furthermore, in the intestinal and colonic epithelium, *H. pylori* induced pro-carcinogenic STAT3 signalling and a loss of goblet cells, changes that have been shown to contribute—in combination with pro-inflammatory and mucus degrading microbial signatures—to tumour development. Similar immune and epithelial alterations were found in human colon biopsies from *H. pylori*-infected patients. Housing of *Apc*-mutant mice under germ-free conditions ameliorated, and early antibiotic eradication of *H. pylori* infection normalised the tumour incidence to the level of uninfected controls.

Conclusions Our studies provide evidence that *H. pylori* infection is a strong causal promoter of colorectal carcinogenesis. Therefore, implementation of *H. pylori* status into preventive measures of CRC should be considered.

frontiers | Frontiers in Immunology

MINI REVIEW
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HP-NAP of *Helicobacter pylori*: The Power of the Immunomodulation

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The miniferritin HP-NAP of *Helicobacter pylori* was originally described as a neutrophil-activating protein because of the capacity to activate neutrophils to generate oxygen radicals and adhere to endothelia. Currently, the main feature for which HP-NAP is known is the ability to promote Th1 responses and revert the immune suppressive profile of macrophages. In this review, we discuss the immune modulating properties of the protein regarding the *H. pylori* infection and the evidence that support the potential clinical application of HP-NAP in allergy and cancer immunotherapy.

medicina

MDPI

Opinion

Controlling the Impact of *Helicobacter pylori*-Related Hyperhomocysteinemia on Neurodegeneration

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Abstract: *Helicobacter pylori* infection consists a high global burden affecting more than 50% of the world's population. It is implicated, beyond substantiated local gastric pathologies, i.e., peptic ulcers and gastric cancer, in the pathophysiology of several neurodegenerative disorders, mainly by inducing hyperhomocysteinemia-related brain cortical thinning (BCT). BCT has been advocated as a possible biomarker associated with neurodegenerative central nervous system disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and/or glaucoma, termed as "ocular Alzheimer's disease". According to the infection hypothesis in relation to neurodegeneration, *Helicobacter pylori* as non-commensal gut microbiome has been advocated as trigger and/or mediator of neurodegenerative diseases, such as the development of Alzheimer's disease. Among others, *Helicobacter pylori*-related inflammatory mediators, defensins, autophagy, vitamin D, dietary factors, role of probiotics, and some pathogenetic considerations including relevant involved genes are discussed within this opinion article. In conclusion, by controlling the impact of *Helicobacter pylori*-related hyperhomocysteinemia on neurodegenerative disorders might offer benefits, and additional research is warranted to clarify this crucial topic currently representing a major worldwide burden.

Citation: Kountouras, J.; Doulberis, M.; Papaefthymiou, A.; Polyzos, S.A.; Zavos, C.; Kazakos, E.; Arapoglou, S.; Kyrailidi, F.; Mouratidou, M.C.; Boziki, M.; et al. Controlling the Impact of *Helicobacter pylori*-Related Hyperhomocysteinemia on Neurodegeneration. *Medicina* **2023**, *59*, 504. https://doi.org/10.3390/medicina59030504

PLOS ONE

RESEARCH ARTICLE

The association of *Helicobacter pylori* infection with serum lipid profiles: An evaluation based on a combination of meta-analysis and a propensity score-based observational approach

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Abstract

Background

Several previous studies have suggested that *Helicobacter pylori* (*H. pylori*) infection affects the serum lipid profile. However, it remains controversial and the mechanism has not been elucidated. The purpose of this study is to use an epidemiological perspective to evaluate the association between *H. pylori* infection and the serum lipid profile.

Methods

Multivariate analysis was performed using the data of serum lipid profile, infection status of *H. pylori*, fitness/lifestyle habits, and various subjects' characteristics which were derived from the 15,679 generally healthy individuals in Japan. The average treatment effects (ATEs) of *H. pylori* infection on the serum lipid profile were estimated using augmented inverse probability weighting (AIPW). A meta-analysis was also performed using the 27 studies worldwide in which the status of *H. pylori* infection and at least one serum examination value (high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), or triglyceride (TG)) were described.

Results

The ATEs determined with AIPW showed that *H. pylori* infection has significant positive effects on LDL-C and TC (ATE (95% confidence interval [95%CI]) = 3.4 (2.36–4.49) and 1.7 (0.58–2.88), respectively) but has significant negative effects on HDL-C and TG (ATE (95% CI) = −1.2 (−1.74 to −0.72) and −3.5 (−5.92 to −1.06), respectively). The meta-analysis to estimate the association between *H. pylori* infection and the serum lipid profile revealed that *H. pylori* infection is positively associated with LDL-C, TC, and TG (standardized mean difference [SMD] (95%CI) = 0.11 (0.09–0.12), 0.09 (0.07–0.10) and 0.06 (0.05–0.08), respectively) and negatively associated with HDL-C (SMD = −0.13 (−0.14 to −0.12)).

Conclusion

Both our multivariate analyses and meta-analysis showed that *H. pylori* infection significantly affects the serum lipid profile, which might lead to various dyslipidemia-induced severe diseases like coronary thrombosis or cerebral infarction.

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

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Competing interests: The authors have declared that no competing interests exist.

Abbreviations: Alb, Albumin; ALP, Alkaline

Obesity Surgery
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ORIGINAL CONTRIBUTIONS

Helicobacter Pylori Infection Prevalence and Histopathologic Findings in Laparoscopic Sleeve Gastrectomy

Gülay Turan[1] · Servet Kocaöz[2]

Abstract

Introduction Helicobacter pylori (*H. pylori*) is a type of bacteria that affects more than half of the world's population and has been associated with gastritis. The relationship between *H. pylori* and obesity is controversial. Laparoscopic sleeve gastrectomy (LSG) is the most commonly used surgery for morbidly obese patients. The aim of this study was to investigate the rate of *H. pylori* in patients undergoing LSG.

Methods Biopsy specimens of 32,743 patients who underwent esophagogastroduodenoscopy (EGD) and resection materials from 1257 patients who underwent LSG were examined histopathologically. The relationships between body mass index (BMI), age, gender, *H. pylori* infection, and intestinal metaplasia (IM) were investigated in patients with gastritis.

Results In patients undergoing EGD, the association of *H. pylori* infection was found to be increased in males and the elderly ($p < 0.001$). The presence of gastritis and IM was significantly higher with *H. pylori* infection ($p < 0.001$ and $p = 0.001$, respectively). *H. pylori* infection was significantly higher in patients over the age of 41 years ($p < 0.001$). There was no significant difference between the results of *H. pylori* before and after LSG surgery ($p = 0.923$). The presence of *H. pylori* together with gastritis and IM was found to be significant ($p < 0.001$).

Conclusions *H. pylori* infection increases with age. No significant difference was found in the examination for *H. pylori* before and after LSG surgery. In addition, no relationship was found between *H. pylori* and excess weight. However, due to the low average age of patients who underwent LSG, further studies are needed in this area.

Keywords Obesity · Sleeve gastrectomy · Pathologic findings · Helicobacter pylori

Unacceptable Antibiotic Resistance Rates for Helicobacter pylori *in Turkey: Something Must Change*

Bilge Müge Gökçekuyu[1,2], Özlem Yılmaz[3], Müjde Soytürk[4], Hülya Ellidokuz[5], Hale Akpınar[4], İlkay Şimşek[4]

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ABSTRACT

Background: *It is known that clarithromycin resistance has increased over the years (success rate 60%). The aim of the study was to investigate the importance of regional antimicrobial resistance rates for full accuracy of both diagnosis and treatment of Helicobacter pylori infection.*

Methods: *This study was carried out in the University Hospital Department of Gastroenterology. A total of 116 patients were evaluated with upper gastrointestinal endoscopy. Gastric antrum and corpus biopsy samples were taken for the rapid urease test (RUT), culture, and antimicrobial susceptibility testing for the presence of H. pylori. Antimicrobial susceptibilities of isolated H. pylori strains for clarithromycin and levofloxacin were determined by the epsilometer test (E-test). Minimal inhibitory concentration values for clarithromycin and levofloxacin were ≥1 and >1 µg/mL, respectively.*

Results: *H. pylori infection was considered clinically positive in 93 (80.2%) patients with either the RUT, culture, or histopathological examination. Seventy (60.3%) of the patients had RUT positivity. Sixty (85.7%) of these 70 patients had RUT positivity within the first 20 min. Among the 90 patients, who had a histopathological examination, HLO was positive in 76 (84.4%) patients. Fifty-two (44.8%) out of 116 patients were culture positive. Resistance rates for both clarithromycin and levofloxacin were high. In these 52 culture-positive patients, resistance rates determined for clarithromycin and levofloxacin were 26.9% and 25.5%, respectively.*

Conclusion: *Clarithromycin or levofloxacin-based treatment regimen may not be an ideal alternative therapy for Turkish patients regardless of culture.*

Keywords: *H. pylori, clarithromycin, levofloxacin, culture susceptibility, diagnosis*

TÜBİTAK

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http://journals.tubitak.gov.tr/medical/

Research Article

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(2021) 51: 1445-1464

doi:10.3906/sag-2101-69

Detection of *Helicobacter pylori* by invasive tests in adult dyspeptic patients and antibacterial resistance to six antibiotics, including rifampicin in Turkey. Is clarithromycin resistance rate decreasing?

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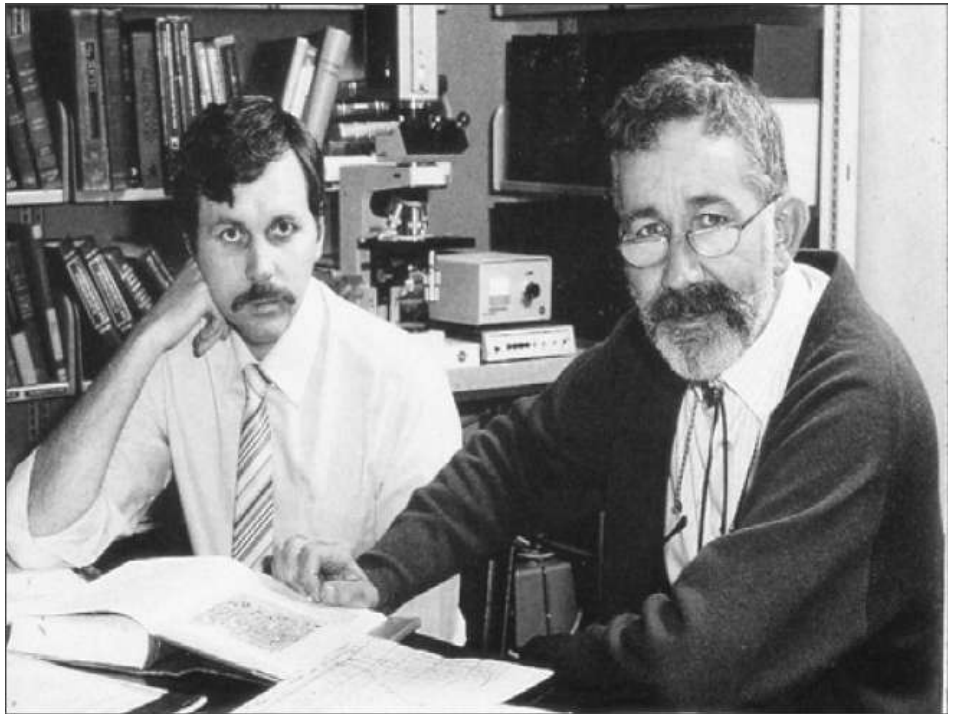
Background/aim: The prevalence of *Helicobacter pylori* is reported to be roughly 80% in Turkey, and only very few culture-based studies are available on antibacterial resistance in adult dyspeptic patients. This study was carried out in adult dyspeptic patients with an aim to: (i) detect *H. pylori* by invasive tests (culture, polymerase chain reaction, and histopathology) and (ii) determine the current resistance rates of *H. pylori* isolates to six antibiotics, including rifampicin.

Materials and methods: This study was conducted in 422 adult dyspeptic patients. The presence of *H. pylori* was demonstrated by culture, polymerase chain reaction, and the histopathology of gastric biopsy material. Antibacterial susceptibility was determined with the E-test.

Results: The mean age of the patients was 50 ± 15 (range 18–90), and 265 (63%) of them were female. By culture, polymerase chain reaction, and histopathology, the presence of *H. pylori* was detected at rates of 35% (148/422), 67% (281/422), and 53% (224/422), respectively. The prevalence of *H. pylori* was determined as 75.6% (319/422). Metronidazole, levofloxacin, clarithromycin, and rifampicin resistance rates were 62%, 36%, 19%, and 12%, respectively. Monodrug, dual-drug, and multidrug resistance rates were ascertained as 36.9%, 29.4%, and 10.5%, respectively. All of the isolates were susceptible to amoxicillin and tetracycline.

Conclusion: This study revealed the current prevalence of *H. pylori* in adult dyspeptic patients as 75.6%, and thereby, showed that infection with this pathogen remains highly prevalent. Although resistance to metronidazole and levofloxacin has increased over time, clarithromycin resistance rate has decreased. The high levels of resistance to metronidazole and levofloxacin limit the empirical use of these antibiotics in the eradication protocol. Owing to the low level of resistance determined for rifampicin, this antibiotic could be included in the eradication protocol, in the event of the need for rescue therapy in Turkey.

Key words: Antibacterial resistance, clarithromycin, *Helicobacter pylori*, invasive test, rifampicin, Turkey



1)2005; Warren ve Marshall, Tıp dalında Nobel Ödülü

2)Marshall içinde H. pylori bulunan deney şişesini içti,

3)Akut Gastrit, 10 gün sonra endoskopide gastrit işaretleri ve *H. pylori*.

Dear Dr. Marshall,

I regret that your research paper was not accepted for presentation...

The number of abstracts we receive continues to increase and **for this meeting 67 were submitted and we could only accept 56.**

GASTROENTEROLOGICAL SOCIETY OF AUSTRALIA

145 Macquarie Street,
SYDNEY. 2000

Telephone 27 3288

17th March, 1983

Dear Dr. Marshall,

I regret that your research paper was not accepted for presentation on the programme of the Annual Scientific Meeting of the Gastroenterological Society of Australia to be held in Perth in May, 1983.

The number of abstracts we receive continues to increase and for this Meeting 67 were submitted and we were able to accept 56.

There were a large number of high quality abstracts which made it extremely difficult to choose those which should be accepted for presentation, and as you know, this is now done by a National Abstract Selection Committee which reviews the abstracts without knowledge of the Authors concerned.

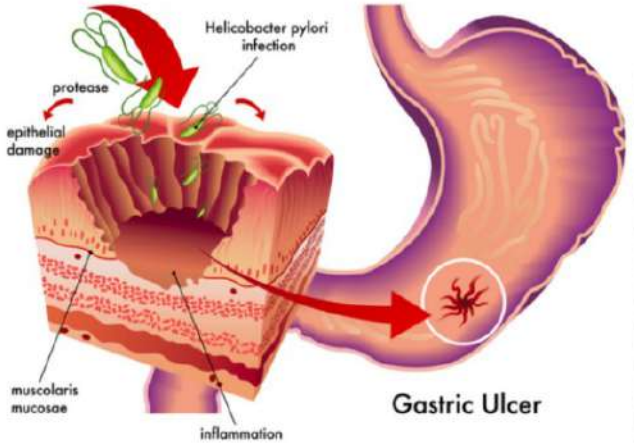
The National Programme Committee would like to thank you for submitting your work, and would hope that this might be re-submitted in the future, perhaps following critical review from your colleagues.

My kindest regards,

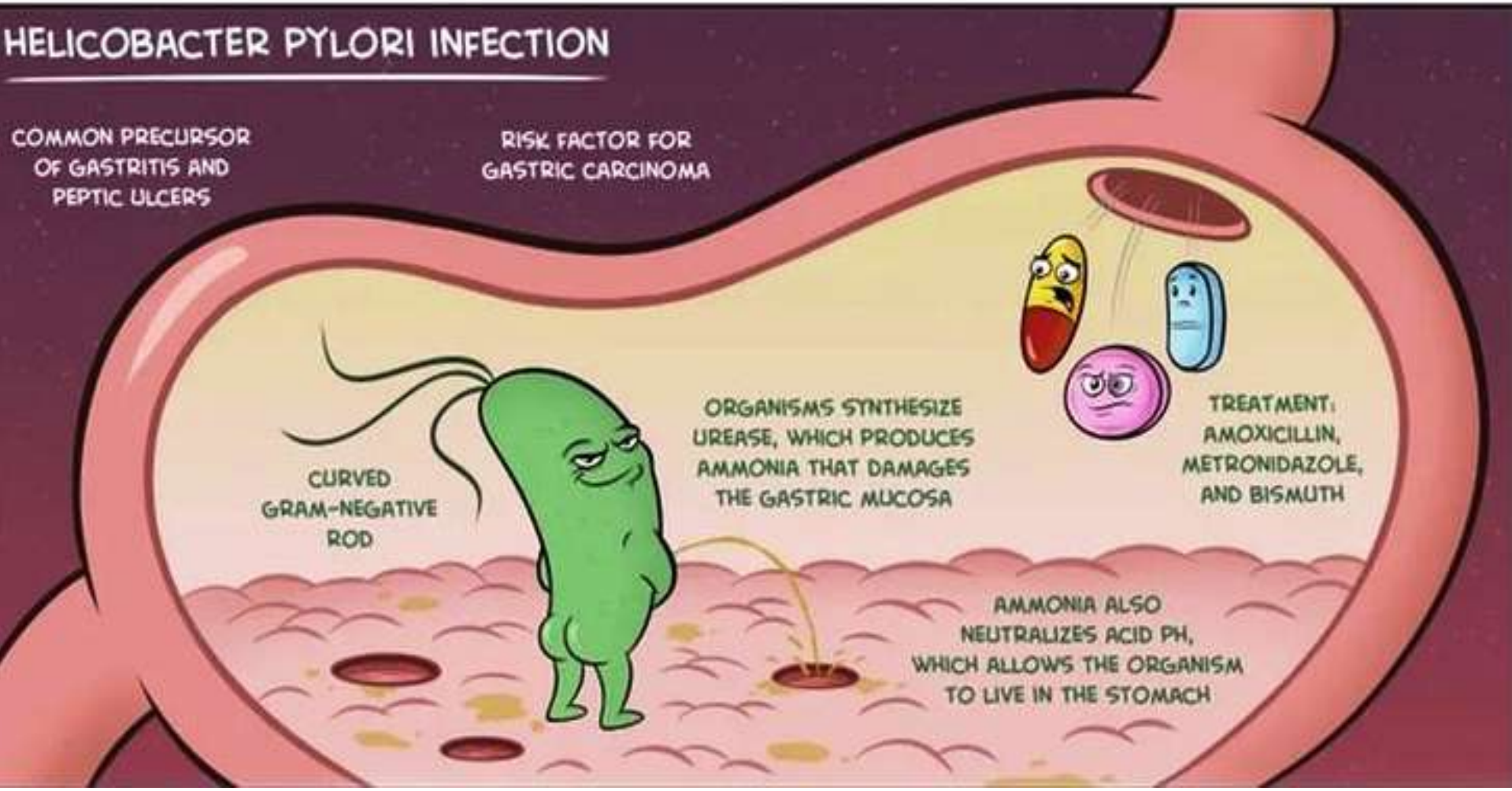
Yours sincerely,

for Terry D. Bolin,
Honorary Secretary.

Barry Marshall receives notification from the Gastroenterological Society in 1983 that his abstract is amongst the bottom 20% for presentation



This is a story of perseverance and the *'never give up'* attitude of a Western Australian by the name of Barry Marshall, who won a Nobel Prize in 2005 for



Sabrınız için teşekkürler…