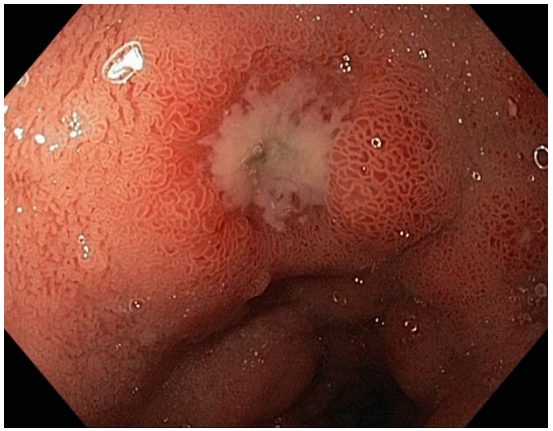
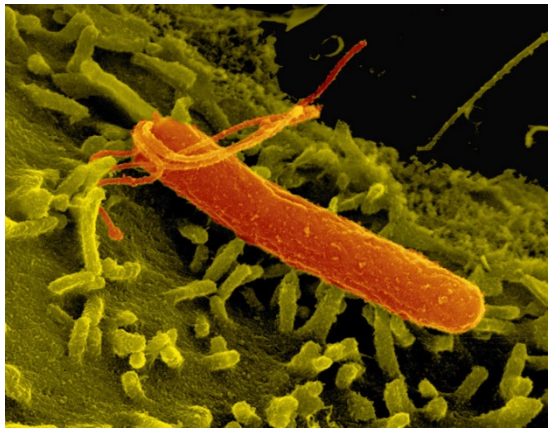
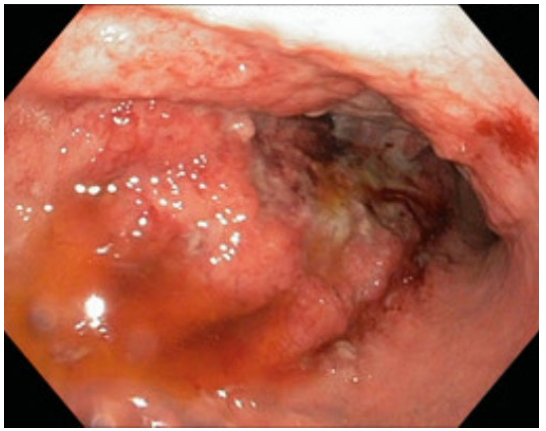
Helicobacter pylori







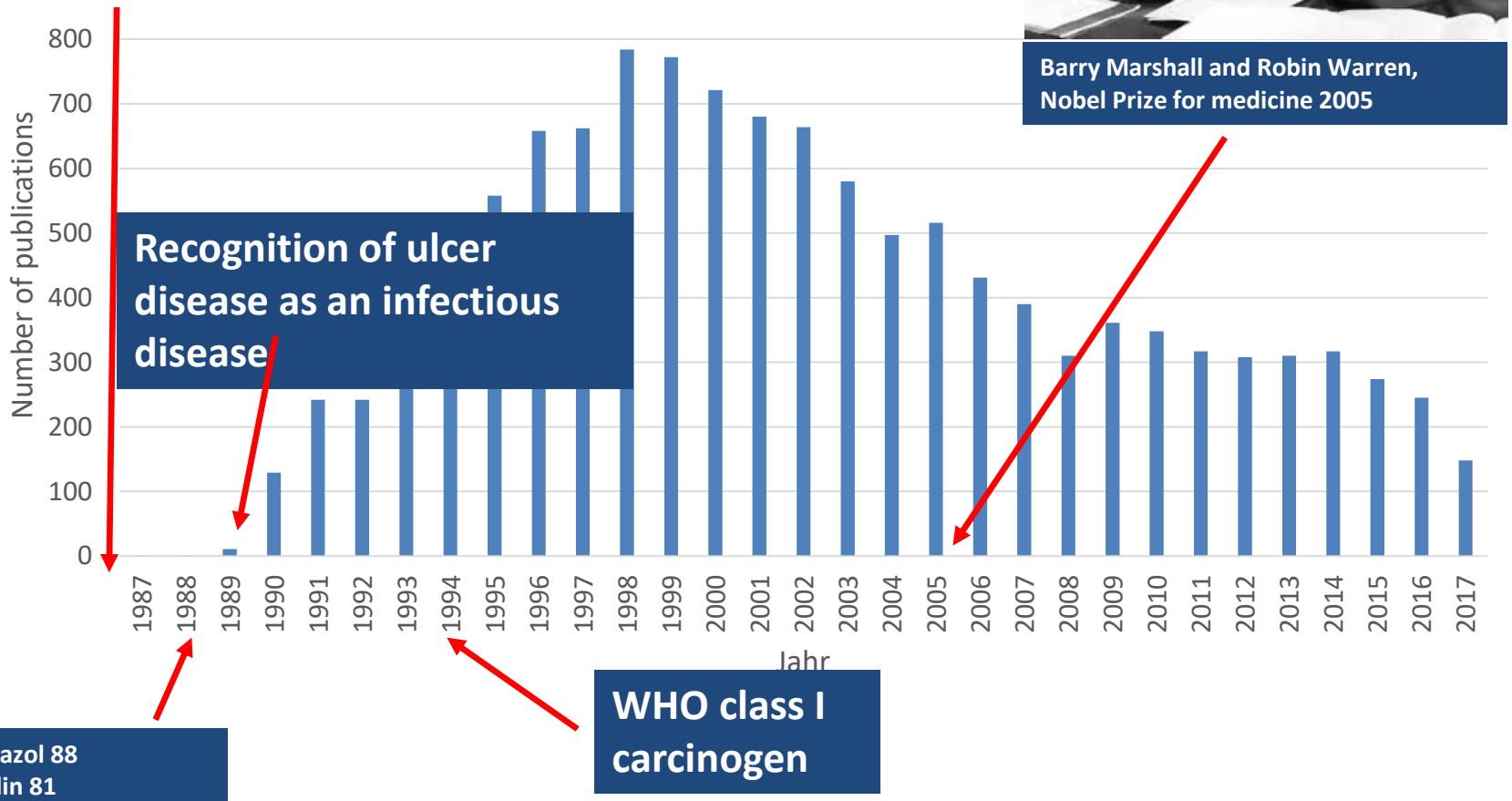
8/2020

History

Discibed by European pathologists already the end of the 19th century

Marshall BJ, Warren JR (June 1984). *"Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration"*. Lancet. 323 (8390): 1311–5.

Barry Marshall and Robin Warren, Nobel Prize for medicine 2005



Recognition of ulcer disease as an infectious disease

Omeprazol 88
Ranitidin 81

WHO class I carcinogen

Acute self-experimental infection - in 1985, microbiologist Barry Marshall took H. pylori and observed:

- First 24 h: Increased intestinal activity
- No further symptoms until day 7
- Day 7: Pain in the stomach area
- Day 8: Vomiting
- Week 2: Soft stools, irritable bowel, stinking breath
- Day 10: Histological diagnosis of gastritis
- Day 14: Spontaneous healing

"The greatest obstacle to discovery is not ignorance—it is the illusion of knowledge."

Daniel J. Boorstin

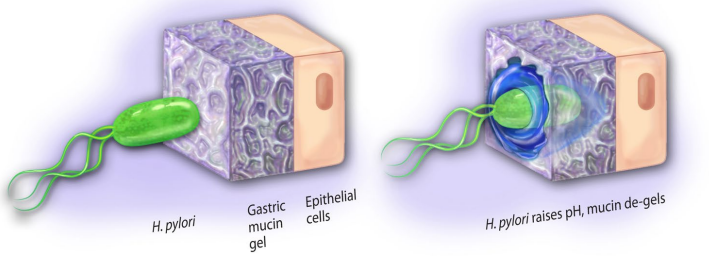
Who is helicobacter pylori

- gram-negative, helically-shaped, microaerophilic bacterium
- has two to six flagella
- Urease – positive

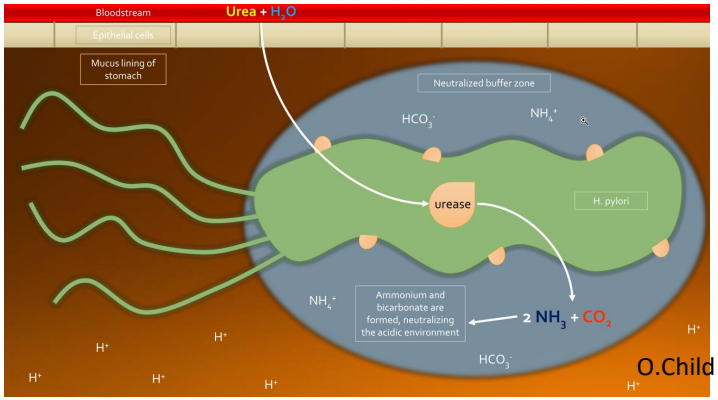
H. pylori senses pH gradient in the mucus and move towards the less acidic region (chemotaxis).

Uses its flagella to burrow into the mucus lining of the stomach to reach the epithelial cells underneath, where it is less acidic

Zina Deretsky NSF



Urease enzyme takes urea and water from the bloodstream and stomach and converts them to ammonia and carbon dioxide. These products neutralize the strong acid of the stomach, and as a result a buffer zone surrounds the bacteria to protect it from the strong acids in its environment.

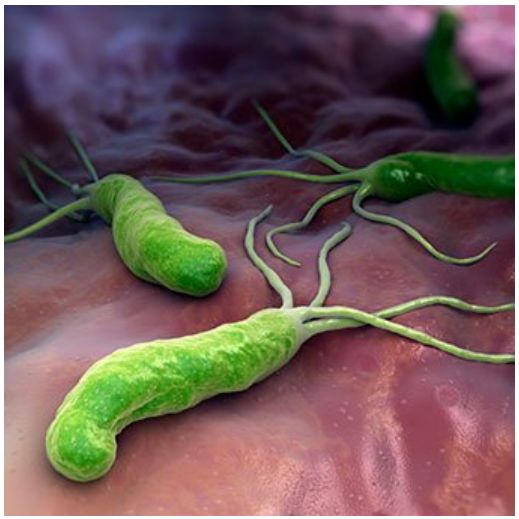


Epidemiology of H. pylori / Transmission? Which are the high risk groups?

- H. pylori infection is chronic, actually one of the most common chronic bacterial diseases, and is usually acquired in childhood. Without treatment persistance trough life

- higher risk:
  - low socioeconomic status
  - increasing number of siblings

Transmission



- Exact path of transmission unclear
- Oral-oral / oral – faecal (culture possible)

- Usually acquired in childhood
  - (transmitted from mother?)

- Contaminated water / food
- Transmission between life partners rare (four times more likely if reflux?)

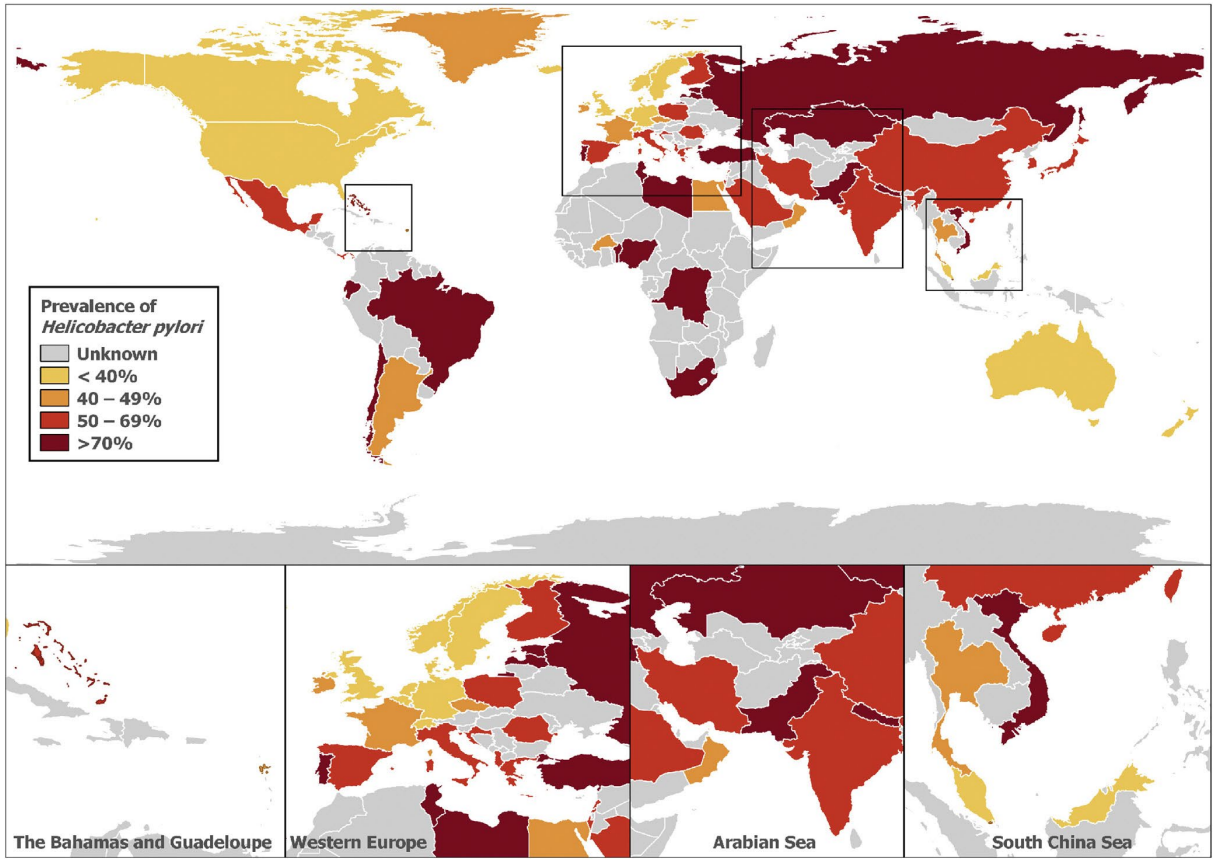
- RR for gastroenterologists 1.6, RR for endoscopy nurses 1.4

- Rate of recurrent infections after successful eradication 2% per year in industrialised countries and 6-12% in developing countries - the global annual recurrence rate of H. pylori is 4.3%.

Bamford KB et al. Gut. 1993 Oct; 34(10): 1348–1350.
Graham DY et al. Gastroenterology 1991; 100: 1495–1501.
Weyermann et at. Am J Gastroenterol 2009; 104: 182–189
Leja 2019, Burucoa 2017

Are we a H. pylori high or low prevalence population?

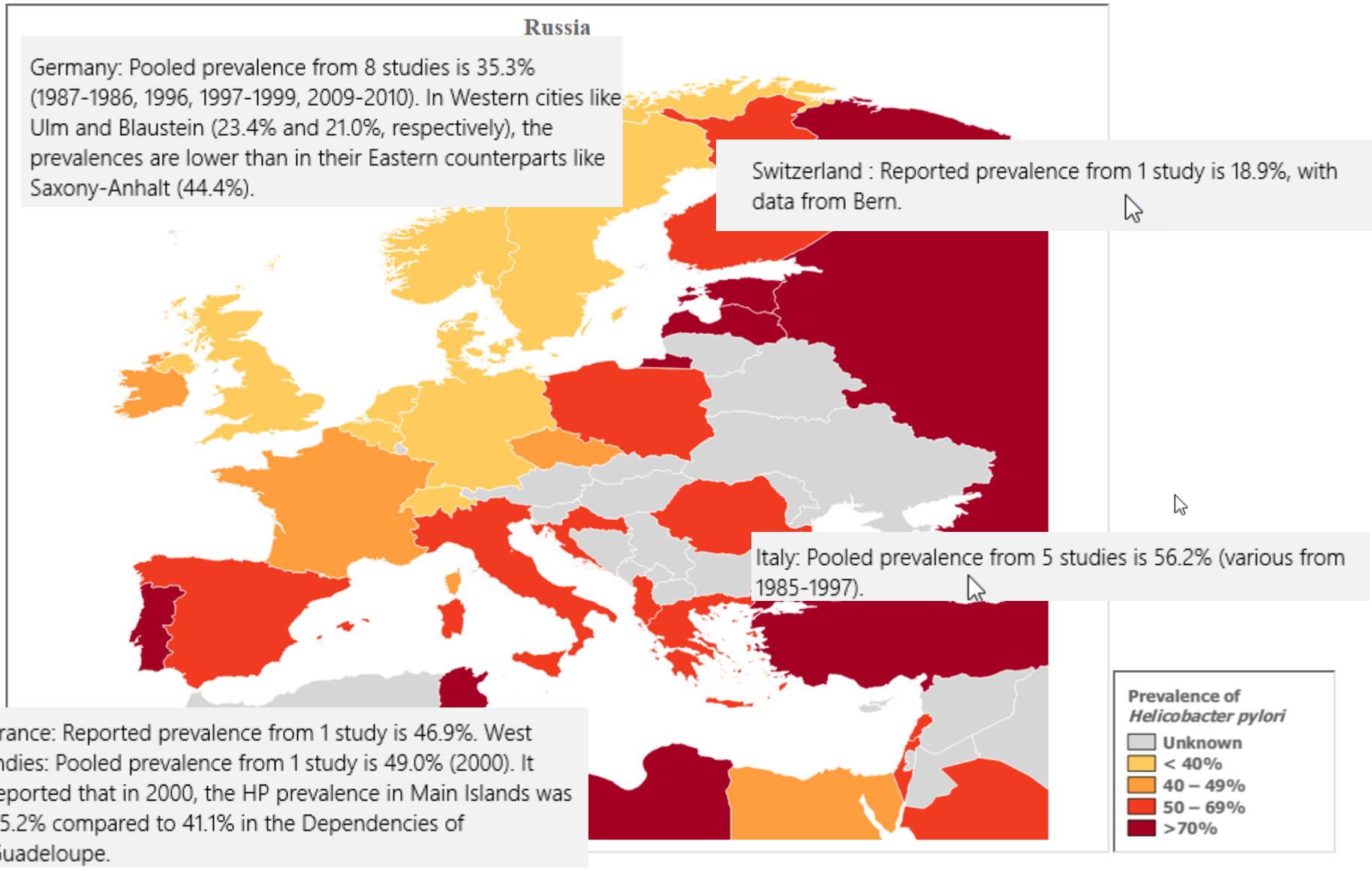
Prevalance

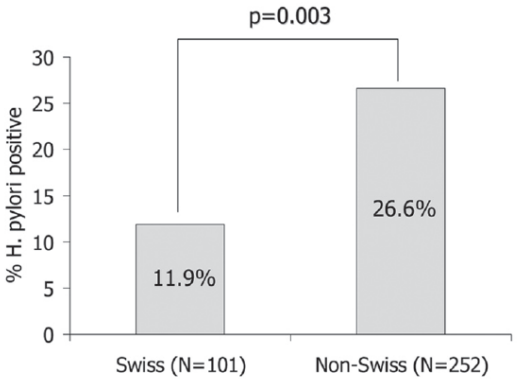


- About 50% of the adult world population infected
- High in Africa 79.1%
- Low prevalence in:
  - Western Europe/North America 35%
  - Switzerland 18.9%

Hooi J. Gastroenterology 2017;153:420–429
https://people.ucalgary.ca/wggkaplan/HP2016.html

Western Europe





H. Pylori positive patients

born in Switzerland 12 %

born outside of the country 27%

Gruber D. J et al. 2005

born in Switzerland 14 %

born outside of the country 40%

Unpublished data (2012)Niess et al

Is the only good *Helicobacter pylori* a dead *Helicobacter pylori?*

Since all patients with a positive test of active infection with H. pylori should be offered treatment irrespective of symptoms, the critical issue **is which patients should be tested** for the infection

Kyoto consensus 2015

Who do you test?

Active peptic ulcer disease (PUD), a past history of PUD (unless previous cure of H. pylori infection has been documented)
Uninvestigated Dyspepsia
Low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma
History of endoscopic resection of early gastric cancer (EGC)
Long-term, low-dose aspirin, testing for H. pylori infection: could be considered to reduce the risk of ulcer bleeding. (low evidence)
NSAID: Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) should be tested for H. pylori infection. The benefit of testing and treating H. pylori in a patient already taking an NSAID remains unclear
Iron deficiency anemia: patients with unexplained iron deficiency anemia despite an appropriate evaluation should be tested for H. pylori infection.
Adults with idiopathic thrombocytopenic purpura (ITP)
Testing for and treatment of H. pylori in asymptomatic individuals with a family history of gastric cancer or patients with lymphocytic gastritis, hyperplastic gastric polyps, and hyperemesis gravidarum: There is insufficient evidence to support routine testing for and treatment of H. pylori

Chey WD et al. **ACG** Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. **Maastricht V** Gut 2017; 66: 6-30.
Crowe SE. N Engl J Med 2019; 380:1158-65

How would you test H. Pylori in case of dyspepsia
and
is eradication an effective therapy for dyspepsia?

H. Pylori and dyspepsia

- If prevalence of *H. pylori* infection is at least 10% - which is almost everywhere – test and treat <45 years of age
- Gastric biopsies should be taken if endoscopy is performed in patients with dyspepsia

- “scope and treat”: trend towards better symptom control and higher patient satisfaction
- "test-and-treat“: cost-effectiveness better
- Because of cost-effectiveness, especially in countries with high H. pylori prevalence, the "test-and-treat" approach is recommended for young patients without alarm symptoms

Ford 2005
Delaney 2005

H. Pylori and dyspepsia

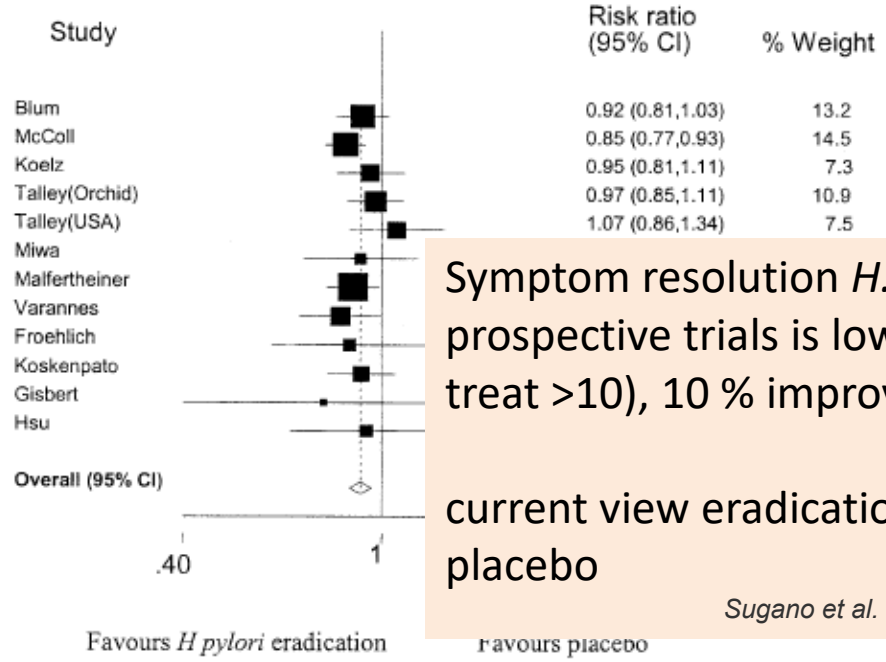
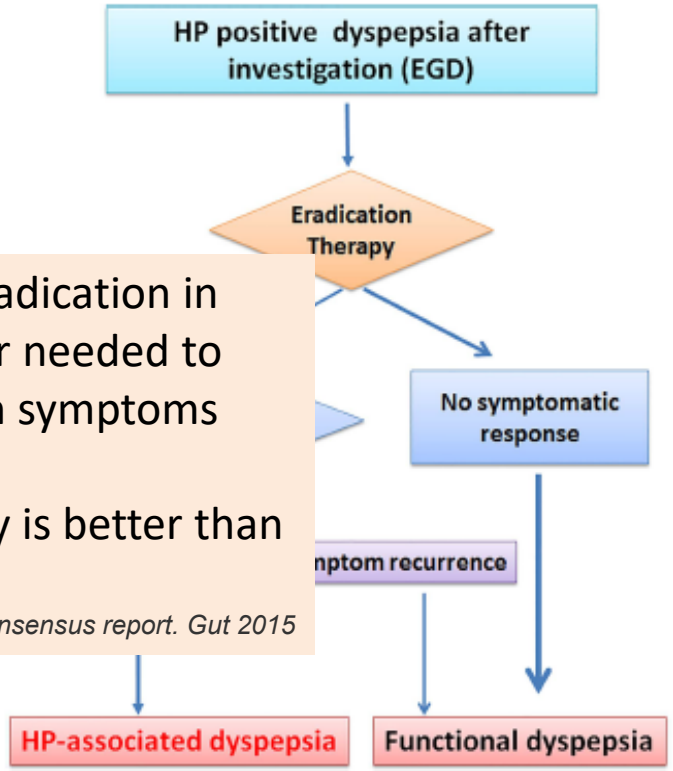


Figure 1. Results of updated Cochrane meta-analysis of randomized controlled trials of *H. pylori* eradication in nonulcer dyspepsia.

Symptom resolution *H. pylori* eradication in prospective trials is low (number needed to treat >10), 10 % improvement in symptoms

current view eradication therapy is better than placebo

Sugano et al. Kyoto global consensus report. Gut 2015



nonulcer dyspepsia relative risk = 0.91

Moayyedi P. et al, AJG 2003

Malfertheiner P et al. **Maastricht V** Gut 2017; 66: 6-30.

Is GORD an contraindication for H.pylori eradication?

- Negative association H. pylori with GORD?:
  - *H. pylori* infection was shown to be present in 39% of GORD sufferers compared with 50% of controls in a review of 26 studies
  - Gastro-oesophageal reflux disease (GORD) is increasing in prevalence worldwide, probably due to of obesity
  - Randomized controlled trials (RCTs) of population-level screening and treatment without evidence of an increase in gastro-oesophageal reflux symptoms

- In most populations, the changes in acid production after H. pylori treatment have no proven clinical relevance and should not be used as an argument to treat or not to treat H. pylori.

O'Connor 1999
Moayyedi 2000
Harvey 2004
Yaghoobi 2010

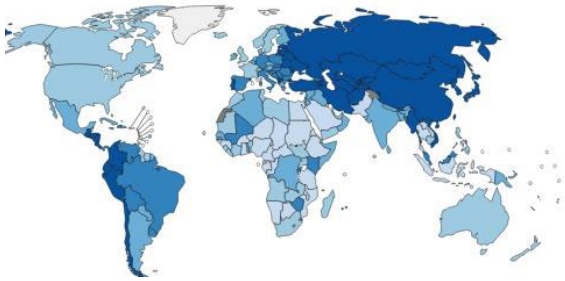
Empfehlung/Statement 3.6

Refluxsymptome oder eine Refluxösophagitis stellen keine Indikation für eine H. pylori-Eradikation dar. Die Entscheidung für eine H. pylori-Eradikation aus anderer Indikation kann unabhängig von etwaigen Refluxsymptomen oder einer Refluxkrankheit getroffen werden.
Konsensusstärke: starker Konsens – keine Empfehlung

Statement 4: *H. pylori* gastritis may increase or decrease acid secretion. Treatment may reverse or partially reverse these effects.

Level of evidence: high **Grade of recommendation: high**

Gastric Cancer



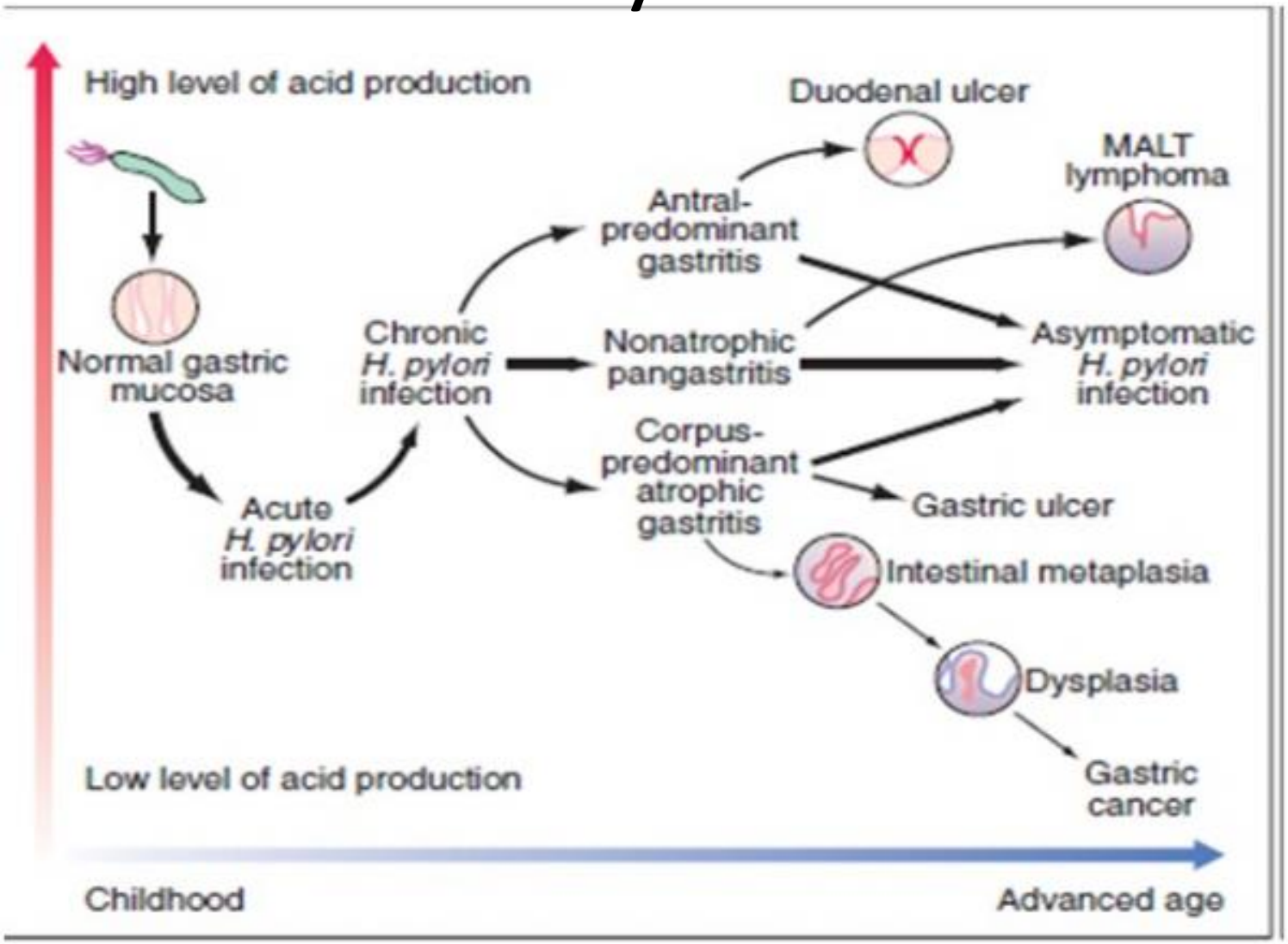
- 5th most common cancer worldwide
- 3rd cause of mortality worldwide
- High incidence in Asia (China, Japan and Korea) eastern Europe, South America
- 5 year survival around 27%, 80% in early cancer

- H. pylori infection is the underlying cause of the majority of cases of gastric cancer worldwide.

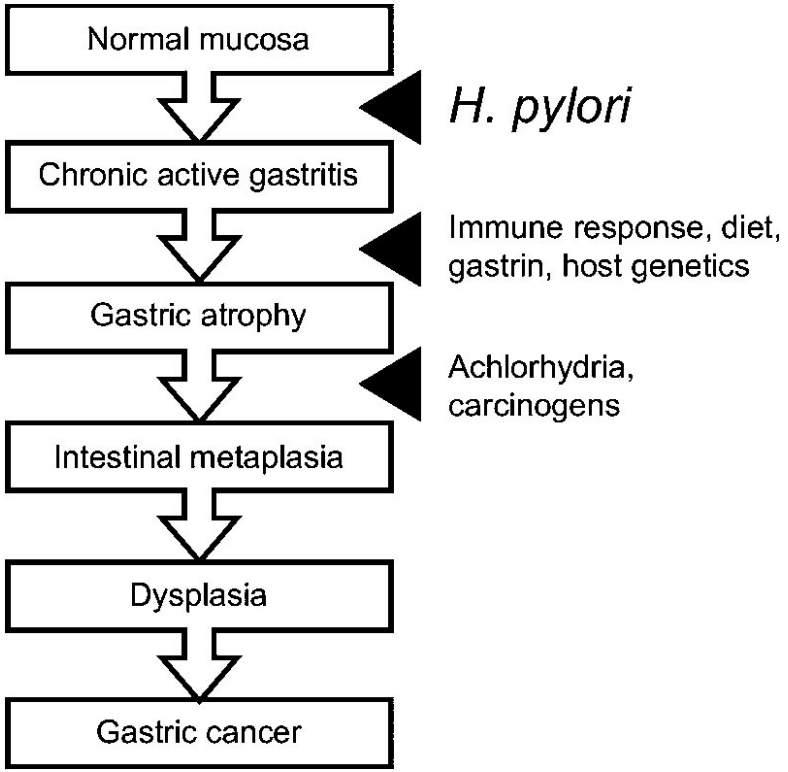
- Overall about 1% to 3% of people infected with *Helicobacter pylori* develop gastric cancer in their lifetime compared to 0.13% of individuals who have had no *H. pylori* infection

Malvezzi M. Ann Oncol. 2016.
Ferlay GLOBOCAN 2018
Kuipers 1999
Wu 2020

Natural history of HP-Infection



- Metanalayses showed H. pylori eradication results in significant improvement of gastritis and gastric atrophy but not of intestinal metaplasia.

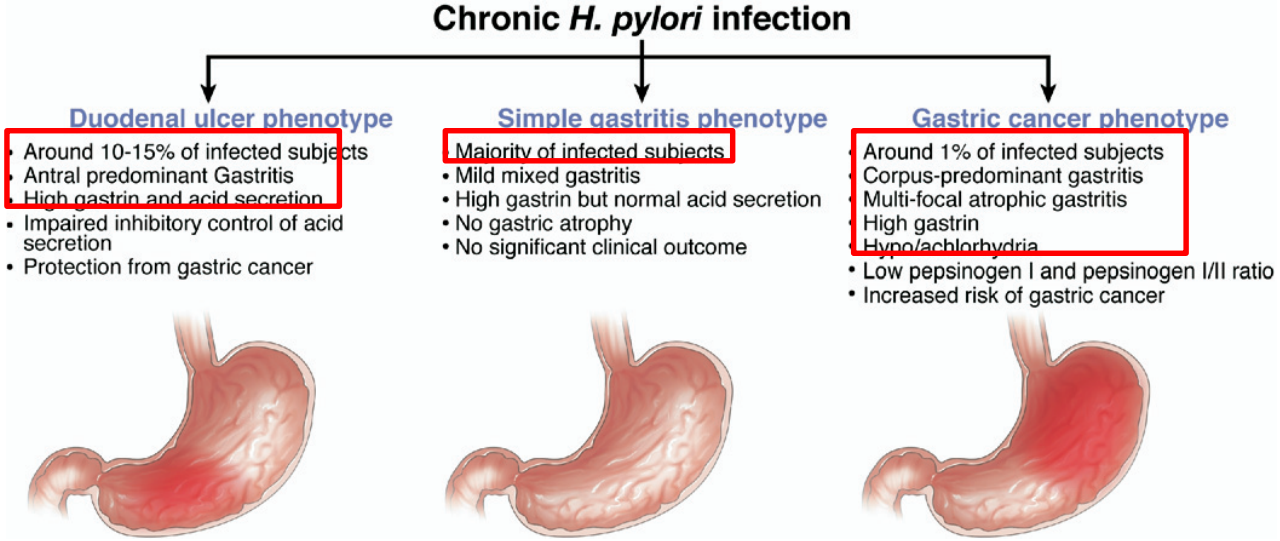


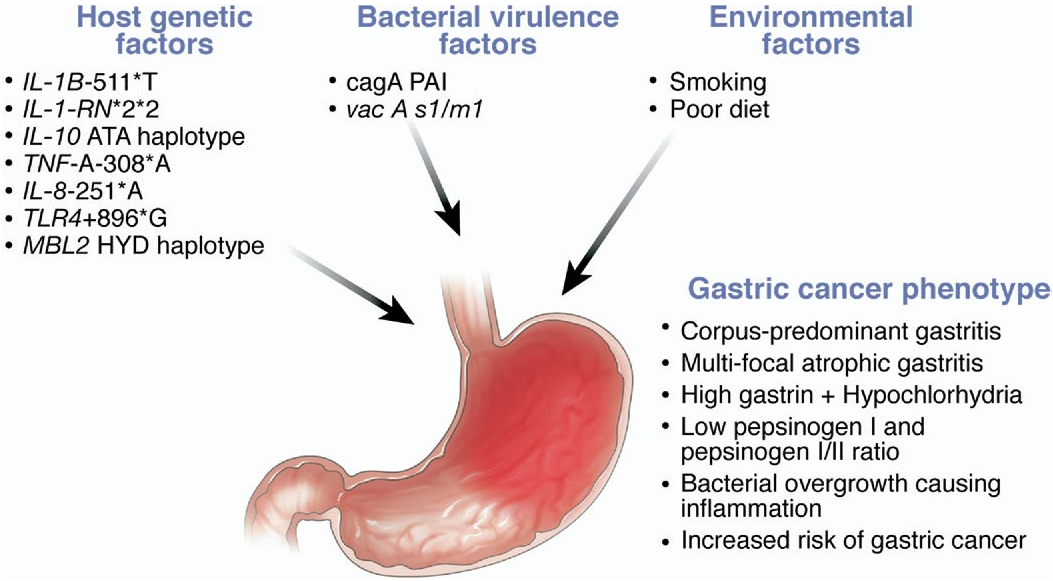
Role of *H. pylori* in gastric carcinogenesis, in cascade proposed by Correa

Rokkas 2007
Wang 2011
Chen 2016

Kusters 2006
Correa 1975

3 potential outcomes - factors contributing to the outcome





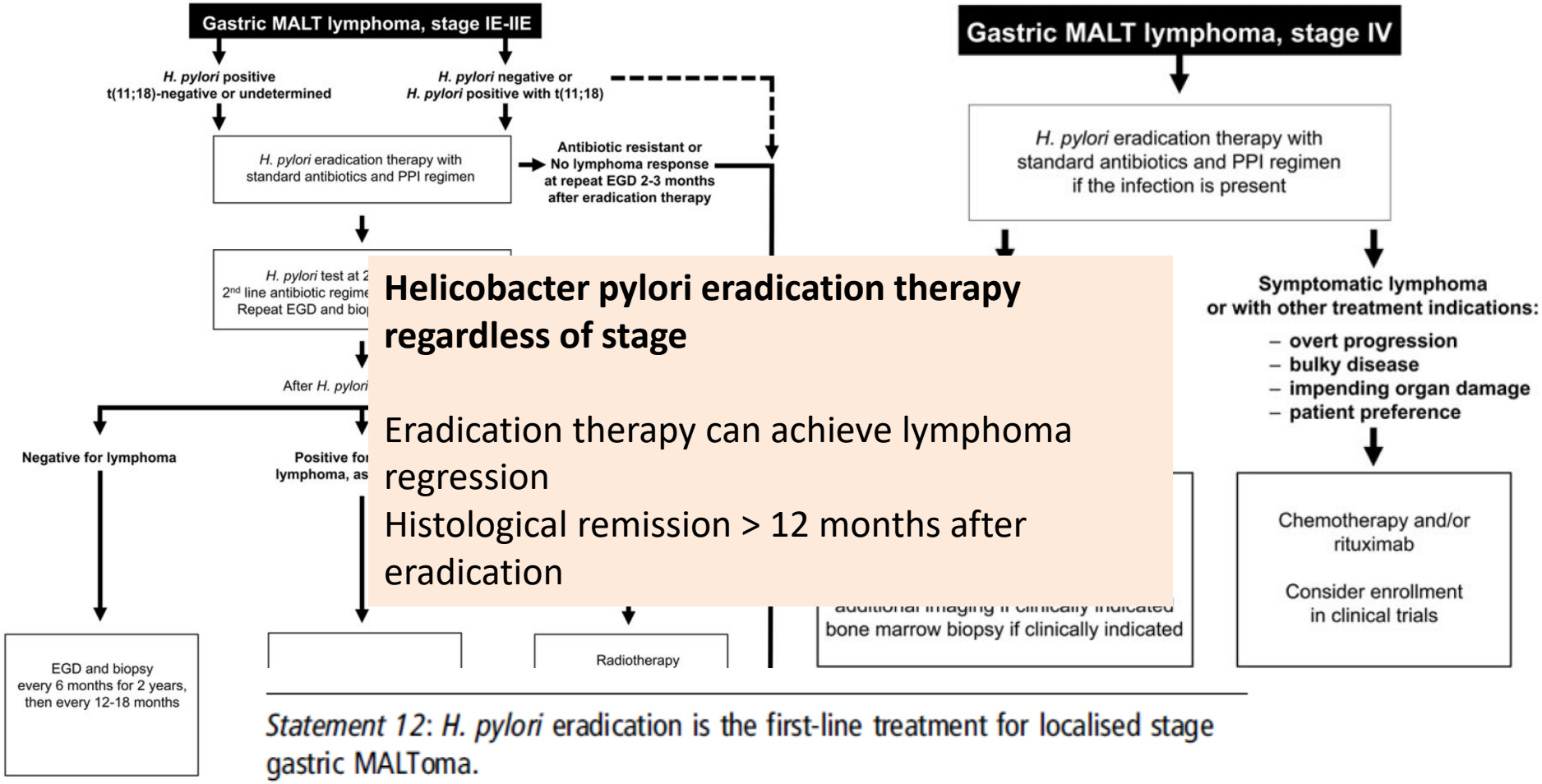
AMIEVA AND EL-OMAR

MALT-Lymphoma

- 1991 first association with gastric lymphoma described
- 1993 is the first year in which complete remission after eradication therapy is reported

H. pylori test in MALT-lymphoma

- Primary Histology
- If histology is negative, then serology



Helicobacter pylori eradication therapy regardless of stage

Eradication therapy can achieve lymphoma regression
Histological remission > 12 months after eradication

Statement 12: *H. pylori* eradication is the first-line treatment for localised stage gastric MALToma.

Level of evidence: moderate **Grade of recommendation: strong**

ıf Oncology 2013; 24(6): vi144–vi148.
NCCN Guidelines Version 5.2019 – Gastric MALT lymphoma.

But is the only good *Helicobacter pylori* a dead *Helicobacter pylori?*

+ Gastric cancer is an inflammation-associated cancer with a multistep carcinogenesis. The process consists of H. pylori infection, ongoing inflammation, development of metaplastic epithelia and genetic instability eventuating in gastric cancer.

+ The Kyoto Global Consensus Report defined H. pylori-associated gastritis as an infectious disease. Currently H. pylori eradication is the only practical method of eliminating gastric cancer and other H. pylori-related diseases.

- Drawback of mass H. pylori eradication programs must be set in relation to other health care priorities - resistance globaly rising!
  - Obesity and asthma and Reflux?

Engler 2014
Sugano 2015
Malfertheiner 2017
Who 2020

How to test?

Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30.

When would you scope and when use which non-invasive Test?

Invasive tests	Non-invasive tests

Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30.

When would you scope and when use which non-invasive Test?

Invasive tests	Non-invasive tests
Iron deficiency anaemia Weight loss Dyspepsia with alarm symptoms Age > 50 years • ACG 60 y, europe ~ 45 – 50 y	Changes associated with H. pylori infection (without indication for endoscopy): Ulcer in the past Immune thrombocytopenia Increased risk of infection Long-term therapy with Aspirin/NSAR

Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30.

	Test	Sensitivity %	Specifity %
Invasive	Histology	80-98	90-98
	Rapid urease test	90-95	90-95
	Culture	70-90	100
	PCR	90-95	90-95
Non-invasive	13C-breath test	85-95	85-95
	Stool antigen	85-95	85-95
	Serology	70-90	70-90

Fischbach W et al. Sk2 Gastroenterol 2016

Non-invasive tests

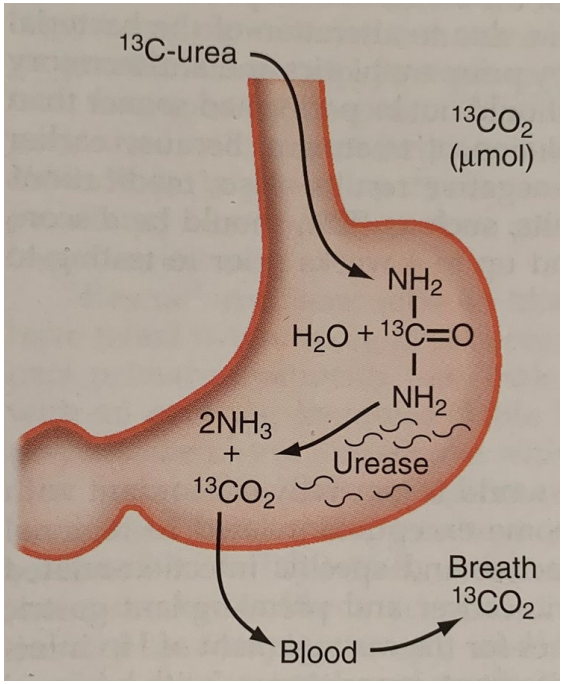
breath test

Detection of isotope-labelled CO2 in breathing air

+ highest sensitivity / specificity among non-invasive methods (95%)
+ suitable for eradication control

– Bacterial overgrowth
– Costs (personnel expenses!)

$$CO(NH_2)_2 + H_2O \xrightarrow{\text{urease}} 2NH_3 + CO_2$$



Fischbach W. Z et al. Gastroenterol. 2016 Apr;54(4):327-63.
Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30.
Walsh JH et al. N Engl J Med 1995; 333:984-91

Non-invasive tests

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$$CO(NH_2)_2 + H_2O \xrightarrow{\text{urease}} 2NH_3 + CO_2$$

Serology

Detection of H. pylori IgG antibodies in serum

+ Not affected by GI bleeding or reduced germ density
– Not suitable for eradication control (antibodies positive for several years

Stool antigen test

Detection of monoclonal antibodies against H. pylori

+ eradication control
+ inexpensive
– Influenced by PPI and antibiotics

Fischbach W. Z et al. Gastroenterol. 2016 Apr;54(4):327-63.
Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30.
Walsh JH et al. N Engl J Med 1995; 333:984-91

Invasive tests

Histology

updated Sydney Classification

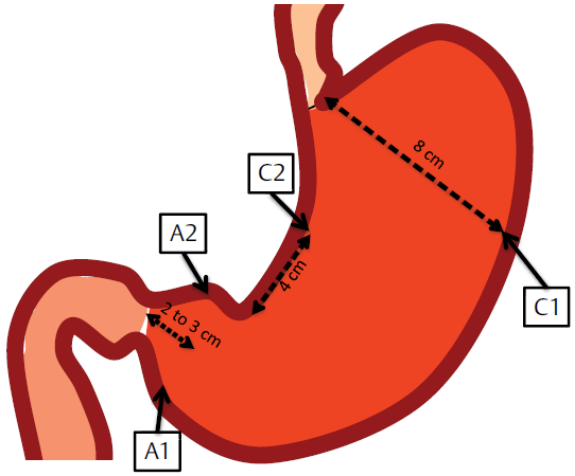
Fischbach W. Z et al. Gastroenterol. 2016 Apr;54(4):327-63.
Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30
Dixon MF et al. Am J Surg Pathol 1996; 20:1161–1181.

Invasive tests

Histology

At least 4 biopsies according to the updated Sydney Classification. Biopsy lesions + incisura separately.

+ Simultaneous diagnosis of inflammation, atrophy, intestinal Metaplasia, dysplasia, neoplasia...
– investigator dependend, invasive



Statement 4: For assessment of *H. pylori* gastritis, a minimum standard biopsy setting is two biopsies from the antrum (greater and lesser curvature 3 cm proximal to the pyloric region) and two biopsies from the middle of the body. Additional biopsy from the incisura is considered for detection of precancerous lesions.

Level of evidence: 2b **Grade of recommendation: B**

detect sites of increased germ density
as well as
sites with increased prevalence of premalignant lesions

Fischbach W. Z et al. Gastroenterol. 2016 Apr;54(4):327-63.
Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30
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Invasive tests

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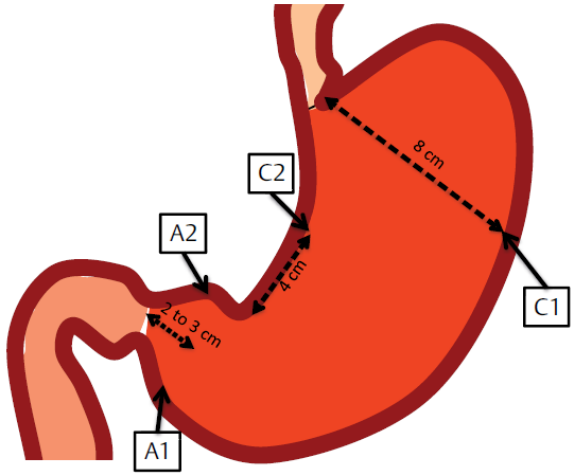


rapid urease test

How many bx and where ?

+ rapid results and immediate therapy
– false negativ in case of GI bleeding or reduced germ density
– False positive rare but possible for urease pos bacteria (eg citrobacter, klebsiella…)
– not recommended as a test for H. pylori eradication assessment after treatment

Culture

How many bx and how transfere to lab?

+ resistance testing

– time-consuming, up to 14 days
– worst sensitivity

Fischbach W. Z et al. Gastroenterol. 2016 Apr;54(4):327-63.
Chey WD, et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30
Dixon MF et al. Am J Surg Pathol 1996; 20:1161–1181.

False positive results

- Serology (current/past infection, cross-reactive AB)
- Other urease pos germs in bacterial overgrowth
- Stool antigen test: bleeding (cross-reaction)

False negative results

- After partial gastric resection (breath test)
- Low colonisation with H. pylori (PPI, antibiotics, atrophy...)
  - PPI discontinued 2 weeks, antibiotics 4 weeks
- Acute bleeding esp. Urease and stool antigen
- Carcinoma, lymphoma

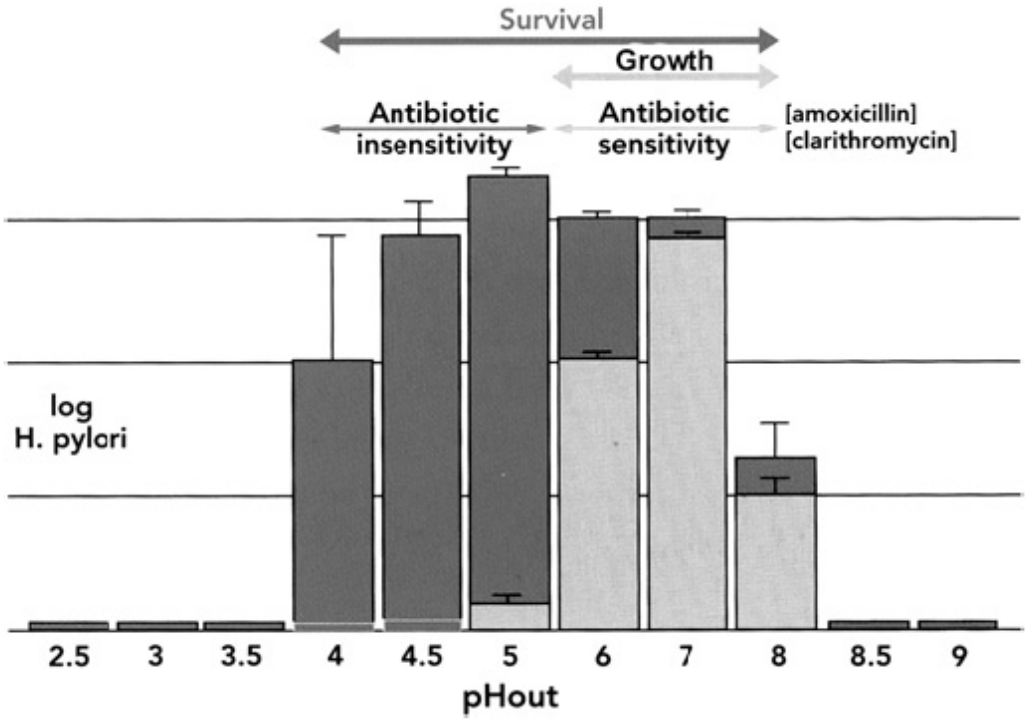
Fischbach 2016
Gisbert JP. 2004 2006
Laine 2005, Brandi G
Kim 2014

Treatment

Why PPI

replication pH 6 and 7

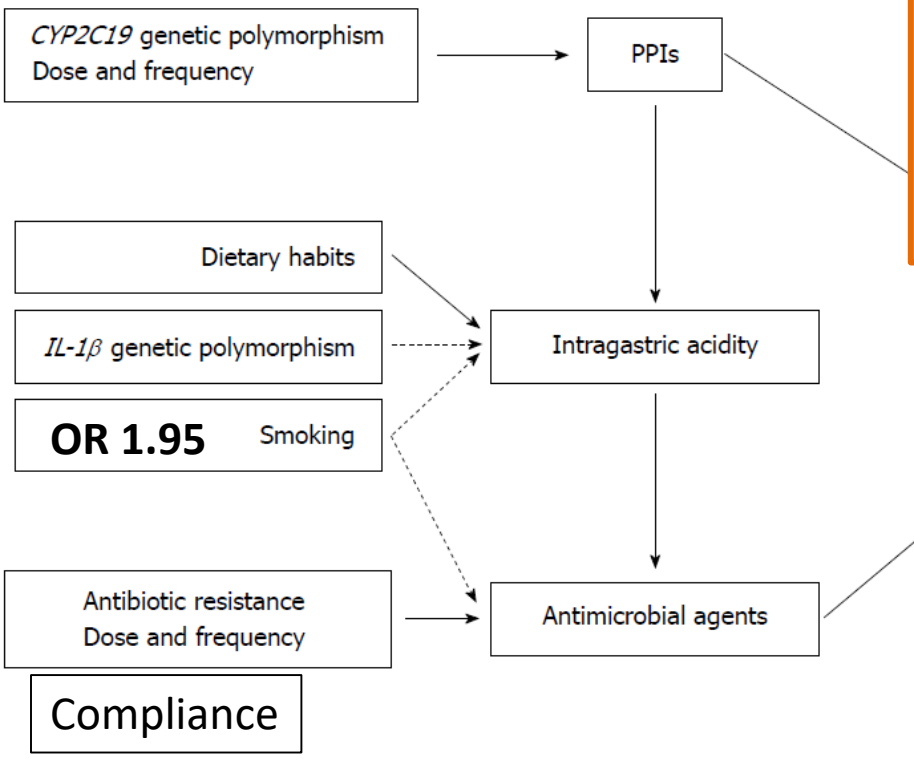
→ susceptible to antibiotics such as clarithromycin or amoxicillin



Graham DY et al. Gut. 2010 Aug;59(8):1143-53.

Factors that influence treatment outcome?

Factors that influence treatment outcome



Impact of cytochrome P450 2C19 genotypes on metabolism of proton pump inhibitors

	Genotype	Ratio (Asian)	Ratio (Caucasian)	Metabolism of PPIs
HomEM	wt/wt	30%-40%	70%	At highest rates
HetEM	wt/m1 or wt/m2	45%-55%	25%-27%	At moderate rates
PM	m1/m2	13%-23%	3%-5%	At lowest rates

HomEM: Homozygous extensive metabolizer; HetEM: Heterozygous extensive metabolizer; PM: Poor metabolizer; PPIs: Proton pump inhibitors; wt: Wild-type allele; m1/m2: Mutated alleles.

Maastricht V / Florence Consensus Report 2016:

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.

Level of evidence: low **Grade of recommendation: weak**

Tang HL. PLoS One. 2013 Apr 30;8(4):e62162.
Chao-Hung K. et al. . World J Gastroenterol. 2014 Nov 21; 20(43): 16029–16036.
Malfertheiner P et al. Gut 2017; 66: 6-30.
Smith 2015, Psarertpetmanee 2013

Main factor ClaR

Statement 6: It is recommended to perform clarithromycin susceptibility testing when a standard clarithromycin-based treatment is considered as the first-line therapy, except in populations or regions with well documented low clarithromycin resistance (<15%). This test can be performed either by a standard method (antibiogram) after culture or by a molecular test directly on the gastric biopsy specimen.

Level of evidence: very low **Grade of recommendation: weak**

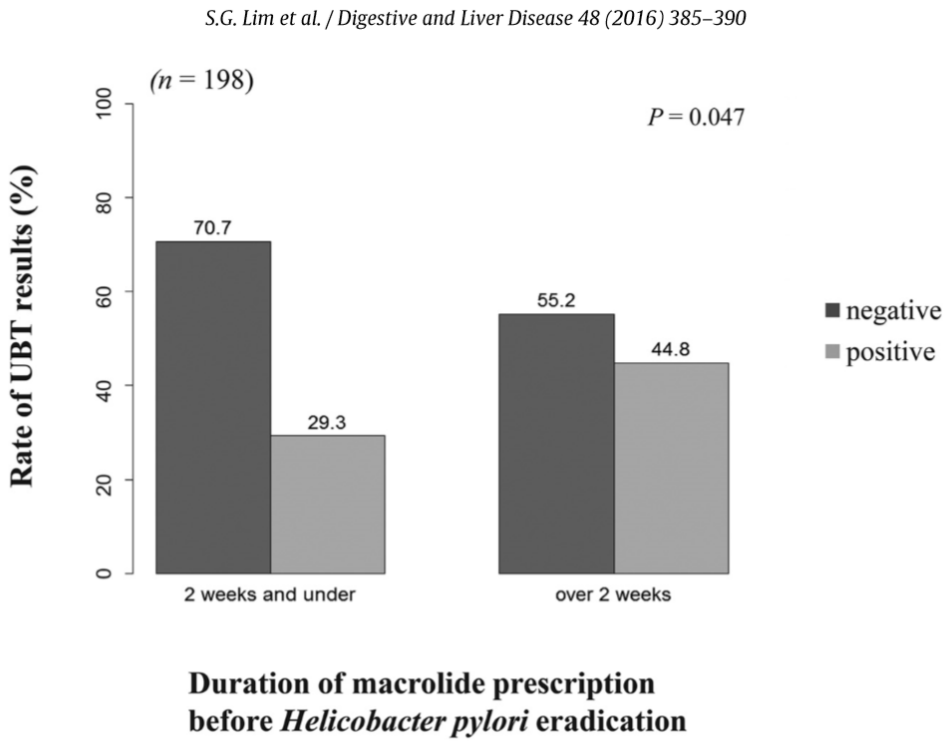
Statement 7: After a first failure, if an endoscopy is carried out, culture and standard antimicrobial susceptibility testing (AST) are recommended to tailor the treatment, except if a bismuth-based quadruple therapy is considered.

Level of evidence: weak **Grade of recommendation: strong**

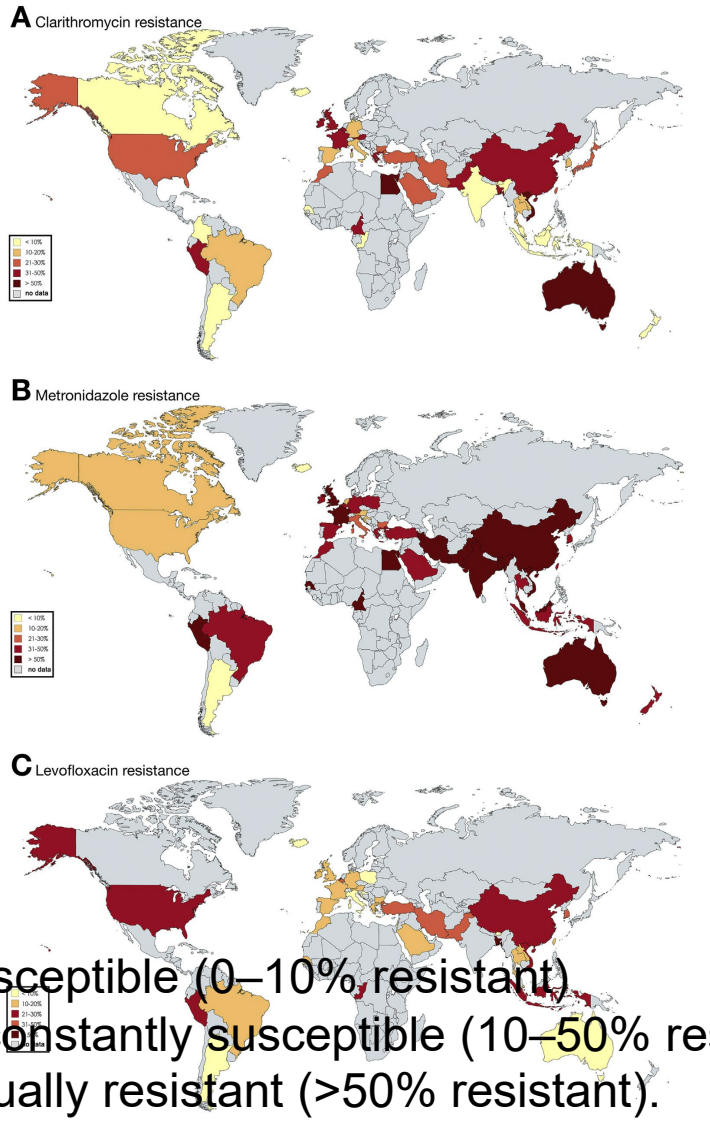
Individual- and population-based susceptibility

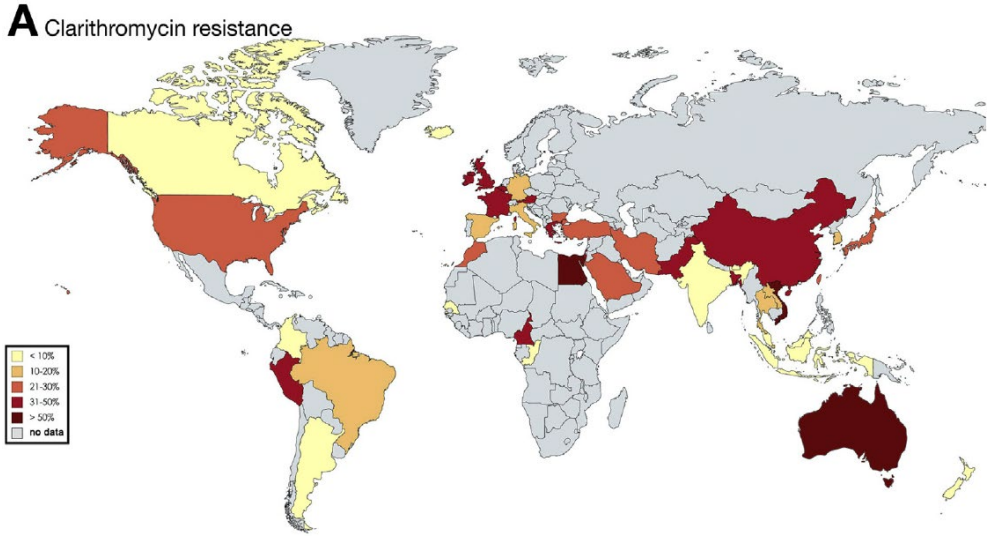
Individual- and population-based susceptibility

- For every patient a history of any prior use of an key antibiotic will identify likely antibiotic resistance



Individual- and **population**-based susceptibility





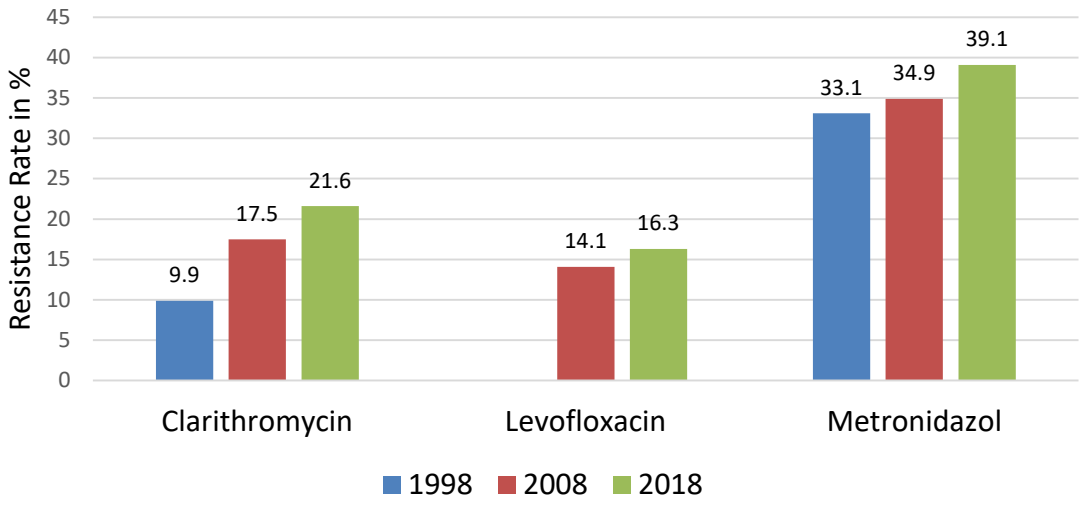
susceptible (0–10% resistant)
inconstantly susceptible (10–50% resistant)
usually resistant (>50% resistant).

Pooled prevalence (2006–2016) of resistance

Savoldi 2018

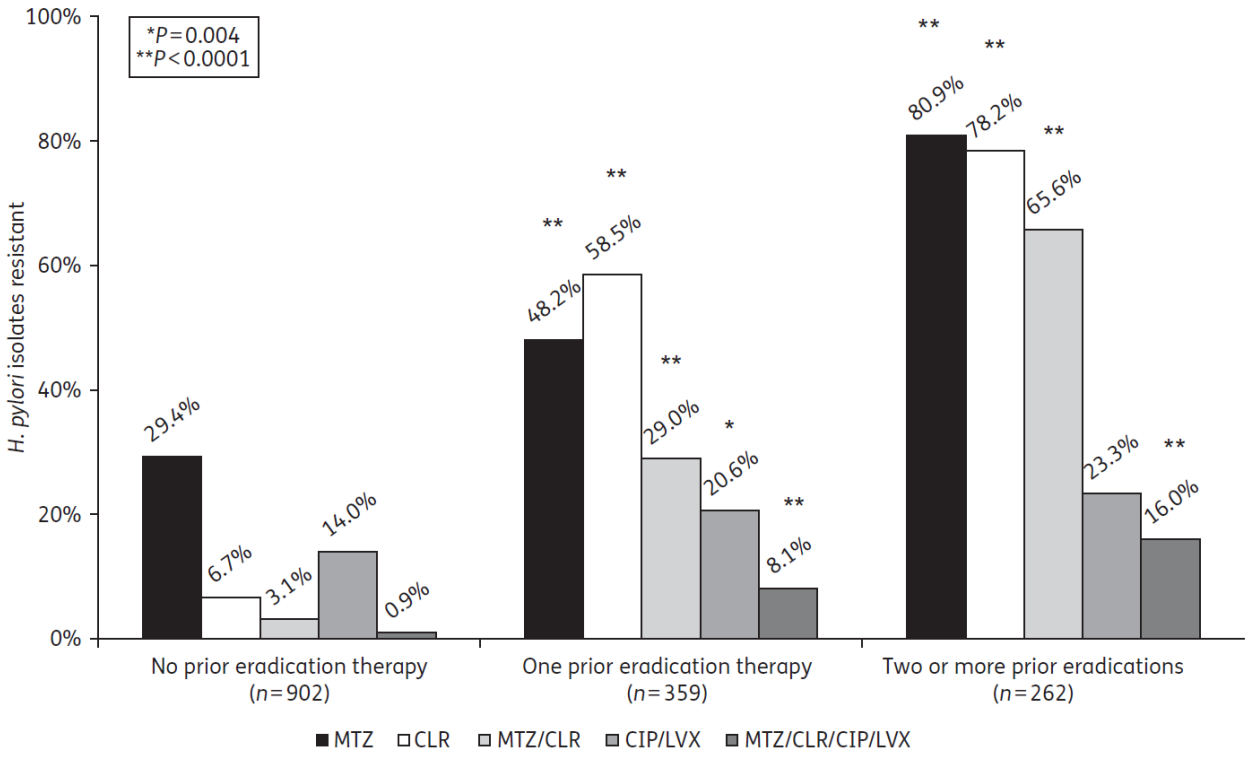
- Increasing resistance in Europe
- Clarithromycin as the main reason for therapy failure in triple therapy
- Resistance to amoxicillin very rare
- Metronidazole resistance can be overcome with higher doses longer duration, in vivo probably still effective

Evolution of primary antimicrobial resistance of H. pylori in Europe (1998-2018)



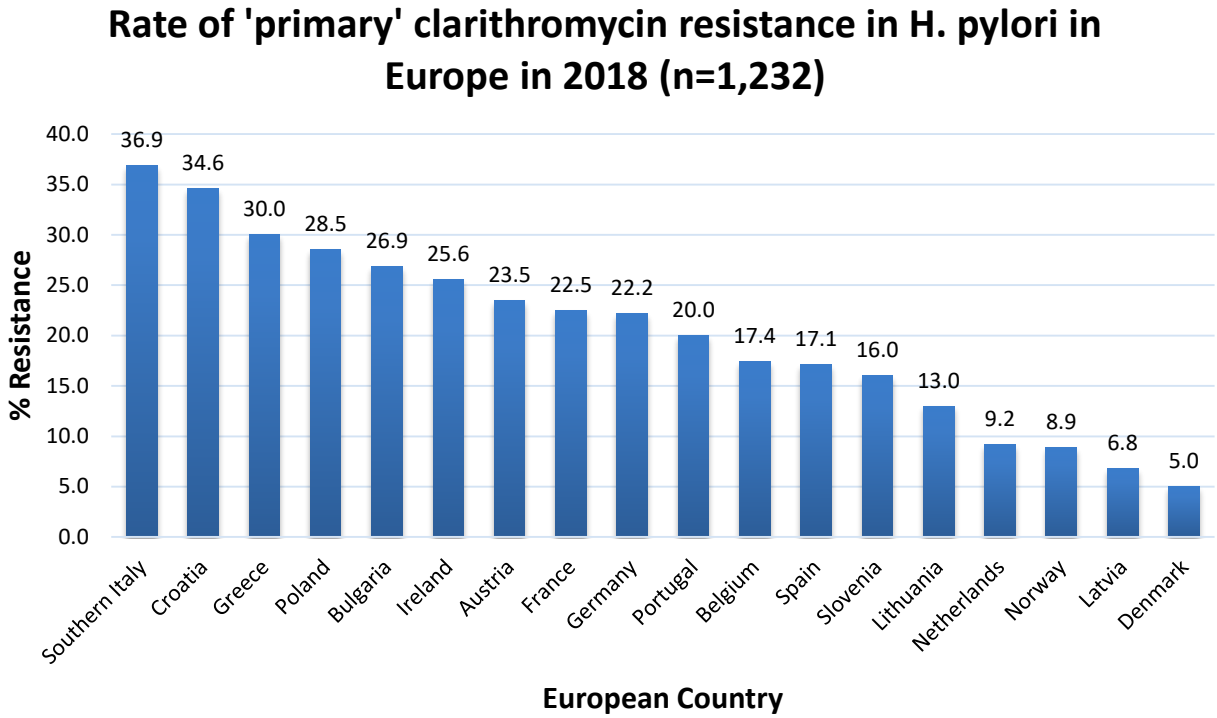
Fischbach W. Z et al. Gastroenterol. 2016 Apr;54(4):327-63.
Savoldi A et al. Gastroenterology. 2018 Nov;155(5):1372-1382.e17.
Megraud F. et al. Presentation UEGW 2019.

Secondary resistance data



Wüppenhorst N et al. J Antimicrob Chemother. 2014 Nov;69(11):3127-33.

H. pylori resistance to clarithromycin



Megraud F. et al. Presentation UEGW 2019.

Primary ClaR

- 7.5% Kantonsspital Basel 2000 (1994 3%)

Lehmann et al 2000

- 12% Tessin 1996-1997

Maggi 2000

Patients	MTZ^R*	CLA^R*	AMO^R*	MTZ^R and CLA^R
Males (n=72)	15 (10.6%)	8 (5.65%)	0	6 (4.2%)
Females (n=70)	26 (18.3%)	9 (6.35%)	0	5 (3.5%
Total (n=142)	41 (28.9%)	17 (12.0%)	0	11 (7.7%)

*MTZ^R, CLA^R, AMO^R, resistant to metronidazole, clarithromycin, amoxycillin, respectively. Values in brackets are percentage of the whole population.

- 9% in Baden Switzerland 2005

Soltermann 2005

Cultural Recovery and Determination of Antimicrobial Susceptibility in *Helicobacter pylori* by Using Commercial Transport and Isolation Media

B. Yuen, R. Zbinden, M. Fried, P. Bauerfeind, M. Bernardi

- Culture of 79 RUT pos Bx in Zurich, successful in 55 of 79
- 22% Resistance to clarithromycin in 12 patients
  - five native Swiss patients (19%) and in seven non-Swiss patients (25%)
- 27 % Resistance to metronidazole
- 9% showed resistance both to metronidazole and to clarithromycin
- No resistance to amoxicillin

Susceptibility data from 1992 to 2003 of Zurich

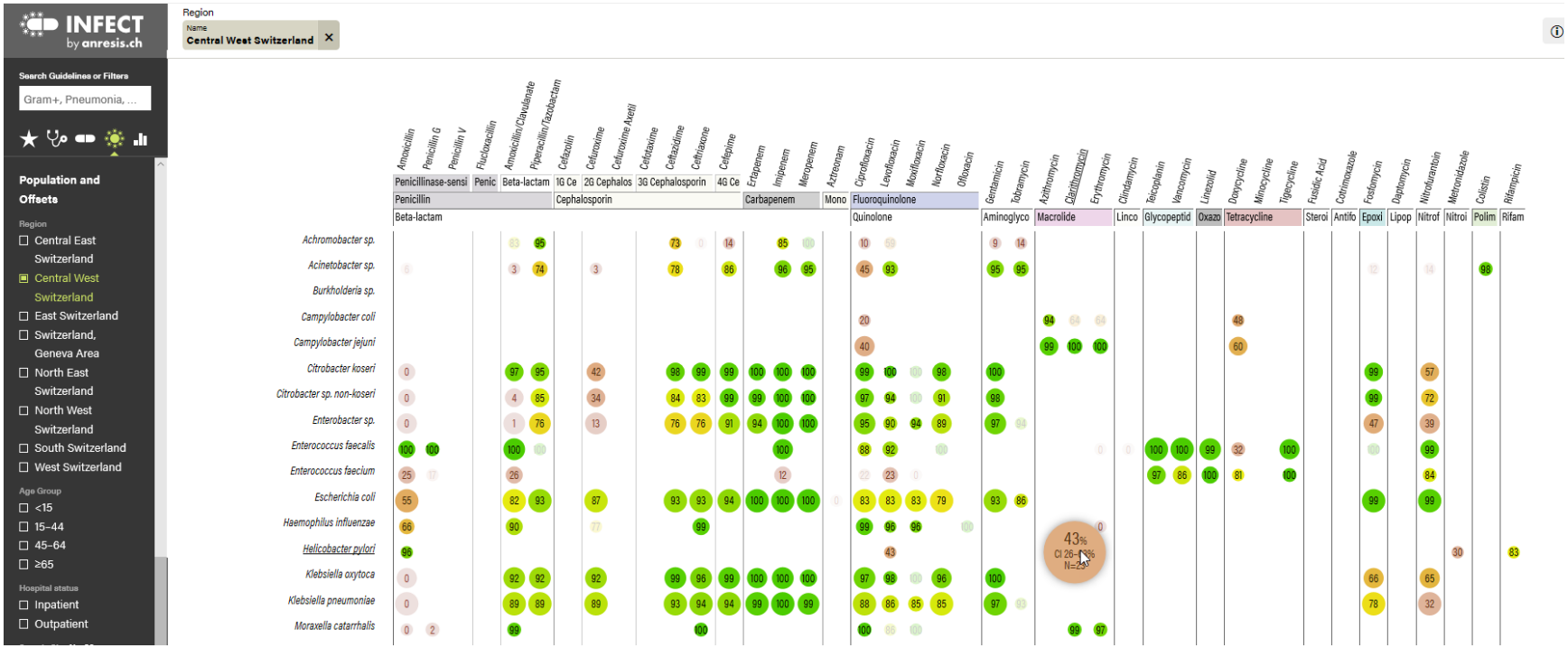
Table 1
Helicobacter pylori **antimicrobial resistance by year in the university hospital (1992–2003) and in a district hospital (2000).**

	Total patients	Positive culture (%)	Susceptibility testing	Metronidazole resistance (%)	Clarithromycin resistance (%)	Amoxicillin resistance
1992	163	91 (56)	82	64 (78)	-	-
1993	314	149 (47)	130	93 (72)	-	-
1994	288	107 (37)	94	43 (46)	-	-
1995	82	42 (51)	34	14 (41)	-	-
1996	48	22 (45)	22	8 (36)	2 (9)	0
1997	256	90 (35)	76	28 (36)	11 (14)	0
1998	69	24 (34)	24	15 (62)	7 (29)	0
1999	19	8 (42)	7	4 (57)	5 (71)	0
2000	21	10 (48)	10	5 (50)	6 (60)	0
2001	25	14 (56)	11	9 (82)	5 (45)	1
2002	34	18 (53)	14	9 (64)	7 (50)	0
2003	27	13 (48)	13	6 (46)	6 (46)	1
2000	79[a]	55 (70)	55[b]	15 (27)	12 (22)	0

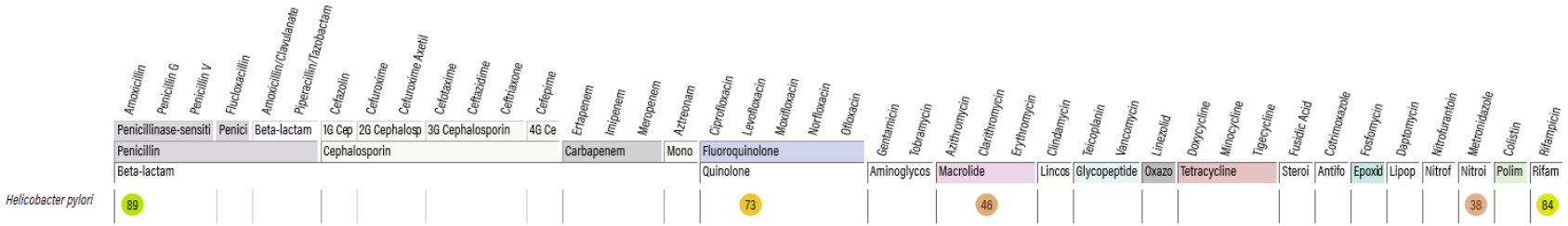
[a] Consecutive patients with positive rapid urease test (HUT test); [b] Positive culture and susceptibility testing

Yuen B. Infection. 2005 Apr;33(2):77-81

Latest 365 days of bacterial resistance data from the Swiss Center for Antibiotic resistance

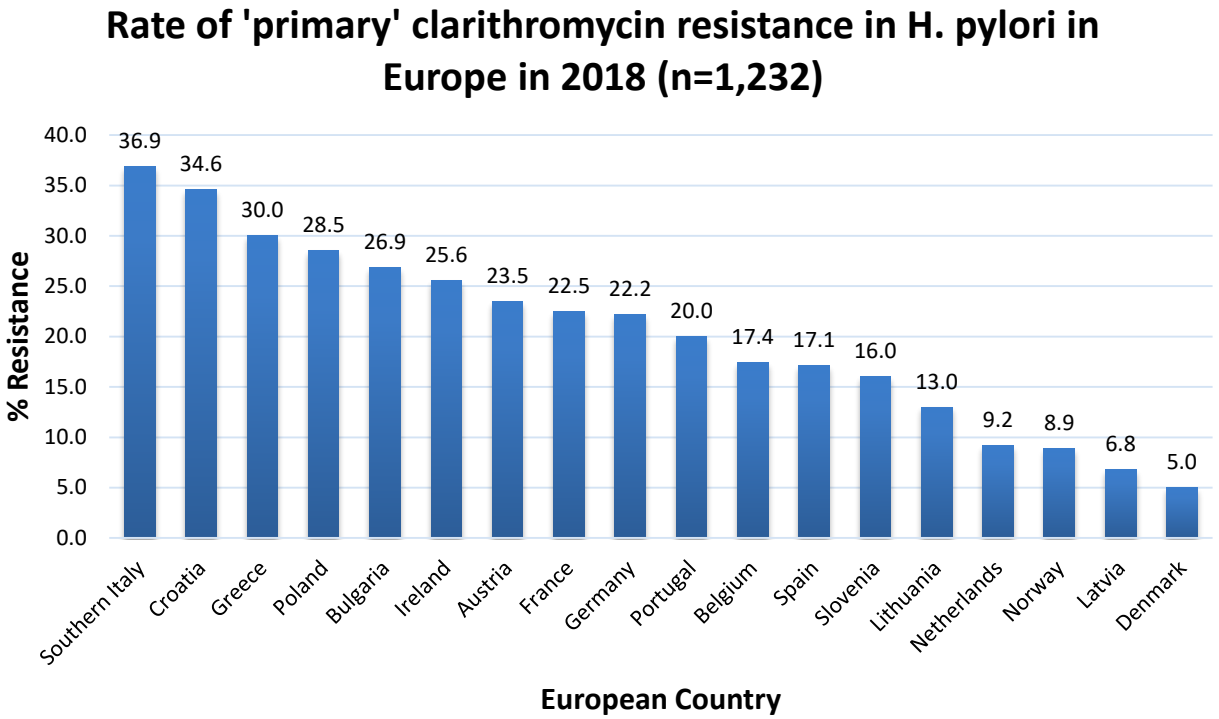


Bern N=23, CH= 243



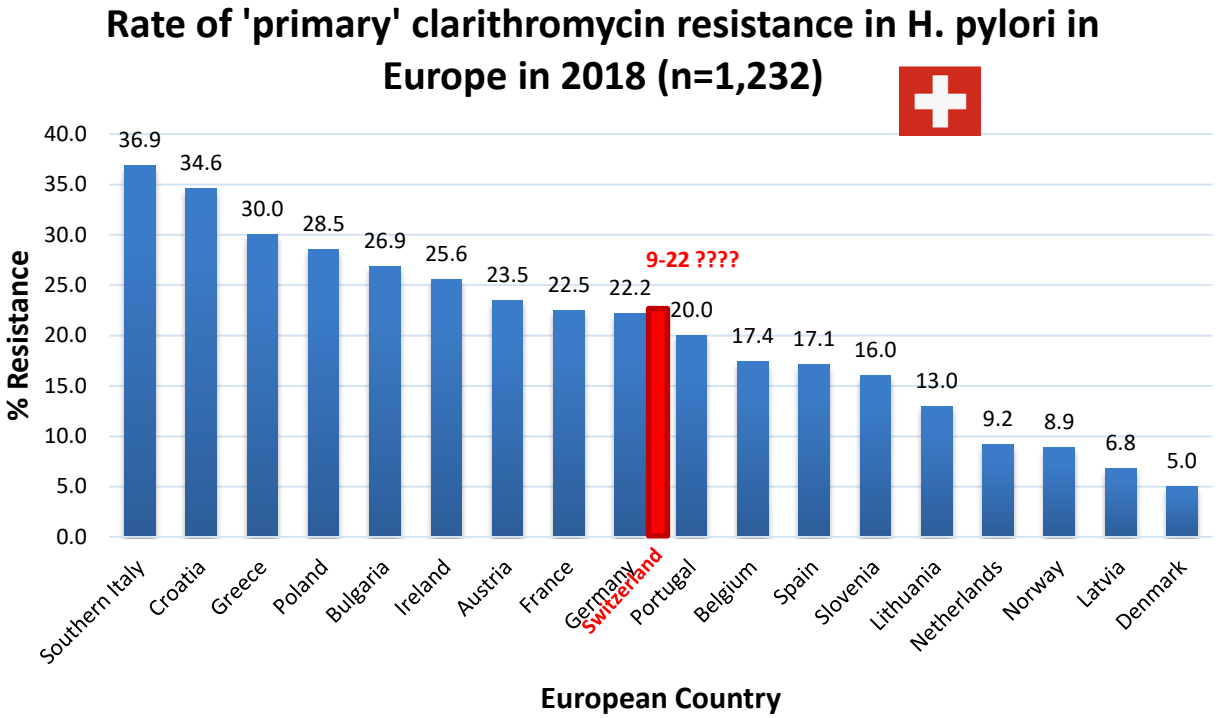
Cave: most probably secondary resistance data – since according to guideline ST only after two failed treatments

ClaR



Megraud F. et al. Presentation UEGW 2019.
Yuen B. Infection. 2005 Apr;33(2):77-81
Soltermann 2005

ClaR



Megraud F. et al. Presentation UEGW 2019.
Yuen B. Infection. 2005 Apr;33(2):77-81
Soltermann 2005

Treatment Maastricht V

Generally only therapy regimes with >80% eradication rate and <5% NWK.

Which treatment strategies does exist? Which antibiotics work for H. pylori?

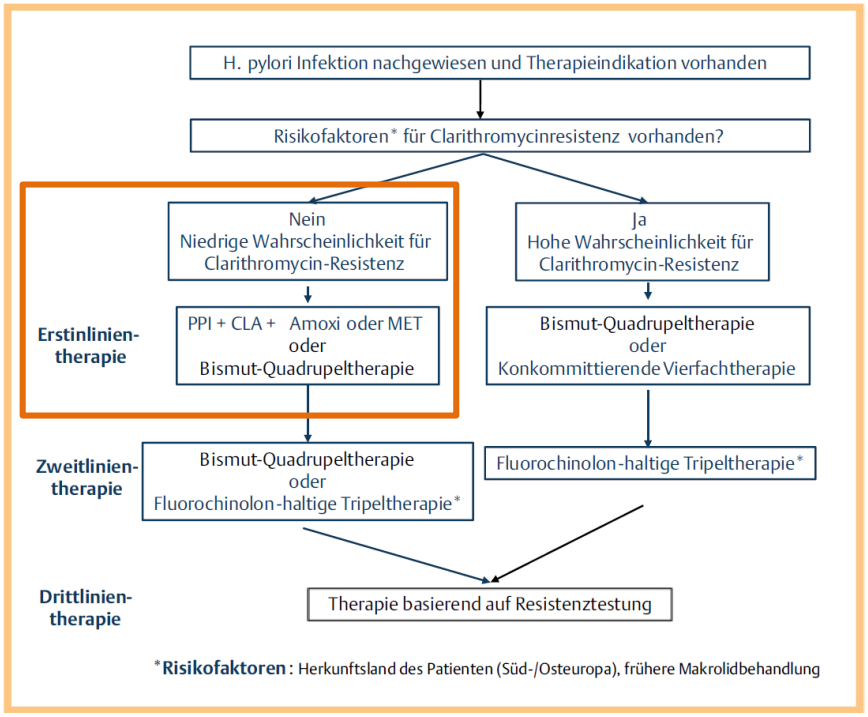
Name	Linie	Schema	Dosierung	Dauer
Standard-Triple-Therapie (italienisch)	1°-Linie	PPI[1] Clarithromycin 250 – 500 mg Metronidazol 400 – 500 mg	1-0-1 1-0-1 1-0-1	7 – 14 Tage
Standard-Triple-Therapie (französich)	1°-Linie	PPI[1] Clarithromycin 500 mg Amoxicillin 1000 mg	1-0-1 1-0-1 1-0-1	7 – 14 Tage
Bismut-haltige Vierfach-therapie[2]	1°-Linie oder 2°-Linie nach Standard-TT	PPI[2] Bismut-Kalium-Salz 140 mg Tetracyclin 125 mg Metronidazol 125 mg	1-0-1 3-3-3-3	10 Tage
kombinierte („konkomit-tierende) Vierfachtherapie	1°-Linie	PPI[1] Clarithromycin 500 mg Amoxicillin 1000 mg Metronidazol 400 – 500 mg	1-0-1 1-0-1 1-0-1 1-0-1	7 Tage
Fluorochinolon-Triple-therapie	2°-Linie	PPI[1] Levofloxacin 500 mg/ Moxifloxacin 400 mg Amoxicillin 1000 mg[3]	1-0-1 1 x 1 1-0-1	10 Tage

[1] Omeprazol 20 mg, Pantoprazol 40 mg, Esomeprazol 20 mg, Lansoprazol 30 mg, Rabeprazol 20 mg.
[2] Fixe Kombination (Pylera®) zugelassen in Kombination mit Omeprazol 20 mg.
[3] Bei Penicillinunverträglichkeit Rifabutin 150 mg 1-0-1.

Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.

First Line (low risk)

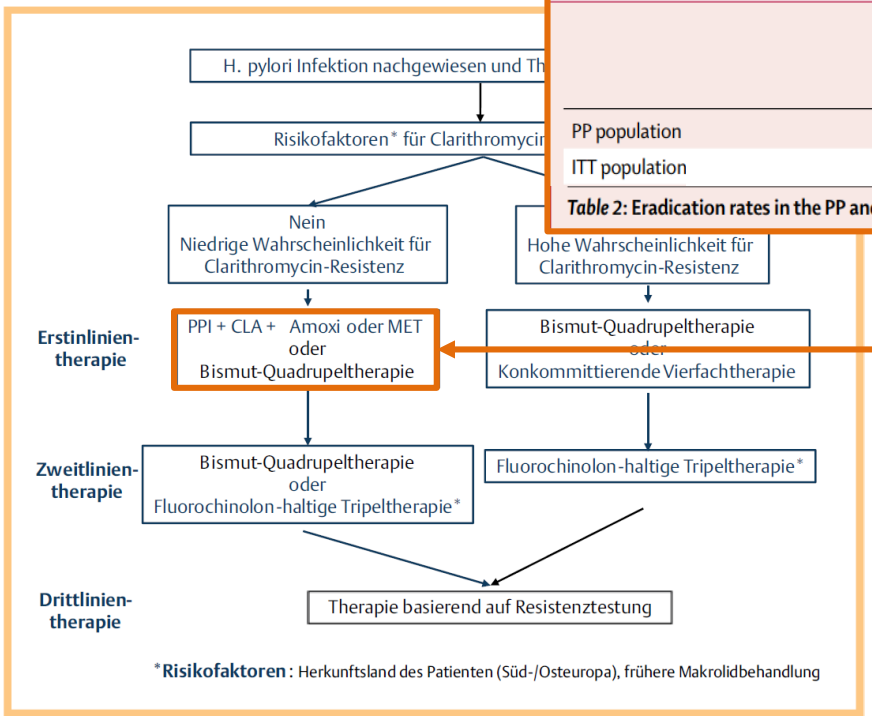
DGVS Leitlinie 2016:



Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Malfertheiner P et al. Gut 2017; 66: 6-30.

First Line (low risk)

DGVS Leitlinie 2016:



Bismuth quadruple therapy (10 d) vs.standard triple therapy (7 d)

	Quadruple therapy	Standard therapy	95% CI for difference between quadruple and standard therapy	p value
PP population	166/178 (93%); 88·5–96·5	112/161 (70%); 61·8–76·6	15·1–32·3	<0·0001
ITT population	174/218 (80%); 73·9–84·9	123/223 (55%); 48·6–62·1	15·5–33·3	<0·0001

Table 2: **Eradication rates in the PP and ITT populations**

Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Mafertheiner P. Lancet. 2011 Mar 12;377(9769):905-13.
Yuan Y. Cochrane Database Syst Rev. 2013 Dec 11;(12):CD008337.

	Triple therapy (n=540)		Concomitant therapy (n=540)		Bismuth quadruple therapy (n=540)		p value
	n (%) or n/N (%)	95% CI	n (%) or n/N (%)	95% CI	n (%) or n/N (%)	95% CI	
Eradication frequency with first-line therapy							
Intention-to-treat analysis	452 (84%)*	80·4–86·6	464 (86%)	82·7–88·6	488 (90%)*	87·6–92·6	0·005
Per-protocol analysis	446/508 (88%)†‡	84·7–90·4	453/494 (92%)‡§	88·9–93·8	461/480 (96%)†§	93·9–97·5	<0·0001
Eradication frequency with second-line therapy							
Intention-to-treat analysis	46/53 (87%)	75·2–93·5	21/28 (75%)	56·6–87·3	11/13 (85%)	57·8–95·7	0·40
Per-protocol analysis	47/48 (98%)	89·1–99·6	20/24 (83%)	64·1–93·3	11/12 (92%)	64·6–98·5	0·08
Overall eradication frequency after two treatments							
Intention-to-treat analysis	499 (92%)	89·9–94·4	485/540 (90%)	87–92·1	499 (92%)	89·9–94·4	0·21
Per-protocol analysis	493/494 (100%)	98·9–100	472/476 (99%)	97·9–99·7	472/473 (100%)	98·8–100	0·21

Of the patients who took less than 80% of the study drugs, *Helicobacter pylori* was successfully eradicated in six (55%) of 11 in the triple therapy group , 11 (61%) of 18 in the concomitant therapy group, and 27 (79%) of 34 in the bismuth quadruple therapy group. However, these individuals were excluded from per-protocol analysis according to our protocol. *p=0·001 for bismuth quadruple therapy versus triple therapy in the intention-to-treat analysis. †p<0·0001 for bismuth quadruple therapy versus triple therapy in the per protocol analysis. ‡p=0·042 for concomitant therapy versus triple therapy in the per-protocol analysis. §p=0·024 for bismuth quadruple therapy versus concomitant therapy in the per-protocol analysis.

***Table 2*: Eradication frequencies with first-line and second-line therapies**

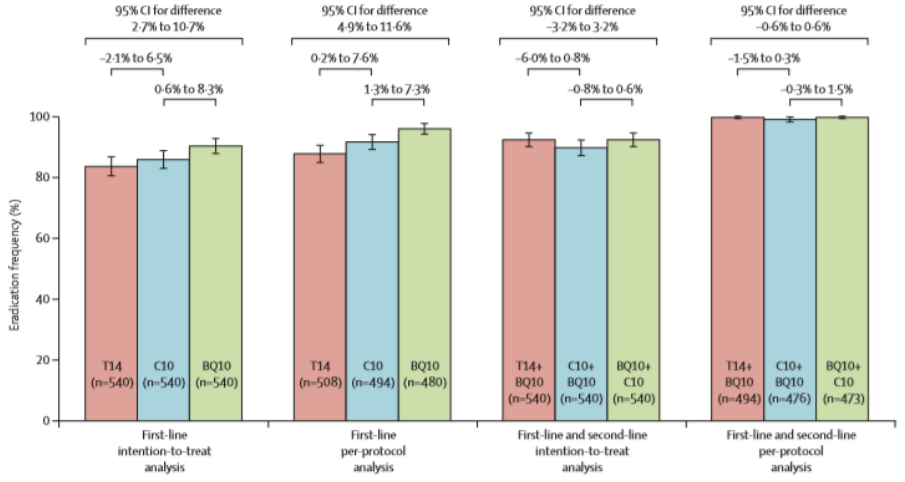


***Figure 2*: Efficacies of first-line and second-line anti-*Helicobacter pylori* treatments**
T14=triple therapy for 14 days. C10=concomitant therapy for 10 days. BQ10=bismuth quadruple therapy for 10 days.

Jyh-Ming Liou, Lancet 2016 (Taiwan)

Pylera

Bismuth-Quadrupel-Therapy

- 140 mg Bismuthcitrat – 125 mg Metro – 125 mg Tetracyclin

$\Rightarrow$ 4x3/day + PPI

$\Rightarrow$ 120 capslues 87.80 CHF => 10 days therapy (14 days in areas of high Metronidazole resistance?)

Malfertheiner et al. Lancet 2011

Standard triple 7 vs 14 d?

Name	Linie	Schema	Dosierung	Dauer
Standard-Triple-Therapie (italienisch)	1°-Linie	PPI[1] Clarithromycin 250 – 500 mg Metronidazol 400 – 500 mg	1-0-1 1-0-1 1-0-1	7 – 14 Tage
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[1] Omeprazol 20 mg, Pantoprazol 40 mg, Esomeprazol 20 mg, Lansoprazol 30 mg, Rabeprazol 20 mg.
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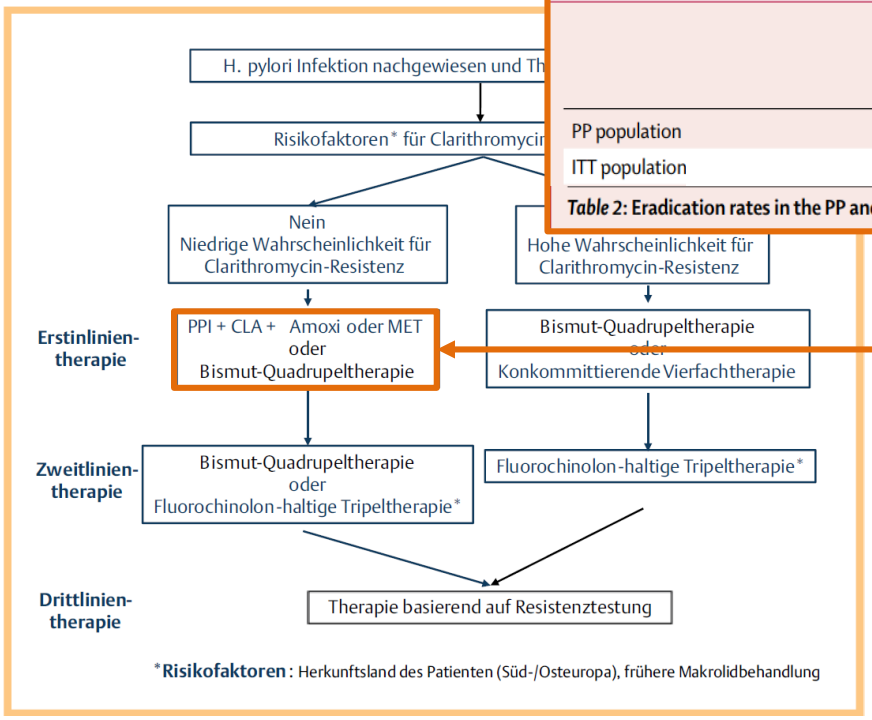
Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.

First Line (low risk)

DGVS Leitlinie 2016:



Bismuth quadruple therapy (10 d) vs.standard triple therapy (7 d)

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Table 2: Eradication rates in the PP and ITT populations

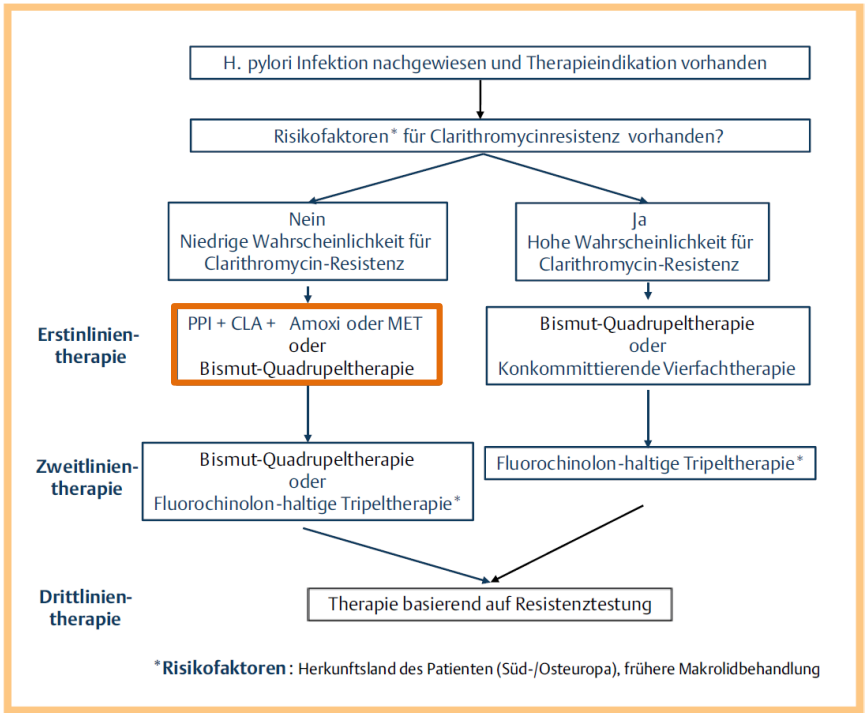
Standard Triple Therapy
7 vs. 10 vs. 14 days

- Eradication rate 7 vs. 14 days: 72.9% vs. 81.9% (45 studies) NNT 11
- Eradication rate 10 vs. 14 days: 78.5 % vs. 84.4% (12 studies) NNT17

Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Mafertheiner P. Lancet. 2011 Mar 12;377(9769):905-13.
Yuan Y. Cochrane Database Syst Rev. 2013 Dec 11;(12):CD008337.

First Line (low risk)

DGVS Leitlinie 2016:



Maastricht V / Florence 2016:

Statement 11: The treatment duration of PPI-clarithromycin based triple therapy should be extended to 14 days, unless shorter therapies are proven effective locally.

Level of evidence: moderate **Grade of recommendation: strong**

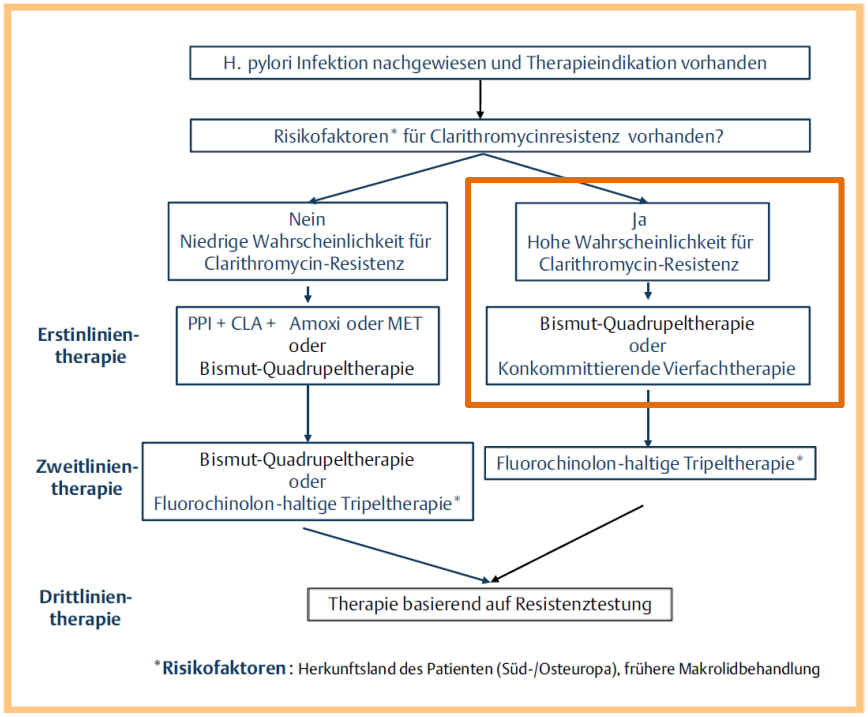
ACG Clinical Guideline 2016:

Regimen	Drugs (doses)	Dosing frequency	Duration (days)
Clarithromycin triple	PPI (standard or double dose)	BID	14
	Clarithromycin (500 mg)		
	Amoxicillin (1 grm) or Metronidazole (500 mg TID)		

Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Chey WD et al. Am J Gastroenterol 2017; 112: 212-39.
Malfertheiner P et al. Gut 2017; 66: 6-30.
Yuan Y. Cochrane Database Syst Rev. 2013 Dec 11;(12):CD008337.

First Line (high risk)

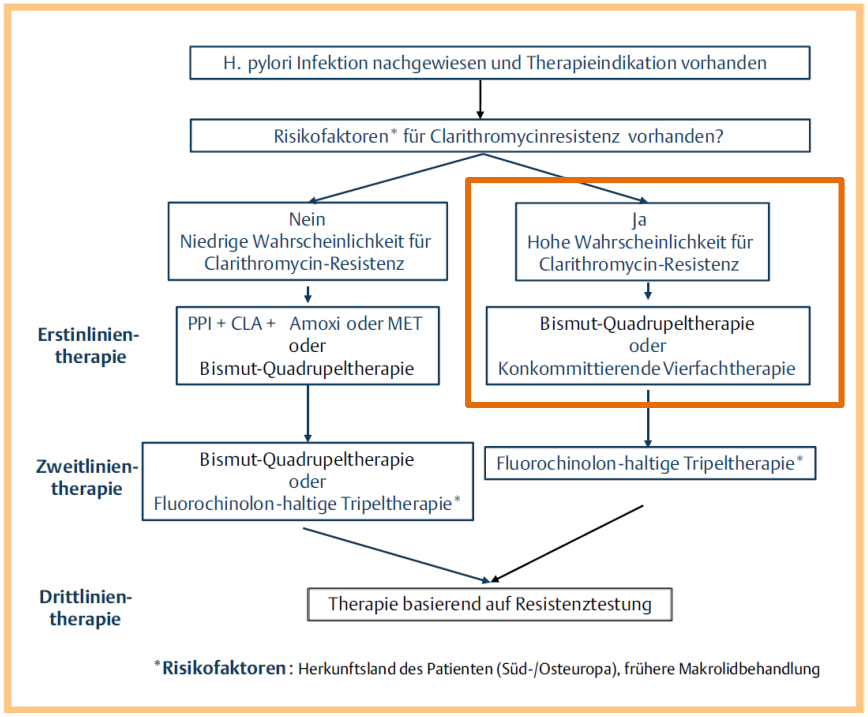
DGVS Leitlinie 2016:

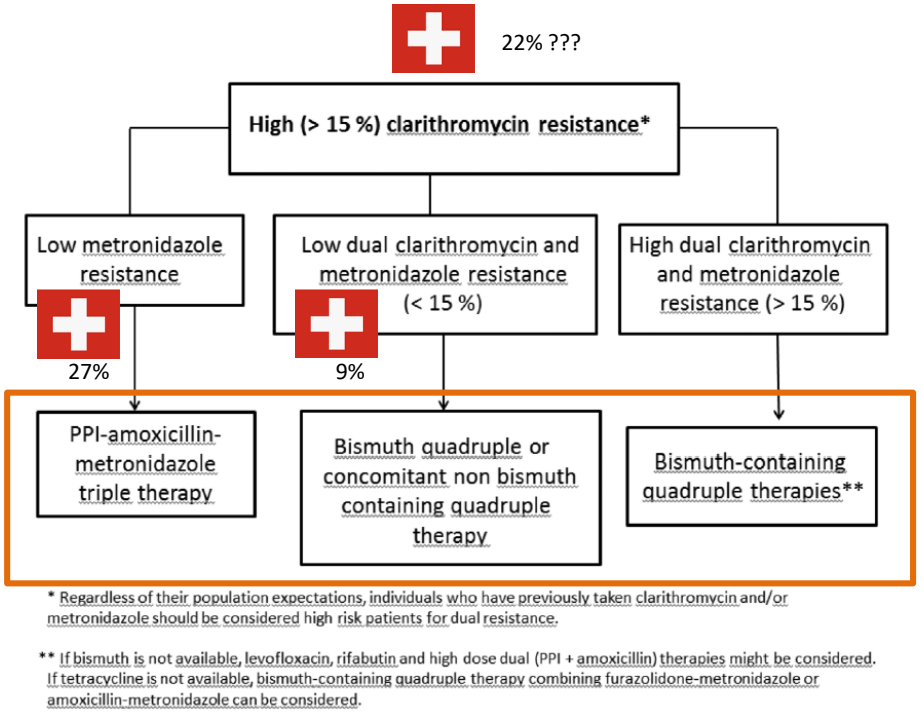


Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Malfertheiner P et al. Gut 2017; 66: 6-30.

First Line (high risk)

DGVS Leitlinie 2016:

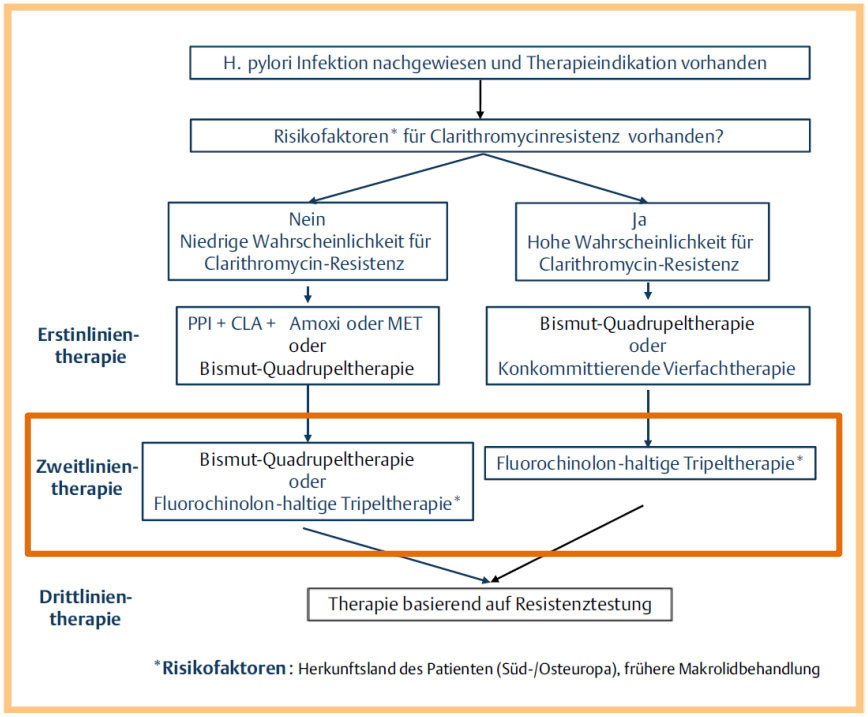


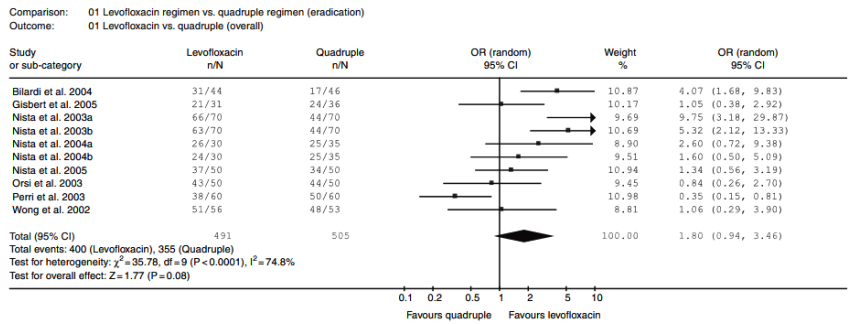


Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Malfertheiner P et al. Gut 2017; 66: 6-30.
Yuen B. Infection. 2005 Apr;33(2):77-81.

2nd Line

DGVS Leitlinie 2016:





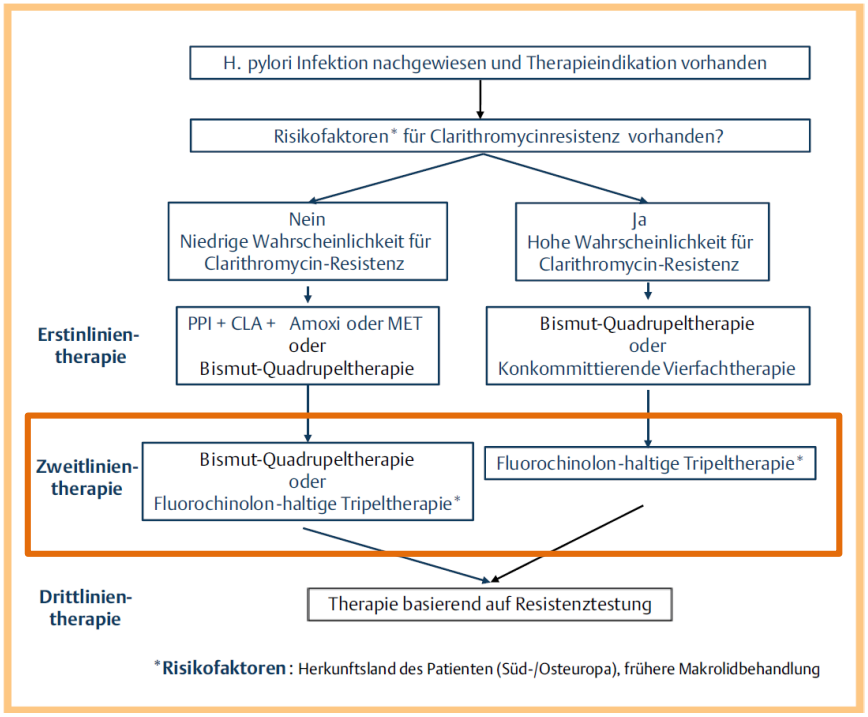
Higher eradication rates with levofloxacin-containing triple compared to quadruple after therapy failure
(81% vs 70%; OR = 1.80)

But no superiority of triple therapy as first-line over quadruple

Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Gisbert JP et all, Aliment Pharmacol, 2006

2nd Line

DGVS Leitlinie 2016:



Maastricht V / Florence 2016:

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.

Level of evidence: very low **Grade of recommendation: weak**

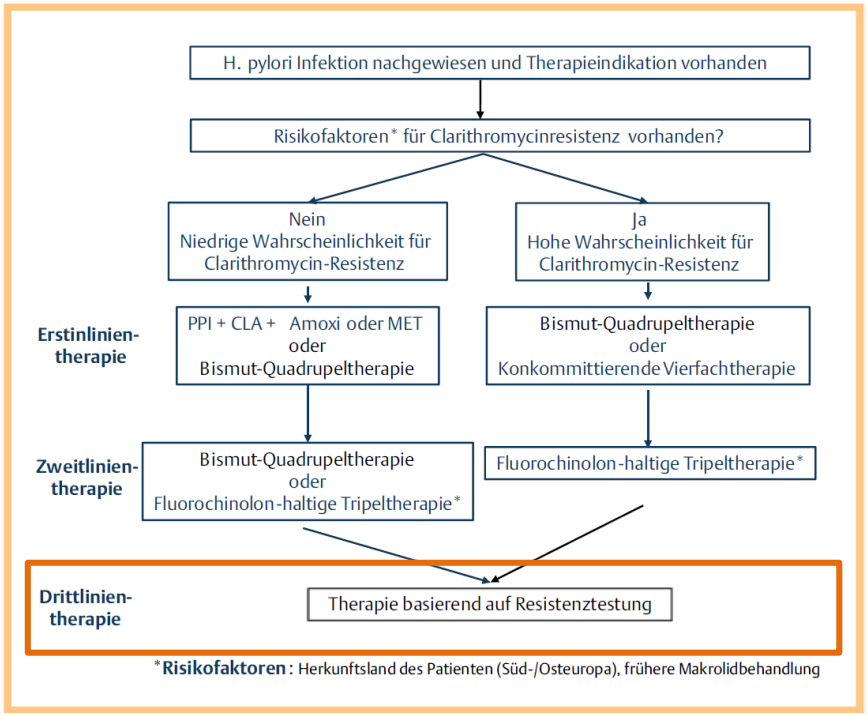
Statement 14: After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended.

Level of evidence: very low **Grade of recommendation: weak**

Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Malfertheiner P et al. Gut 2017; 66: 6-30.

3rd Line

DGVS Leitlinie 2016:



Maastricht V / Florence 2016:

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.

Level of evidence: very low **Grade of recommendation: weak**

- Evidence on efficacy of susceptibility-guided treatment for rescue therapy is very scarce.

Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Malfertheiner P et al. Gut 2017; 66: 6-30.

Meta-analysis, 1008 patients

Rifabutin-containing therapy (including PPI and amoxicillin, 10 d)

Eradication rate (ITT) total 73% (2nd 79%, 3rd 66%, 4th/5th 70%)

But: side effects (22%; myelotoxicity)

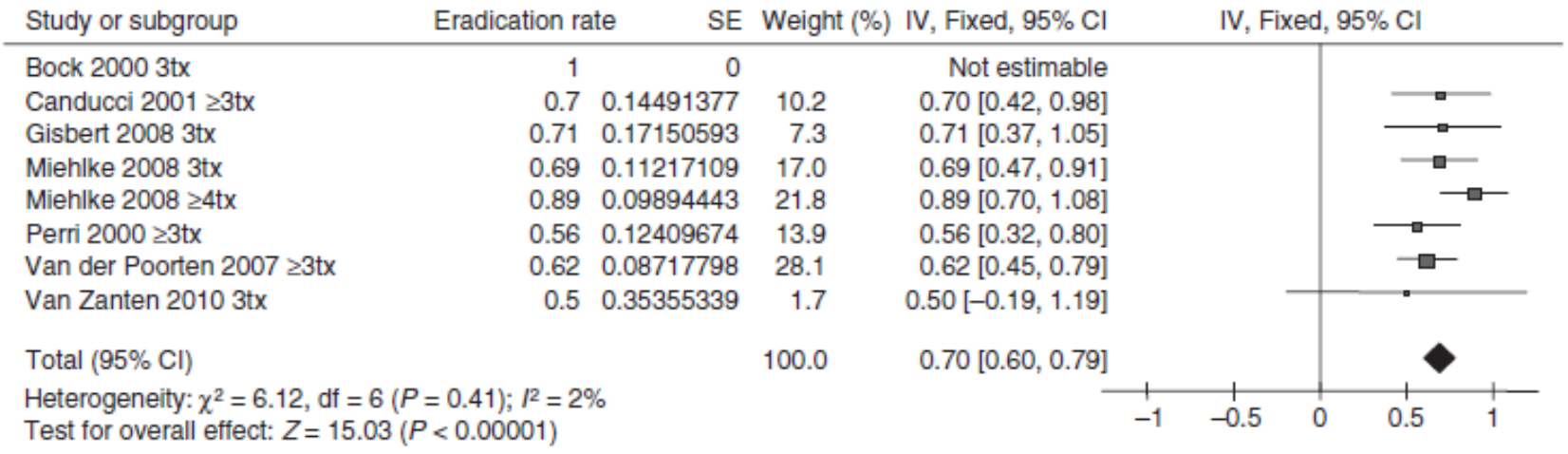


Figure 4 | Efficacy (intention-to-treat analysis) of fourth- or fifth-line rifabutin-containing therapies for the eradication of *Helicobacter pylori* in patients with at least three previous eradication failures.

Gisbert JP, Clavet X. Aliment Pharmacol Ther 2012

Annals of Internal Medicine ORIGINAL RESEARCH

Rifabutin-Based Triple Therapy (RHB-105) for *Helicobacter pylori* Eradication

A Double-Blind, Randomized, Controlled Trial

David Y. Graham, MD; Yamil Canaan, MD; James Maher, MD; Gregory Wiener, MD; Kristina G. Hulten, PhD; and Ira N. Kalfus, MD

Background: Although consensus supports eradication of *Helicobacter pylori* infections, antimicrobial resistance has substantially reduced eradication rates with most current therapies.

Objective: To as
based therapy (RH

Design: Phase 3,
Trials.gov: NCT031

Setting: 55 clinica

Participants: 455
comfort and confir

Intervention: RHB-105 (amoxicillin, 3 g; omeprazole, 120 mg; and rifabutin, 150 mg) versus active comparator (amoxicillin, 3 g, and omeprazole, 120 mg), given as 4 capsules every 8 hours for 14 days.

Measurements: Between-group difference for *H pylori* eradication rate, demonstrated by ^{13}C urea breath test 4 weeks after treatment, analyzed by using the χ^2 test.

Results: In the intention-to-treat population, the eradication rate was higher with RHB-105 than with the active comparator (228 vs. 227 patients, respectively; 83.8% [95% CI, 78.4% to 88.0%] vs.). Eradication rates
ycin or metronida-
he most commonly
ere diarrhea (10.1%
or), headache (7.5%

ere excluded be-
cytochrome P450

Conclusion: These findings suggest potential for RHB-105 as first-line empirical *H pylori* therapy, addressing an unmet need in the current environment of increasing antibiotic resistance.

Primary Funding Source: RedHill Biopharma Ltd.

Ann Intern Med. 2020;172:795-802. doi:10.7326/M19-3734 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 5 May 2020.

Rifabutin is a valuable salvage therapy

But

increasing multi-resistant Tbc germs, so that rifabutin should be used very cautiously

Penicillin allergy?

- Most patients do not have true penicillin hypersensitivity
- After failure of first-line therapy referral for allergy testing for amoxicillin-containing salvage regimens should be considered

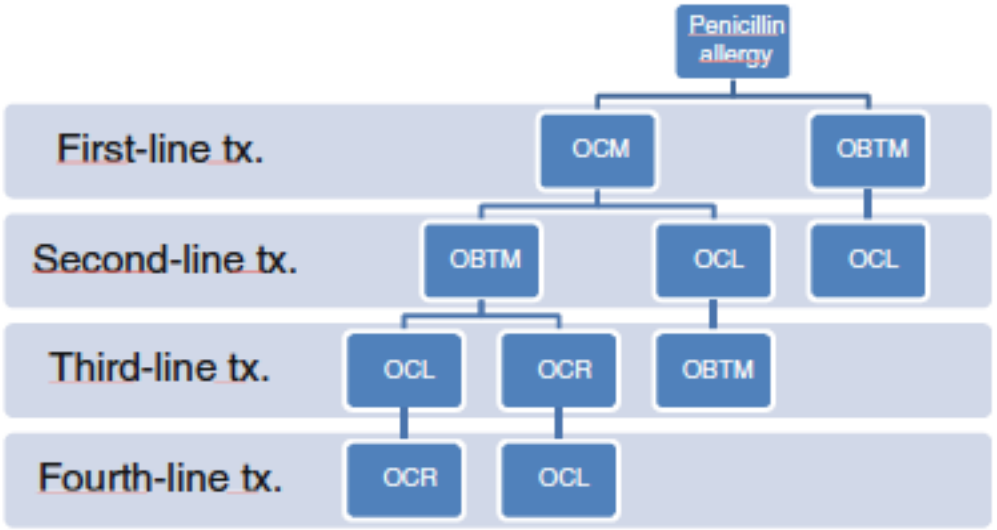


Fig. 1 Flow diagram of subject progress through the phases of the study. *O* omeprazole, *C* clarithromycin, *M* metronidazole, *B* bismuth, *T* tetracycline, *L* levofloxacin, *R* rifabutin

Chen et al 2017 (ACG)
Gisbert JP et al. Dig Dis Sci 2015

Should we test for treatment success after H. pylori eradication therapy?

- After every eradication therapy
  - 4 weeks after the end of antibiotic therapy
  - 2 weeks after end of PPI therapy
- Reality: only 35% of patients are retested
- Non - invasive methods sufficient (except ulcus ventriculi and MALT lymphoma)

Weyermann M. Am J Gastroenterol. 2009 Jan;104(1):182-9.
Fischbach W. Z Gastroenterol. 2016 Apr;54(4):327-63.
Parsonnet J. JAMA. 1999 Dec 15;282(23):2240-5.

You perform a repeat upper endoscopy in a 56-year old man who received a 3 drug (omeprazole, clarithromycin, amoxicillin) eradication therapy for *H pylori* positive duodenal ulcer 2 months ago. At endoscopy an ulcer is found in first part of duodenum. It is biopsied and the only finding is *H pylori* organisms. There is no evidence of malignancy. Which is the most appropriate regime to treat *H pylori* at this time?

- ○ Lansoprazole, clarithromycin, amoxicillin
- ○ Omeprazole, bismuth, metronidazole, doxycycline for one week
- ○ Omeprazole, bismuth, metronidazole for one week
- ○ Omeprazole, clarithromycin, amoxicillin for two weeks
- ○ Omeprazole, metronidazole,

Unless proven effective in the local population doxycycline is not recommended as a substitute for tetracycline hydrochloride.

- ○ Lansoprazole, clarithromycin — 1 %
- ○ Omeprazole, bismuth, metronidazole, doxycycline for one week — 36 %
- ○ Omeprazole, bismuth, metronidazole for one week — 5 %
- ○ Omeprazole, clarithromycin, amoxicillin for two weeks — 11 %
- ◉ Omeprazole, metronidazole, amoxicillin for one week ✔ Richtige Antwort ausgewählt — 46 %

Further Reading

NICE CG184 (2014) Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management

Take – Home – Messages

- Be familiar with individual resistance rate
- Longer therapy duration
- Eradication control at the earliest 4 weeks after stopping antibiotics and 2 weeks after stopping PPI


220
210
200
190
180
170
160
150
140
130
120
110
100
QUESTIONS?

The following regimens can be considered for use as salvage treatment ACG:

- Bismuth quadruple therapy for 14 days is a recommended salvage regimen.
- Levofloxacin triple regimen for 14 daysis a recommended salvage regimen.
- Concomitant therapy for 10–14 days is a *suggested* salvage regimen.
- Clarithromycin triple therapy *should be avoided* as a salvage regimen.
- Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a *suggested* salvage regimen
- High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a *suggested* salvage regimen

Inselspital

Selektivkultur

H. pylori Keim 1 Helicobacter pylori

Für die H. pylori Resistenzprüfung existieren abgesehen von Clarithromycin KEINE durch das amerikanische Clinical and Laboratory Standards Institute (CLSI) festgelegten Richtlinien.
Zur Orientierung können folgende Werte dienen:
Amoxicillin >/= 1.5 mg/L; resistent
Tetracyclin >/= 4.0 mg/L; resistent
Metronidazol >/= 8.0 mg/L; resistent

Ref: Samara Z et al, JAC 2002; 49: 1023-1026

Resistenzprüfung

	Keim 1
Amoxicillin MHK (E-Test)	
	0.016 mg/l
Minimalwert dieser Analysenserie. Der wahre Wert liegt tiefer.	
Tetracyclin MHK (E-Test)	
	0.023 mg/l
Metronidazol MHK (E-Test)	
	256.000 mg/l
Maximalwert dieser Analysenserie. Der wahre Wert liegt höher.	
Clarithromycin MHK (E-Test)	sensibel
	0.016 mg/l
Minimalwert dieser Analysenserie. Der wahre Wert liegt tiefer.	

Table 1 Proposed clinical antimicrobial breakpoints for *Helicobacter pylori*

Antibiotic	Susceptible (mg/L)	Resistant (mg/L)
Amoxicillin	⩽ 0.12	> 0.12
Clarithromycin	⩽ 0.25	> 0.5
Metronidazole	⩽ 8	> 8
Levofloxacin	⩽ 1	> 1
Rifampicin[1]	⩽ 1	> 1
Tetracycline	⩽ 1	> 1

[1]Although rifabutin is used clinically, rifabutin *E* tests are not available routinely and rifampicin is used to screen for rifabutin resistance. Adapted from European Committee on Antimicrobial Susceptibility Testing[48].

E-test is a quantitative variant of the disc diffusion method and is useful for slow-growing bacteria

sensitivity 45%

specificity 98%

Thung 2011

The rate of metronidazole resistance detected by an E-test might be overestimated by 10%-20% according to agar dilution-based results. (Lack of an anaerobic pre-incubation of plates in the E-test)