Diagnosis and treatment of *H. pylori* infection

Prof. Uday C Ghoshal MD, DNB, DM, FACG, RFF, FAMS, FRCP (Edin), MISG
Professor and Head, Dept. of Gastroenterology, SGPGI, Lucknow, India
President, Indian Motility & Functional Diseases Association
Former Editor-in-Chief, Indian J Gastroenterol
www.spreadhealth.in, www.sgpgi.edu.in

Outline of presentation

- Outline of pathogenesis of *H. pylori* infection
- In whom diagnostic work-up and treatment for *H. pylori* infection needs to be undertaken?
- What are the tests for *H. pylori* infection?
- How to treat *H. pylori* infection?
- Adverse effects, compliance, eradication rates and how to improve it?
- Re-infection

Outline of the pathogenesis

Environmental factors

Multifocal atrophic gastritis

Gastric cancer

Gastric ulcer

PGL

Acute gastritis

Chronic active gastritis

DU

Antral predominant

PGL

Genetic, socioeconomic and nutrition of host

Age of the child

Outline of gastric physiology in *H. pylori* infection

Inflammatory cells

Cytokines

Acid

\+

Parietal cell

\+

Histamine cells

Inflammatory cells

Cytokines

\+

G cells: gastrin

\+

\-

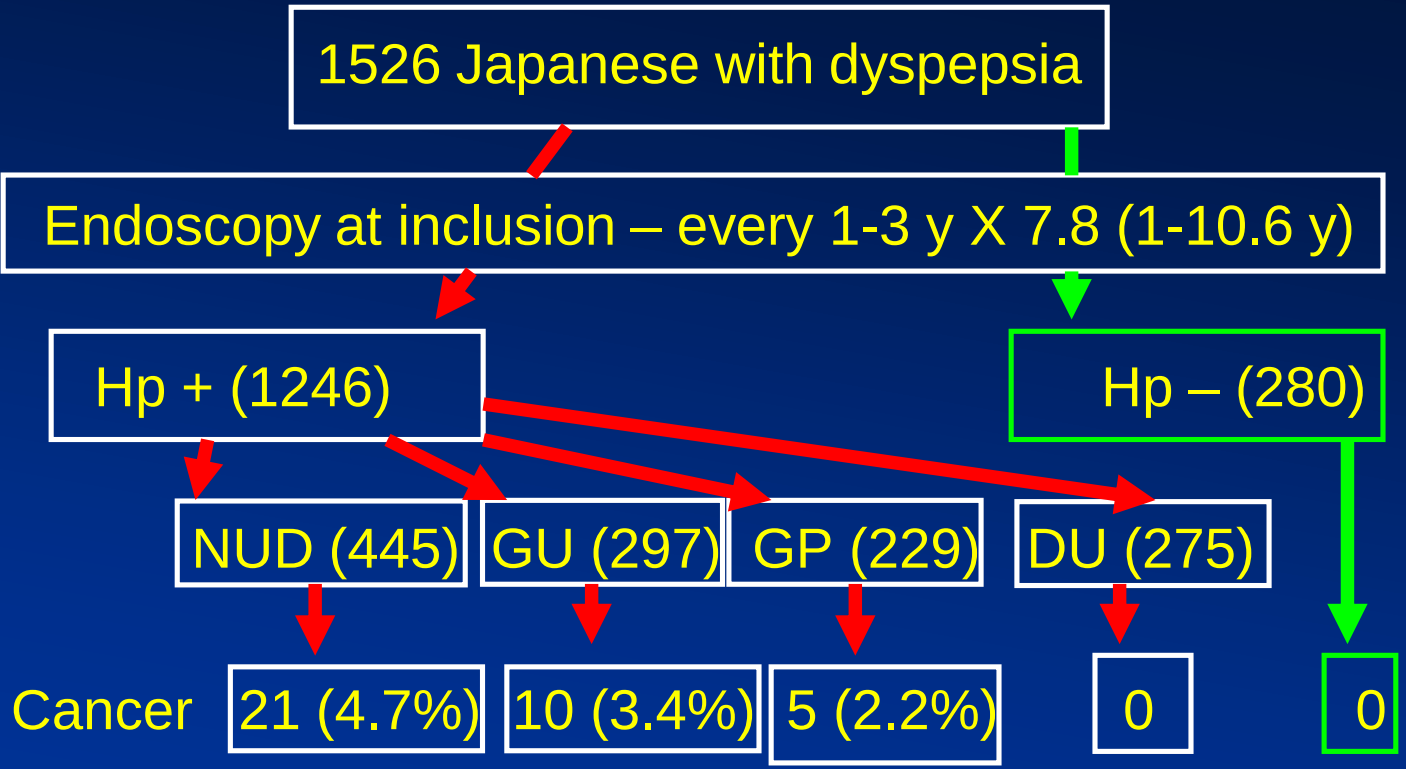
\-

\-

D cells: somatostatin

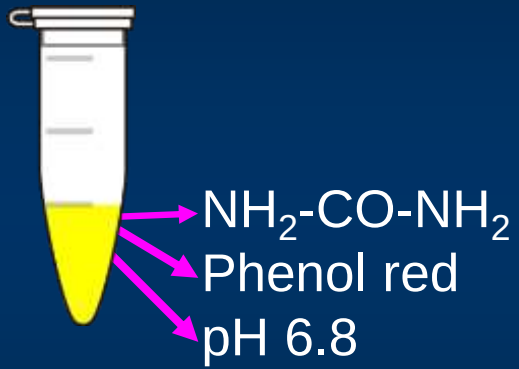
\+

H. Pylori and gastric cancer



Uemura N. NEJM 2001; 345: 784-9

Diagnosis of *H. pylori* infection: Principle of RUT



Urease of *H. pylori* (if present in the biopsy)

NH_2-CO-NH_2

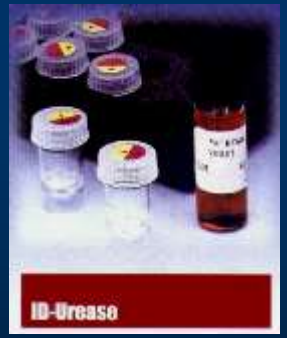
NH_4+ NH_4+ CO_2

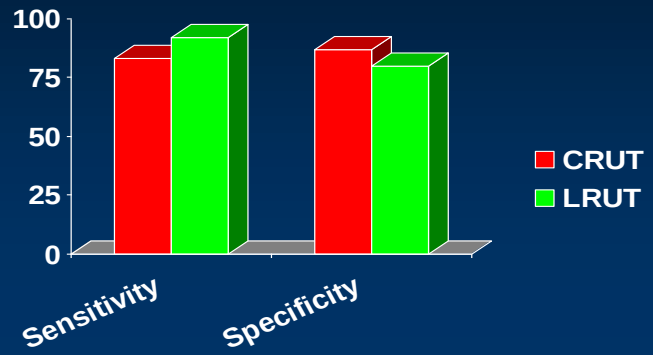
Phenol red in alkaline medium

Yellow → Red

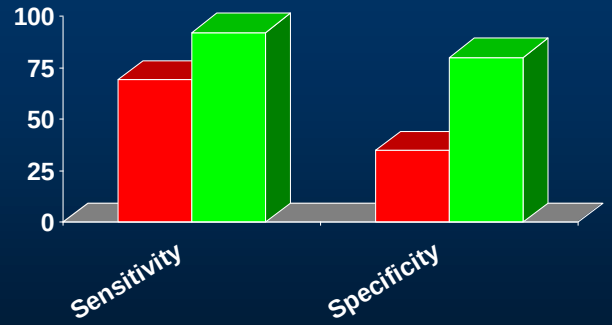
RUT: Sol vs. gel

Observation: LRUT 4-h, CRUT 24-h



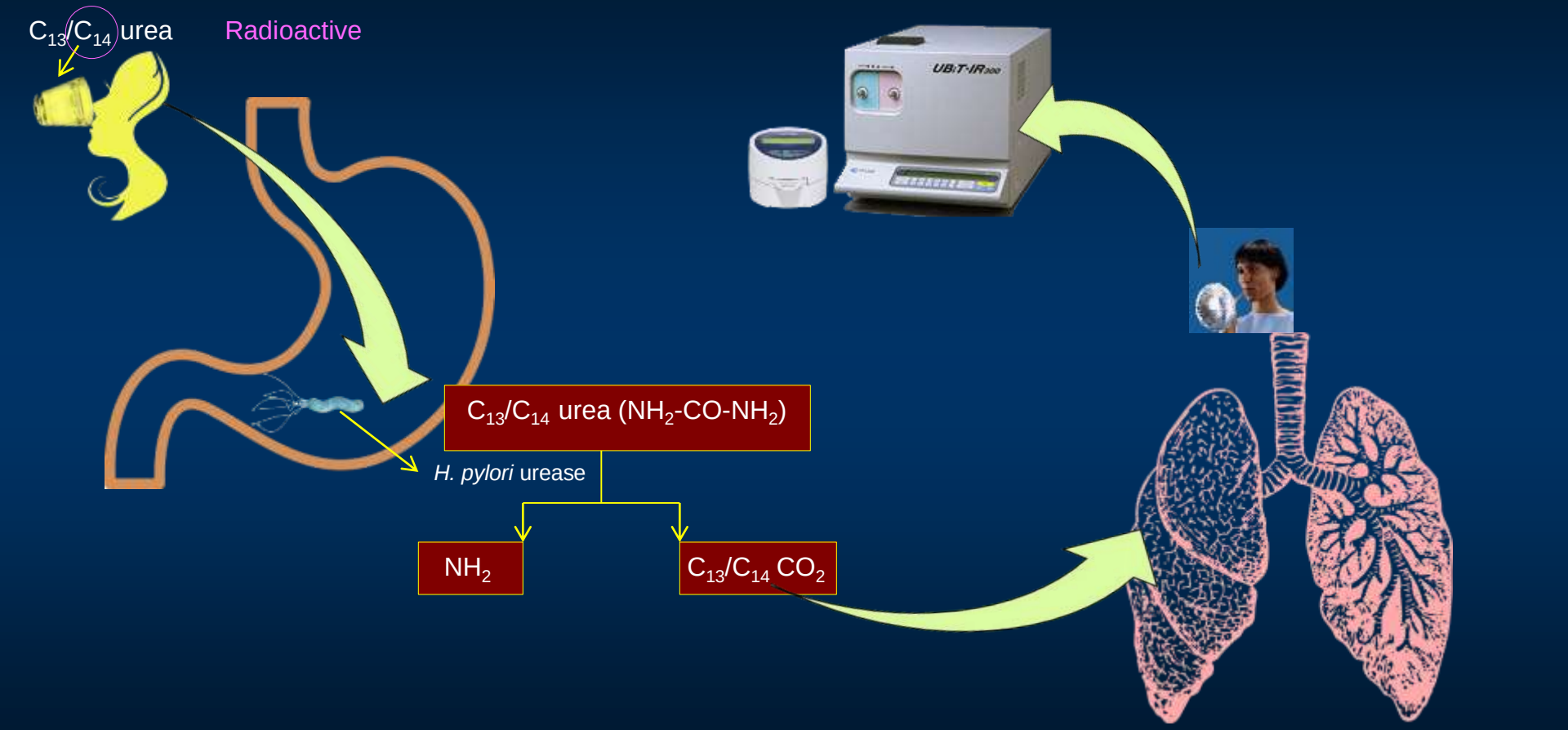


Observation: 4-h for both LRUT & CRUT



Ghoshal et al. Indian J Gastroenterol 1999; 18: 183

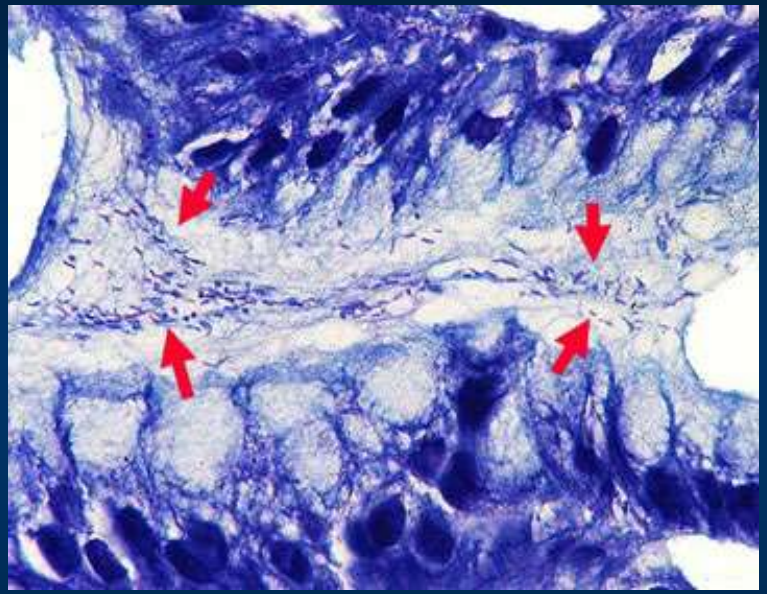
Urea breath test



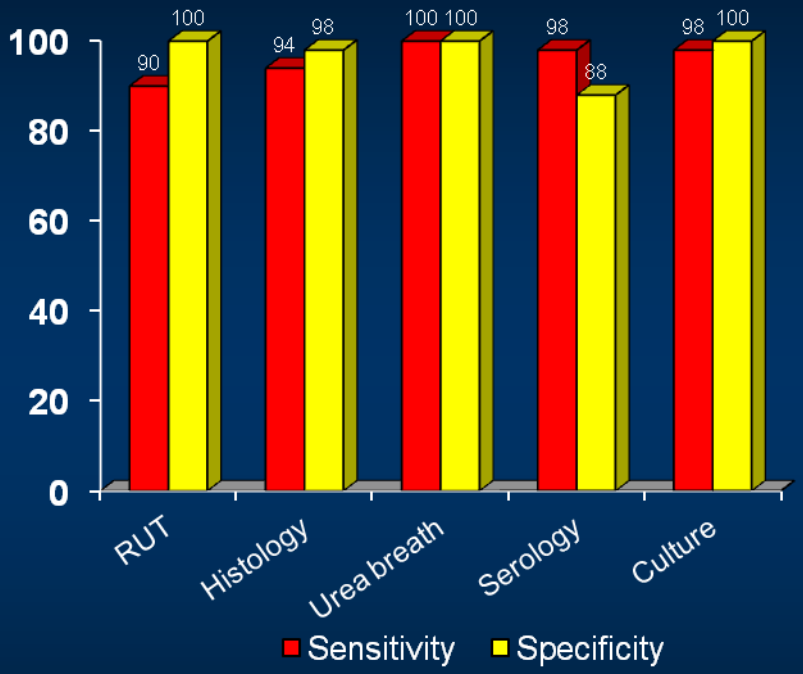
Histopathology & other tests

- Gram's stain: Gram's negative bacilli
- Giemsa stain
- Genta stain
- Methylene blue

- Fecal antigen test
- *H. pylori* culture
- *H. pylori* serology



Sensitivity and specificity of different tests



Sensitivity of RUT reduces if

- Patients present with acute GI bleed
- Prior use of PPI

Scand J Gastro 1996; 31 (suppl 215): 57-62

Stool antigen assay (HpSA)

HpSA test for pre-treatment diagnosis of *H. pylori* infection

References	Patients (no)	Gold standard	Sensitivity (%)	Specificity (%)
Adult populations				
Vaira *et al.*[11]	501	RUT, H, C	94	92
Ohkura *et al.*[12]	309	RUT, H, UBT	94	96
Trevisani *et al.*[13]	300	RUT, H	97	90
Forné *et al.*[14]	188	RUT, H, UBT	89	78
Trevisani *et al.*[15]	146	RUT, H	94	90
Vakil *et al.*[16]	108	RUT	86	91
Monteiro *et al.*[17]	104	RUT, H, C	89	94
Lehman *et al.*[18]	102	RUT, H, C	96	93
Makristathis *et al.*[19]	100	UBT, S	89	95
Braden *et al.*[20]	90	UBT	92	97
Fanti *et al.*[21]	84	H, C	98	96
Puspök *et al.*[22]	72	H	80	98
Agha-Amiri *et al.*[23]	54	RUT, H, UBT, S	96	92
Chang *et al.*[24]	62	H, C, UBT, RUT	94	89
Child populations				
Kato *et al.*[27]	264	UBT	96	97
Oderda *et al.*[28]	203	RUT, H	100	93
Braden *et al.*[29]	162	UBT	92	99
Konstantopoulos *et al.*[30]	145	RUT, H, C	89	94
Shepherd *et al.*[31]	119	UBT	88	82
Gosciniak *et al.*[32]	107	RUT, C	89	96
van Doorn *et al.*[33]	106	H, C	100	92
Makristathis *et al.*[34]	78	UBT, S	94	97
Rothenbacher *et al.*[35]	69	UBT	85	98
Husson *et al.*[36]	58	H, C	87	97

Polyclonal anti-*H. pylori* antibody as a capture reagent
Monoclonal antibody improves efficacy

HpSA test for post-treatment diagnosis of *H. pylori* infection

References	Patients (no)	Time (weeks)	Gold standard	Sensitivity (%)	Specificity (%)
Adult populations					
Vaira *et al.*[38]	235	4	UBT	96	95
	162	4	RUT, H, C	93	95
Ishihara *et al.*[39]	112	4	UBT	90	98
Manes *et al.*[40]	106	4	UBT	87	95
Braden *et al.*[20]	115	4	UBT	91	95
Makristathis *et al.*[19]	55	4	H,C	86	68
Arents *et al.*[41]	65	4	UBT	40	95
Leodolter *et al.*[42]	30	4–6	UBT	93	94
Vaira *et al.*[43]	84	5	RUT, H, C	94	97
Odaka *et al.*[44]	43	2	H,C,UBT	89	91
		6		89	97
Trevisani *et al.*[15]	116	8	RUT, H, UBT	93	82
Forné *et al.*[14]	142	6	UBT	70	82
Costa *et al.*[45]	155	4	RUT, UBT, H	92	82
	153	13		96	97
Child populations					
Gosciniak *et al.*[32]	62	4–6	RUT, C	89	96
Oderda *et al.*[46]	60	2	UBT	100	100
		6		100	94
Makristathis *et al.*[34]	40	4	UBT	100	93
		8		100	100
Husson *et al.*[36]	11	5–6	H, C	67	100

C, culture; H, histology; RUT, rapid urease test; UBT, urea breath test.

Kabir S. Aliment Pharmacol Ther 2003; 17: 1345–1354

Salivary and urinary antigen tests

Salivary antigen test for *H. pylori* infection

References	Patients (no)	Salivary ELISA Sensitivity (%)	Salivary ELISA Specificity (%)
Patel *et al.*[77]	119	85	85
Luzza *et al.*[78]	213	81	73
Luzza et al.[85]	152	82	71
Christie *et al.*[86]	86	88	71
Simor *et al.*[87]	195	81	75
Fallone *et al.*[88]	106	66	74
Reilly *et al.*[89]	303	84	70
Loeb *et al.*[90]	157	86	58
Marshall *et al.*[79,*]	81	94	85

n.d., not determined; * Oral fluid used.

Urinary enzyme immunoassays for *H. pylori* infection

Reference	Patients (no)	Gold standard	Sensitivity (%)	Specificity (%)
Urinary ELISA				
Alemohammad *et al.*[63]	306	H, RUT, C	96	90
Kato *et al.*[64]	238	H, RUT, C	96	79
Miwa *et al.*[65]	132	UBT	86	91
Katsuragi *et al.*[66]	119	UBT	99	100
Adachi *et al.*[67]	100	UBT	91	95
Kato *et al.*[68]	816*	S	85	95
Immunochromatography				
Miwa *et al.*[69]	155	UBT	96	88
Wong *et al.*[70]	123	H, RUT	97	95
Yamamoto *et al.*[71]	117	H, S	92	93
Graham & Reddy[72]	104	UBT	95	97
Wu *et al.*[73]	93	H, RUT, C, UBT	95	90
Fujisawa *et al.*[74]	21	H, RUT, C	100	67

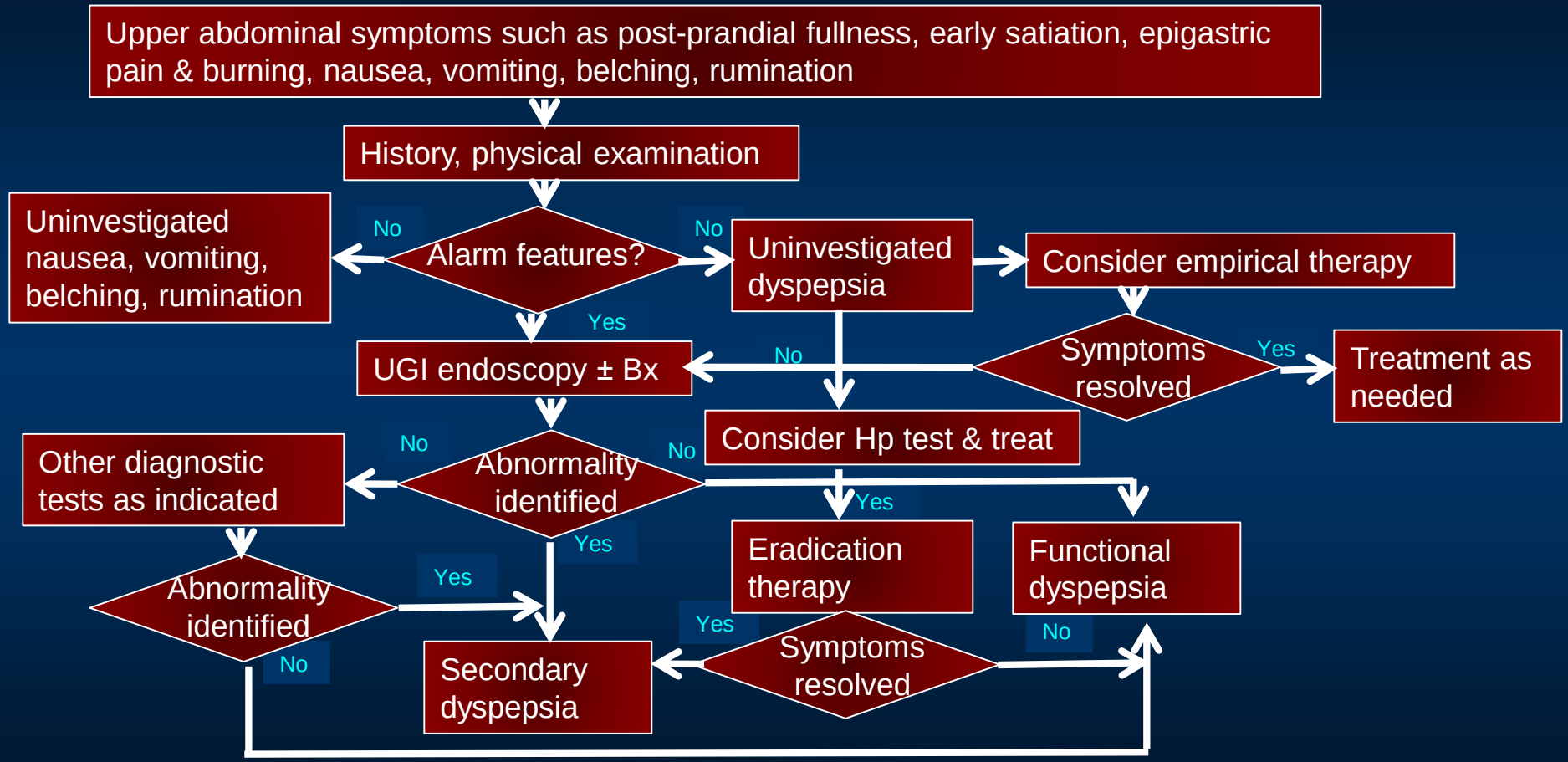
C, culture; H, histology; RUT, rapid urease test; S, serology; UBT, urea breath test. *Children.

Kabir S. Aliment Pharmacol Ther 2003; 17: 1345–1354

Indications for treatment of *H. pylori* infection

- Duodenal ulcer (number needed to treat [NNT] to prevent recurrence 2)
- Gastric ulcer (NNT to prevent recurrence 3)
- Low-grade MALT lymphoma (high-grade requires additional chemotherapy)
- After gastric cancer resection (to prevent metachronous cancer)
- Family history of gastric cancer
- In high-risk individuals before long-term NSAID and low-dose aspirin
- Univestigated dyspepsia?

Functional dyspepsia: Rome IV algorithm



Stanghellini V. Gastroenterology. 2016 Feb 15.

H. Pylori eradication in FD: A randomized controlled trial

FD with or without IBS (n=2640)

FD only (n=2000)

H. pylori (RUT + histology) +ve FD (n=1160; 58%)

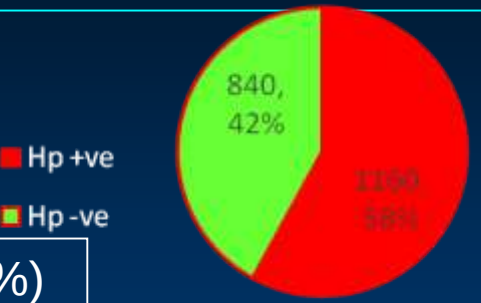
FD patients with moderate-severe symptoms (n=556%)

Triple therapy (n=259)

12-mo follow-up (n=259)

Placebo (n=260)

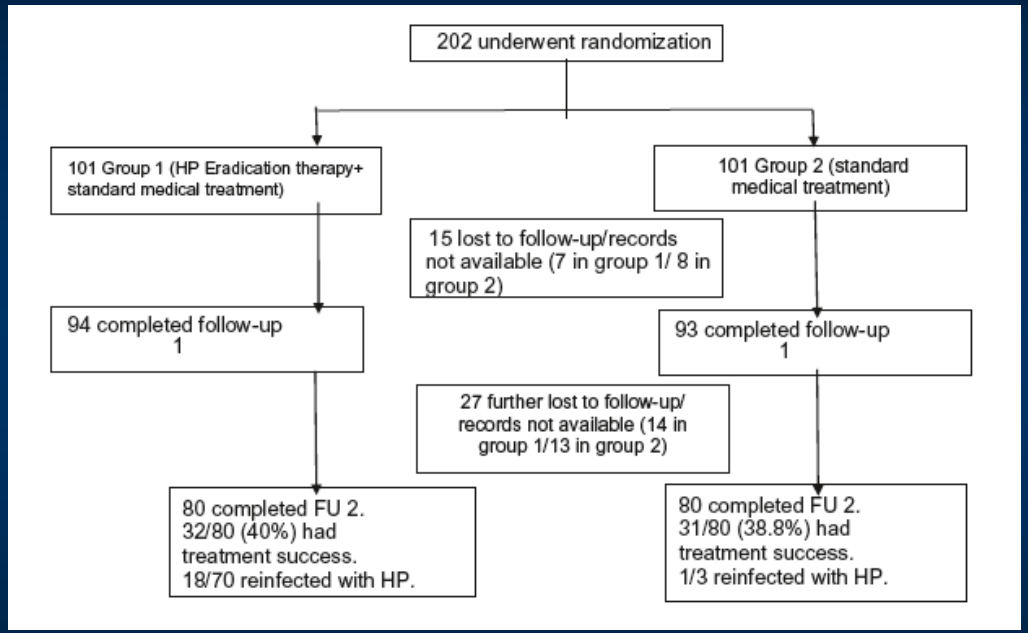
12-mo follow-up (n=180)

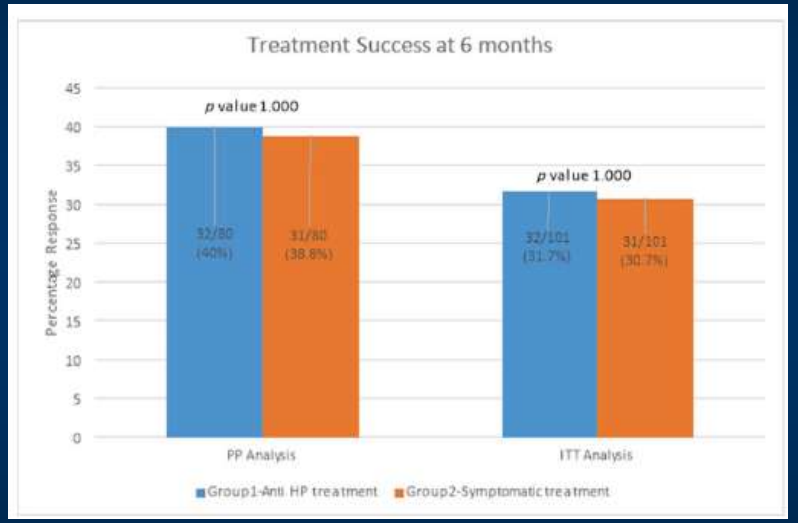


Variables	Triple therapy group	Placebo group	*P* value
Resolution of symptoms†			
4 weeks (%)	60.6	52.3	0.38
1 year (%)	43.7	36.9	0.13
Eradication of *Helicobacter pylori*			
6 weeks (%)	69.9	5.0	0.001
1 year (%)	66.6	6.6	0.001
Healing of gastritis			
6 weeks (%)	36.3	5	0.001
1 year (%)	75.9	6.2	0.001

Sodhi JS. J Gastroenterol Hepatol 2013: 28; 808-13

H. Pylori eradication in FD: A randomized controlled trial





Padole P. Indian J Gastroenterol 2021: 40; 492-501

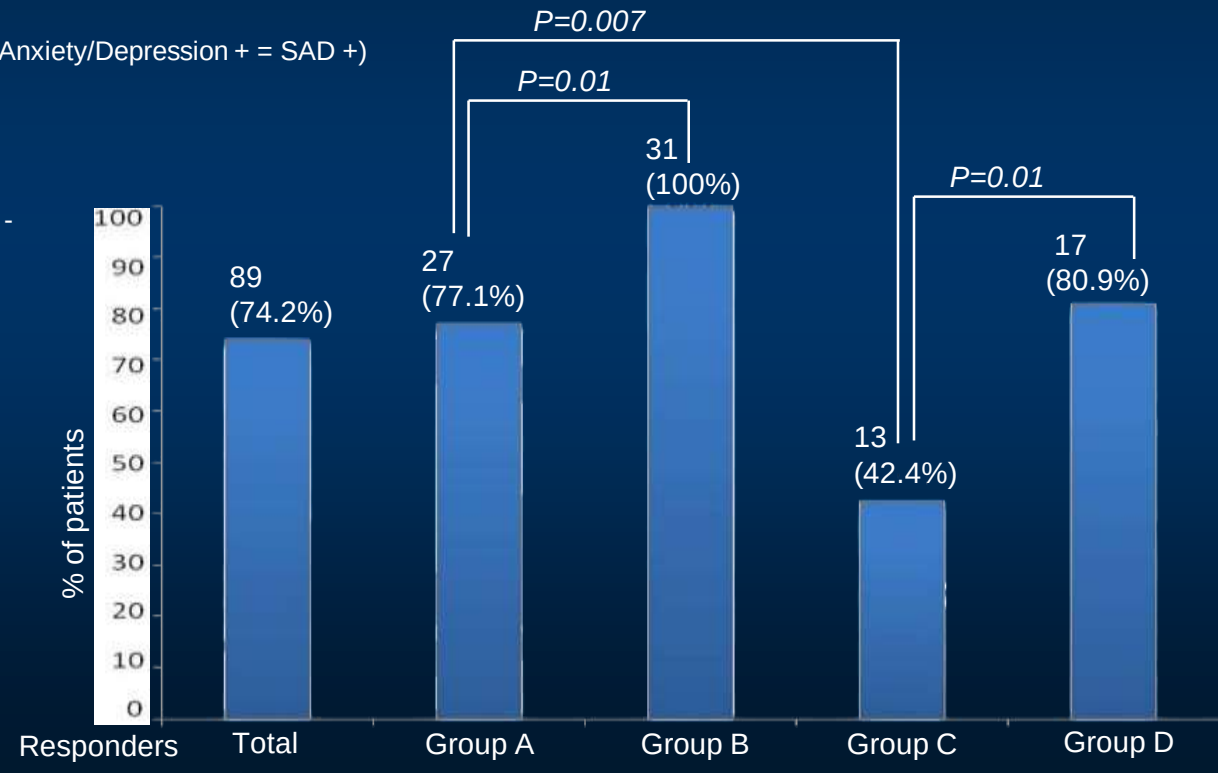
H. Pylori eradication in FD: Another Indian study

120 FD patients

- Endoscopy-based Hp test (2 +ve)
- Patient health questionnaire 9
- General anxiety disorder 7
- Perceived stress scale
- Any of above 3 (Stress/Anxiety/Depression + = SAD +)

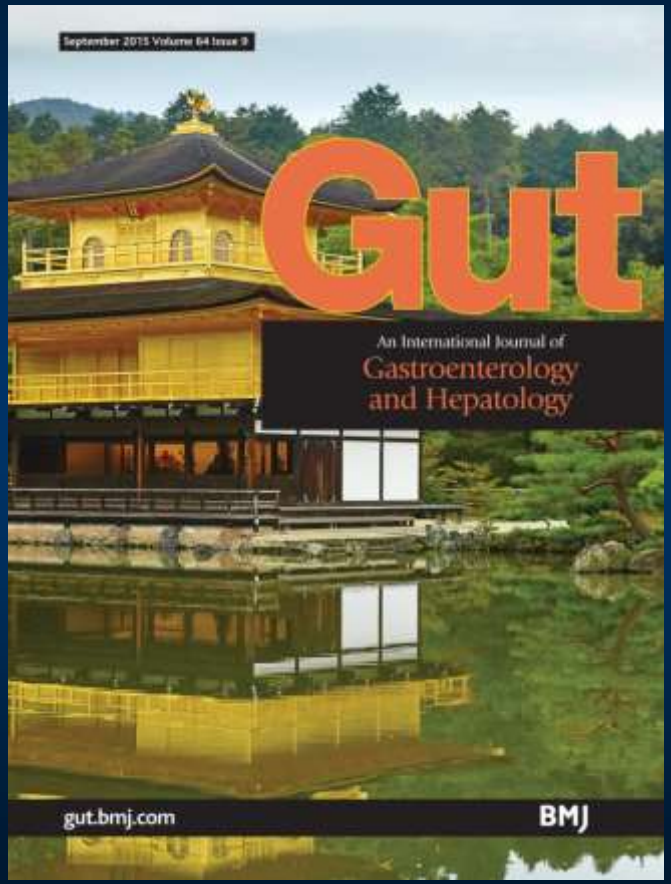
Group A	Group B	Group C	Group D
Hp +, SAD +	Hp +, SAD -	Hp -, SAD +	Hp -, SAD -
N=35	N=31	N=31	N=21
Hp eradication & psycho intervention	Hp eradication only	Psycho intervention only	PPI

Response at 3 month

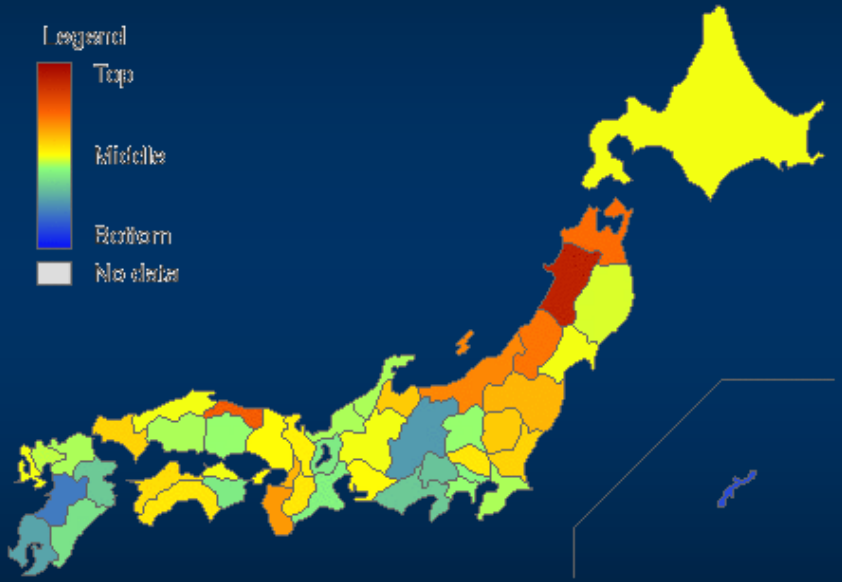


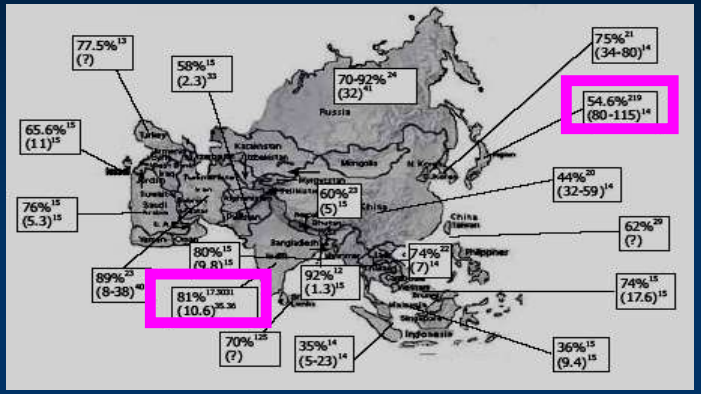
Kabeer KK. J Clin Diagn Res. 2017; 11: VC11-VC15

Kyoto consensus



What other factor influenced Kyoto consensus?
Frequency of gastric cancer

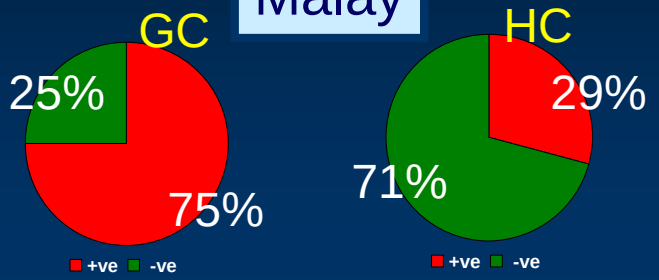




Singh K, Ghoshal UC. World J Gastroenterol 2006; 12: 1346-51
Ghoshal UC, Chaturvedi R, Correa P. Indian J Gastroenterol 2010; 29: 95-100
Kumar S, Patel G, Ghoshal UC. Pathogens 2021

Ethnicity & *H. Pylori* as Risk Factors for GC: Indians vs. Malay vs. Chinese

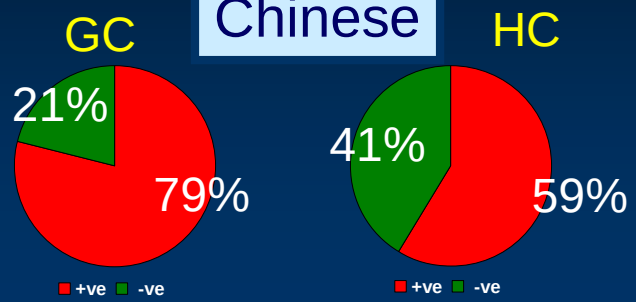
Malay



N = 4

N = 48

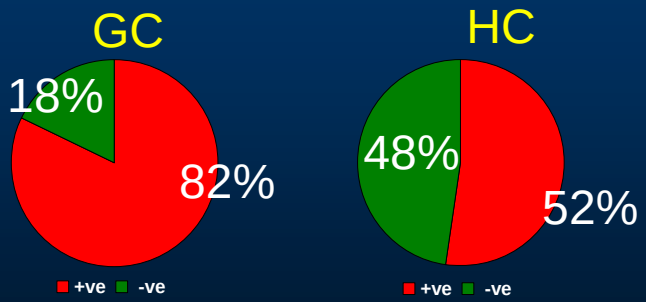
Chinese



N = 66

N = 58

Indians



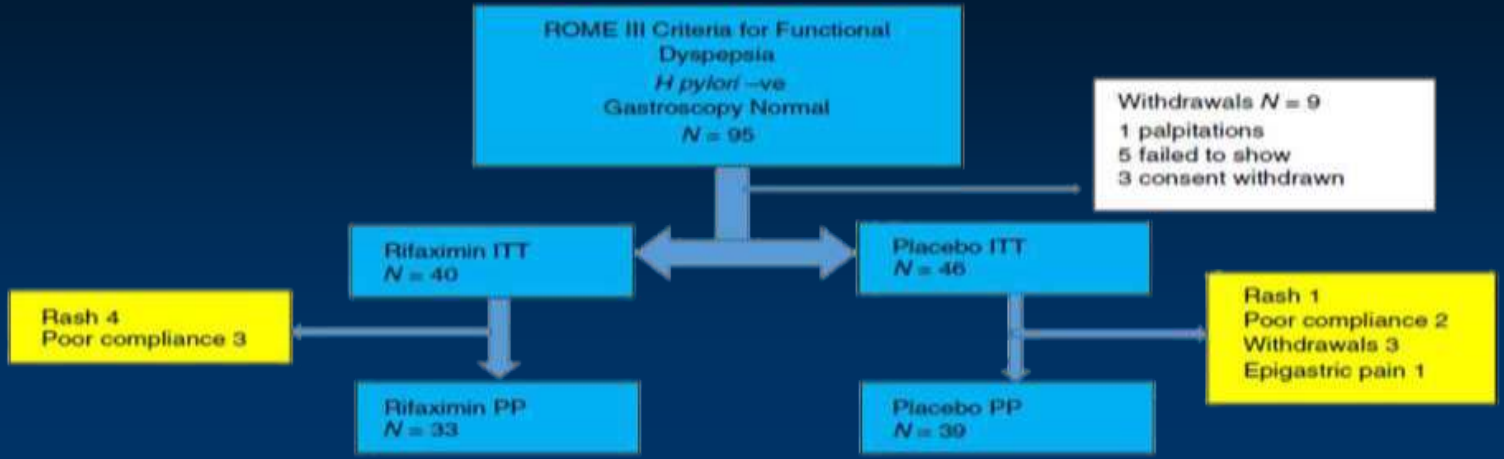
N = 17

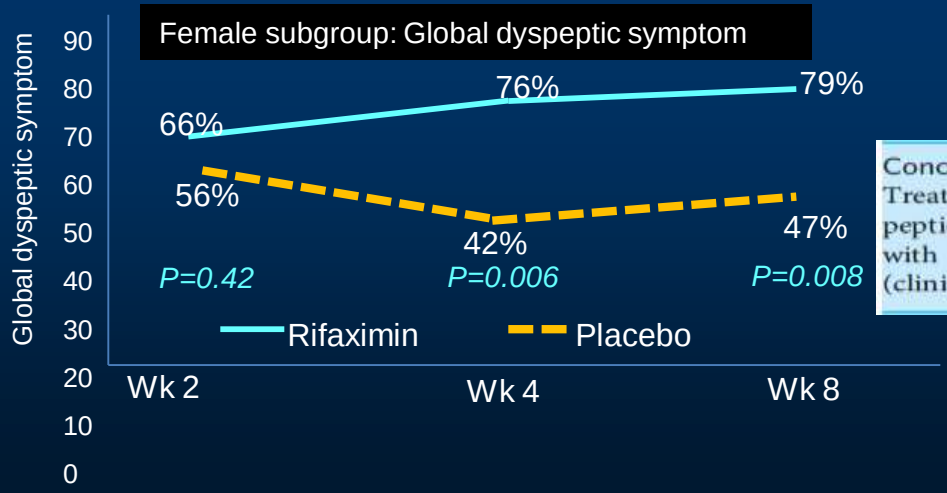
N = 68

H. Pylori positive Indians develop GC less frequently compared to Chinese & Malays

Goh K-L et al . Am J Gastroenterol, 2007

Rifaximin in functional dyspepsia





Conclusions

Treatment with 2 weeks of rifaximin led to adequate relief of global dyspeptic symptoms, belching and post-prandial fullness/bloating in subjects with functional dyspepsia. The difference was more marked in females. (clinicaltrials.org NCT01643083).

Tan VP. Aliment Pharmacol Ther 2017; 45: 767–776

Regimens

P-A-C

P-M-C

O-B-M-T

O-B-F-T

P-A-R

P: PPI
C: clarithromycin
O: ofloxacin
T: tetracycline
R: rifabutin

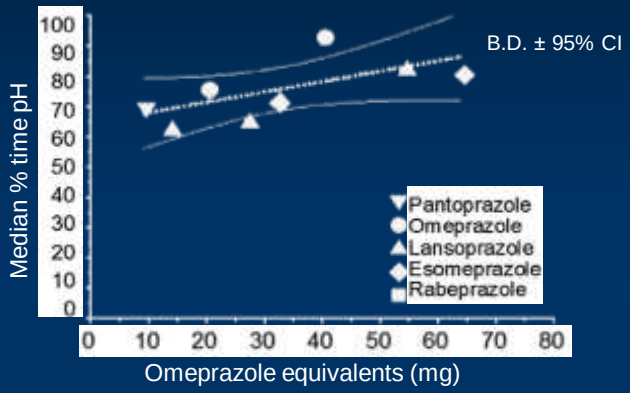
A: amoxycillin
M: metronidazole
B: bismuth salt
F: furazolidone

GCNA 2000; 29 (4): 759-773

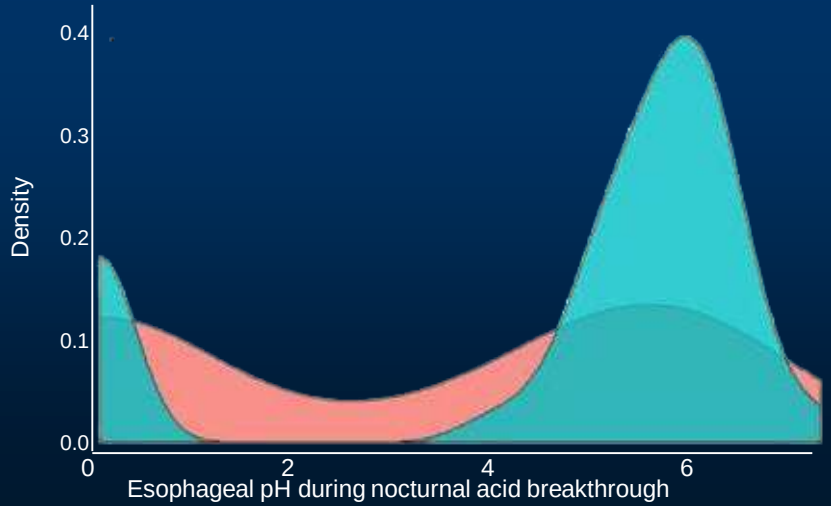
Which proton pump inhibitor?

- Newer PPIs and those not affected by CYP2C-19 polymorphism (e.g. rabeprazole, esomeprazole, vonoprazan) have greater efficacy
- Higher dose, greater efficacy

PPI + amoxycillin	Eradication rates
Omeprazole 20 mg BD	20%
Omeprazole 40 mg BD	40%
Esomeprazole 40 mg BD	60%
Vonoprazan 20 mg BD	90%

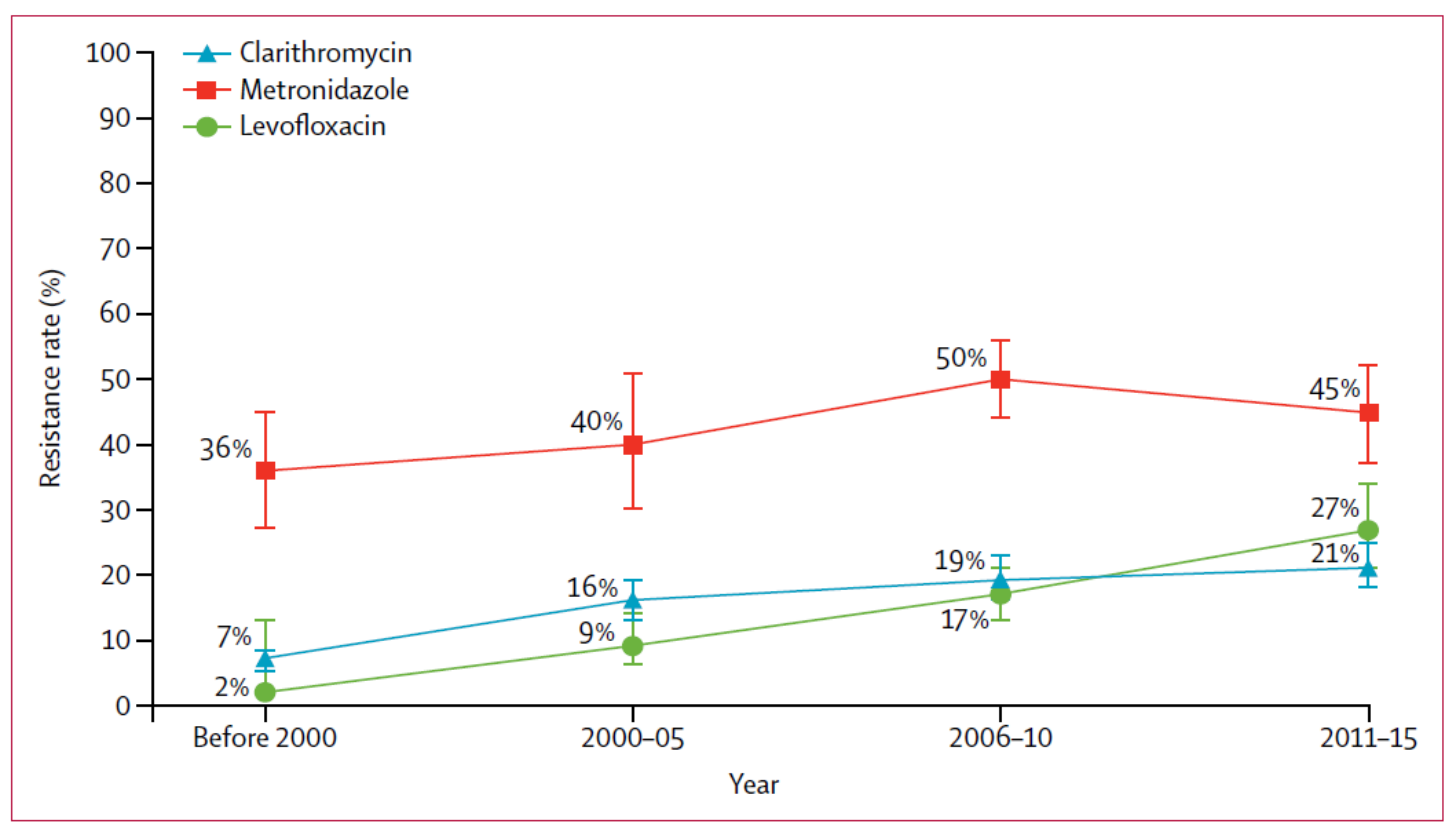


Graham DY. Helicobacter 2019 Feb;24(1):e12554



Ghoshal UC. Indian J Gastroenterol 2022; 41: 405-14

Primary clarithromycin, metronidazole, and levofloxacin resistance in the Asia-Pacific region

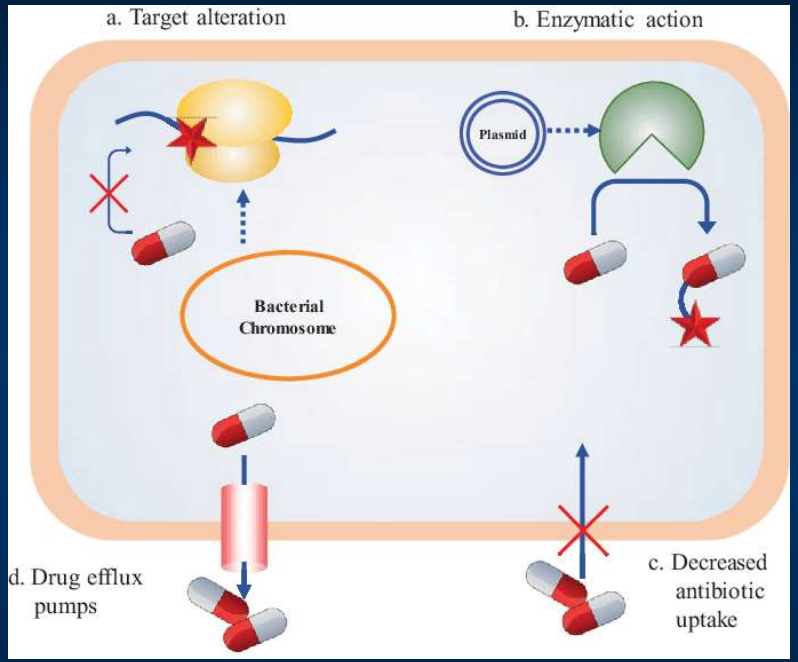


Kuo YT. Lancet Gastroenterol Hepatol 2017

Mechanisms of antibiotic resistance in *H. pylori*

Coccoid transformation

Biofilm formation



Genetic mechanisms of antibiotic resistance in *H. pylori*

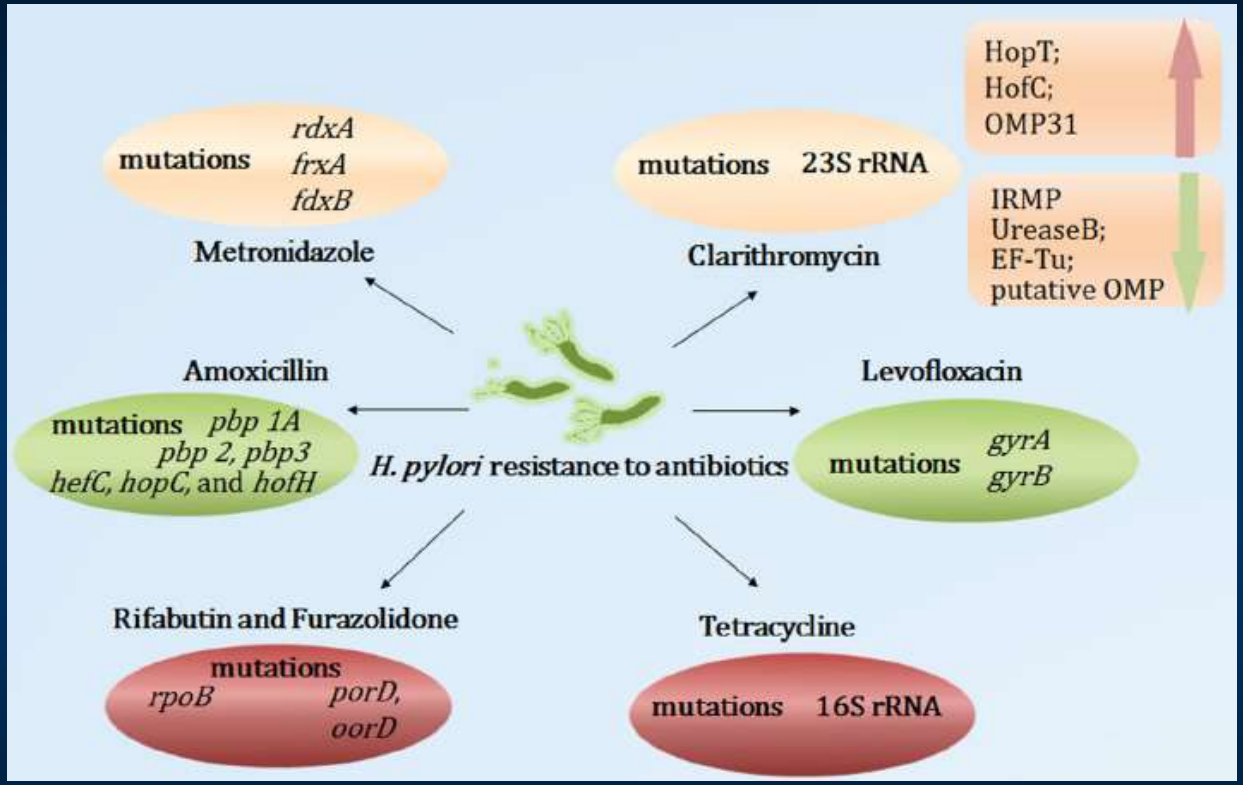
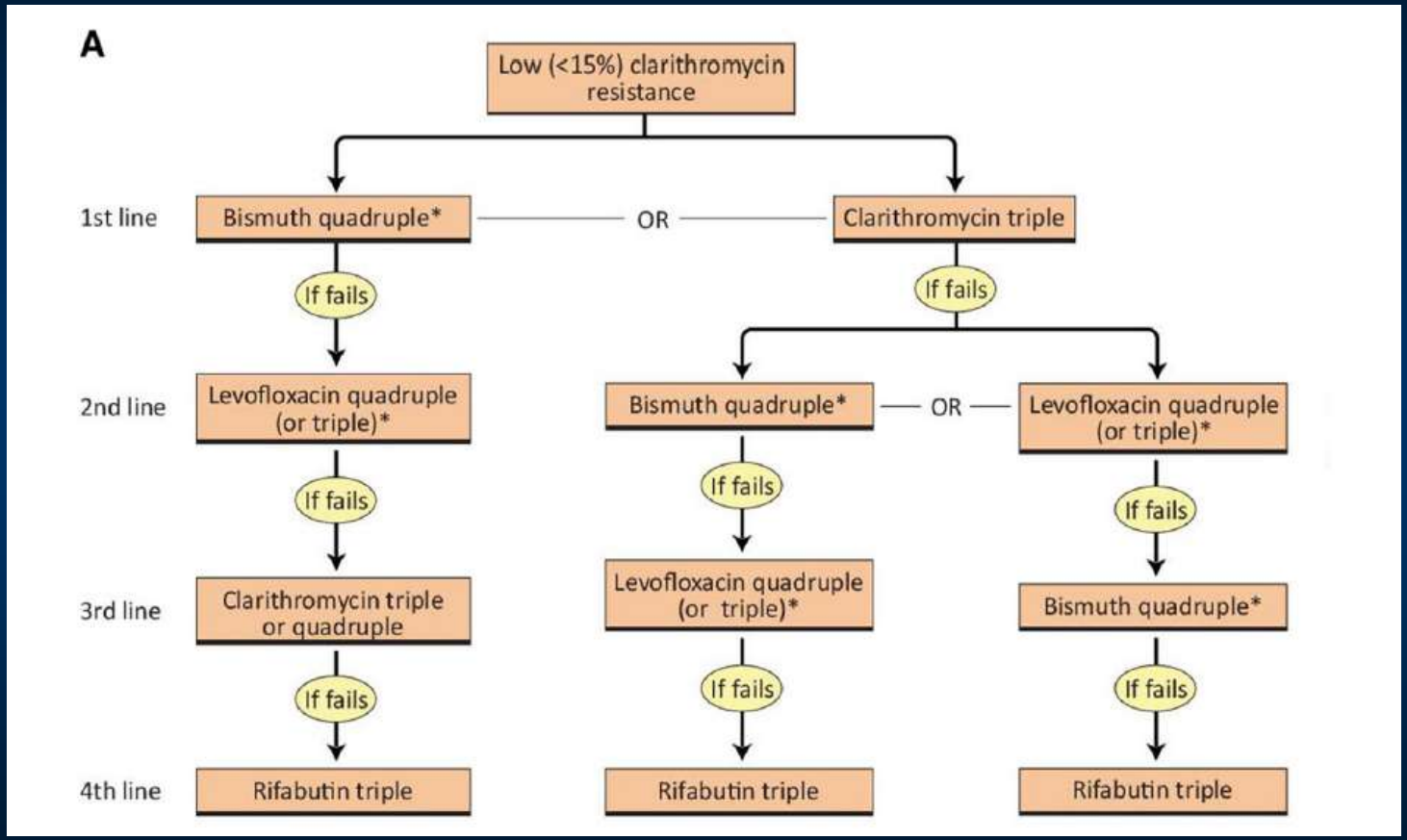


FIGURE 2 | Summary of mutations and novel mechanisms involved in *H. pylori* antibiotic resistance. OMP, outer membrane protein; IRMP, iron-regulated membrane protein; EF-Tu, elongation factor thermo unstable.

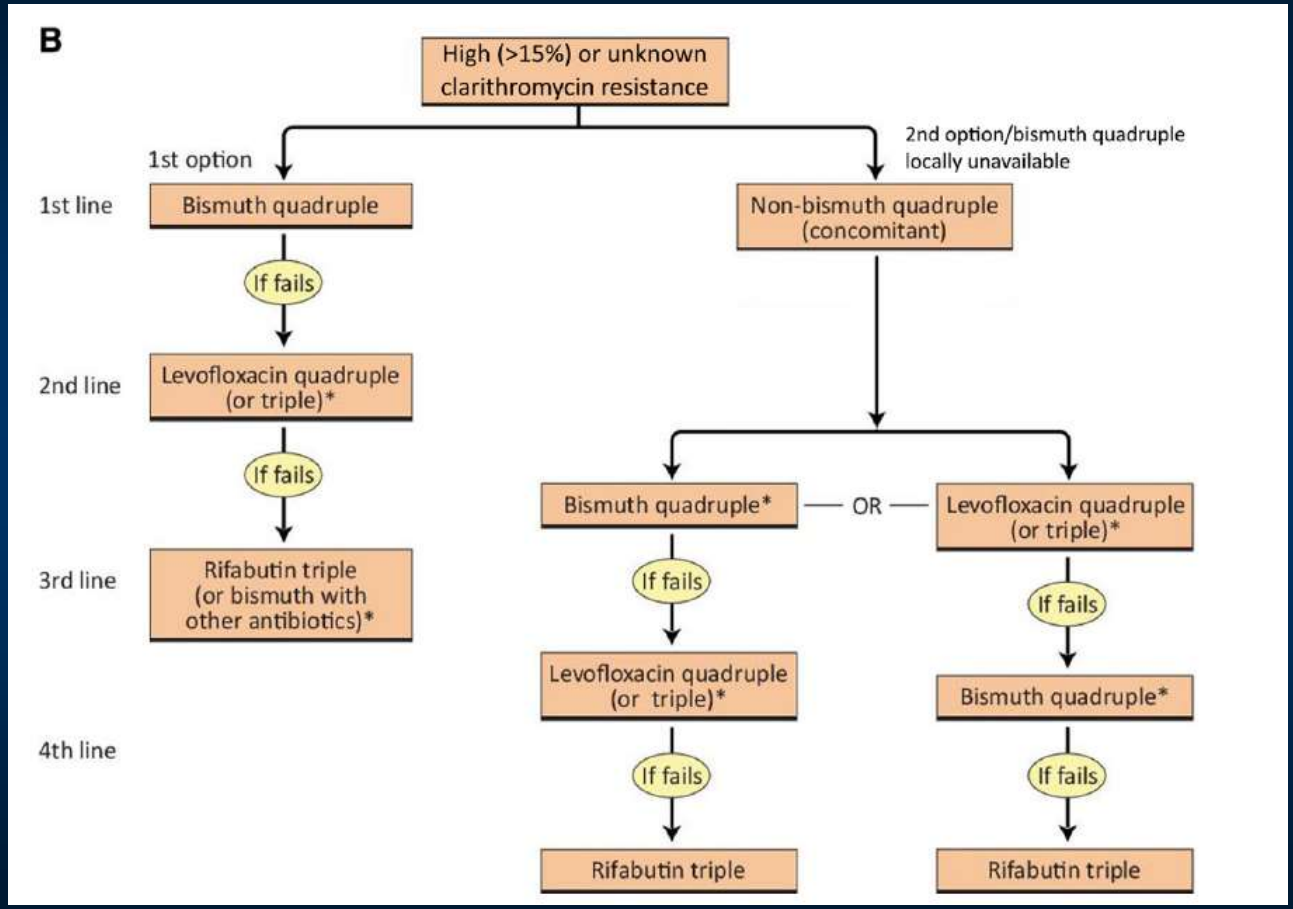
Zhu YHY. Front. Cell. Infect. Microbiol. 7:168

Maastricht VI/Florence consensus



Malfertheiner P. Gut 2022;71:1724–1762

Maastricht VI/Florence consensus



Malfertheiner P. Gut 2022;71:1724–1762

Short & long treatment & triple vs. quadruple therapies

- Longer duration of triple therapy is superior to shorter duration therapy (1 week therapy 48% eradication, 2 week: 80%; Chaudhary A. Helicobacter 2004; 9: 124-29)

- Quadruple therapy (PPI, bismuth, metronidazole, tetracycline, eradication in 73%) does not offer any advantage over the standard triple therapy (PPI, amoxycillin, clarithromycin, eradication in 83%; p=ns). Pai G. Indian J Gastroenterol 2003; 22: 85-87

- Standard triple therapy (pantoprazole, clarithromycin, amoxycillin) was less effective (62%) than sequential therapy (pantoprazole 40 mg plus amoxicillin 1 g twice daily for 5 days followed by 40 mg pantoprazole, 500 mg clarithromycin, and 500 mg tinidazole each administered twice daily for 5 days; 76%). Javid G. Indian J Gastroenterol 2013; 32: 190-94

APAC consensus recommendations: Use of probiotic with anti-Hp therapy reduces side effect & improve eradication

Indications	Recommendation	Level of agreement on Likert scale	Consensus
Helicobacter pylori infection	Concomitant probiotic administration reduces side effects related to antibiotic therapy in adults undergoing eradication therapy for *H. pylori*.	4.2	Agreed
	A) Certain strains are more effective than others	4.4	
	Concomitant probiotic administration increases eradication rates in adults undergoing eradication therapy for *H. pylori.*	3	Agreed
	A) Certain strains are more effective than others	3,2	

Ghoshal UC et. al. J Gastroenterol Hepatol. 2017. doi: 10.1111/jgh.13840

Regimens

Regimens	Drugs		Efficacy
	1st week	2nd week	
Standard triple therapy	P + A + C	P + A + C	76%
Sequential therapy	P + A	P + C + M	83%
Concomitant therapy	P + A + C + M	P + A + C + M	85%
Hybrid therapy	P + A	P + A + C + M	81%
Bismuth quadruple therapy	P + M + T + B	P + M + T + B	87%

P: PPI
C: clarithromycin
O: ofloxacin
T: tetracycline

A: amoxicillin
M: metronidazole
B: bismuth salt
F: furazolidone

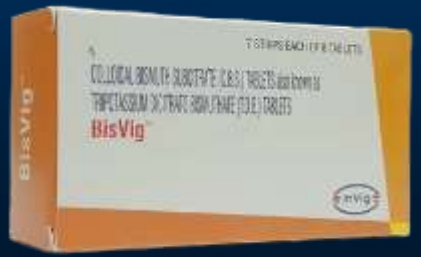
R: rifabutin

A few words about bismuth salt for *H. pylori*

- Again available in India
- Dose 420 mg Q.I.D.
- Inhibits *H. pylori* urease, catalase, and lipase
- Inhibits ability of *H. pylori* to adhere to epithelial cells
- Overcomes clarithromycin and levofloxacin resistance
- No relationship with metronidazole resistance

Side effect	BLAC (%)
Darkening of stool	32.9
Metallic taste	18.5
Nausea	15.4
Diarrhea	11.3
Itching	8.2
Headache	8.2
Abdominal pain	6.1
Vomiting	6.1
Skin rash	6.1
Constipation	5.1

BLAC, bismuth subcitrate, lansoprazole, amoxicillin, clarithromycin.




Thank you