Helicobacter pylori: Rise of the resistance

Zachias Hopkins, Jason Diab, Kumari Obeyesekera, Tim Tse, Bosco Wu

CASE

A man, aged 40 years, from Bangladesh presented to his general practitioner (GP) following a 12-month history of intermittent epigastric discomfort and dyspepsia. The symptoms of mild nausea and bloating increased daily, albeit without weight loss, fatigue or melaena. His past medical history included reflux treated with omeprazole, hypertension and hyperlipidaemia, controlled with telmisartan and atorvastatin respectively. He was a non-smoker, non-drinker and last travelled overseas 18 months ago to Bangladesh. Physical examination was unremarkable with no abdominal mass or lymphadenopathy. A urea breath test (UBT) was performed because of the presence of chronic dyspepsia and associated symptoms, which returned positive for *Helicobacter pylori* (*H. pylori*).

QUESTION 1

What is the prevalence of *H. pylori* in Australia?

QUESTION 2

What are the possible complications of *H. pylori*?

QUESTION 3

What is the non-invasive test of choice for diagnosing *H. pylori*?

QUESTION 4

What is the initial management of *H. pylori*?

ANSWER 1

The prevalence of *H. pylori* is 7.3 cases per 100,000, with incidence increasing with age; there is also an inverse correlation to socioeconomic living conditions.[1,2] In Australia, a pooled meta-analysis reported the general population prevalence for adults was 24.8% (95% [confidence interval; CI], 21.7–55.9), with Aboriginal and Torres Strait Islander peoples and Asian communities disproportionately represented with prevalence as high as 50–80%.[1–3]

Table 1. Complications of *Helicobacter pylori* infection and their lifetime risk[4]

Complication	Lifetime risk (%)
Peptic ulcer disease	10
Gastric adenocarcinoma	1–3
Mucosa-associated lymphoid tissue lymphoma	<0.1

ANSWER 2

Although most patients with *H. pylori* remain asymptomatic, nearly all will develop chronic gastritis. Chronic gastritis can further progress to several severe complications with varying lifetime risk rates (Table 1). Early detection and eradication of *H. pylori* remains vital to preventing these complications and reducing individual disease burden.[4]

ANSWER 3

The non-invasive test of choice in diagnosing *H. pylori* is a UBT; however, preparation is required before undertaking the test (Table 2).[5]

ANSWER 4

Clarithromycin-based triple therapy is the initial treatment of choice for *H. pylori* eradication (Table 3).[5] A Cochrane review found extending the treatment duration to 14 days significantly increased the eradication rate compared to a seven-day regimen.[6] This presents logistical and financial challenges for patients, as the Pharmaceutical Benefits Scheme permits a single prescription without repeats. A follow-up review at seven days is recommended to consider the need for an additional prescription, providing a total treatment duration of 14 days. A repeat UBT is recommended as a test of cure at least four weeks after completion of therapy to evaluate

Table 2. Urea breath test considerations[5,8,13]

Preparation and washout duration of medications[A]	
Medication	**Washout duration**
Antibiotics and bismuth compounds	4 weeks
Cytoprotective agents (sucralfate)	2 weeks
Proton pump inhibitors	2 weeks
H2 antagonists and antacids	Fasting period only

Limitations

- Must cease all antibiotics, cytoprotective agents and proton pump inhibitors prior to testing as they can cause false negative results
- Sensitivity and specificity in paediatric populations significantly decreases when a urea breath test is conducted (sensitivity and specificity both 75–100% and 77.5–100, respectively)

Alternatives

- A monoclonal stool antigen test is an acceptable alternative to a urea breath test in adults and is preferred in paediatric patients because of increased sensitivity and specificity (96.6–98.0% and 94.1–100%, respectively)
- Serological tests might be considered as an alternative in adults who are unable to cease antibiotics, cytoprotective agents or proton pump inhibitors (sensitivity and specificity 55.6–85% and 79%, respectively)

[A] Always refer to individual laboratory guidelines as institutional policies might differ.

Table 3. First-line *Helicobacter pylori* eradication therapy[5]

Standard first-line therapy (dose and duration)		
Esomeprazole	20 mg twice daily	14 days
Clarithromycin	500 mg twice daily	
Amoxicillin	1 g twice daily	
First-line therapy for patients with a penicillin allergy (dose and duration)		
Esomeprazole	20 mg twice daily	14 days
Clarithromycin	500 mg twice daily	
Metronidazole	400 mg twice daily	

the effectiveness of eradication therapy.[5] Referral for endoscopy should be made if red flags or clinical concern is present (Table 4).[7]

CASE CONTINUED

The patient completed a combined course of esomeprazole, clarithromycin and amoxicillin for seven days; however, he presented with mild gastric symptoms several weeks later. A subsequent UBT was positive, which is consistent with refractory *H. pylori* infection.

QUESTION 5

What are the factors that contribute to treatment failure for *H. pylori*?

QUESTION 6

What is the management of a patient with refractory *H. pylori* infection?

ANSWER 5

In Australia, treatment failure for *H. pylori* is primarily caused by poor adherence and increasing clarithromycin resistance.

Table 4. Indications for endoscopy referral[7]

Red flag indications (urgent endoscopy referral)
• Unexplained iron deficiency anaemia
• Unintentional weight loss with gastrointestinal symptoms
• Dysphagia or odynophagia
• Gastrointestinal bleeding
• Persistent vomiting

Other indications

- Treatment failure
- New symptoms in people aged >50 years
- Severe or frequent symptoms
- Changing or atypical symptoms

Patient education on common side effects and the importance of completing the full course of treatment is fundamental to improve adherence. The most common side effects of *H. pylori* therapy are diarrhoea, altered taste and gastrointestinal upset (Table 5).[8] It is recommended to assess side effects and monitor adherence at the seven-day review to support antibiotic completion and promote antimicrobial stewardship. Previous use of proton pump inhibitors (PPIs) and macrolides are also associated with increased rates of treatment failure, emphasising the need to prescribe according to the guidelines.[9,10] There is a positive association with smoking and treatment failure, in addition to an increased risk of developing gastric cancer with a concurrent *H. pylori* infection.[4,11] Family members with upper gastrointestinal symptoms or a positive family history of gastric cancer should be offered screening, treatment and follow-up to reduce the risk of progression.[5]

ANSWER 6

Patients with refractory *H. pylori* should avoid repeat eradication with first-line clarithromycin-based triple therapy because of low repeat success rates and the potential for further resistance.[5] Clarithromycin resistance has significantly increased over the last 20 years in Australia.[12] In refractory cases, the management includes various salvage therapies, which are either restricted or available through special access schemes; these include levofloxacin, colloidal bismuth

Table 5. Common and/or serious side effects of first-line *Helicobactor pylori* therapy by drug[8]

Drug	Common side effects
Esomeprazole	• Abdominal pain • Diarrhoea • Gastrointestinal upset • Headache
Amoxicillin	• Diarrhoea • Gastrointestinal upset • Headache • Maculopapular rash • Anaphylaxis
Clarithromycin	• Altered taste • Diarrhoea • Gastrointestinal upset • QT prolongation
Metronidazole	• Metallic taste • Dyspepsia • Alcohol interactions can cause headache, flushing, nausea and vomiting

subcitrate and tetracycline, whereas rifabutin and moxifloxacin are alternative options depending on the context.[5] In these cases, patients should be referred to a specialist for further management including gastroscopy.

CASE CONTINUED

The patient was referred to a gastroenterologist who performed a gastroscopy and confirmed no underlying peptic ulcer disease or malignancy. He was commenced on salvage quadruple therapy including levofloxacin, tetracycline, amoxicillin and a PPI for 14 days. The treatment successfully eradicated the infection, confirmed by a UBT, with resolution of symptoms.

Key points

- Duration of treatment should be 14 days with clarithromycin-based triple therapy in confirmed *H. pylori* infections.
- A test of cure four weeks post-treatment with a UBT is recommended to confirm the eradication of *H. pylori*.
- Family members with upper gastrointestinal symptoms or a positive family history of gastric cancer should be offered screening for *H. pylori*.

Authors

Zachias Hopkins BMedSc (Hons), Medical Student, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW

Jason Diab BMedSc, MIPH, MBBS, MSurg, Surgical Registrar, Upper Gastrointestinal Surgery, St George Hospital, Sydney, NSW; Clinical Associate Lecturer, School of Medicine, University of Notre Dame, Sydney, NSW; Clinical Associate Lecturer, University of New South Wales, School of Medicine, Sydney, NSW

Kumari Obeyesekera MBBS, FRACGP, General Practitioner, Hills Doctors, Sydney, NSW

Tim Tse BMed, MD, MMed, FRACGP, General Practitioner, MQ Health General Practice, Discipline of Primary Care, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW

Bosco Wu MBBS, BMedSci (Hons), FRACGP, General Practitioner, MQ Health General Practice, Discipline of Primary Care, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW

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Correspondence to:
Zachias.hopkins@live.com

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correspondence **ajgp@racgp.org.au**