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Nawal Al Nahdi

Overview of H. Pylori Management

22-April-2024 04:45 - 05:10 PM

Dubai World Trade Centre

Dr. Nawal Al Nahdi Biography

- Internal Medicine Residency – Canada
- Gastroenterology and Hepatology Fellowship - Canada
- Hepatology and Liver Transplant – Canada
- Advance Therapeutic Endoscopy Fellowship – Canada
- Program Director Adult Gastroenterology Fellowship Program – Saudi Board Dubai Health
- President NIHS Gastroenterology
- EMA Gastroenterology and Hepatology Scientific Committee

Disclosure

- This lecture is sponsored by NewBridge Pharmaceuticals.
- Advisory board of AbbVie, Gilead

Outline

- Origin and microbiology
- Epidemiology and transmission
- Etiology and clinical presentation
- Burden/ importance of eradication/ indication to test for *H. pylori*
- Treatment guidelines
- Bismuth based quadruple therapy
- Factors predicting successful eradication of *H. pylori*

Origin of *H. pylori*

1

- Gastric organisms were first observed more than 100 years ago

2

- Spiral shaped organisms were visualized in gastric mucous layer
- No evidence of disease association

3

- In 1982, Marshall and Warren identified and cultured gastric Campylobacter pyloridis
- In 1985, the association with peptic ulcer was discovered
- In 1989, it was named ***Helicobacter pylori***
- In 2005, Nobel prize awarded to Marshall and Warren for their discovery
- It is now classified by WHO as group one carcinogen due to its association with gastric carcinoma

Graham World J Gastroenterol. 2014 , Marshall, et al. Can J Gastroenterol. 2008

Microbiology: *H. pylori* Bacteria

Spiral-shaped

Gram-negative bacteria

Bacteria are same size

(length: 2.5-4 micron width: 0.5-1 micron)

Motile bacterium

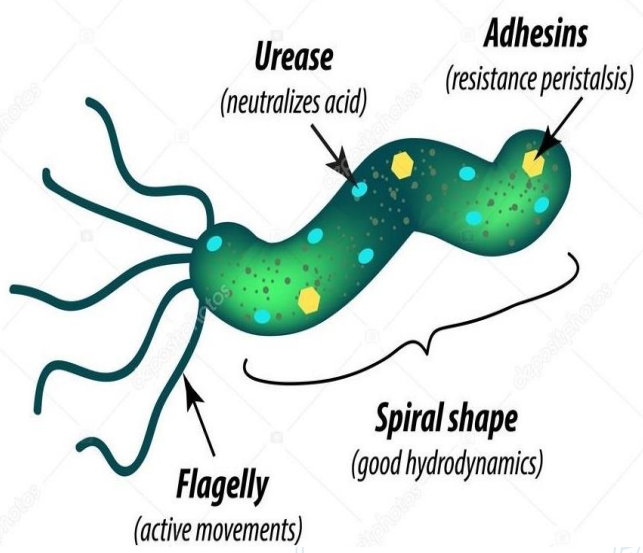
2-7 unipolar flagella

Positive

Urease, Oxidase

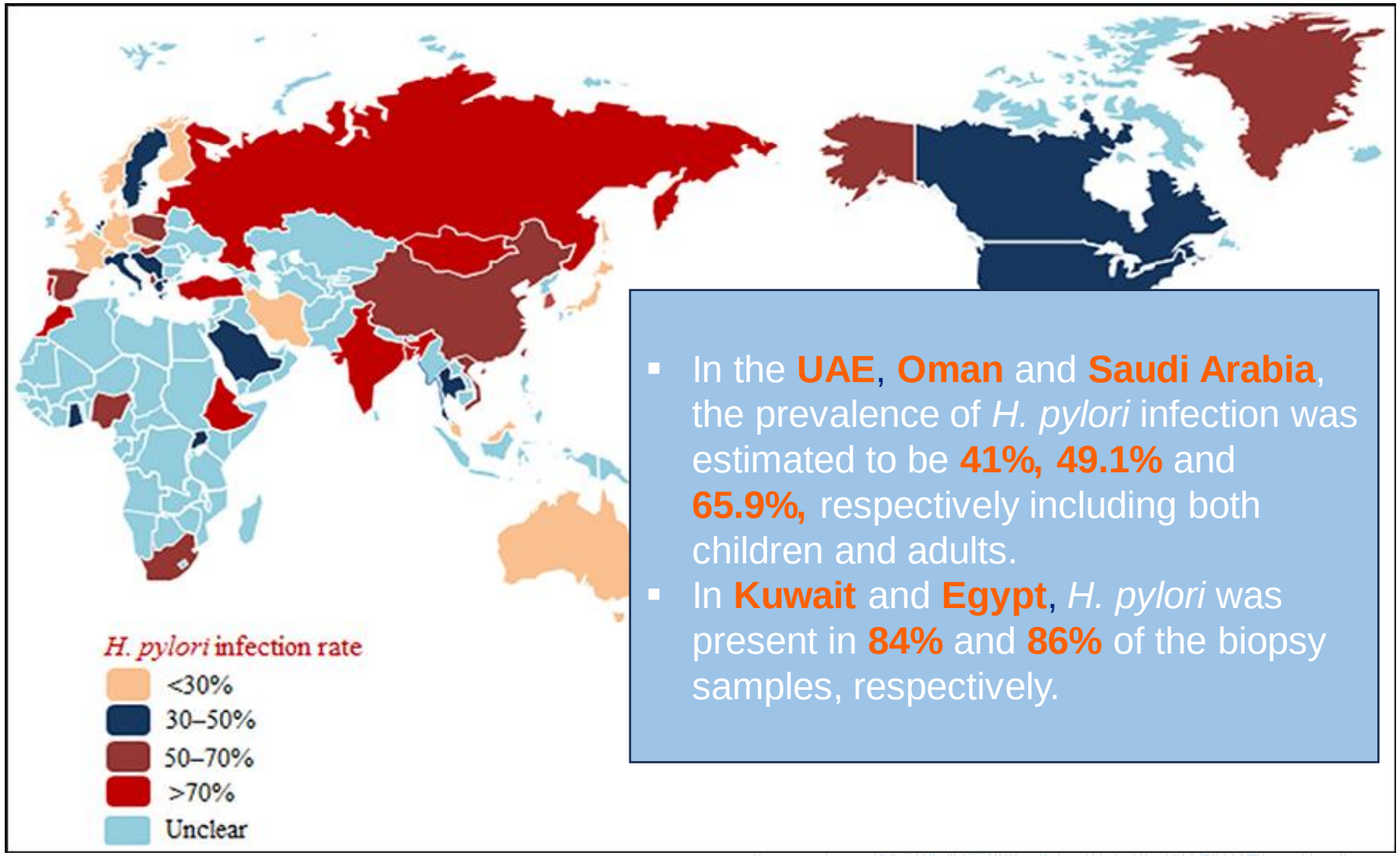
Catalase

Microaerophilic



Dunn et al. Clinical microbiology Reviews 1997.

Epidemiology : Worldwide Prevalence

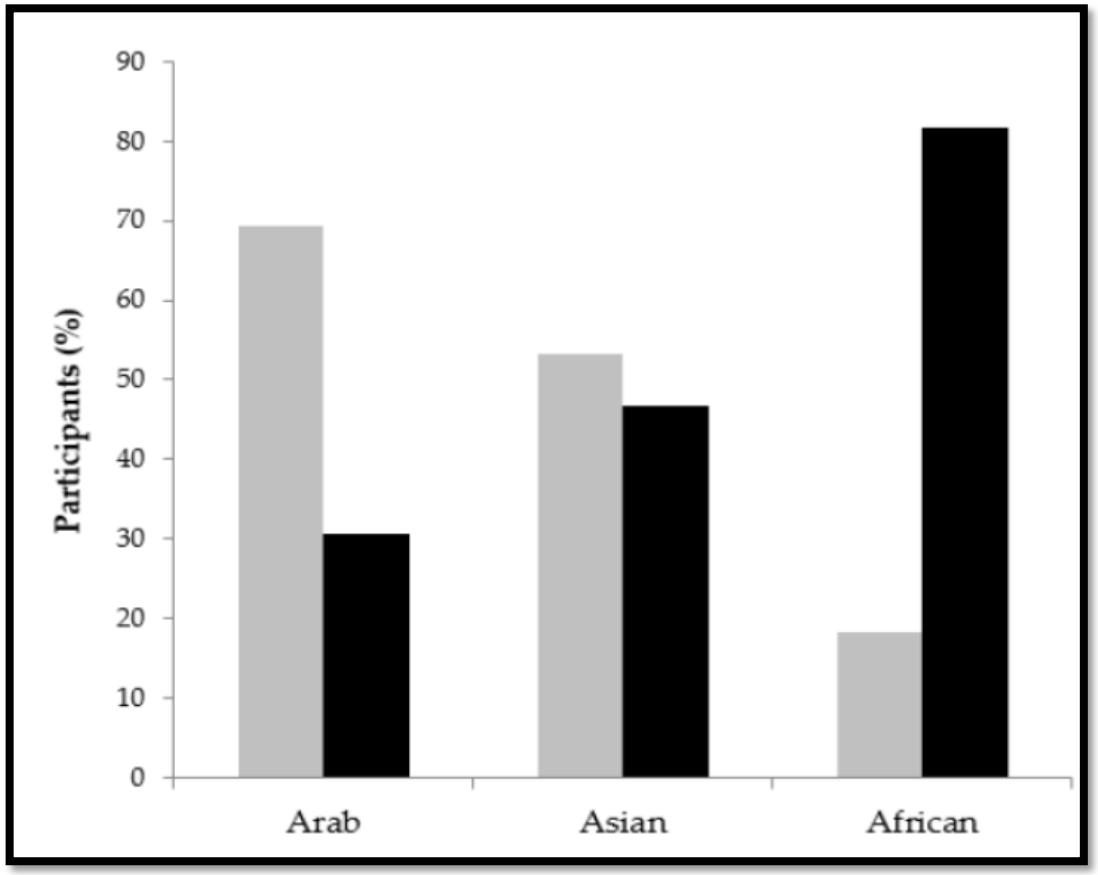


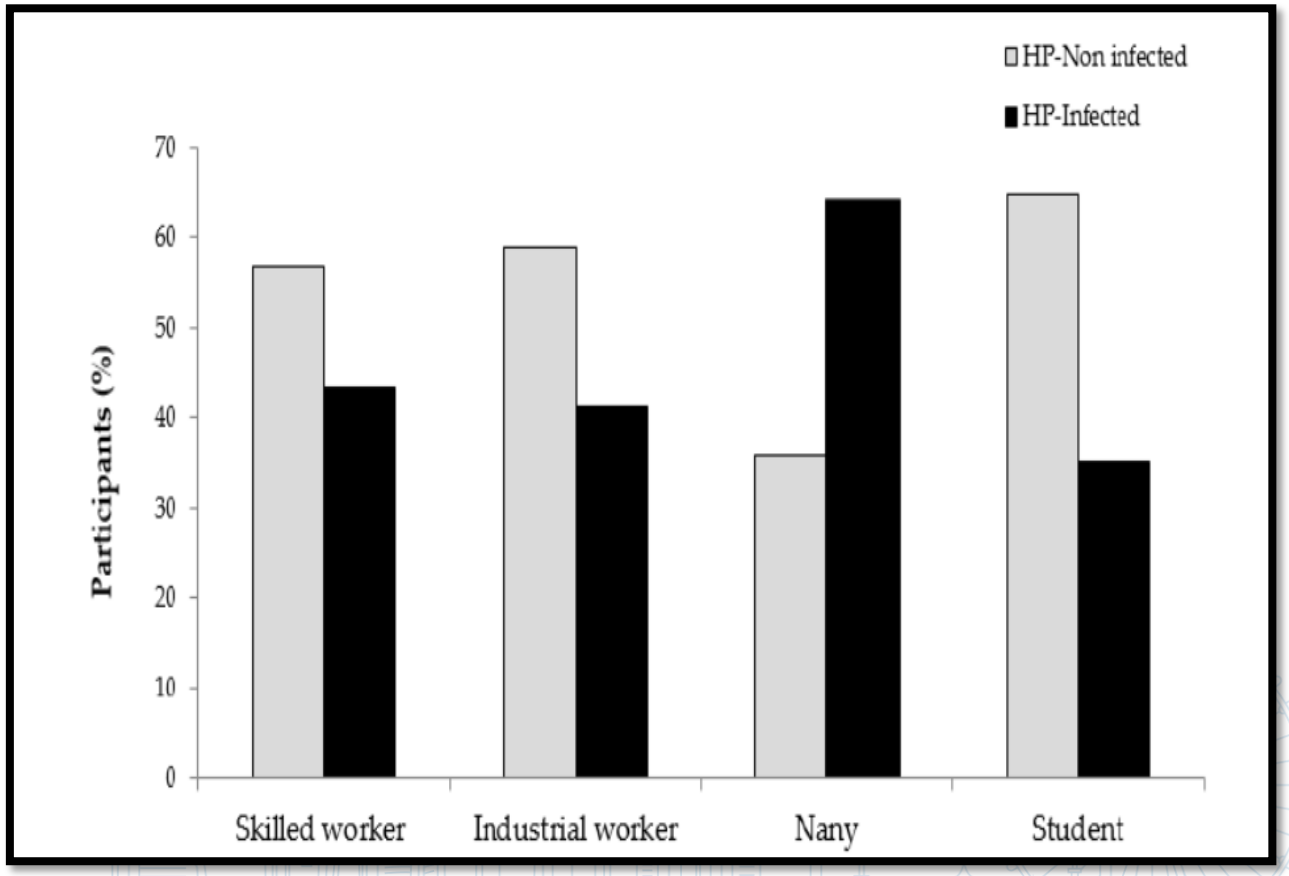
- In the **UAE**, **Oman** and **Saudi Arabia**, the prevalence of *H. pylori* infection was estimated to be **41%, 49.1%** and **65.9%,** respectively including both children and adults.
- In **Kuwait** and **Egypt**, *H. pylori* was present in **84%** and **86%** of the biopsy samples, respectively.

Hu et al. Frontiers in Cellular and Infection Microbiology 2017.
Peery et al. Gastroenterology 2015; Mentis et al. Helicobacter 2015; Khoder et al. Pathogens 2019; Hooi, et al. Gastroenterology 2017;Al Qabandi, et al. Acta Trop 2005; Mahmoud, et al. Am J Immunol. 2006.

Epidemiology (4): Prevalence in UAE

Prevalence of H. pylori in 350 healthy asymptomatic residents in UAE





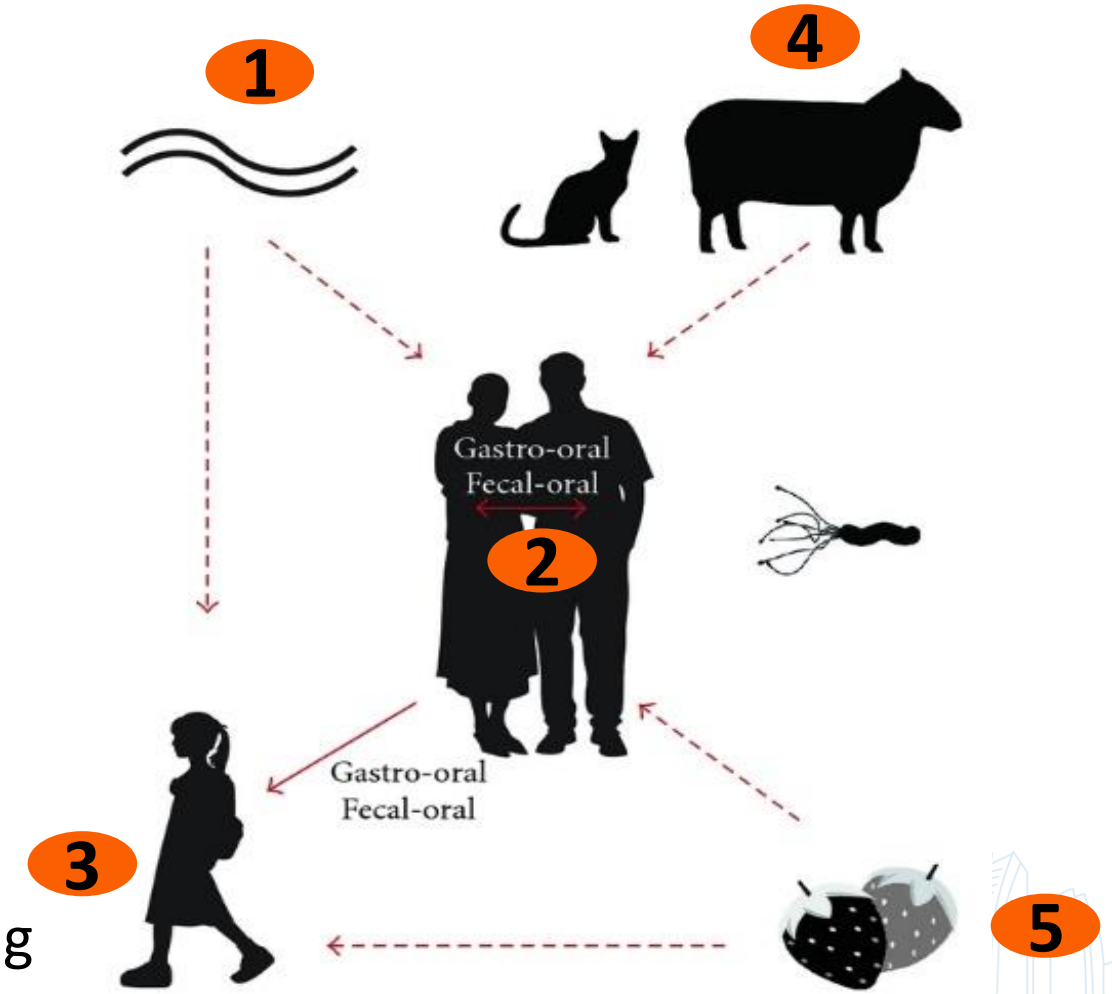
Khoder et al. Pathogens 2019.

Transmission

1) Contaminated water supplies

2) Person to person fecal/oral (diarrhea) or oral/oral(vomitus)

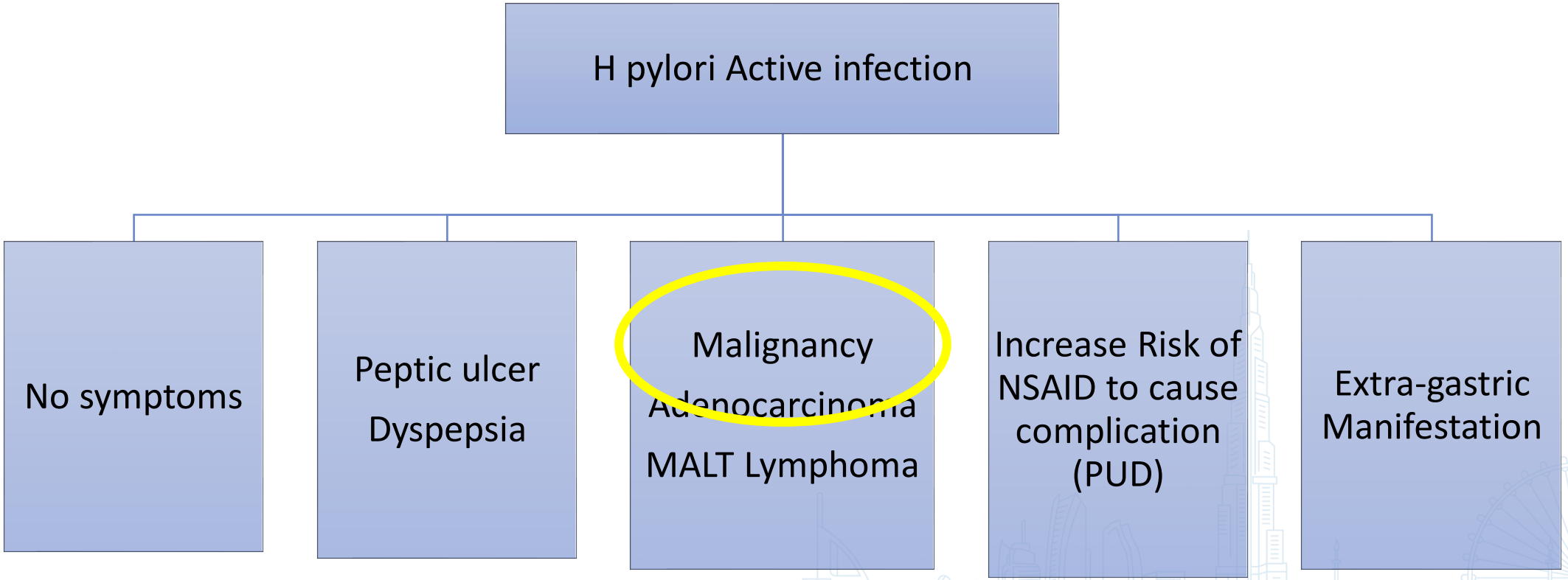
3) Person to person Intrafamilial clustering of infection



4) Zoonotic
Milk of the sheep
Saliva of the cat

5) Eat uncooked vegetables or unwashed fruit

H Pylori Infection Presentation



Extra gastric Manifestation of H pylori

- Iron Deficiency Anemia
- Vitamin B12 Deficiency
- ITP
- Urticaria
- Rosacea
- Increase risk of Metabolic Syndrome
- Increase risk of cardiovascular disease
- Neurological disorder none specific

Diagnosis Tests

Non-Invasive

- Urea Breath Test
- **Stool Antigen Test**
  - -Enzyme immunoassay
  - - Immuno-chromatography
- Serology

Invasive Endoscopy

- Rapid Urease Test
- Histology
- Culture

Garza-Gonzalez et al. World J Gastroenterol. 2014; Sabbagh et al. European Journal of Clinical Microbiology & Infectious Diseases 2019.

Diagnosis

- Invasive Test
  - rapid urease test (through gastroscopy and CLO application kit)
  - histology, culture, and PCR. (through gastroscopy and tissue sample)

- The major disadvantage of the invasive tests is that they require endoscopic examination for obtaining the diagnostic sample.

- Several studies have demonstrated that stool monoclonal tests are reliable for diagnosing *H. pylori* infection

Burucoa C. *Helicobacter.* 201
Megraud F. *Eur. J. Gastroenterol. Hepatol.* 2001
Queiroz D.M. *J. Clin. Microbiol.* 2013

Urea Breath Test and Stool Antigen Test

- Patient should be off anti-acid for 14 days to increase the test sensitivity
- Stool Antigen Test dose not require patient to be off anti-acid

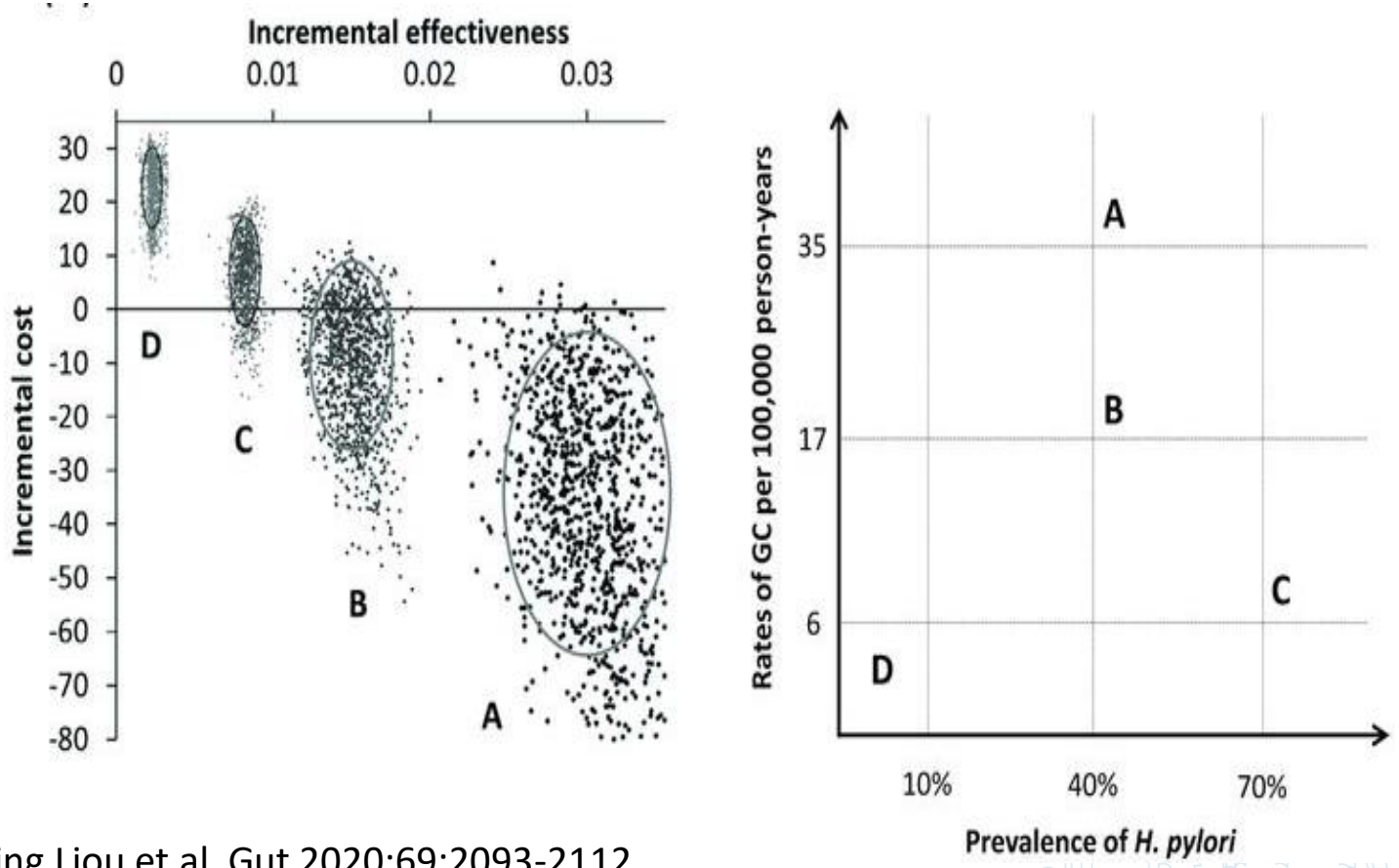
H pylori Serology test

- Serum H pylori antibodies is positive in active infection and previously treated h pylori

- Serum H pylori antibodies could be used as screening test in countries with increasing risk of gastric cancer

Is screening program for H pylori is coast effective?

Screening Program for H pylori is Coast effective in high and intermediate risk of gastric cancer - regions

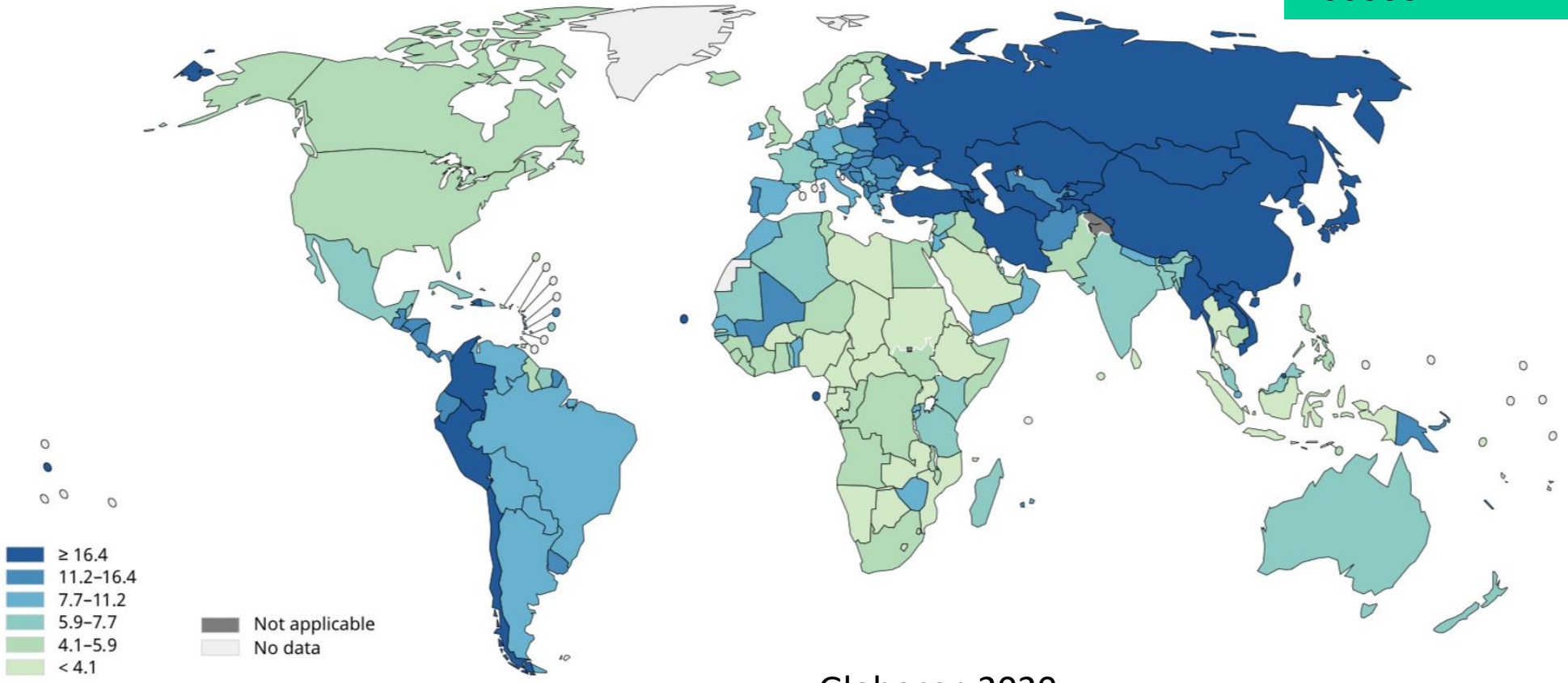


A) High rate of Gastric Cancer (35 per 100000) and high prevalence of H pylori (>40%)
B) Intermediate rate of Gastric Cancer (17 per 100000) and high rate of H pylori (> 40%)
C) Low rate of gastric cancer (7 per 100000) but high rate of H pylori (> 70%)
D) Both low rate of gastric cancer and H pylori

Jyh-Ming Liou et al. Gut 2020;69:2093-2112

Incidence of Gastric Cancer

UAE rate of GC 4.1 – 5.9 per 100000



Globocan 2020

Which patient to be tested for h pylori

ACG guideline: which patient to be tested

- Active peptic ulcer disease (PUD), a past history of PUD
- Dyspepsia
- Patients taking long-term low-dose aspirin.
- Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID)
- Patients with unexplained iron deficiency (ID) anemia.
- Adults with idiopathic thrombocytopenic purpura (ITP)
- Low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma
- History of endoscopic resection of early gastric cancer (EGC)

ACG guideline: which patient to be tested

- Patients with typical symptoms of gastroesophageal reflux disease (GERD) who do not have a history of PUD or dyspepsia need not be tested for *H. pylori* infection.

- Most of the patients seen in clinics do not have GERD symptoms alone and mostly having associated dyspeptic symptoms. Therefore, testing for H pylori found to be common in GERD patients.

Based on Studies:

- Insufficient evidence to support routine testing and treating of *H. pylori* in
  - Asymptomatic individuals with a family history of gastric cancer (in region with low rate of gastric cancer)
  - Patients with lymphocytic gastritis
  - Hyperplastic gastric polyps
  - Hyperemesis gravidarum

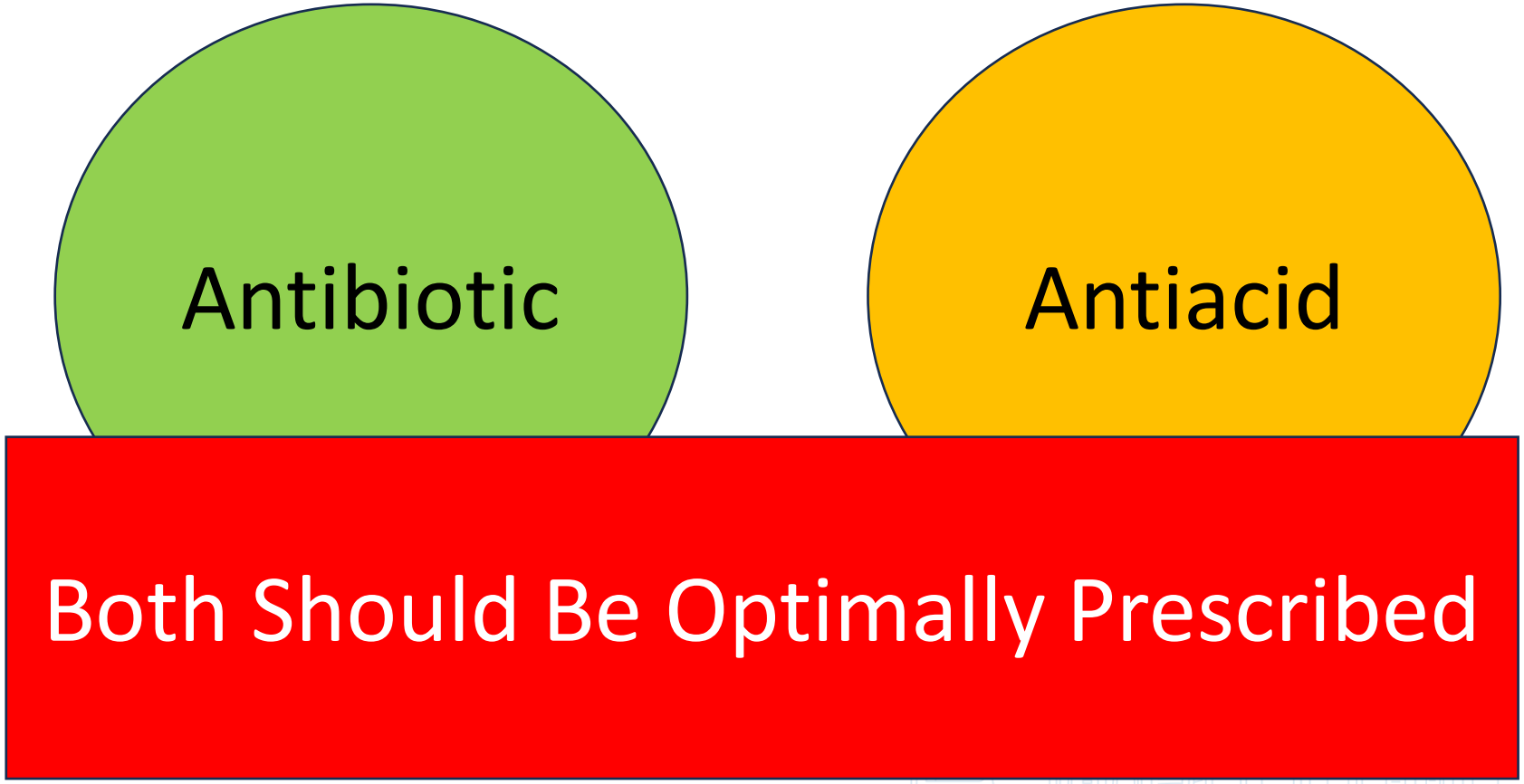
Management of H pylori

- Given the carcinogenic effect of this organism, it is recommended to:

Treat the All patients with a positive test of active infection with *H. pylori*

Eradication Therapy

Eradication Therapy Based on Two Concepts



Clarithromycin Based Triple Therapy

- Clarithromycin 500 mg bid + Amoxicillin 1 gm bid + PPI bid for 14 days

Bismuth Based Quadruple Therapy

- Bismuth 525 mg QID + Metronidazole 250 mg QID + Tetracycline 500 mg QID + PPI bid for 10 - 14 days

Concomitant Therapy

- clarithromycin 500 mg bid + amoxicillin1 gm bid and a metronidazole 500 mg tid + PPI bid for 10–14 days

Sequential therapy

- amoxicillin 1gm bid for 5–7 days followed by clarithromycin 500 mg bid + metronidazole 500 mg tid for 5–7 days Plus PPI bid all time

Hybrid Therapy

- Amoxicillin 1 gm bid for 7 days followed by a PPI, amoxicillin, clarithromycin and metronidazole for 7 days

Levofloxacin based Therapy

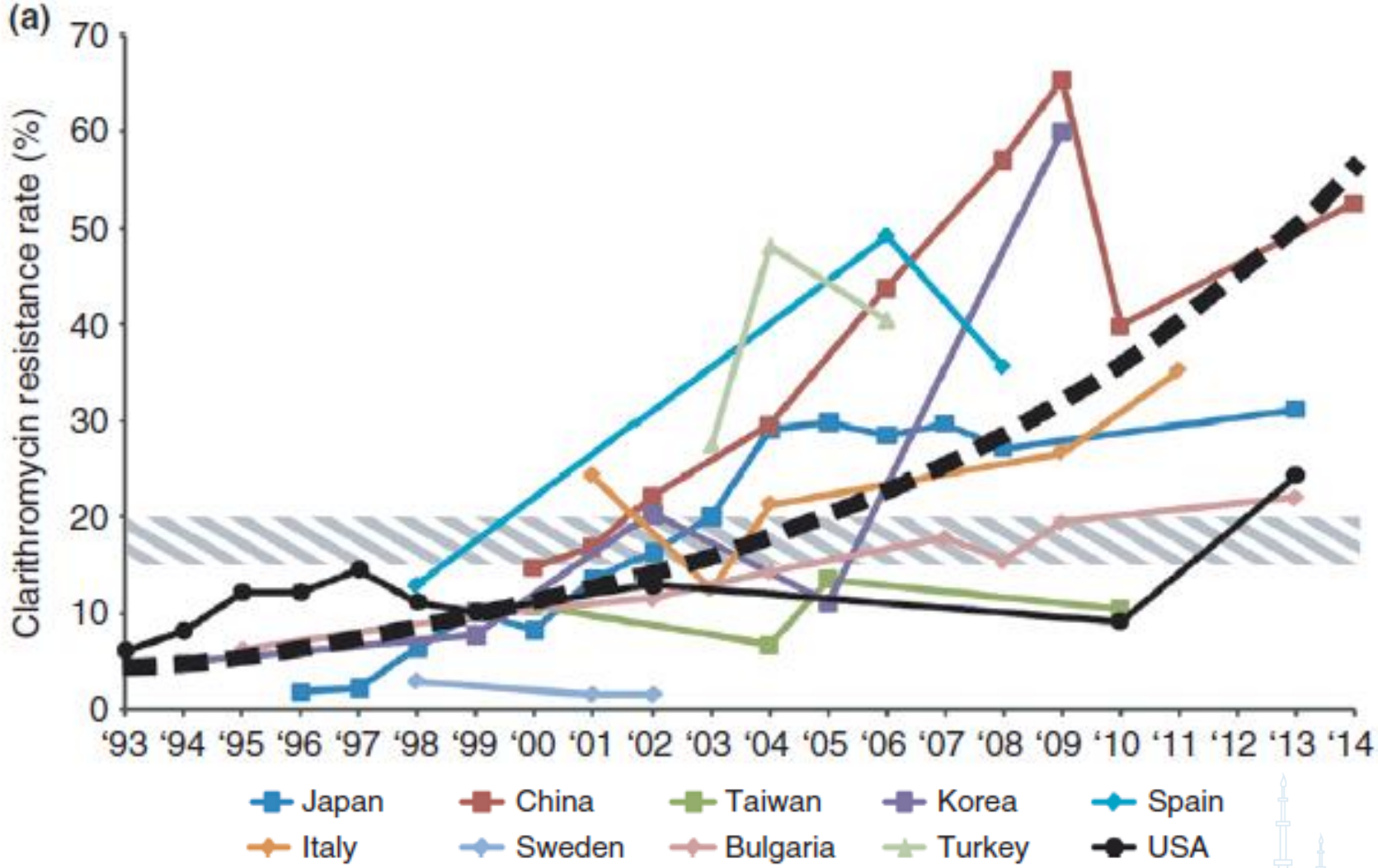
- levofloxacin 500 mg bid + amoxicillin 1gm bid + PPI bid for 10–14 days

Antibiotics in Eradication Therapy

- H pylori almost develops no resistence to amoxicillin (tetracyclin) and the resistence rate is very low < 5%

- Rate of antibiotic Resistance > 15% is considered High

Global Prevalence of Clarithromycin Antibiotic Resistance by Country & Year

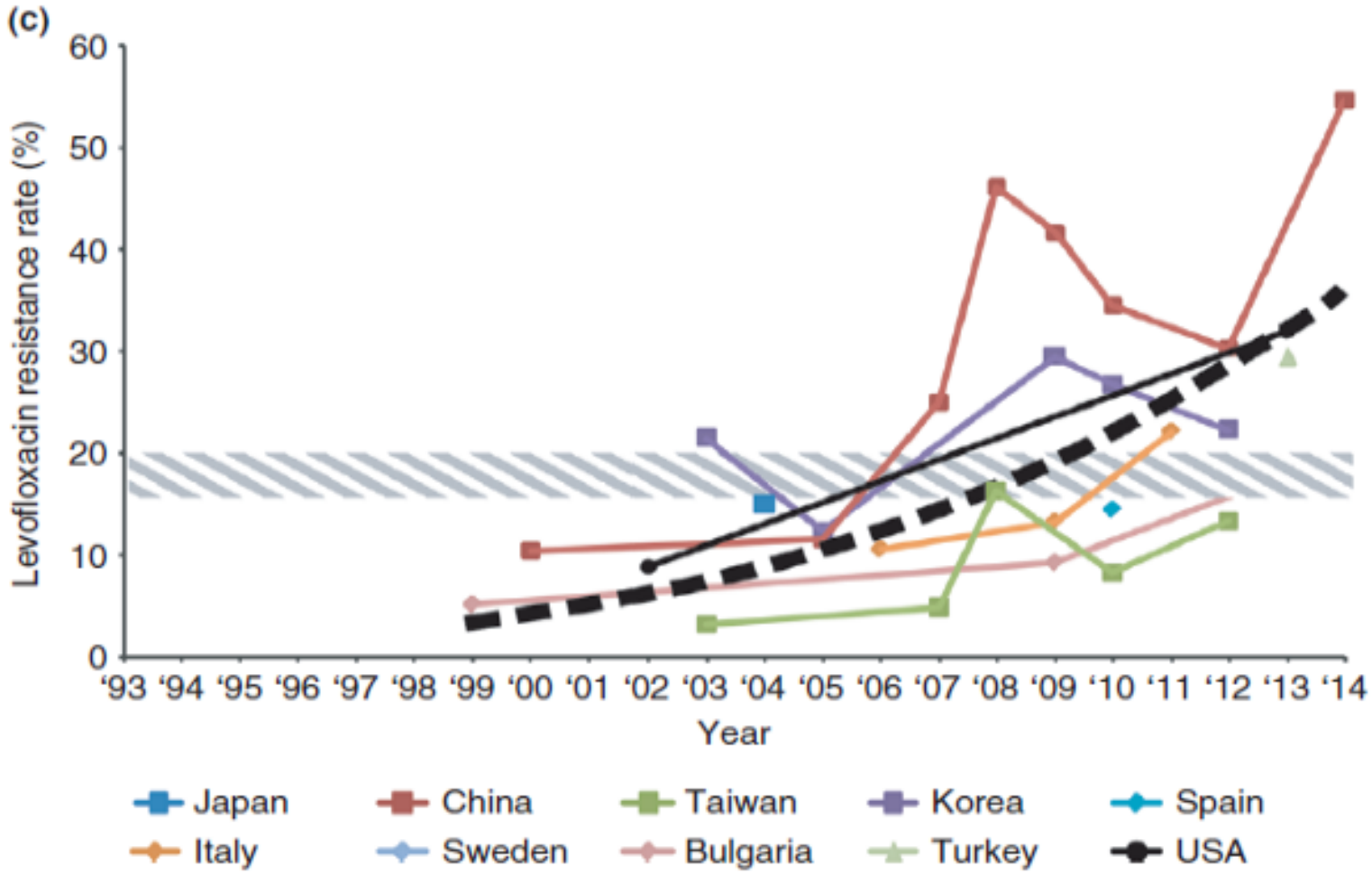


Thung et al. Aliment Pharmacol Ther. 2016.

Clarithromycin Antibiotic Resistance Rates in Middle-East Countries

Country	Resistance rate	Year	Reference
Egypt	55.7%	2016	Ramzy Iman et al. Revista do Instituto de Medicina Tropical de Sao
Iran	22.4%	2015	Khademi et al. IJBMS.
Iraq	16.2%	2015	Hussein et al. New Microbes New Infect.
KSA	23.3%	2015	Alsohaibani et al. Saudi J Gastro.
Tunisia	15.4%	2010	Ben Mansour et al. Ann Clin Microbiol Antimicrob.
UAE	19.2%	2010	Alfaresi M & Elkoush A. Indian J Gastroenterol.
Jordan	22.4%	2016	Diab et al. The Int Arabic J Of Antimicrobial Agents

Global Prevalence of Levofloxacin Antibiotic Resistance



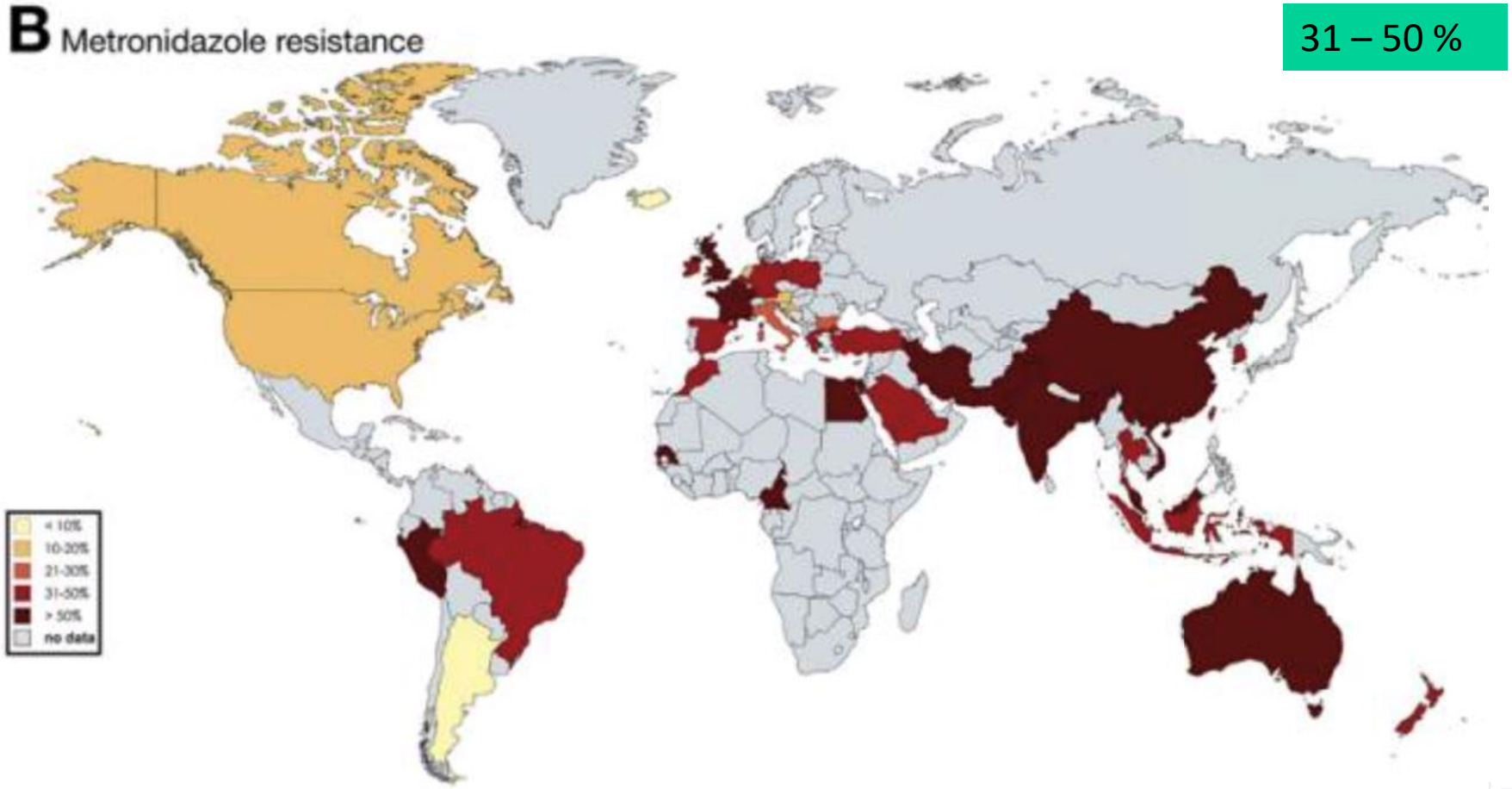
Thung et al. Aliment Pharmacol Ther. 2016.

Levofloxacin Antibiotic Resistance Rates in Middle-East Countries

Country	Resistance rate	Year	Reference
Egypt	6.7%	2020	Awad YMMM et al. QJM: An International J of Medicine.
Iran	5.3%	2015	Khademi F et al. IJBMS.
Iraq	13.4%	2014	Saeed AY et al. IOSR-JDMS.
KSA	11.1%	2015	Alsohaibani F et al. Saudi J Gastroenterol.
Turkey	29.5%	2015	Caliskan R et al. Rev. Soc. Bras. Med. Trop.

Thung et al. Aliment Pharmacol Ther. 2016.

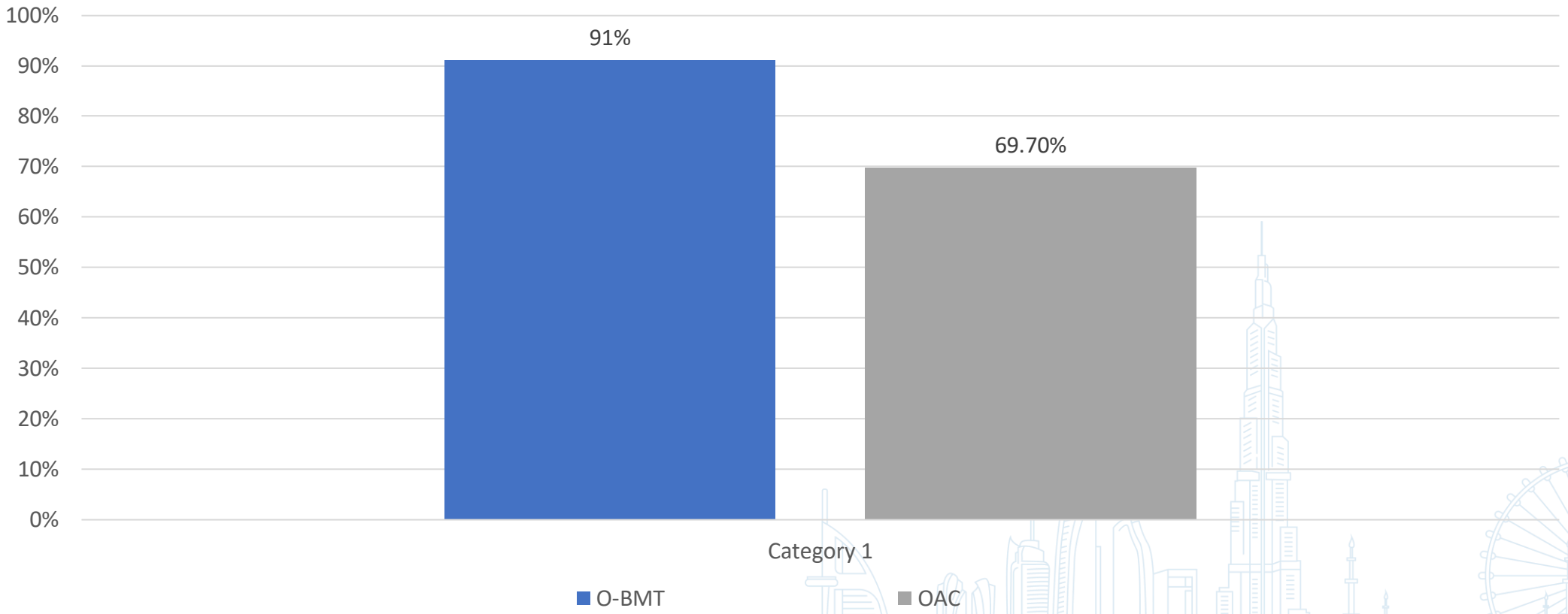
Global Prevalence of Metronidazole Antibiotic Resistance



31 – 50 %

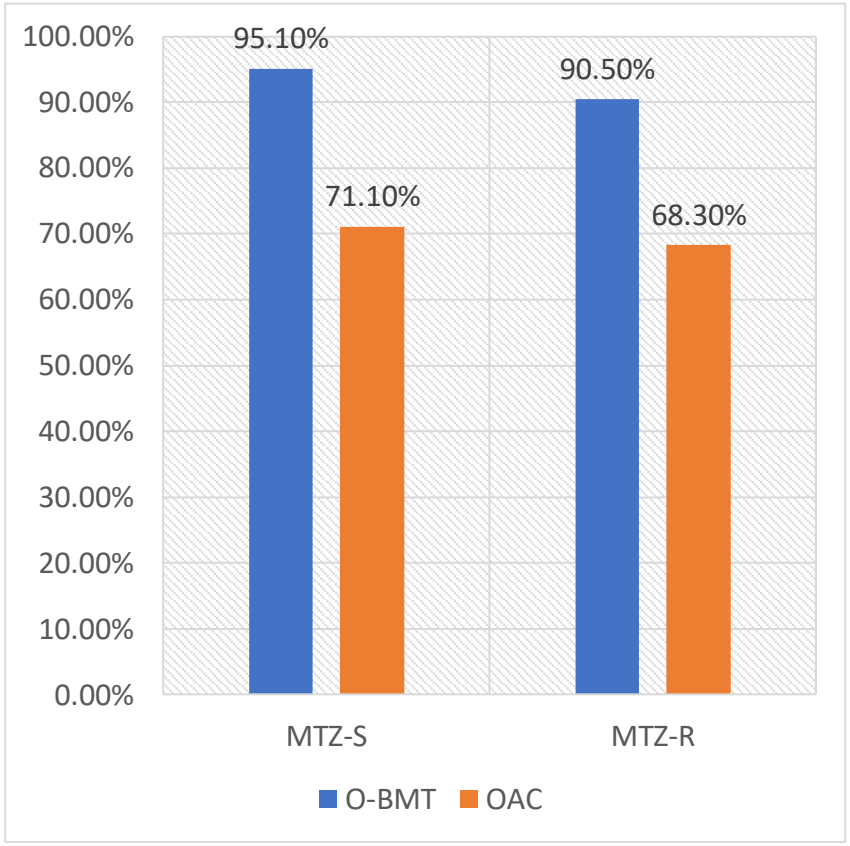
WHO 2019

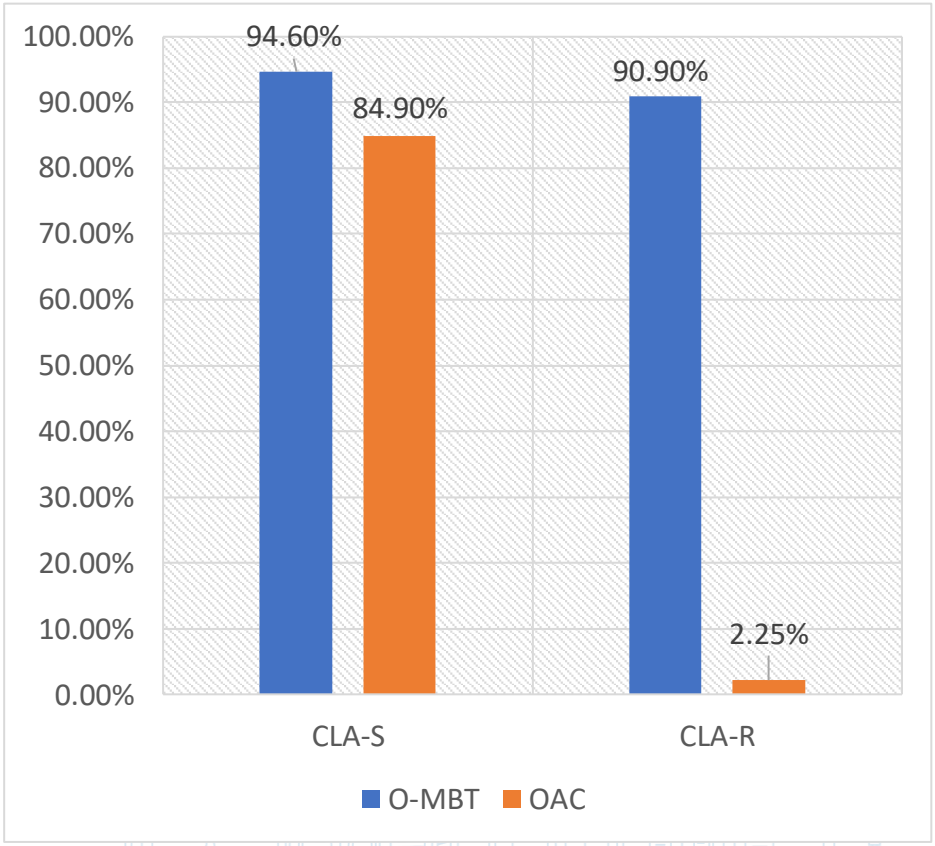
Comparison Between Bismuth Based quadruple therapy vs Clarithromycin Triple Therapy



Malfertheiner et al lancet 2011

Bismuth based quadruple therapy not affected by antibiotics resistance

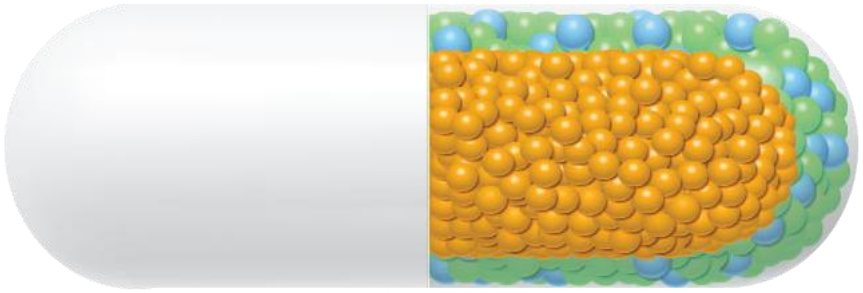




Malfertheiner et al lancet 2011

Bismuth Based Quadruple Therapy
PYLERA: 3 in 1 Treatment

Simply administered via an innovative 3-in-1 capsule[1,2,3]



- **125 mg** tetracycline HCl
- **125 mg** metronidazole
- **140 mg** bismuth subcitrate potassium

\+

PPI

1. Pylera Summary of Product Characteristics, October 2018. 2. Malfertheiner P, et al. Lancet 2011; 377: 905-913.
3. O'Morain C, et al. Aliment Pharmacol Ther 2003; 17: 415-420.

Treatment Guidelines & Consensus

First Line Treatment

2016

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]

[1]Division of Gastroenterology, McGill University Health Centre, McGill University, Montreal, Quebec, Canada; [2]Guelph GI and Surgery Clinic, Guelph, Ontario, Canada; [3]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; [4]Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [5]Department of Epidemiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; [6]Gastroenterology Service, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; [7]Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [8]Division of Gastroenterology, Hepatology, and Nutrition, The Hospital for Sick Children, Departments of Paediatrics and Physiology, University of Toronto, Toronto, Ontario, Canada; and [9]Kelowna General Hospital, Kelowna, British Columbia, Canada

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e25. Learning Objective: Upon completion of this examination, successful learners will be able to establish a treatment plan for patients with *H pylori* infection.

BACKGROUND & AIMS: *Helicobacter pylori* infection is increasingly difficult to treat. The purpose of these consensus statements is to provide a review of the literature and specific, updated recommendations for eradication therapy in adults. **METHODS:** A systematic literature search identified studies on *H pylori* treatment. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Statements were developed through an online platform, finalized, and voted on by an international working group of specialists chosen by the Canadian Association of Gastroenterology. **RESULTS:** Because of increasing failure of therapy, the consensus group strongly recommends that all *H pylori* eradication regimens now be given for 14 days. Recommended first-line strategies include concomitant nonbismuth quadruple therapy (proton pump inhibitor [PPI] + amoxicillin + metronidazole + clarithromycin [PAMC]) and traditional bismuth quadruple therapy (PPI + bismuth + metronidazole + tetracycline [PBMT]). PPI triple therapy (PPI + clarithromycin + either amoxicillin or metronidazole) is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. Recommended rescue therapies include PBMT and levofloxacin-containing therapy (PPI + amoxicillin + levofloxacin). Rifabutin regimens should be restricted to patients who have failed to respond to at least 3 prior options. **CONCLUSIONS:** Optimal treatment of *H pylori* infection requires careful attention to local antibiotic resistance and eradication patterns. The quadruple therapies PAMC or PBMT should play a more prominent role in eradication of *H pylori* infection, and all treatments should be given for 14 days.

Keywords: Helicobacter pylori; Eradication; Resistance; Proton Pump Inhibitor; Amoxicillin; Bismuth; Clarithromycin; Metronidazole; Tetracycline; Levofloxacin; Rifabutin.

Most current article

© 2016 by the AGA Institute
0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.04.006

Although the prevalence of *H pylori* is decreasing in some parts of the world, the infection remains present in 28% to 84% of subjects depending on the population tested.[1] Even studies in Western nations, which tend to have the lowest general prevalence,[2–4] report high proportions of infected individuals in certain communities (eg, 38%–75% of Alaskan or Canadian aboriginal populations).[2,4,5–8]

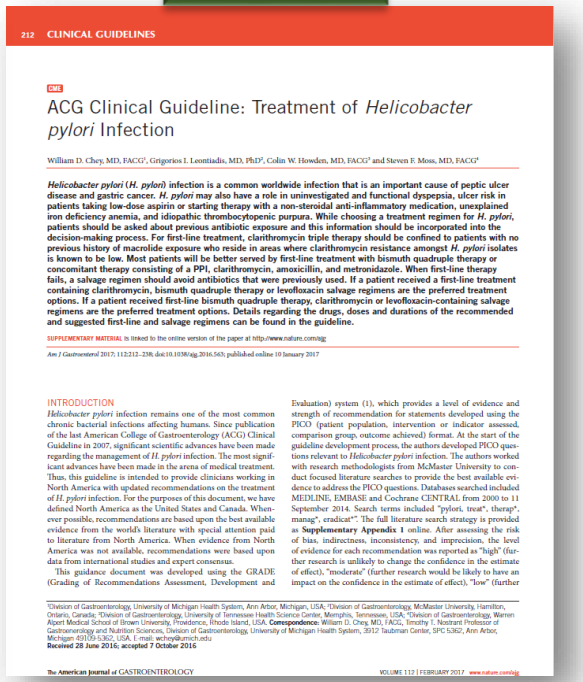
H pylori is implicated in the development of and its eradication is recommended in the treatment of duodenal or gastric ulcers, early gastric cancer, and gastric mucosa-associated lymphoid tissue lymphomas (in <0.01%).[4,9–14] Treatment has been suggested for prevention of gastric cancer in high-risk individuals,[11–13,15] as well as in patients with uninvestigated[16] and functional dyspepsia,[17] given evidence that eradication of the infection leads to sustained improvements in symptoms in a proportion of patients.[14,16,17]

The increasing prevalence of antibiotic-resistant strains of *H pylori* has led to reduced success with traditional *H*

Abbreviations used in this paper: BPAL, bismuth compounds + proton pump inhibitor + amoxicillin + levofloxacin; CAG, Canadian Association of Gastroenterology; CI, confidence interval; GRADE, Grading of Recommendation Assessment, Development and Evaluation; ITT, intention-to-treat; NNT, number needed to treat; PA, proton pump inhibitor + amoxicillin; PAC, proton pump inhibitor + amoxicillin + clarithromycin; PAL, proton pump inhibitor + amoxicillin + levofloxacin; PAM, proton pump inhibitor + amoxicillin + metronidazole + clarithromycin; PAN, PPI + amoxicillin + nitrofurantoin; PBMT, proton pump inhibitor + bismuth compounds + metronidazole + tetracycline; PICO, Population, Intervention, Comparator, Outcomes; PMC, proton pump inhibitor + metronidazole + clarithromycin; PPI, proton pump inhibitor; RCT, randomized controlled trial; RD, risk difference.

Toronto Consensus

2017



212 CLINICAL GUIDELINES

CME

ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

William D. Chey, MD, FACG[1], Grigorios I. Leontiadis, MD, PhD[2], Colin W. Howden, MD, FACG[3] and Steven F. Moss, MD, FACG[4]

***Helicobacter pylori* (*H. pylori*) infection is a common worldwide infection that is an important cause of peptic ulcer disease and gastric cancer. *H. pylori* may also have a role in uninvestigated and functional dyspepsia, ulcer risk in patients taking low-dose aspirin or starting therapy with a non-steroidal anti-inflammatory medication, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura. While choosing a treatment regimen for *H. pylori*, patients should be asked about previous antibiotic exposure and this information should be incorporated into the decision-making process. For first-line treatment, clarithromycin triple therapy should be confined to patients with no previous history of macrolide exposure who reside in areas where clarithromycin resistance amongst *H. pylori* isolates is known to be low. Most patients will be better served by first-line treatment with bismuth quadruple therapy or concomitant therapy consisting of a PPI, clarithromycin, amoxicillin, and metronidazole. When first-line therapy fails, a salvage regimen should avoid antibiotics that were previously used. If a patient received a first-line treatment containing clarithromycin, bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options. If a patient received first-line bismuth quadruple therapy, clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options. Details regarding the drugs, doses and durations of the recommended and suggested first-line and salvage regimens can be found in the guideline.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Am J Gastroenterol 2017; 112:212–238. doi:10.1038/ajg.2016.563; published online 10 January 2017

INTRODUCTION

Helicobacter pylori infection remains one of the most common chronic bacterial infections affecting humans. Since publication of the last American College of Gastroenterology (ACG) Clinical Guideline in 2007, significant scientific advances have been made regarding the management of *H. pylori* infection. The most significant advances have been made in the arena of medical treatment. Thus, this guideline is intended to provide clinicians working in North America with updated recommendations on the treatment of *H. pylori* infection. For the purposes of this document, we have defined North America as the United States and Canada. Whenever possible, recommendations are based upon the best available evidence from the world's literature with special attention paid to literature from North America. When evidence from North America was not available, recommendations were based upon data from international studies and expert consensus.

This guidance document was developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (1), which provides a level of evidence and strength of recommendation for statements developed using the PICO (patient population, intervention or indicator assessed, comparison group, outcome achieved) format. At the start of the guideline development process, the authors developed PICO questions relevant to *Helicobacter pylori* infection. The authors worked with research methodologists from McMaster University to conduct focused literature searches to provide the best available evidence to address the PICO questions. Databases searched included MEDLINE, EMBASE and Cochrane CENTRAL from 2000 to 11 September 2014. Search terms included "pylori, treat*, therap*, manag*, eradicat**. The full literature search strategy is provided as **Supplementary Appendix 1** online. After assessing the risk of bias, indirectness, inconsistency, and imprecision, the level of evidence for each recommendation was reported as "high" (further research is unlikely to change the confidence in the estimate of effect), "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect), "low" (further

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ACG

2022

Guidelines

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

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2022-327745).

For numbered affiliations see end of article.

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1724

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 considered.

Progress made in the management of *H. pylori* infection is covered in the present sixth edition of the Maastricht/Florence 2021 Consensus Report, key aspects related to the clinical role of *H. pylori* infection were re-evaluated and updated. Forty-one experts from 29 countries representing a global community, examined the new data related to *H. pylori* infection in five working groups: (1) indications/associations, (2) diagnosis, (3) treatment, (4) prevention/gastric cancer and (5) *H. pylori* and the gut microbiota. The results of the individual working groups were presented for 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 various clinical fields.

INTRODUCTION

The Maastricht VI/Florence Consensus Report was published in 2017[1] and substantial developments have ensued to necessitate an update that captures the progress and addresses the challenging clinical issues in the field of *Helicobacter pylori*. The increasing *H. pylori* resistance to previously effective antibiotic treatments has become of great concern and requires careful selection of therapies and revision of therapeutic strategies. In this edition, a new focus is set on molecular testing for *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.

New studies conducted to demonstrate feasibility and efficacy of primary and secondary gastric cancer prevention strategies are presented and discussed in their complexity at the individual and population level. Endoscopy-based enhanced imaging is taken note of for its contributions in early detection and treatment of small neoplastic foci and surveillance.

The role of *H. pylori* infection has also been assessed for potential interactions with other microbiota in the upper and lower digestive tract, as the gut microbiome emerges as a critical player in human health and disease.

The aim of this consensus report is to provide a state-of-the-art guide for the management of *H. pylori* infection and related clinical manifestations and as an inspiration for new clinical research in the area. In the current Maastricht VI/Florence Consensus Report, 41 experts from 29 countries convened for 2 days for a face-to-face meeting after having been actively involved in a previous Delphi process.

The working groups (WG) were set under the following topics: WG1: indications/associations, WG2: diagnosis, WG3: treatment, WG4: prevention/gastric cancer, WG5: *H. pylori* and the gut microbiota.

METHODS

Meeting logistics and coordination

The evidence-based Delphi process developed consensus statements following proposals by

Malfertheiner P, *et al*. *Gut* 2022;71:1724–1762. doi:10.1136/gutjnl-2022-327745

BMJ

Maastricht VI Consensus

2023

WGO GUIDELINE

Helicobacter pylori World Gastroenterology Organization Global Guideline

Peter Katelaris, MD, Richard Hunt, MD,† Franco Bazzoli, MD,‡ Henry Cohen, MD,§ Kwong Ming Fock, MD,‖ Marek Gemilyan, MD,¶ Peter Malfertheiner, MD,# Francis Mégraud, MD,** Alejandro Piscoya, MD,†† Due Quach, MD,‡‡ Nimish Vakil, MD,§§ Louis G. Vaz Coelho, MD,‖‖ Anton LeMair, MD,¶¶ and Jim Melberg, MA##*

Key Words: Helicobacter pylori, guidelines, gastritis, peptic ulcer disease, gastric cancer, treatment

(*J Clin Gastroenterol* 2023;57:111–126)

Helicobacter pylori has been recognized as a major pathogen of humankind for nearly 4 decades. However, despite the impact of treatment of infected individuals and the reduced transmission of infection in communities where socioeconomic living standards have improved, it remains the most common human bacterial pathogen, infecting perhaps half the population of the world.[1] As a result, it remains a major cause of morbidity and mortality worldwide.

H. pylori infection invariably causes active chronic gastritis. In most people, this may be clinically silent throughout life, but in a substantial minority, it causes gastroduodenal diseases, most importantly peptic ulcer disease and noncardia gastric cancer and gastric mucosa-associated lymphoid (MALT) lymphoma. It also increases the risk of gastroduodenal ulceration and bleeding in patients taking nonsteroidal antiinflammatory drugs (NSAIDs) and aspirin and is responsible for symptoms in a subset of patients with functional dyspepsia.

H. pylori has been studied intensively. A literature search reveals more than 45,000 publications. A great deal has been learned about the epidemiology of infection, biology, genetics, pathophysiology, disease expression, diagnosis, and treatment. Yet major challenges to our knowledge remain. The precise mode of transmission of infection remains unclear, despite many epidemiological studies that identify risk factors for infection. The determinants of disease expression remain incompletely understood, including many aspects of the host-pathogen interaction. The pathophysiology of this interaction is complex and has been reviewed in detail elsewhere.[2,3] The optimal clinical management pathways in different settings remain debated, and refinements in diagnostic modalities continue to be sought. The quest for the most effective, safe, and simple therapy remains the major issue for clinicians, and the problem of antimicrobial resistance to therapy is a major challenge. Optimal surveillance of adverse histologic gastric mucosal changes has not been determined, and the quest for an effective vaccine is ongoing.

There are many reviews and clinical guidelines about *H. pylori*,[4–12] As the field rapidly changes, there is a need for periodic updating and revision of these position papers. Moreover, a major challenge for guidelines is to be relevant

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WGO

PYLERA is recommended as first line treatment option for H. pylori

Chey, et al. American Journal of Gastroenterology 2017; Malfertheiner P, et al. Gut 2022;71:1724–1762. doi:10.1136/gutjnl-2022-327745; Fallone, et al. Gastroenterology 2016. J Clin Gastroenterol Volume 57, Number 2, February 2023

Treatment Guidelines – ACG

Regimen	Drugs (doses)	Dosing frequency	Duration (days)	FDA approval
Clarithromycin triple	PPI (standard or double dose)	BID	14	Yes[a]
	Clarithromycin (500 mg)			
	Amoxicillin (1 grm) or Metronidazole (500 mg TID)			
Bismuth quadruple	PPI (standard dose)	BID	10–14	No[b]
	Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)	QID		
	Tetracycline (500 mg)	QID		
	Metronidazole (250–500 mg)	QID (250)		
Hybrid	PPI (standard dose)+Amox (1 grm)	BID	7	No
	PPI, Amox, Clarithromycin (500 mg), Nitroimidazole (500 mg)[c]	BID	7	
Levofloxacin triple	PPI (standard dose)	BID	10–14	No
	Levofloxacin (500 mg)	QD		
	Amox (1 grm)	BID		
Levofloxacin sequential	PPI (standard or double dose)+Amox (1 grm)	BID	5–7	No
	PPI, Amox, Levofloxacin (500 mg QD), Nitroimidazole (500 mg)[c]	BID	5–7	
LOAD	Levofloxacin (250 mg)	QD	7–10	No
	PPI (double dose)	QD		
	Nitazoxanide (500 mg)	BID		
	Doxycycline (100 mg)	QD		

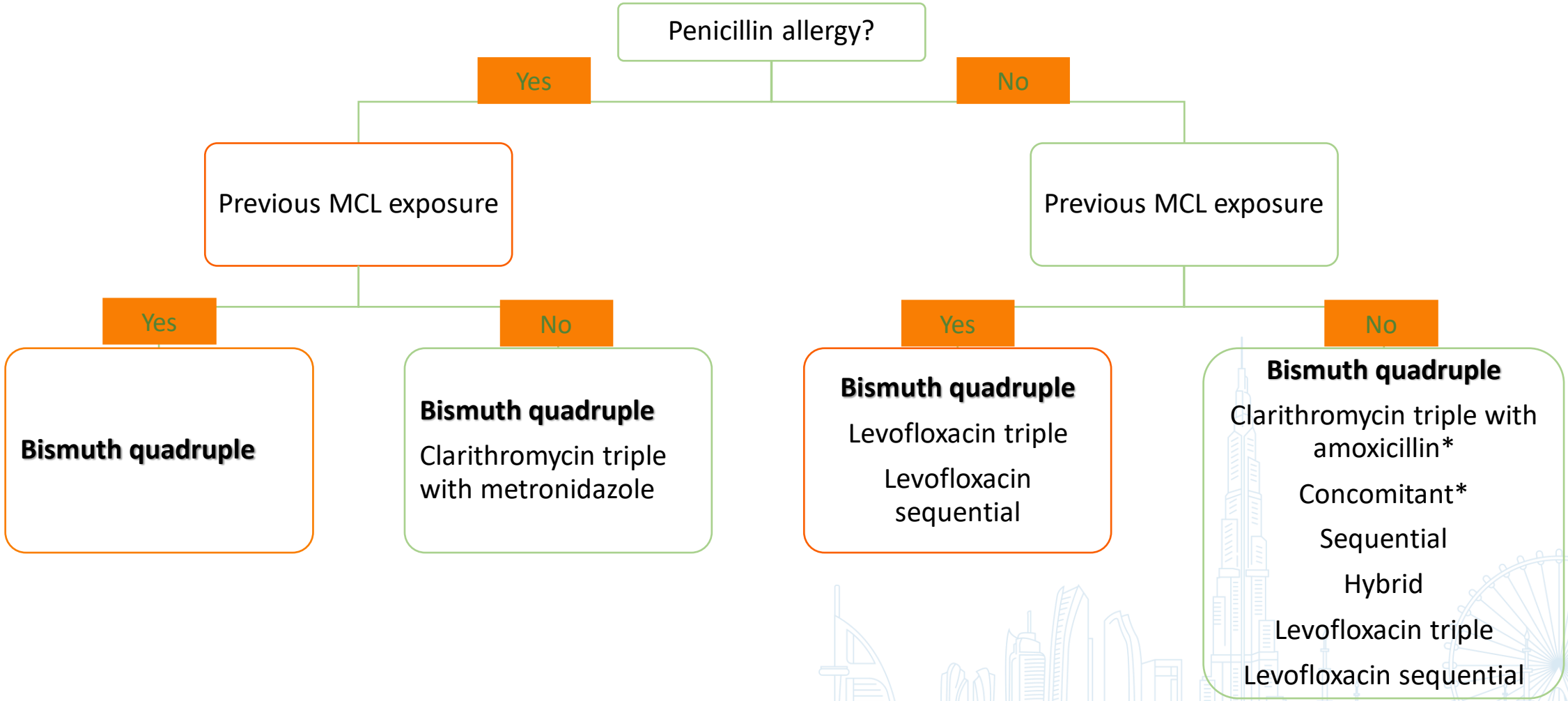
BID, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily.
[a]Several PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin and metronidazole is not an FDA-approved treatment regimen.
[b]PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.
[c]Metronidazole or tinidazole.

[b]PPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

Chey et al. Am J Gastroenterol 2017.

Treatment Guidelines – ACG (2017)

First Line Treatment



Chey et al. Am J Gastroenterol 2017.

Treatment Guidelines – Maastricht VI (2022)

- **The <u>first-line</u>** recommended treatment in areas of **high (>15%) or unknown clarithromycin resistance** is **<u>bismuth quadruple therapy (bQT)</u>.** If this is not available, non-bismuth concomitant quadruple therapy may be considered.

- **In areas of low clarithromycin resistance**, **<u>bismuth quadruple therapy (bQT)</u>** or clarithromycin-containing triple therapy may be recommended as **<u>first-line</u>** empirical treatment, if proven effective locally.

Malfertheiner P, et al. Gut 2022;71:1724–1762. doi:10.1136/gutjnl-2022-327745

WGO 2023

First Line Treatment

WGO GUIDELINE

2023

Helicobacter pylori World Gastroenterology Organization Global Guideline

Peter Katelaris, MD, Richard Hunt, MD,† Franco Bazzoli, MD,‡ Henry Cohen, MD,§ Kwong Ming Fock, MD,‖ Manik Gemilyan, MD,¶ Peter Malfertheiner, MD,# Francis Mégraud, MD,** Alejandro Piscoya, MD,†† Duc Quach, MD,‡‡ Nimish Vakil, MD,§§ Louis G. Vaz Coelho, MD,‖‖ Anton LeMair, MD,¶¶ and Jim Melberg, MA###*

Abstract: *Helicobacter pylori* remains a major health problem worldwide, causing considerable morbidity and mortality due to peptic ulcer disease and gastric cancer. The burden of disease falls disproportionally on less well-ensconced populations. As with most infectious diseases, the largest impact on reducing this burden comes from improvement in socioeconomic status, which interrupts transmission. This has been observed in many regions of the world, but the prevalence of infection remains high in many regions where improvements in living standards are slow to occur. Meanwhile, the optimal clinical management and treatment pathways remain unsettled and are evolving with changing antimicrobial resistance patterns. Despite decades of research and clinical practice, major challenges remain. The quest for the most effective, safe, and simple therapy remains the major issue for clinicians. The search for an effective vaccine appears to be elusive still. Clinical guidelines do not infrequently proffer discordant advice. A major challenge for guidelines is for relevance across a variety of populations with a varying spectrum of disease, antimicrobial resistance rates, and vastly different resources. As local factors are central to determining the impact and management strategies for *H. pylori* infection, it is important that pathways are based on the best available local knowledge rather than solely extrapolating from guidelines formulated in other regions, which may be less applicable. To this end, this revision of the World Gastroenterology Organisation (WGO) *H. pylori* guideline uses a "Cascades" approach that seeks to summarize the principles of management and offer advice for pragmatic, relevant and achievable diagnostic and treatment pathways based on established key treatment principles and using local knowledge and available resources to guide regional practice.

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The authors declare that they have nothing to disclose.

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DOI: 10.1097/MCG.0000000000001719

Key Words: Helicobacter pylori, guidelines, gastritis, peptic ulcer disease, gastric cancer, treatment

(*J Clin Gastroenterol* 2023;57:111–126)

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There are many reviews and clinical guidelines about *H. pylori*.[4–12] As the field rapidly changes, there is a need for periodic updating and revision of these position papers. Moreover, a major challenge for guidelines is to be relevant

The other core choice for first-line therapy, especially in regions of high primary CR, remains bismuth-based quadruple therapy.

The best-studied regimen involves a PPI, bismuth, tetracycline, and metronidazole (PPI-BTM). This treatment has stood the test of time because it results in reliable and acceptable eradication rates irrespective of primary MR, as the addition of a PPI to BTM appears to overcome MR.

Consensus - TORONTO

First Line Treatment

- Because of increasing failure of therapy, the consensus group strongly recommended that all H. pylori eradication regimens now be given for 14 days.

- **Quadruple therapies** recommended as a **first-line strategies** including:
  - ✓ Bismuth quadruple therapy (PBMT)
  - ✓ Concomitant non-bismuth quadruple therapy

- PPI **triple therapy** (PPI +clarithromycin and either amoxicillin or metronidazole) was **restricted to** areas with known **low clarithromycin resistance** or high eradication success with these regimens.

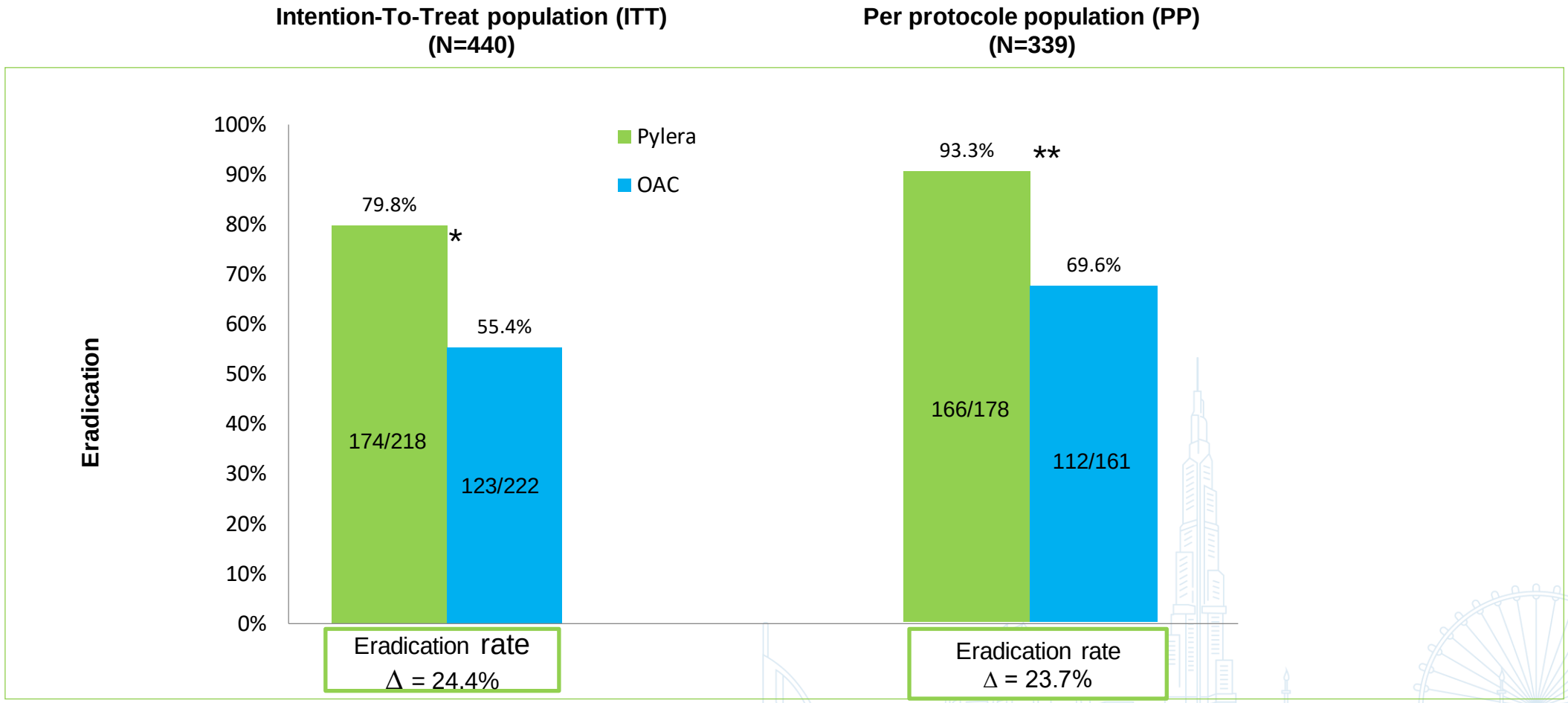
Pylera Phase 3 Trial

Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial

Peter Malfertheiner, Franco Bazzoli, Jean-Charles Delchier, Krysztof Celiński, Monique Giguère, Marc Rivière, Francis Mégraud, for the Pylera Study Group

Malfertheiner et al. Lancet 2011.

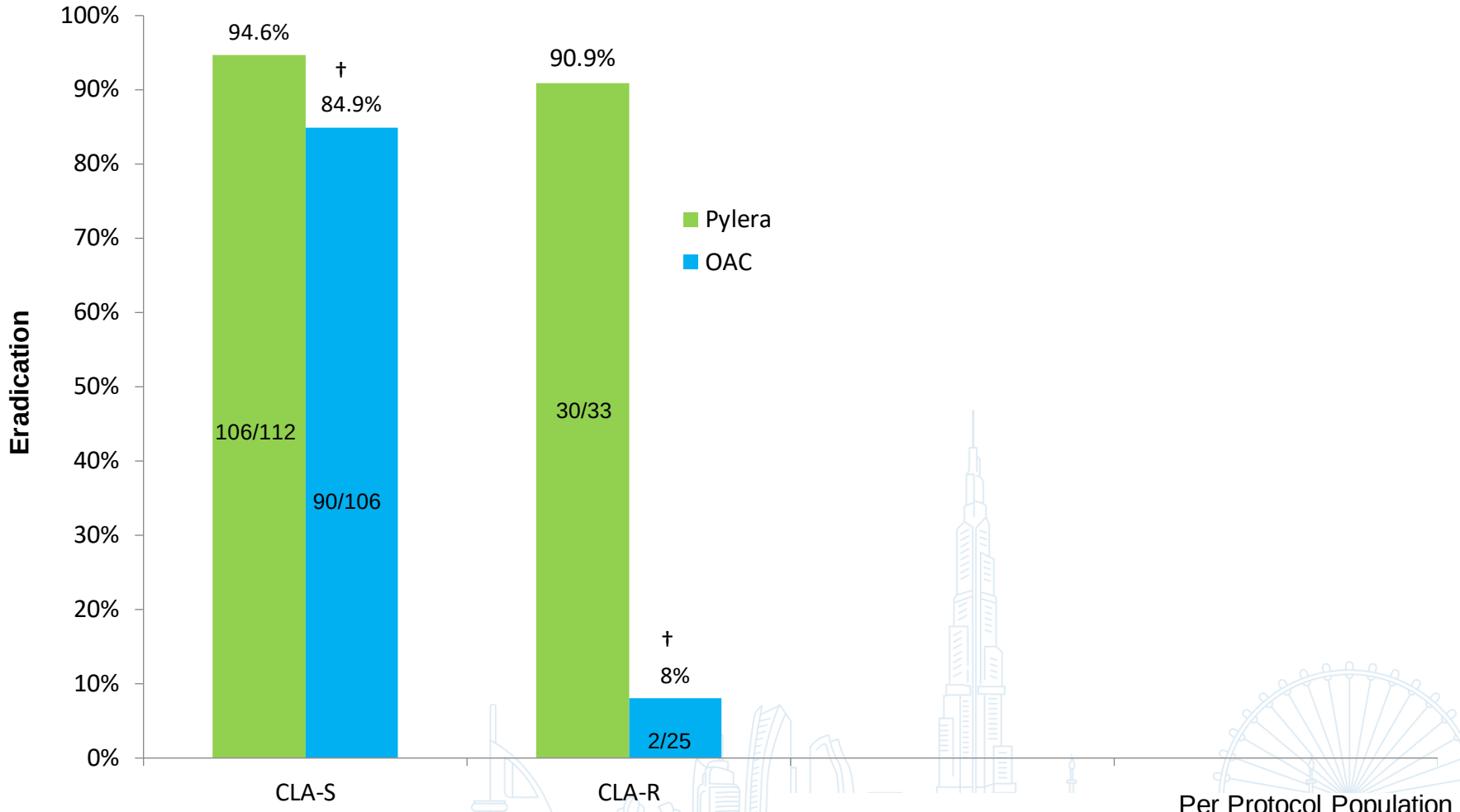
Pylera Achieved Significant High Rates of Eradication Compared to OAC



*p<0.001, ** p<0.01
OAC = omeprazole, amoxicillin and clarithromycin

Malfertheiner et al. Lancet 2011.

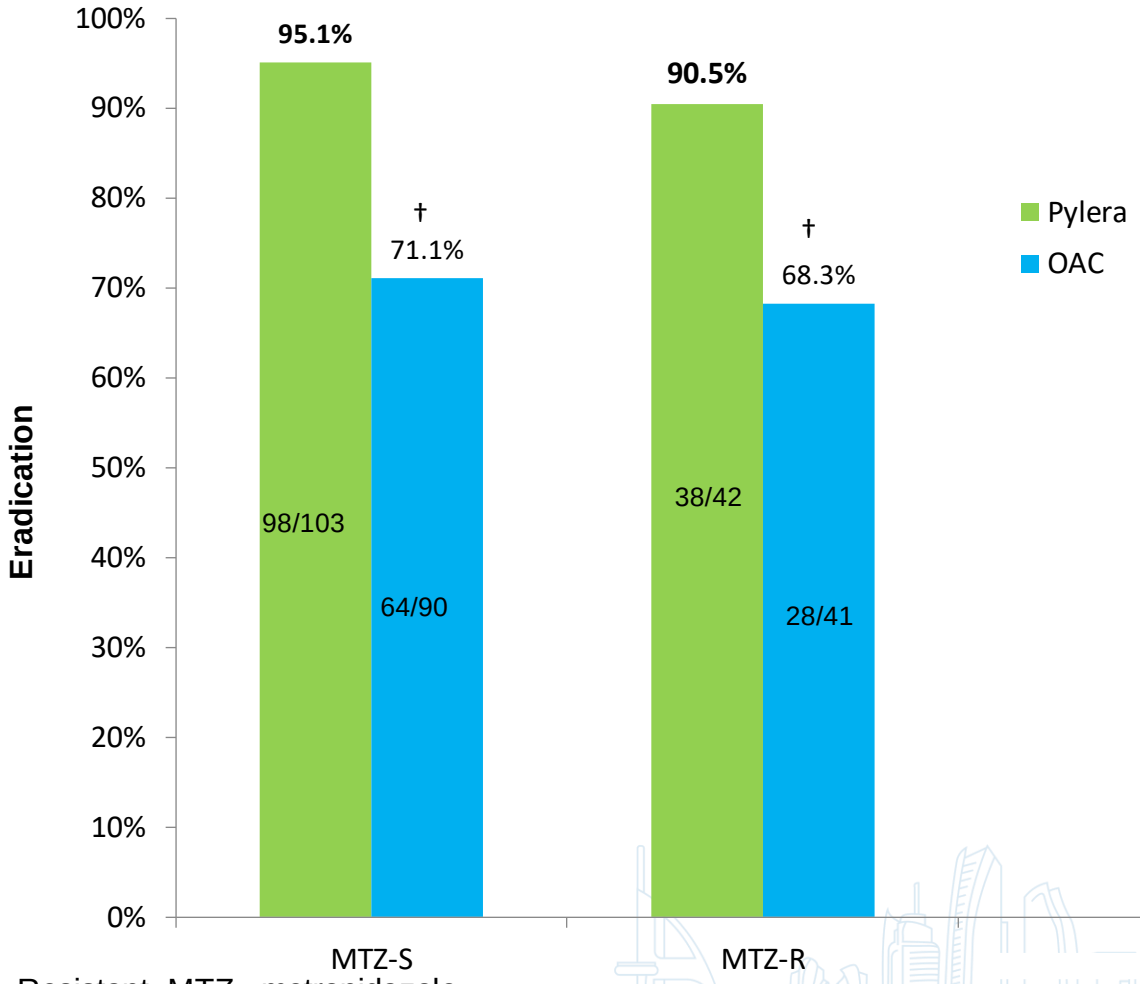
Clarithromycin Resistance Doesn't Impact Pylera® Efficacy (PP)



*p= 0.43 , † p <0.001 , S= Susceptible, R= Resistant, CLA= clarithromycin,
OAC= omeprazole, amoxicillin, and clarithromycin,
OBMT= omeprazole, bismuth, metronidazole, and tetracycline

Malfertheiner et al. Lancet 2011.

Metronidazole resistance Doesn't Impact Pylera® Efficacy (PP)



*p= 0.28 , † p=0.84, S= Susceptible, R= Resistant, MTZ= metronidazole, OAC= omeprazole, amoxicillin, and clarithromycin
OBMT= omeprazole, bismuth, metronidazole, and tetracycline

Malfertheiner et al. Lancet 2011.

Safety (1/2)

	Quadruple Therapy (N=216)	Standard Therapy (N=222)
Treatment –emerged adverse events (TEAE)	258	223
Patients with a TEAE	101(47%)	112(51%)
Gastrointestinal disorders	65 (30%)	82 (37%)
Dyspepsia	22 (10%)	30 (14%)
Diarrhea	14 (7%)	28 (13%)
Upper abdominal pain	18 (8%)	16 (7%)
Nausea	14 (7%)	2 (1%)
Vomiting	8 (4%)	6 (3%)
Faeces discoloured	9 (4%)	1 (1%)
Flatulence	3 (1%)	5 (2%)
Abdominal pain	3 (1%)	1 (1%)
Eructation	3 (1%)	1 (1%)
Central nervous system disorders	33 (15%)	29 (13%)
Dysgeusia	12 (6%)	22 (10%)
Headache	18 (8%)	7 (3%)
Dizziness	4 (2%)	1 (1%)
Somnolence	3 (1%)	0

Malfertheiner et al. Lancet 2011.

Safety (2/2)

	Quadruple Therapy (N=216)	Standard Therapy (N=222)
Infections and infestations	17 (8%)	18 (8%)
Nasopharyngitis	6 (3%)	7 (3%)
Upper respiratory tract infection	3 (1%)	2 (1%)
Influenza	0	4 (2%)
General disorders and administration-site conditions	14 (7%)	7 (3%)
Malaise	5 (2%)	3 (1%)
Pyrexia	3 (1%)	1 (1%)
Respiratory, thoracic, and mediastinal disorders	8 (4%)	3 (1%)
Cough	4 (2%)	1 (1%)
Musculoskeletal and connective tissue disorders	7 (3%)	3 (1%)
Back pain	4 (2%)	1 (1%)
Psychiatric disorders	3 (1%)	5 (2%)
Insomnia	0	3 (1%)

Malfertheiner et al. Lancet 2011.

Conclusion

Interpretation: Quadruple therapy should be considered for first-line treatment in view of the rising prevalence of clarithromycin-resistant *H pylori*, especially since quadruple therapy provides superior eradication with similar safety and tolerability to standard therapy.

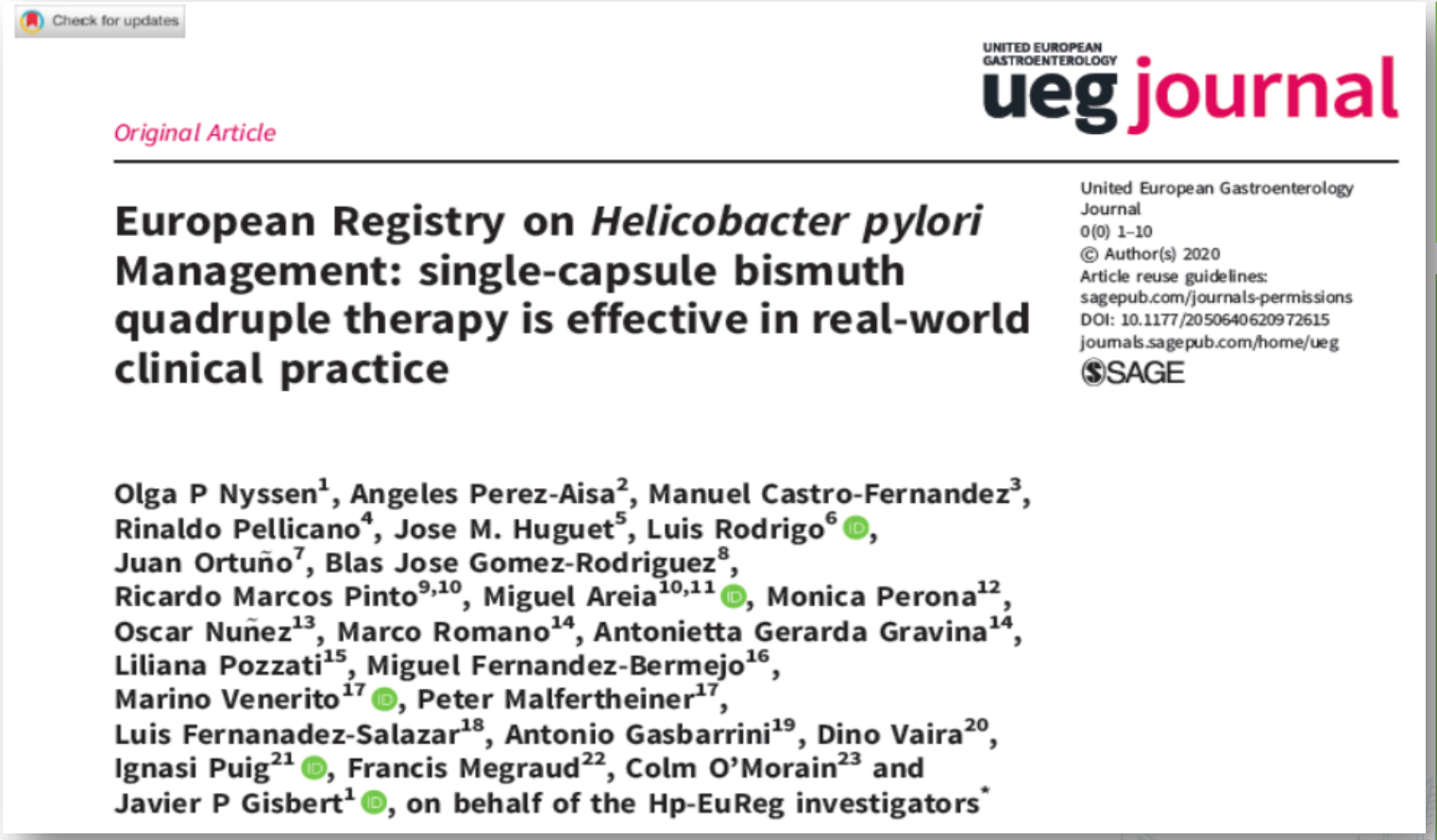
Clarithromycin resistance doesn't affect the efficacy of Pylera®

Metronidazole resistance doesn't affect the efficacy of Pylera®

Malfertheiner et al. Lancet 2011.

European registry on *H. pylori* management:

Single-capsule bismuth quadruple therapy is effective in real-world clinical practice



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Original Article

European Registry on *Helicobacter pylori* Management: single-capsule bismuth quadruple therapy is effective in real-world clinical practice

United European Gastroenterology Journal
0(0) 1–10

DOI: 10.1177/2050640620972615
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SAGE

Olga P Nyssen[1], Angeles Perez-Aisa[2], Manuel Castro-Fernandez[3], Rinaldo Pellicano[4], Jose M. Huguet[5], Luis Rodrigo[6], Juan Ortuño[7], Blas Jose Gomez-Rodriguez[8], Ricardo Marcos Pinto[9,10], Miguel Areia[10,11], Monica Perona[12], Oscar Nuñez[13], Marco Romano[14], Antonietta Gerarda Gravina[14], Liliana Pozzati[15], Miguel Fernandez-Bermejo[16], Marino Venerito[17], Peter Malfertheiner[17], Luis Fernanadez-Salazar[18], Antonio Gasbarrini[19], Dino Vaira[20], Ignasi Puig[21], Francis Megraud[22], Colm O'Morain[23] and Javier P Gisbert[1], on behalf of the Hp-EuReg investigators*

*The Hp-EuReg is an international, multicenter, prospective, non-interventional registry that has been recording information on the management of H. pylori infection since 2013

Objective:
To evaluate the effectiveness and safety of the single-capsule bismuth quadruple therapy

European Registry on H. pylori Management (Hp-EuReg)*

34,460 cases from 28 countries

3,439 cases were treated with single-capsule BQT

2100 were prescribed this treatment according to the regimen indicated in the technical sheet
(3 capsules q.i.d. for 10 days)

Single-Capsule Bismuth Quadruple Therapy Effectiveness by Line of Treatment

	ITT		PP		mITT	
	N (%)	95% CI	*N* (%)	95% CI	*N* (%)	95% CI
Overall	1724 (85.2)	(83.6–86.7)	1761 (92.8)	(91.6–94.0)	1777 (91.9)	(90.6–93.1)
First-line	1135 (88.1)	(86.3–89.9)	1158 (95.5)	(94.2–96.6)	1166 (94.6)	(93.2–95.8)
Second-line	361 (81.5)	(77.7–85.2)	370 (90.2)	(87.2–93.2)	375 (89.3)	(86.2–92.3)
Rescue treatment from third-line to sixth-line	228 (85.2)	(73.2–82.9)	233 (85.0)	(80.6–89.4)	236 (91.9)	(79.5–88.4)

ITT: intention-to-treat; PP: per protocol; mITT: modified intention-to-treat.
The χ^2 test showed statistical significant differences in effectiveness for the different treatment lines as measured by ITT, PP and mITT ($P < 0.001$).

- Single-capsule BQT eradicates H. pylori in approximately 90% of patients in real world clinical practice, with a favorable safety profile
- The development of a three-in-one single-capsule formulation has led to a resurgence in the use of bismuth quadruple therapy (BQT) to treat Helicobacter pylori infection.
- In the largest study carried out to date, the effectiveness of single-capsule BQT was optimal both as a first line and as a rescue therapy.
- Compliance was the factor most closely associated with treatment effectiveness.

Nyssenet al. United European Gastroenterol J. 2021

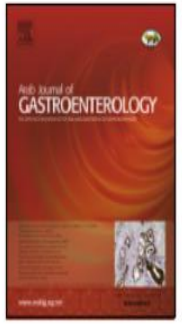
Evidence from Kuwait: Bismuth Quadrable Therapy (Pylera®)

Arab Journal of Gastroenterology 16 (2015) 131–135

Contents lists available at ScienceDirect

Arab Journal of Gastroenterology

journal homepage: www.elsevier.com/locate/ajg



Gastroenterology in Arab Countries

Quadruple therapy versus standard triple therapy for eradication of *Helicobacter pylori* in Kuwait

Mohamed Alboraie [a,b,*], Motaz Saad [a], Jaber Al-Ali [a,c], Mohammad Malik [a], Noha Asem [d], Imre Schmidt [a], Ahmad A. Alfadhli [a]

[a] Haya Al-Habeeb Gastroenterology Center, Department of Internal Medicine, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait
[b] Department of Internal Medicine, Al-Azhar University, Cairo, Egypt
[c] Department of Internal Medicine, Kuwait University, Kuwait City, Kuwait
[d] Department of Public Health and Community Medicine, Cairo University, Giza, Egypt

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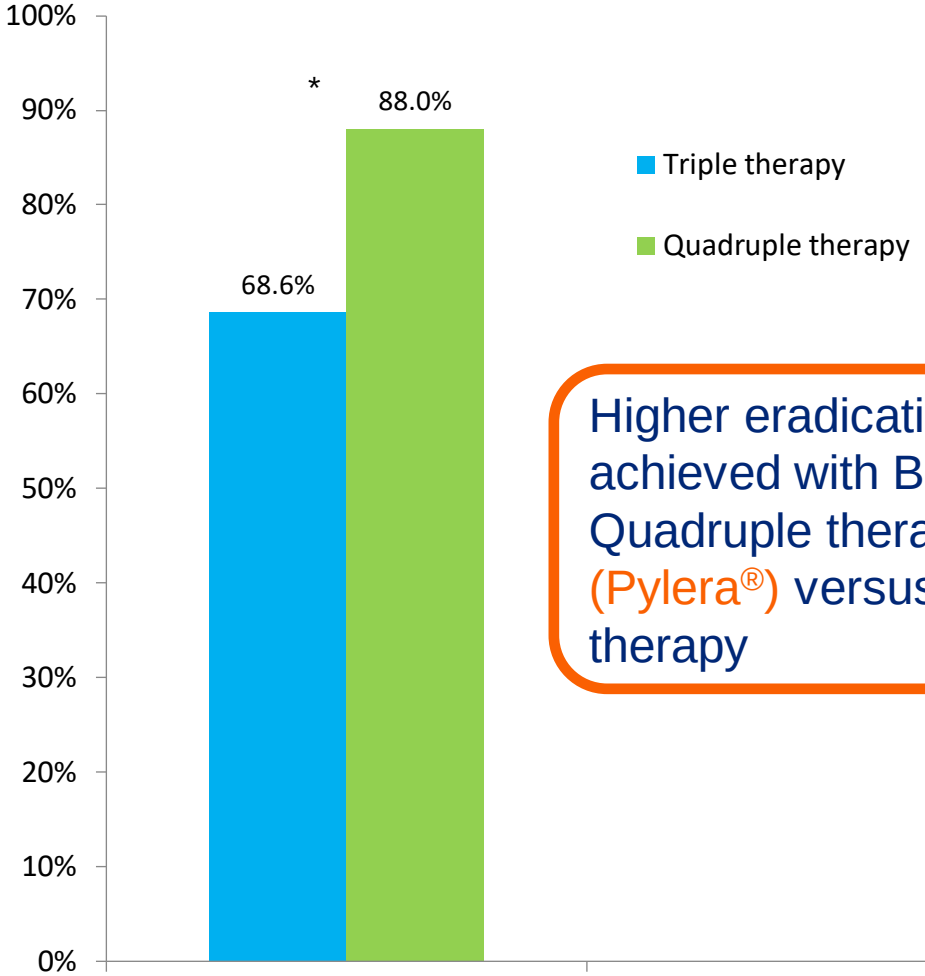
dyspeptic patients from different countries who were proved to have chronic gastritis by endoscopy and gastric biopsy

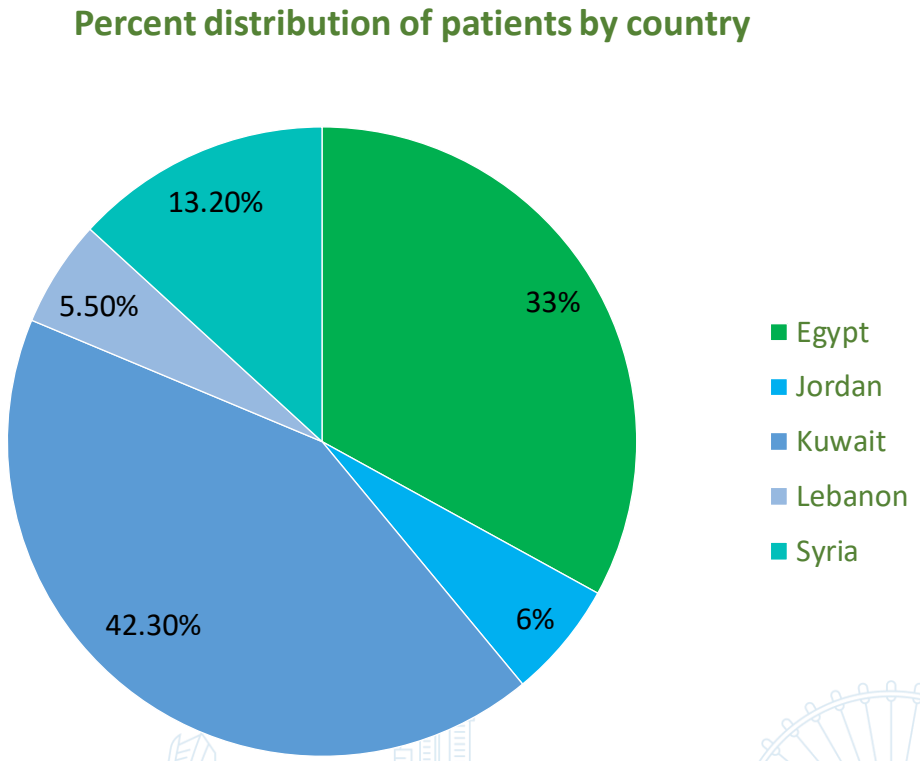
All of them were naïve to H. pylori eradication therapy.

Alboraie al. Arab J Gastroenterol 2015.

Efficacy of Bismuth Quadrable Therapy (Pylera®) versus Triple Therapy



Higher eradication rate is achieved with Bismuth Quadruple therapy (Pylera®) versus triple therapy



*p< 0.001 , triple therapy (omeprazole, amoxicillin, and clarithromycin) for 10 days, quadruple therapy (omeprazole, bismuth subcitrate potassium, tetracycline, and metronidazole) for 10 days

Alboraie al. Arab J Gastroenterol 2015.

Evidence from Saudi Arabia: Bismuth Quadrable Therapy (Pylera®)

Original Article

Efficacy of a bismuth-based quadruple therapy regimen for *Helicobacter pylori* eradication in Saudi Arabia

Fahad Alsohaibani, Mohammed Alquaiz, Khalid Alkahtani, Hamad Alashgar, Musthafa Peedikayil, Abdulrahman AlFadda, Majid Almadi[1]

Department of Medicine, Section of Gastroenterology, King Faisal Specialist Hospital and Research Center, [1]Department of Medicine, Division of Gastroenterology, King Saud University Medical City, College of Medicine, King Saud University, Riyadh, Saudi Arabia

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Patients with
H. pylori diagnosed by endoscopy and rapid urease test (RUT) or histology.

80% naïve

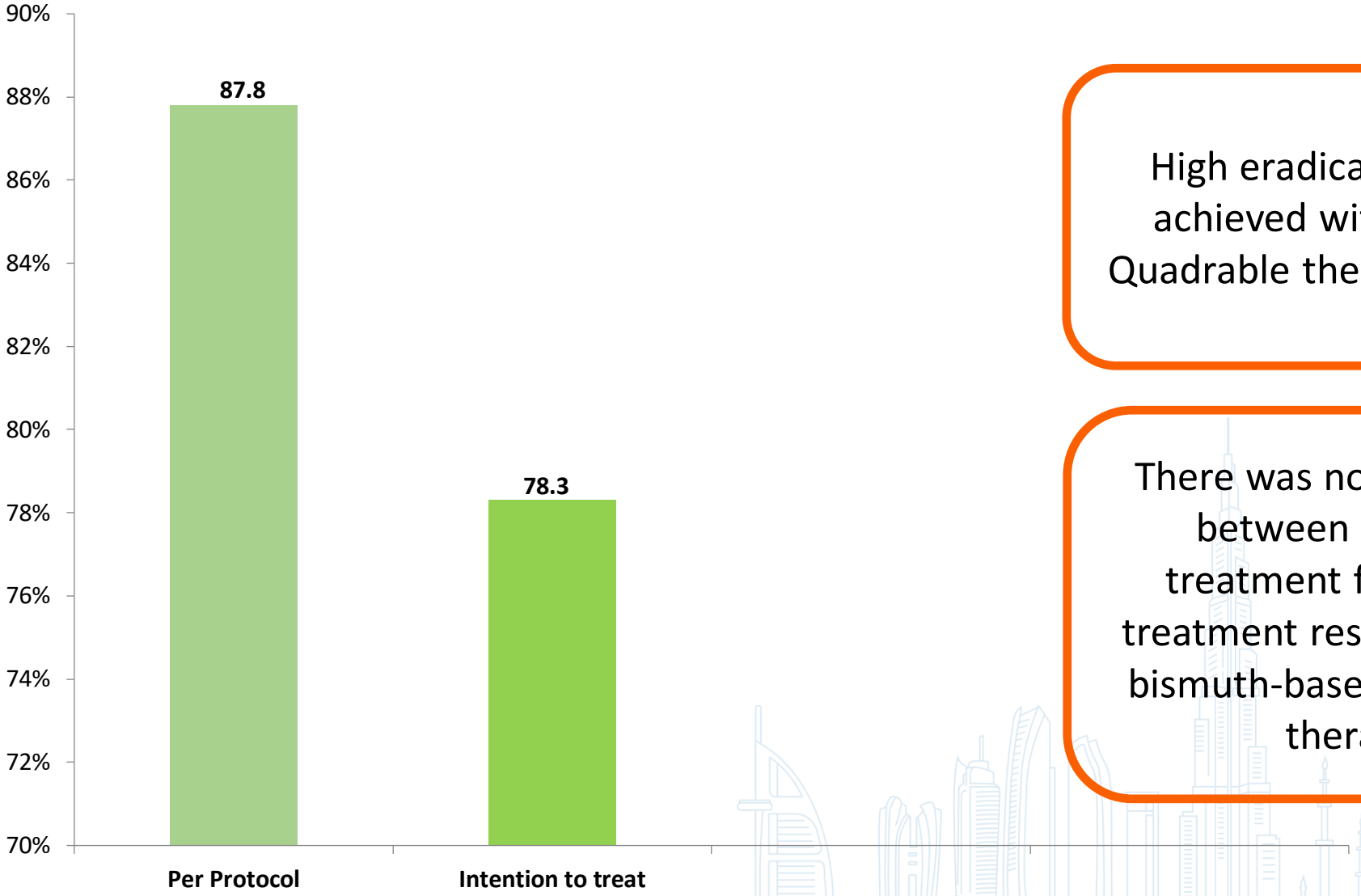
20% had previous treatment*

Prospective, open-label, non-randomized controlled trial

*4 patients had failed previous treatment with the sequential regimen and 12 patients had treatment with clarithromycin-based triple therapy

Alsohaibani et al. Saudi JGastroenterol 2020

Efficacy: Per-Protocol and Intention-To-Treat Analysis



High eradication rate is achieved with Bismuth Quadrable therapy (Pylera®)

There was no correlation between previous treatment failure and treatment response to the bismuth-based quadruple therapy

Alsohaibani et al. Saudi JGastroenterol 2020

Factors Affecting Success rate of Eradication therapy

Host Related Factors

- Adherence
    - was identified as an important factor predicting *H. pylori* eradication success rate
- Genetic factors leading to high acidity
    - Polymorphisms of *CYP2C19* in cytochrome P450 system, determine the rate at which PPIs metabolized
- cigarette smoking and diabetes mellitus have been associated with treatment failure in separate meta-analyses

Lee M. Arch Intern Med 1999. Tang HL,PLoS One 2013
Horikawa C, Diabetes Res Clin Pract 2014. Dore MP, Dig Dis Sci 2000
Fischbach L. Aliment Pharmacol Ther 2007. Graham DY, Clin Gastroenterol Hepatol 2014

Organism Related Factors

- Prior use of macrolides, metronidazole, and levofloxacin increase risk of resistance.
- Clarithromycin resistance has a greater effect on treatment efficacy as compared with metronidazole resistance.
- Metronidazole resistance can be overcome by increasing the dose, duration, or frequency of administration. At least 1.5 – 2 gm divided in 3 – 4 times a day
- Resistance rates to amoxicillin, tetracycline, and rifabutin are low (<5 percent).
- Amoxicillin should be at least 2 gm total divided in 2 to 3 times a day

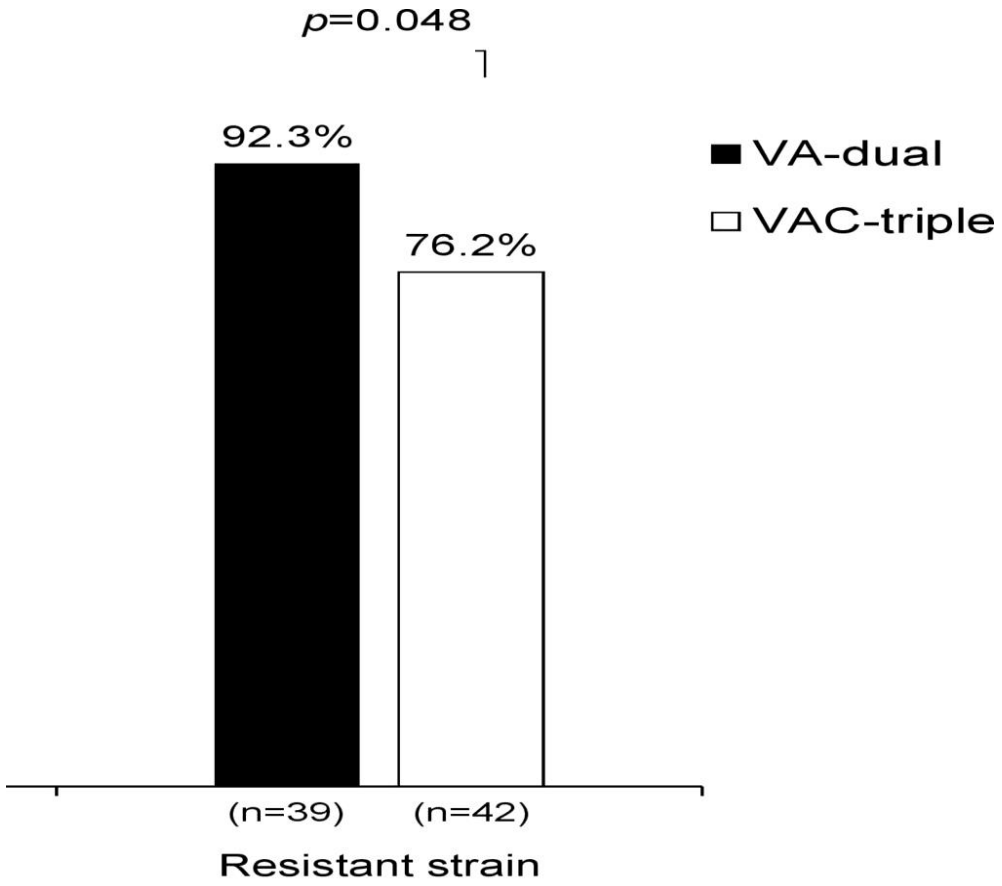
Anti- Acid Factor in Eradication Therapy

- PPIs are an important component of *H. pylori* eradication regimens. They have inhibitory effects on *H. pylori replication*
  - Alkaline media has bacteriostatic properties
  - Decreasing intragastric acidity enhancing antibiotic effects

- The bismuth is anti-acid and has added effect to PPI in eradicating the bacteria

- More profound acid inhibition significantly improved *H. pylori* eradication rates.

Eradication rate using Potent Anti-acid



- Using new potent anti acid: potassium – competitive acid blocker which is more potent than PPI class (Vonoprazan)

- Amoxicillin plus Vonoprazan compaired with Clarithromycin based Triple therapy plus Omeprazole

Sho Suzuki, Gut 2020

Lessons from the European Registry

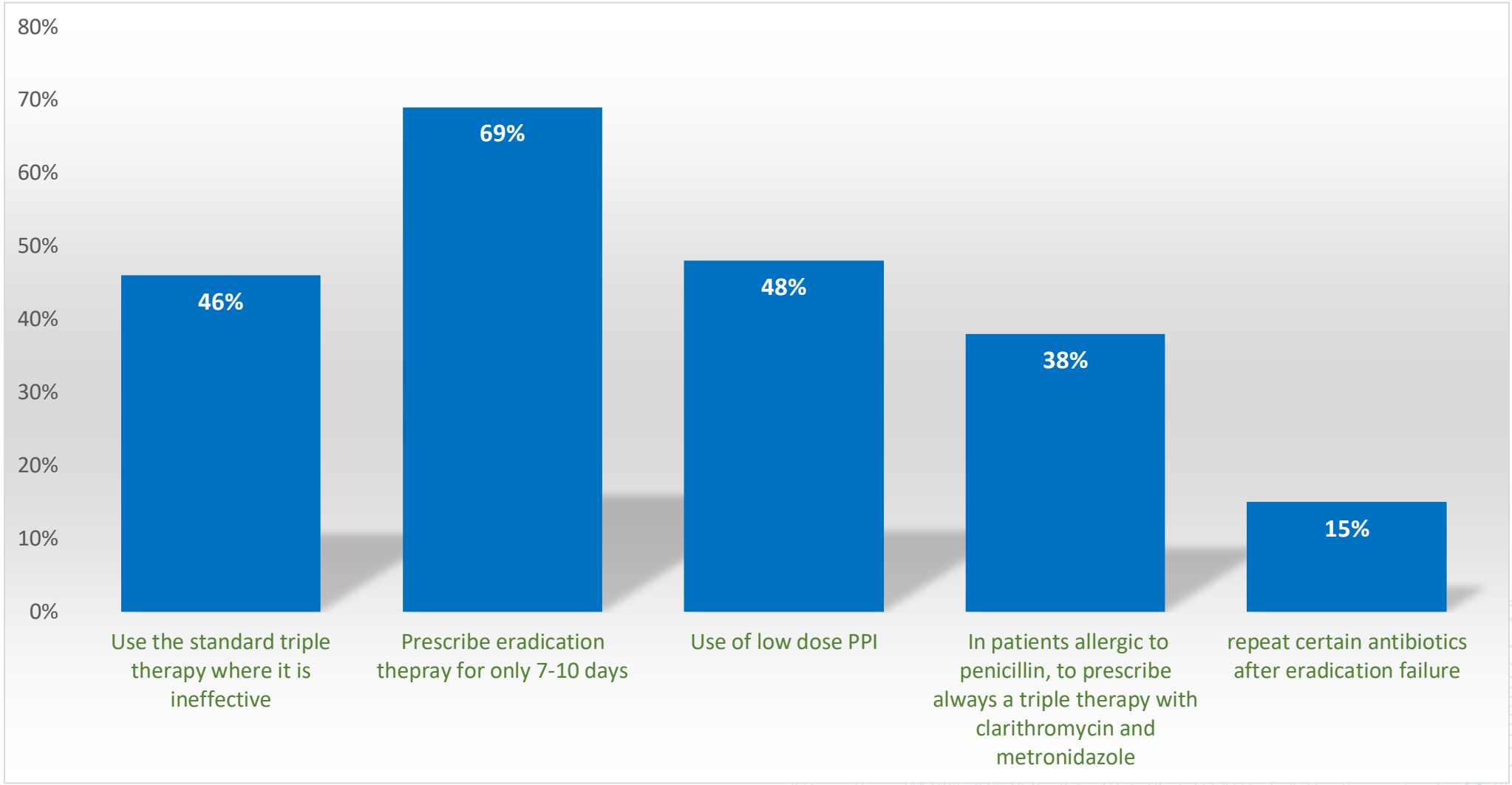
J Clin Gastroenterol. 2021 Jan 5;Publish Ahead of Print. doi: 10.1097/MCG.0000000000001482.
Online ahead of print.

Room for Improvement in the Treatment of Helicobacter pylori Infection: Lessons from the European Registry on H. pylori Management (Hp-EuReg)

Olga P Nyssen [1], Dino Vaira, Bojan Tepes, Limas Kupcinskas, Dmitry Bordin, Ángeles Pérez-Aisa, Antonio Gasbarrini, Manuel Castro-Fernández, Luis Bujanda, Ana Garre, Alfredo Lucendo, Liudmila Vologzhanina, Natasa B Jurecic, Luis Rodrigo-Sáez, Jose M Huguet, Irina Voynovan, Jorge Perez-Lasala, Pilar Mata Romero, Miroslav Vujasinovic, Rustam Abdulkhakov, Jesús Barrio, Luis Fernandez-Salazar, Francis Mégraud, Colm O'Morain, Javier P Gisbert

Nyssen OP, et al. J Clin Gastroenterol. 2021.

The Most Common Mistakes in European Practice



Nyssen OP, et al. J Clin Gastroenterol. 2021.

PYLERA Dosing

PYLERA®: a 10-days schedule that fits into daily life[1]

- Three capsules of **PYLERA®**
- 4 times a day
- With breakfast, lunch, dinner and a bedtime snack
- Plus omeprazole twice daily

1. Pylera USPI, October 2018.

PYLERA

- **Pylera should be considered for first line treatment in view of the rising prevalence of clarithromycin-resistant H. pylori, especially since it provides superior eradication with similar safety and tolerability to standard therapy.**

1. Pylera USPI, October 2018. 2. Malfertheiner P, et al. Lancet 2011; 377: 905-913.

Summary

- H pylori prevelance is high all over the world
- Treat all positive patients
- Bismuth based quadruple therapy is first line in all international guidelines and all studies provine supperior effecacy and safty profile
- Bismuth based quadruple therapy avoid clarithromycin resistence, over come metronidazole resistance and bismuth is potent anti-acid adding to PPI the efficacy of bactericidal action and improve antibiotic effect.

Thank you...