

Recent Trends and Predictors of Antibiotic Resistance in *Helicobacter pylori* in Israel

Asaf Ness MD^{1,3}, Noa Eliakim-Raz MD^{1,2}, Rachel Gingold Belfer MD^{2,3}, Ram Dickman MD^{2,3}, Zohar Levi MD^{2,3}, and Doron Boltin MBBS^{2,3}

¹Department of Internal Medicine E, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel

²Division of Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel

³Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Rising rates of antibiotic resistance pose a major challenge in the treatment of *Helicobacter pylori* (*H. pylori*) infection. Current treatment guidelines emphasize the importance of acquiring local resistance data to select an effective empirical regimen.

Objectives: To analyze trends in *H. pylori* antibiotic resistance over two decades in Israel.

Methods: Data from Clalit Health Services for *H. pylori* isolates cultured from gastric biopsies between January 2007 and December 2023 were included. Susceptibility to clarithromycin, amoxicillin, metronidazole, tetracycline, and levofloxacin was determined using E-tests. Demographic and clinical variables were retrieved to identify predictors of resistance.

Results: We identified 2521 *H. pylori* isolates (71.6% females, mean age 44.4 ± 15.8 years). Most individuals were residents of central Israel (84.6%) and of Jewish ethnicity (87.8%). Antibiotic resistance was observed in 71.6% of isolates for clarithromycin, 64.3% for metronidazole, and 19.4% for levofloxacin. Resistance to tetracycline and amoxicillin was minimal (0.2% and 1.2%, respectively). Dual clarithromycin-metronidazole resistance occurred in 50.4%, and triple resistance (clarithromycin-metronidazole-levofloxacin) was found in 12.0%. Between 2007 and 2012, clarithromycin resistance increased 5.3% annually, then tapered (odds ratio [OR] 1.05, 95% confidence interval [95%CI] 3.84–6.85, $P < 0.001$). Age and prior antibiotic use were predictors of resistance for all antibiotics, with the greatest effect observed for drugs in the same class. Female sex was associated with higher resistance to levofloxacin (OR 1.62, 95%CI, 1.28–2.05, $P < 0.001$).

Conclusions: Antibiotic resistance to *H. pylori* is high in our geographical region. Nevertheless, resistance rates have remained steady over recent years.

IMAJ 2025; 27: 731–737

KEY WORDS: antibiotic use, clarithromycin, culture, *Helicobacter pylori* (*H. pylori*), resistance

Helicobacter pylori (*H. pylori*) is one of the most common bacterial pathogens leading to infection of the digestive tract. It affects over 40% of the global population. Infection is highest in developing countries. *H. pylori* is an important factor in the development of upper gastrointestinal diseases including gastritis, duodenitis, gastric and duodenal ulcers, gastric cancer, and gastric mucosa-associated lymphoid-tissue lymphoma [1]. Treatment of *H. pylori* infection typically involves the use of antibiotics, and traditional regimens include triple therapy based on a proton-pump inhibitor (PPI) and two antibiotics (clarithromycin and amoxicillin or metronidazole), or quadruple therapy with PPI, bismuth, metronidazole, and tetracycline.

In response to high rates of treatment failures with triple therapies, especially those containing clarithromycin, many national and international guidelines, including the most recent Israeli guidelines from 2019, recommend against using triple therapy and advise the more complex, frequently dosed bismuth-quadruple therapy for first-line empirical therapy. The most common cause of treatment failure is antibiotic resistance. Previous studies have described a persistent, linear rise in antibiotic resistance rates in patients with *H. pylori* both in Israel and around the world [2,3]. Resistance to treatment varies across different geographic regions and often across different areas of the same region [4]. This variability is closely associated with rates of prior antibiotic use, particularly the use of macrolides for respiratory tract infections. The choice of appropriate antibiotics is crucial for the success of treatment, but treatment is usually empirical as bacterial culture and antibiotics sensitivity are often not part of routine management. Knowledge of the sensitivity of *H. pylori* in specific geographic areas and among specific populations can significantly improve treatment success

rates. Therefore, current guidelines, including the Maas-tricht VI consensus report [1], emphasize that the choice of empirical treatment in a particular geographical region depends on local resistance data. For this reason, antibiotic resistance data for *H. pylori* are crucial, and must be monitored from time to time. That said, epidemiological data regarding antibiotic resistance in patients infected with *H. pylori* in Israel are limited, making a rational use of antibiotics challenging. Local resistance data may be especially important in Israel, given the socioeconomic and demographic differences between central and peripheral regions, which may lead to differences in previous antibiotic exposure, access to healthcare, antibiotic stewardship, and health literacy. Aside from prior antibiotic use, several factors have been associated with increasing antibiotic resistance, including age and sex.

We examined resistance rates of *H. pylori* to different antibiotics during two decades in Israel and define predictors of resistance. Since susceptibility testing is generally reserved for cases of treatment failure, we did not assess *H. pylori* resistance among patients not previously treated.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

In this retrospective cohort study of *H. pylori* isolates cultured from gastric biopsies of adult patients in Israel, we used data from the Rabin Medical Center and Clalit Health Care databases. We assumed that all cultures were acquired from non-naïve individuals since *H. pylori* culture and sensitivity testing is only reimbursed and approved in Israel following at least one treatment failure; however, in practice and in accordance with the guidelines of the Israeli Association of Gastroenterology and Liver Diseases, susceptibility testing is usually performed after at least two treatment failures. Available data included information gathered from four specialized laboratories (Rabin Medical Center, Kaplan Medical Center, Carmel Medical Center, and Emek Medical Center) during a 16-year period (1 January 2007 to 31 December 2023). Antibiotic susceptibility to clarithromycin, amoxicillin, metronidazole, tetracycline, and levofloxacin was determined by E-test. Additional data included general demographic characteristics (age, sex), body mass index, smoking history, alcohol use, co-morbidities (Charlson Comorbidity Index), and prior antibiotic treatments.

Inclusion criteria were age ≥ 18 years with gastric tissue culture and available data for *H. pylori* antibiotic susceptibility and resistance. Sterile samples and repeat cultures from the same individual were excluded.

BIOPSY AND CULTURE

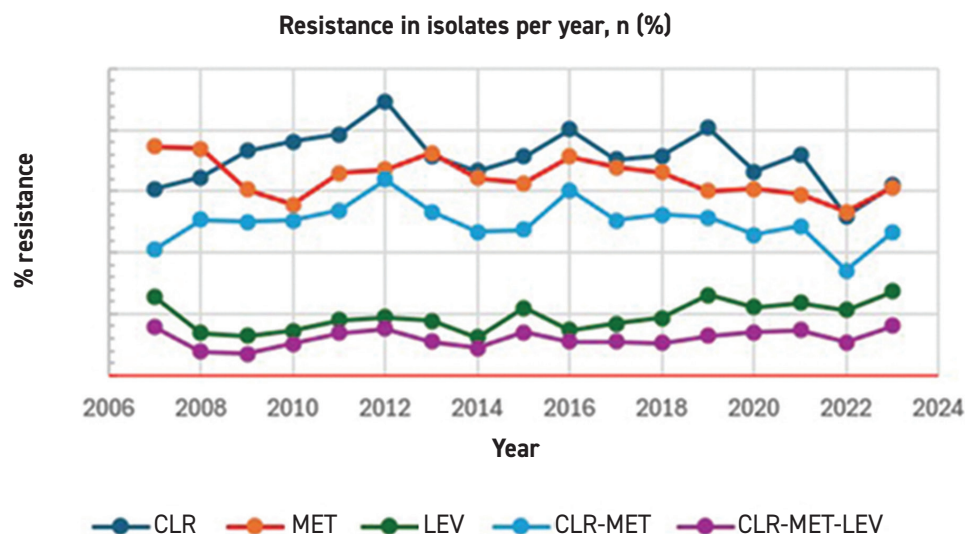
Gastric biopsy specimens were obtained for culture, antimicrobial susceptibility testing, and histologic examination for *H. pylori*. Specimens were stored in cysteine freeze medium at -80°C , ground in a sterile tissue grinder, and inoculated onto blood agar, chocolate agar, and brucella agar. Cultures were incubated at 37°C under microaerophilic conditions for up to 10 days, with positive colonies typically identified within 3–5 days. *H. pylori* was confirmed based on catalase, oxidase, and urease reactions as well as characteristic colony morphology and Gram staining.

Minimum inhibitory concentrations (MICs) for clarithromycin, metronidazole, levofloxacin, tetracycline, and amoxicillin were determined using agar diffusion gradient strips (E-test). Susceptibility test results were interpreted according to the guidelines and criteria of the European Committee of Antibiotic Susceptibility Testing (EUCAST) breakpoints [5], which defined susceptibility as MIC ≤ 0.25 mg/L for clarithromycin, ≤ 8 mg/L for metronidazole, ≤ 1 mg/L for tetracycline, ≤ 1 mg/L for levofloxacin, and ≤ 0.25 mg/L for amoxicillin. Higher MICs indicated resistance.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize demographic and clinical characteristics. They were presented as means $\pm$ standard deviation for continuous variables and frequencies (%) for categorical variables. Univariate analyses were conducted using chi-square tests for categorical variables and independent *t*-tests for continuous variables to assess associations between antibiotic resistance and potential predictors. Temporal trends in resistance were analyzed using linear regression models. Multivariate logistic regression was used to identify independent predictors of resistance, with results expressed as odds ratios (OR) and 95% confidence intervals (95%CI). Annual linear trends were evaluated. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). The study was performed in accordance with the principles of good clinical practice and was approved by the Rabin Medical Center internal review board (RMC-0034-24).

Figure 1. Antibiotic resistance prevalence in *Helicobacter pylori* isolates by year
CLR = clarithromycin, MET = metronidazole, LEV = levofloxacin



RESULTS

PATIENTS

The cohort included a total of 2521 patient cultures, 1806 (71.64%) from females. The mean age was 44.41 ± 15.78 years. In total, 2133 (84.61%) were residents of central Israel, 186 (7.38%) were Arab, and 2213 (87.78%) were Jewish. Patient characteristics are displayed in Table 1.

CULTURE AND SUSCEPTIBILITY

A total of 2521 positive *H. pylori* cultures were performed in 4 laboratories, 2045 (81.12%) at Rabin Medical Center, 306 (12.14%) at Kaplan Medical Center, and the remainder at Carmel Medical Center and Emek Medical Centre. A total of 1805 (71.60%) isolates were resistant to clarithromycin, 490 (19.44%) to levofloxacin, 1620 (64.26%) to metronidazole, 5 (0.2%) to tetracycline, and 30 (1.19%) to amoxicillin. Testing for amoxicillin and tetracycline resistance was mostly stopped after March 2009 due to minimal resistance. Combined clarithromycin-metronidazole resistance was seen in 1267 (50.4%) of isolates, while resistance for clarithromycin-levofloxacin was seen in 400 (15.9%), and clarithromycin-levofloxacin-metronidazole were seen in 304 (12.0%). Resistance prevalences in isolates by year displayed in Table 2.

Table 1. Patient characteristics

Patient characteristic		Number
Total number		2521
Female, n (%)		1806 (71.64%)
Age in years, mean $\pm$ SD		44.41 $\pm$ 15.78
Demographic district, n (%)		
	Center	2133 (84.61%)
	North	227 (9%)
	South	150 (5.95%)
	Jerusalem	10 (0.4%)
Ethnicity		
	Jewish	2213 (87.78%)
	Arab	186 (7.38%)
Body mass index, mean $\pm$ SD		25.77 $\pm$ 5.43
Charlson Comorbidity Index (total score mean $\pm$ SD)		1.49 $\pm$ 1.98
Previous antibiotic therapy within 3 years*, n (%)		
	Yes	1917 (76.05%)
	No	604 (23.95%)

*Antibiotic dispensation as part of eradication regimen for *H. pylori*

FACTORS ASSOCIATED WITH ANTIBIOTIC RESISTANCE

Multivariate analysis identified increasing age and prior antibiotic use as independent predictors of resistance, for all antibiotics, with the greatest effect observed for drugs in the same class. Female sex was associated with higher

Antibiotic	Total (% of total)	Resistance in isolates, n (%)																
		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Total	2521	51	65	86	97	117	158	221	171	150	136	220	210	218	194	136	141	150
No resistance*	324 (12.85%)	3 (5.88%)	8 (12.30%)	14 (16.27%)	18 (18.55%)	9 (7.69%)	12 (7.59%)	18 (8.14%)	25 (14.61%)	18 (12.0%)	11 (8.08%)	26 (11.81%)	27 (12.85%)	17 (7.79%)	31 (15.97%)	21 (15.44%)	37 (26.24%)	29 (19.33%)
CLR	1805 (71.60%)	31 (60.78%)	42 (64.62%)	63 (73.26%)	74 (76.29%)	92 (78.63%)	141 (89.24%)	158 (71.49%)	114 (66.67%)	107 (71.33%)	109 (80.15%)	155 (70.45%)	150 (71.43%)	176 (80.73%)	129 (66.49%)	98 (72.06%)	73 (51.77%)	93 (62.00%)
MET	1620 (64.26%)	38 (74.51%)	48 (73.85%)	52 (60.47%)	54 (55.67%)	77 (65.81%)	106 (67.09%)	160 (72.40%)	110 (64.33%)	94 (62.67%)	97 (71.32%)	149 (67.73%)	139 (66.19%)	131 (60.09%)	118 (60.82%)	80 (58.82%)	75 (53.19%)	92 (61.33%)
LEV	490 (19.44%)	13 (25.49%)	9 (13.85%)	11 (12.79%)	14 (14.43%)	21 (17.95%)	30 (18.99%)	39 (17.65%)	21 (12.28%)	33 (22.00%)	20 (14.71%)	37 (16.82%)	39 (18.57%)	57 (26.15%)	43 (22.16%)	32 (23.53%)	30 (21.28%)	41 (27.33%)
CLR-MET	1267 (50.4%)	21 (41.17%)	33 (50.76%)	43 (50%)	49 (50.51%)	63 (53.84%)	101 (63.92%)	118 (53.39%)	80 (46.78%)	71 (47.33%)	82 (69.29%)	111 (50.45%)	110 (52.38%)	112 (51.37%)	89 (45.87%)	66 (48.52%)	48 (34.04%)	70 (46.66%)
CLR-MET-LEV	304 (12.0%)	8 (15.68%)	5 (7.69%)	6 (6.97%)	10 (10.3%)	16 (13.67%)	24 (15.18%)	24 (10.85%)	15 (8.77%)	21 (14%)	15 (11.02%)	24 (10.9%)	22 (10.47%)	28 (12.84%)	27 (13.91%)	20 (14.79%)	15 (10.63%)	24 (16%)

*No resistance to clarithromycin, metronidazole or levofloxacin

temporal trends in antibiotic resistance: 2007–2012 CLR resistance increased 5.3% annually (odds ratio 1.05, 95% confidence interval 3.84–6.85, $P < 0.001$); following 2012 resistance rates plateaued; linear regression modeling did not identify a linear trend for any other antibiotic during any time period

Notably, 23.95% of our cohort lacked documentation of prior antibiotic treatment. It is unlikely that these patients were truly naïve, as it is uncommon to perform gastric culture on adult patients who are treatment naïve. Furthermore, the high resistance rates to various antibiotics observed in our study are consistent with those from prior studies on secondary antibiotic resistance in our region [2]. This high percentage of patients is likely due to documentation errors such as purchases from private pharmacies not connected to the electronic medical system of Clalit Health Services or examples of eradication treatment administered more than 3 years before the endoscopy.

Table 3. Predictors of antibiotic resistance, multivariate analysis

Risk factor	CLR		LEV		MET		CLR-MET		CLR-MET-LEV	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Increasing age	1.009 (1.004–1.015)	0.001	1.034 (1.027–1.041)	< 0.0001	1.011 (1.005–1.016)	< 0.0001	1.012 (1.007–1.017)	< 0.0001	1.031 (1.023–1.039)	< 0.0001
Female sex	1.03 (0.85–1.25)	0.720	1.62 (1.28–2.05)	< 0.001	1.001 (0.83–1.20)	0.989	1.065 (0.89–1.26)	0.476	1.76 (1.30–2.38)	0.0002
Past antibiotic therapy										
Clarithromycin within 6 months	1.43 (1.04–1.95)	0.023	0.84 (0.60–1.19)	0.349	1.01 (0.77–1.33)	0.898	1.23 (0.94–1.60)	0.11	0.96 (0.64–1.44)	0.857
Clarithromycin within 3 years	2.11 (1.77–2.53)	< 0.001	0.92 (0.76–1.13)	0.465	1.06 (0.90–1.25)	0.423	1.59 (1.36–1.87)	< 0.0001	1.30 (1.03–1.65)	0.032
Metronidazole within 6 months	1.19 (0.89–1.60)	0.234	1.15 (0.84–1.57)	0.37	2.43 (1.77–3.34)	< 0.0001	2.01 (1.54–2.63)	< 0.0001	1.52 (1.07–2.16)	0.018
Metronidazole within 3 years	1.42 (1.19–1.71)	0.0001	1.42 (1.16–1.73)	0.0005	2.52 (2.11–3.01)	< 0.0001	2.17 (1.84–2.55)	< 0.0001	2.12 (1.66–2.70)	< 0.0001
Levofloxacin within 6 months	0.23 (0.02–2.42)	0.223	2.47 (0.23–25.72)	0.447	0.91 (0.09–9.52)	0.943	0.14 (0.00–4.27)	0.259	1.03 (0.03–31.8)	0.982
Levofloxacin within 3 years	0.26 (0.08–0.95)	0.041	2.87 (0.81–10.18)	0.101	0.79 (0.22–2.82)	0.726	0.45 (0.12–1.72)	0.248	3.41 (0.98–12.99)	0.071
Tetracycline within 6 months	0.90 (0.67–1.22)	0.531	0.96 (0.68–1.36)	0.845	1.76 (1.28–2.40)	0.0004	1.37 (1.04–1.81)	0.023	1.13 (0.75–1.69)	0.538
Tetracycline within 3 years	1.15 (0.96–1.38)	0.125	1.20 (0.98–1.47)	0.075	1.61 (1.35–1.92)	< 0.0001	1.50 (1.2–1.77)	< 0.0001	1.45 (1.14–1.85)	0.002
FQ within 6 months	1.43 (0.84–2.18)	0.088	2.78 (1.94–4.00)	< 0.0001	1.23 (0.84–1.78)	0.275	1.40 (0.98–1.99)	0.058	2.89 (1.93–4.31)	< 0.0001
FQ within 3 years	1.39 (1.12–1.72)	0.002	3.52 (2.85–4.34)	< 0.0001	1.28 (1.05–1.56)	0.011	1.36 (1.13–1.63)	0.001	N/A	N/A
Macrolides within 6 months	1.83 (1.40–2.41)	< 0.0001	1.32 (1.02–1.71)	0.033	1.18 (0.93–1.48)	0.153	1.50 (1.21–1.87)	0.0002	1.52 (1.12–2.05)	0.006
Macrolides within 3 years	2.30 (1.93–2.75)	< 0.0001	1.12 (0.91–1.37)	0.263	1.14 (0.96–1.35)	0.111	1.73 (1.47–2.03)	< 0.0001	1.61 (1.24–2.09)	0.0003
CS within 6 months	1.08 (0.78–1.50)	0.618	1.56 (1.12–2.17)	0.008	1.07 (0.79–1.45)	0.636	1.11 (0.83–1.48)	0.461	1.56 (1.06–2.31)	0.023
CS within 3 years	1.35 (1.12–1.64)	0.001	1.63 (1.33–2.00)	< 0.0001	1.16 (0.97–1.39)	0.086	1.28 (1.08–1.52)	0.003	1.80 (1.41–2.30)	< 0.0001

CLR = clarithromycin, MET = metronidazole, LEV = levofloxacin, TET = tetracycline, FQ = fluoroquinolone, CS = cephalosporin, OR = odds ratio, 95%CI = 95% confidence interval

Multivariate analysis identified increasing age as an independent predictor of resistance for all antibiotics, likely due to greater past antibiotic exposure. Previous studies have shown similar findings with respect to levofloxacin; however, clarithromycin and metronidazole resistance have not previously been associated with age and may reflect regional antibiotic practices. Studies from Italy and China reported higher resistance rates among older patients, often attributed to increased quinolone use for urinary tract infections [10,11].

Prior antibiotic exposure was also found to be an independent predictor of resistance for all antibiotics, with the greatest effect observed for drugs within the same class, except for levofloxacin. This association has been demonstrated in multiple studies across diverse geographical regions [12-16]. Clinical cohort studies revealed that prior use of macrolides, fluoroquinolones, and metronidazole significantly increased the odds of resistance and treatment failure and have identified associations between *H. pylori* clarithromycin resistance and community-level macrolide consumption, and between levofloxacin resistance and consumption of quinolones [6]. In addition, prior exposure to macrolides has been shown to adversely affect the success of clarithromycin-based triple therapy, with a significant reduction in efficacy. For example, in a recent study by our group, we demonstrated that clarithromycin-based triple therapy success dropped to 55.5% among patients with prior clarithromycin exposure (OR 0.31, 95%CI 0.24–0.39, $P < 0.0001$), with similar effects observed with other macrolides [17].

It is noteworthy that past use of levofloxacin was not associated with increased levofloxacin resistance, while prior use of quinolones as a class was strongly associated with increased resistance. This discrepancy may be attributed to the relatively small sample size for patients with prior levofloxacin use. In addition, indirect effects of covariables, such as macrolide use, may contribute to this finding. Other quinolones, such as ciprofloxacin, are used more broadly, whereas in Israel, levofloxacin is typically reserved for the treatment of refractory or atypical pneumonias. The stronger association observed for the quinolone group likely reflects cumulative selective pressure across multiple agents, emphasizing the importance of considering class-wide effects. Overall, these results support the continued use of levofloxacin for the empirical treatment of *H. pylori* following at least one treatment failure, without over-concern that this practice will increase levofloxacin resistance.

Increased resistance of *H. pylori* to levofloxacin was associated with prior macrolide use within 6 months and with prior cephalosporin use. A possible explanation is

concurrent or sequential prescribing of multiple antibiotics for respiratory illnesses. This finding would suggest that quinolone exposure is covariate with macrolide and cephalosporin exposure and that it is the quinolone exposure that is the true driver of levofloxacin resistance. Similarly, the association between female sex and levofloxacin resistance may relate to higher quinolone use in females, particularly for urinary tract infections. This result differs from what is known from previous cohort studies, which found significantly higher rates of metronidazole and clarithromycin but not quinolone resistance among women, with only one study from China identifying increased quinolone resistance among women [18,19]. This difference might be related to population-specific variations and antibiotic prescribing practices.

Our study has several limitations. Its retrospective design and reliance on electronic medical files may introduce biases due to incomplete or imprecise data. Certain variables, such as prior antibiotic use were inferred and may be subject to documentation error or omission, and detailed information regarding dosage or duration of use was not available, which influenced resistance development. Moreover, our cohort is heavily skewed toward central Israel and predominantly includes Jewish patients, thus limiting generalizability.

Despite these limitations, our findings have clinical implications. The high resistance rate for clarithromycin suggest that empirical rescue treatment with clarithromycin should be abandoned unless susceptibility testing is performed. This finding would be a departure from current Israeli guidelines, which recommend clarithromycin-based concomitant therapy for first and second line treatment in some situations. Our results also emphasize the value of avoiding repeated empirical triple therapy, especially in older patients or those with known prior antibiotic exposure. Continued resistance surveillance and antibiotic stewardship remain essential to combat resistance in high-prevalence regions. In the future, polymerase chain reaction-based methods may offer advantages over traditional culture for assessing resistance, and especially for detecting clarithromycin mutations, with advantages including higher technical success, rapid results, and the possibility for non-invasive testing.

Correspondence

Prof. D. Boltin

Division of Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel

Phone: (972-3) 937-6506

Fax: (972-3) 937-6505

Email: dboltin@gmail.com

References

1. Malfertheiner P, Megraud F, Rokkas T, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. *Gut* 2022; 71 (9): 1724-62.
2. Boltin D, Ben-Zvi H, Perets TT, et al. Trends in secondary antibiotic resistance of *Helicobacter pylori* from 2007 to 2014: has the tide turned? *J Clin Microbiol* 2015; 53 (2): 522-7.
3. Bujanda L, Nyssen OP, Vaira D, et al. Antibiotic resistance prevalence and trends in patients infected with *Helicobacter pylori* in the period 2013-2020: results of the European Registry on H. pylori Management (Hp-EuReg). *Antibiotics* 2021; 10 (9): 1058.
4. Hultén KG, Lamberth LB, Kalfus IN, Graham DY. National and regional US antibiotic resistance to *Helicobacter pylori*: lessons from a clinical trial. *Gastroenterology* 2021; 161 (1): 342-4.e1.
5. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 15.0, 2025. [Available from <https://www.eucast.org>]. [Accessed 4 February 2025].
6. Megraud F, Bruyndonckx R, Coenen S, et al. *Helicobacter pylori* resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. *Gut* 2021; 70 (10): 1815-22.
7. Hong TC, El-Omar EM, Kuo YT, et al; Asian Pacific Alliance on *Helicobacter* and Microbiota. Primary antibiotic resistance of *Helicobacter pylori* in the Asia-Pacific region between 1990 and 2022: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2024; 9 (1): 56-67.
8. Ho JJC, Navarro M, Sawyer K, Elfanagely Y, Moss SF. *Helicobacter pylori* antibiotic resistance in the United States Between 2011 and 2021: a systematic review and meta-analysis. *Am J Gastroenterol* 2022; 117 (8): 1221-30.
9. Armitage R, Nellums LB. Antibiotic prescribing in general practice during COVID-19. *Lancet Infect Dis* 2021; 21 (6): e144.
10. Zullo A, Perna F, Hassan C, et al. Primary antibiotic resistance in *Helicobacter pylori* strains isolated in northern and central Italy. *Aliment Pharmacol Ther* 2007; 25 (12): 1429-34.
11. Ji Z, Han F, Meng F, Tu M, Yang N, Zhang J. The association of age and antibiotic resistance of *Helicobacter pylori*: a study in Jiaxing City, Zhejiang Province, China. *Medicine* 2016; 95 (8): e2831.
12. Haas CE, Nix DE, Schentag JJ. In vitro selection of resistant *Helicobacter pylori*. *Antimicrob Agents Chemother* 1990; 34 (9): 1637-41.
13. Jenks PJ, Labigne A, Ferrero RL. Exposure to metronidazole in vivo readily induces resistance in *Helicobacter pylori* and reduces the efficacy of eradication therapy in mice. *Antimicrob Agents Chemother* 1999; 43 (4): 777-81.
14. Shiota S, Reddy R, Alsarraj A, El-Serag HB, Graham DY. Antibiotic resistance of *Helicobacter pylori* among male United States Veterans. *Clin Gastroenterol Hepatol* 2015; 13 (9): 1616-24.
15. McMahon BJ, Hennessy TW, Bensler JM, et al. The relationship among previous antimicrobial use, antimicrobial resistance, and treatment outcomes for *Helicobacter pylori* infections. *Ann Intern Med* 2003; 139 (6): 463.
16. McNulty CAM, Lasseter G, Shaw I, et al. Is *Helicobacter pylori* antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther* 2012; 35 (10): 1221-30.
17. Boltin D, Levi Z, Gingold-Belfer R, et al. Impact of previous exposure to macrolide antibiotics on *Helicobacter pylori* infection treatment outcomes. *Am J Gastroenterol* 2019; 114 (6): 900-6.
18. Tveit AH, Bruce MG, Bruden DL, et al. Alaska Sentinel Surveillance Study of *Helicobacter pylori* Isolates from Alaska Native Persons from 2000 to 2008. *J Clin Microbiol* 2011; 49 (10): 3638-43.
19. Shao Y, Lu R, Yang Y, Xu Q, Wang B, Ye G. Antibiotic resistance of *Helicobacter pylori* to 16 antibiotics in clinical patients. *J Clin Lab Anal* 2018; 32 (4): e22339.

Wrongs are often forgiven, but contempt never is. Our pride remembers it forever.

Philip Dormer Stanhope, 4th Earl of Chesterfield (1694–1773), British politician, diplomat and writer

Capsule

Accelerated vascular ageing after COVID-19 infection

This prospective, multicentric, cohort study by **Bruno** and co-authors included 34 centers in 16 countries with 4 groups of participants: COVID-19-negative controls plus three groups of individuals with recent (6 ± 3 months) exposure to SARS-CoV-2: not hospitalized, hospitalized in general wards, and hospitalized in intensive care units. The main outcome was carotid-femoral pulse wave velocity (PWV), an established biomarker of large artery stiffness. In total, 2390 individuals (age 50 ± 15 years, 49.2% women) were recruited. After adjustment for confounders, all COVID+ groups showed higher PWV (+0.41, +0.37, and +0.40 m/s, $P < .001$, $P = .001$, and $P = .003$, respectively) vs. controls (PWV 7.53, 95CI 7.09–

7.97 m/s adjusted mean). In sex-stratified analyses, PWV differences were significant in women (PWV +0.55, +0.60, and +1.09 m/s for the COVID+ groups, $P < .001$ for all), but not in men. Among the COVID+ groups, persistent symptoms were associated with higher PWV, regardless of disease severity and cardiovascular confounders (adjusted PWV 7.52, 95%CI 7.09–7.96) vs. 7.13 (95%CI 6.67–7.59) m/s, $P < .001$. A stable or improved PWV after 12 months was found in the COVID+ groups, whereas progression was observed in the COVID+ groups.

Europ Heart J 2025; ehaf430

Eitan Israeli