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GI ReConnect

Case-Based Presentation: Latest Advances in *H. pylori*

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Faculty Disclosures

- Consultant: Phathom, ISOThrive, Allakos, EndoStim, Neurogastrx
- Consultant/Speaker: RedHill Biopharma
- Speaker: Alnylam

Guidelines are evolving …

ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

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Question 1

To which of the following antibiotics is *H. pylori* least likely to be resistant?

A: Clarithromycin
B: Levofloxacin
C: Metronidazole
D: Rifabutin

Case

A 35-year-old woman with a 2 year history of dyspeptic symptoms had upper endoscopy for evaluation. Endoscopic appearances were normal but gastric mucosal biopsies were positive for *H. pylori* infection. She received a 14-day course of lansoprazole, clarithromycin and amoxicillin that she successfully completed.

4 weeks after completing treatment, she was seen back in the office. She reported that her symptoms had resolved. She was not taking any medicines at that time.

What next?

Question 2: What next?

A: No further testing since her symptoms have resolved

B: Check *H. pylori* status by urea breath test

C: Other

Treatment of *H. pylori* infection: General considerations

- Require a positive test of active infection
- Offer treatment to all who test positive
- Explain the treatment, possible side effects *etc.*
- Choice of treatment?
  - Availability of antimicrobial sensitivity testing?
  - History of macrolide / quinolone use?
  - True penicillin allergy?
- **Always re-test after treatment**

What are the recent advances in *H. pylori* management?

- Contemporary information on resistance rates
- Next generation sequencing on stool samples for determining resistance
- Consideration of intragastric antibiotic levels
- Recent FDA approval of vonoprazan-based regimens
  - role of high intragastric pH in optimizing treatment

Antimicrobial resistance – US

		Years of study	CLA	MET	AMOX	TET	LEVO	RIF
1	Houston VA	2009-13	16	20	0	1	31	N/A
2	Alaska	2000-16	30	43	2	< 1	14	N/A
3	Delaware valley	2009-19	43	42	N/A	N/A	69	N/A
4	US RCT	2017-18	17	44	6	3	58	0
5	Rhode Island	2018-19	30	33	1	< 1	30	< 1
6	US RCT	2019-21	22	65	2	N/A	N/A	N/A

1. Shiota et al, Clin Gastroenterol Hepatol 2015; 13: 1616 *2. Mosites et al, J Glob Antimicrob Resist 2018; 15: 148* *3. Kumar et al, GastroHep 2020; 2: 6*
4. Hulten et al, Gastroenterology 2021; 161: 342 *5. Argueta et al, Gastroenterology 2021; 160: 2181* *6. Mégraud et al, Am J Gastroenterol 2023; 118: 269*

Antimicrobial resistance – Europe

1211 adults, 2008 - 2017

24 centers in 18 European countries

Prior macrolide use → CLA resistance
(P = 0.0003)

Prior quinolone use → LEVO resistance
(P = 0.0002)

	Resistance (%)
Clarithromycin	21.4
Levofloxacin	15.8
Metronidazole	38.9
Amoxicillin	0.2
Tetracycline	0

Mégraud et al, Gut 2021; 70: 1815

H. pylori resistance: US isolates, 2011 – 2021

- **19 studies; 2660 samples**
- **Marked heterogeneity**
  - **I^2 > 50% for all except rifabutin (only 2 studies)**

	Pooled prevalence	95% CI
Clarithromycin	31.5%	23.6% - 40.6%
Metronidazole	42.1%	27.3% - 58.6%
Levofloxacin	37.6%	26.3% - 50.4%
Amoxicillin	2.6%	1.4% - 5.0%
Tetracycline	0.9%	0.2% - 3.8%
Rifabutin	0.2%	0.0% - 10.9%
CLA + MET	11.7%	0.1% - 94.0%

Ho et al, Am J Gastroenterol 2022; 117: 1221

Question 1 - Answer

To which of the following antibiotics is *H. pylori* least likely to be resistant?

A: Clarithromycin
B: Levofloxacin
C: Metronidazole
D: Rifabutin

Rates of antimicrobial resistance in *H. pylori* isolates from clinical trial patients in US and Europe

- 103 sites across US and 7 European countries
- 907 treatment-naïve patients

	Overall prevalence in US *	Range among different regions
Clarithromycin	**22.2%**	**15.2% - 24.9%**
Metronidazole	**69.2%**	**54.5% - 73.3%**
Amoxicillin	**1.2%**	**1.1% - 4.0%**

* **Similar results found in European sites**

Mégraud et al, Am J Gastroenterol 2023; 118: 269

Testing for *H. pylori* resistance with next generation sequencing

	Mutation detected on biopsy (N = 64)	Mutation detected in stool (N = 64)	kappa
Clarithromycin	**53.1%**	**53.1%**	**0.94**
Levofloxacin	**29.7%**	**25.0%**	**0.88**
Metronidazole	**31.3%**	**26.6%**	**0.89**
Tetracycline	**9.4%**	**9.4%**	**1.00**
Amoxicillin	**6.3%**	**6.3%**	**1.00**
Rifabutin	**0%**	**0%**	**1.00**

Moss et al, Gastroenterology 2022; 162: 2095

Consideration of intragastric antibiotic levels

- Do antibiotics against *H. pylori* act systemically, locally or both?
- Local instillation of antibiotics for 2 hours with occlusion of pylorus led to >90% cure rates. [1,2]
- Some antibiotics are re-secreted back into stomach after systemic absorption. [3]

1. Satoh, Scand J Gastroenterol 1996; 214 (Suppl.): 56 – 60
2. Kihira et al, J Gastroenterol 1996; 31 (Suppl. 9): 66 – 68
3. Howden et al, Aliment Pharmacol Ther 2023; in press

Intragastric rifabutin exposure

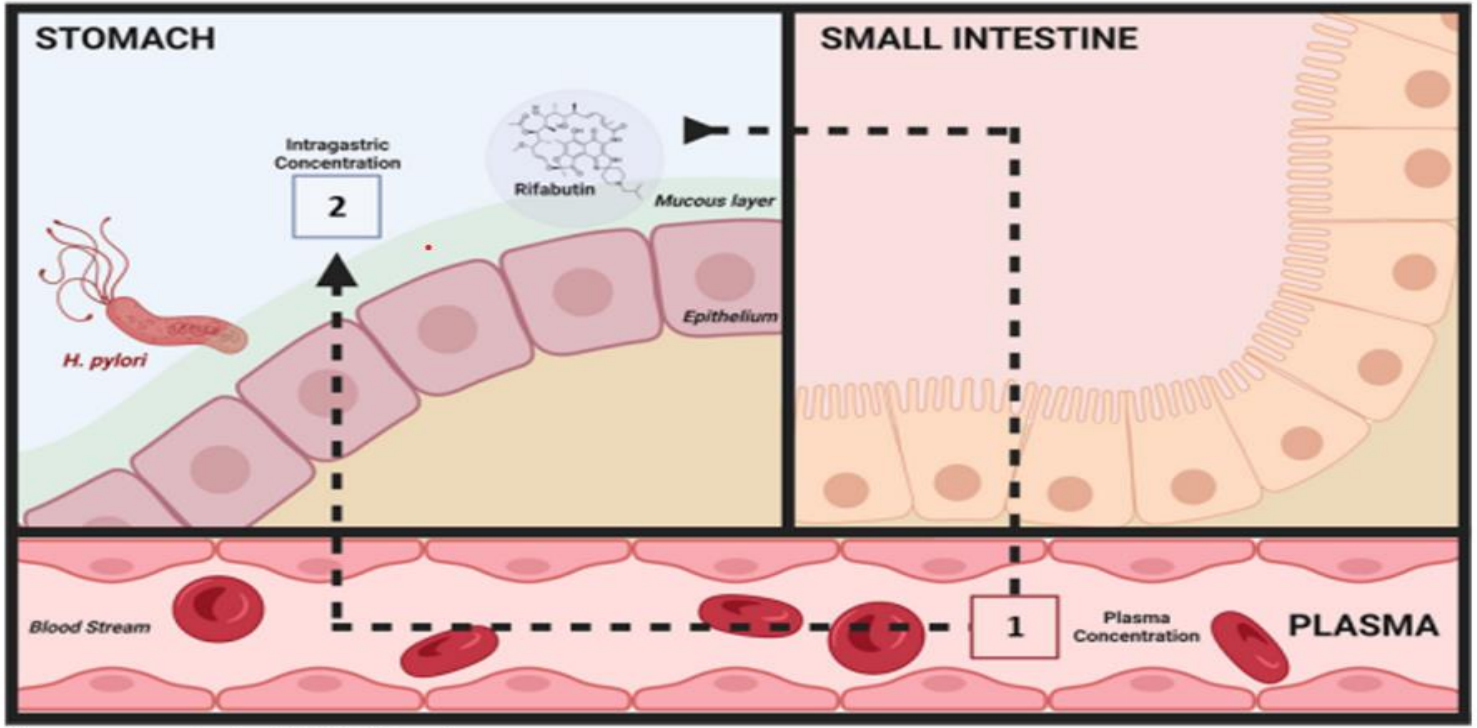
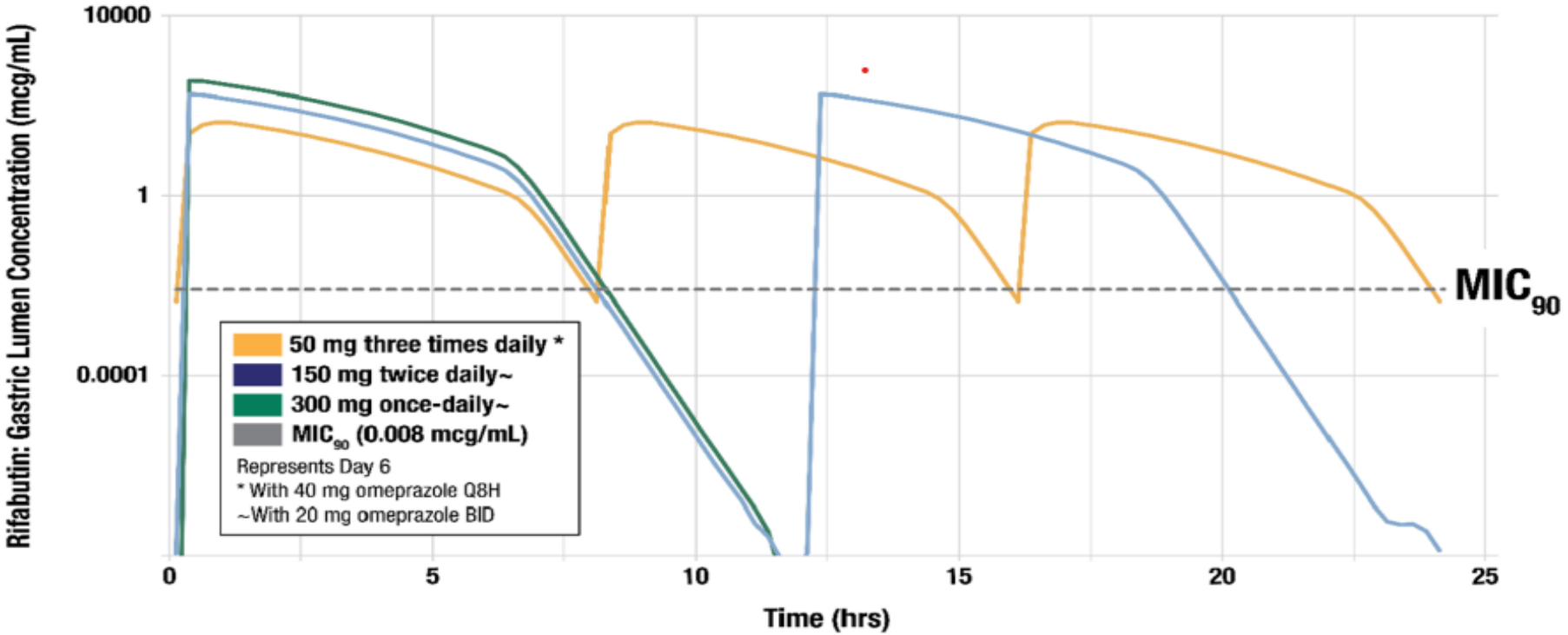


*Image created with BioRender.com

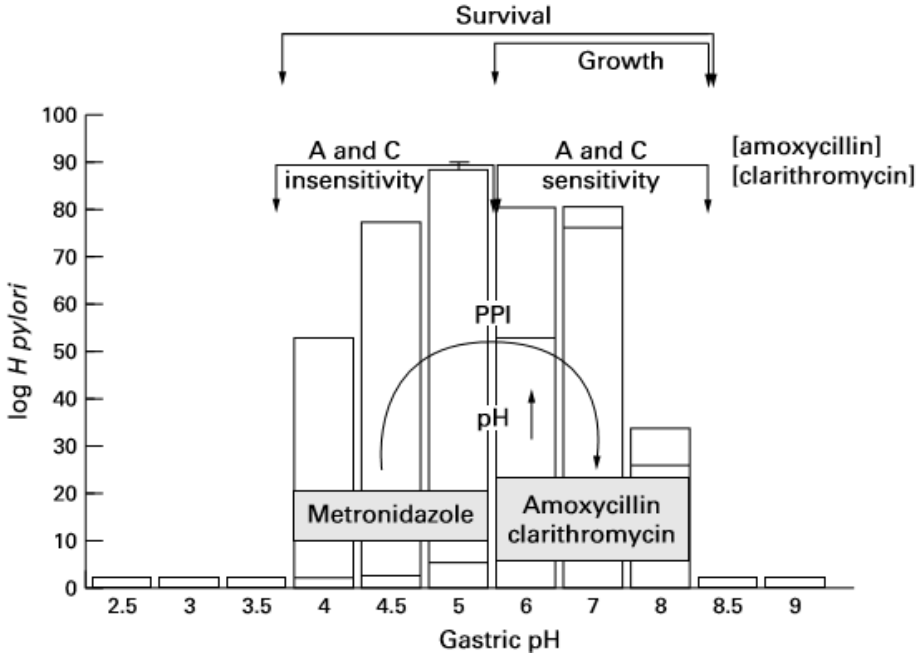
Howden et al, Aliment Pharmacol Ther 2023; in press

Physiologically-based pharmacokinetic modeling of intragastric rifabutin concentrations



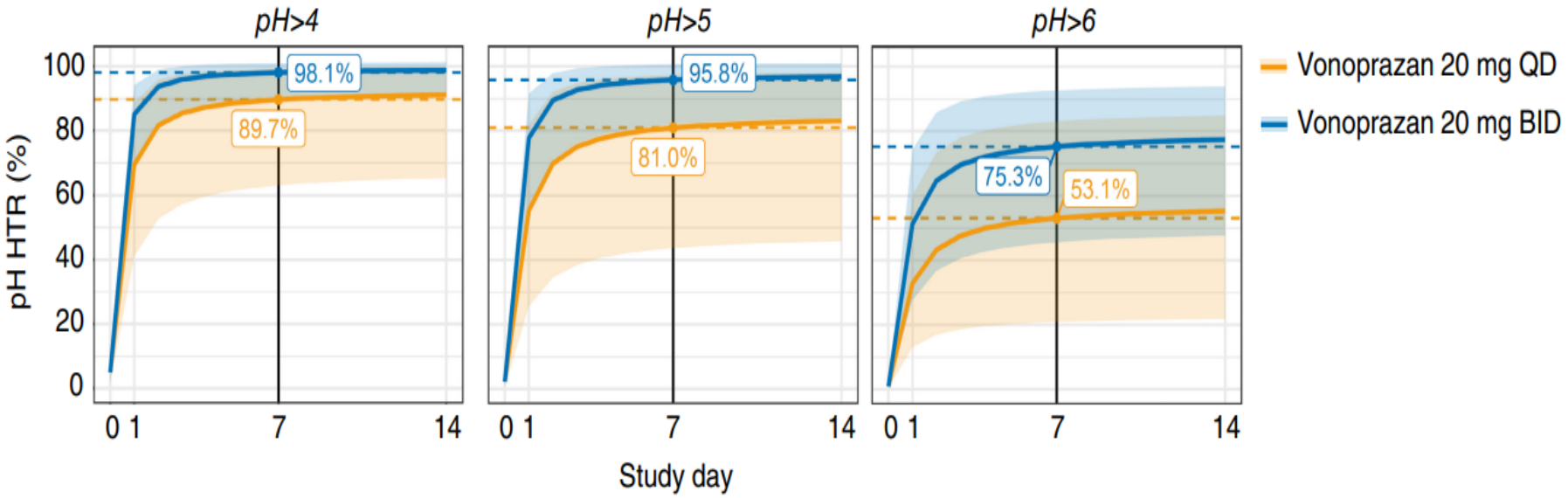
Howden et al, Aliment Pharmacol Ther 2023; in press

Life and death of *H. pylori*: Why elevating pH helps in eradication



Scott et al, Gut 1998; 43: S56

Pharmacokinetic / pharmacodynamic modelling for vonoprazan dosage

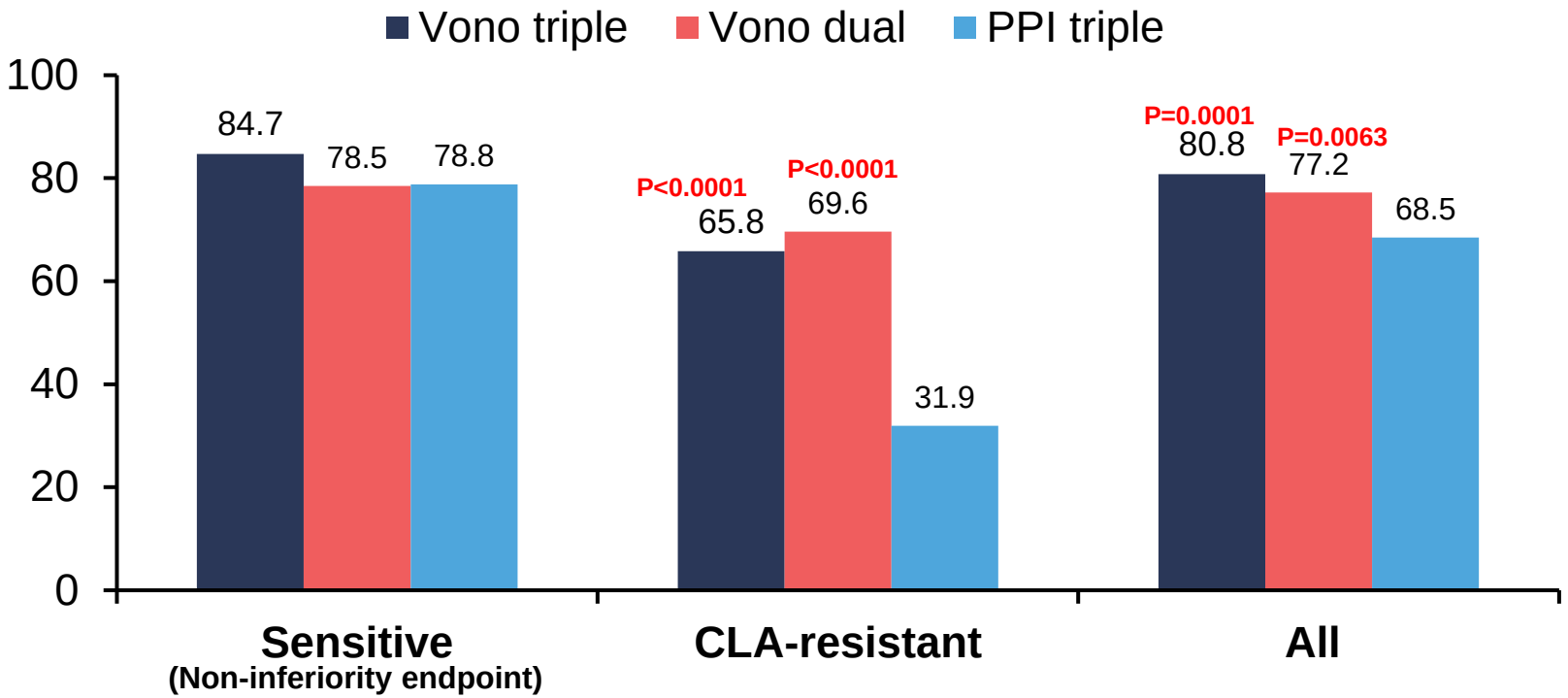


Scarpignato, Howden et al, Aliment Pharmacol Ther 2023; in press

Vonoprazan-based regimens

- FDA approval of vonoprazan-based regimens for treatment of *H. pylori* infection in adults, May 2022
- Dual regimen
  - vonoprazan 20 mg *b.i.d*. + amoxicillin 1000 mg *t.i.d*.
- Triple regimen
  - vonoprazan 20 mg *b.i.d*. + clarithromycin 500 mg *b.i.d*. + amoxicillin 1000 mg *b.i.d*.
- Both approved as 14-day treatments

Comparison of vonoprazan- and PPI-based regimens (US and European RCT)



Chey et al, Gastroenterology 2022; 163: 608

Maastricht VI / Florence consensus statements on *H. pylori*: Role of P-CABs

P-CAB – antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections.

100% agreement; Grade B2
(Moderate quality / weak recommendation)

Malfertheiner et al, Gut 2022; 71: 1724

Summary: The most recent advances

- Better understanding of prevailing resistance rates
  - but still no US national registry …
- Likely availability of stool-based testing for antimicrobial resistance?
- High intragastric antibiotic concentrations may be important for treatment success
  - % time with intragastric concentration > MIC_{90}
- Importance of maintaining intragastric pH > 6
  - P-CABs > PPIs