Public Health England

Protecting and improving the nation's health

Test and treat for *Helicobacter pylori* (HP) in dyspepsia

Quick reference guide for primary care: For consultation and local adaptation

About Public Health England

Public Health England (PHE) exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships, and the delivery of specialist public health services. PHE is an executive agency of the Department of Health, and is a distinct delivery organisation with operational autonomy to advise and support government, local authorities, and the NHS, in a professionally independent manner.

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Foreword – Aims and adaptations

Audience
- primary care prescribers in general practice and out of hours settings; including doctors, nurses and pharmacists
- those giving first point of contact for test and treat of *Helicobacter pylori* in adults

Aims
- to provide a simple, effective, economical and empirical approach to the test and treat of *Helicobacter pylori*
- to minimise the emergence of antibiotic resistance in the community

Implications
- the guidance should lead to more appropriate antibiotic use
- use of this guidance may influence laboratory workload, which may have financial implications for laboratories and primary care commissioners

Production
- the guidance has been produced in consultation with the Association of Medical Microbiologists, general practitioners, nurses, specialists, and patient representatives
- the guidance is in agreement with other publications, including CKS, SIGN and NICE
- the guidance is fully referenced and graded
- the guidance is not all-encompassing, as it is meant to be 'quick reference'
- if more detail is required we suggest referral to the websites and references cited
- the guidance will be updated every three years; or more frequently if there are significant developments in the field

Poster Presentation of Guidance
- the summary table is designed to be printed out as a poster for use in practice
- the rationale and evidence is designed to be used as an educational tool for you, and your colleagues and trainees, to share with patients as needed

Local Adaptation
- we would discourage major changes to the guidance, but the format allows minor changes to suit local service delivery and sampling protocols
- to create ownership agreement on the guidance locally, dissemination should be agreed and planned at the local level between primary care clinicians, laboratories and secondary care providers

We welcome opinions on the advice given. Please email any evidence or references that support your requests for change so that we may consider them at our annual review. Comments should be submitted to Professor Cliodna McNulty, Head of PHE Primary Care Unit, Microbiology Laboratory, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN. Email: TARGETAntibiotics@phe.gov.uk

Quick reference guide

NICE	☐ Patients over the age of 55, with recent onset, unexplained and persistent dyspepsia (over 4-6 weeks) should be referred urgently for endoscopy to exclude cancer.[1D]

WHEN SHOULD I TEST FOR *HELICOBACTER PYLORI*?

☐ Patients with uncomplicated dyspepsia unresponsive to lifestyle change and antacids, following a single one month course of proton pump inhibitor (PPI), without alarm symptoms.[2D,3A-,4A-,5A-,6A-]

Note: Options should be discussed with patients, as the prevalence of HP in developed countries is falling,[7B+,8B-,9B+] and is lower than 15% in many areas in the UK.[10B+,11D] A trial of PPI should usually be prescribed before testing, unless the likelihood of HP is higher than 20%[11A-] (older people; people of North African ethnicity;[8B-,9B+] those living in a known high risk area), in which case the patient should have a test for HP first, or in parallel with a course of PPI.

☐ Patients with a history of gastric or duodenal ulcer/bleed who have not previously been tested.[11C]

☐ Patients before taking NSAIDs, if they have a prior history of gastro-duodenal ulcers/bleeds.

Note: Both HP and NSAIDs are independent risk factors for peptic ulcers, so eradication will not remove all risk.[11A-]

☐ Patients with unexplained iron-deficiency anaemia, after negative endoscopic investigation has excluded gastric and colonic malignancy, and investigations have been carried out for other causes, including: cancer; idiopathic thrombocytopenic purpura; vitamin B12 deficiency.[11D]

WHEN SHOULD I NOT TEST FOR *HELICOBACTER PYLORI*?

☐ Patients with proven oesophagitis, or predominant symptoms of reflux, suggesting gastro-oesophageal reflux disease (GORD).[2D,11D,12A+]

☐ Children with functional dyspepsia.[13A+,14A+]

WHICH NON-INVASIVE TEST SHOULD BE USED IN UNCOMPLICATED DYSPEPSIA?

☐ Urea breath tests (UBTs)[15A+,16C,17B+] and stool antigen tests (SATs) are the preferred tests.[11A+]

Urea Breath Test (UBT): most accurate test.[2D,15A+,16C,17B+]
- needs a prescription and staff time to perform

Stool Helicobacter Antigen Test (SAT): check test availability.[18A+,19A+]
- pea-sized piece of stool sent to local laboratory

DO NOT perform UBT or SAT within two weeks of PPI,[20B+,21B+] or four weeks of antibiotics,[19A+,22A+] as these drugs supress bacteria and can lead to false negatives.

Serology: whole blood in plain bottle; low cost, lower accuracy.[2D,16A-,23A+]
- not recommended for most patients, and positives should be confirmed by a second test such as UBT, SAT[24D] or biopsy[11D,15A+]
- has very good negative predictive value at current; low prevalence in the developed countries[7B+,8B-,9B+,10B+,11D]
- most useful in patients with acute gastrointestinal bleed, to confirm negative UBT or SAT, when blood and PPI use interacts with tests[19A+]
- detects IgG antibody;[25A+] does not differentiate active from past infection[19A+]

DO NOT use near patient serology tests, as they are not accurate.[2D,11D,16A-]

DO NOT use serology post-treatment.

DO NOT use serology in the elderly or in children.[13A+,14A+]

WHEN SHOULD I TREAT *HELICOBACTER PYLORI*?

HP POSITIVE → Treat *H. pylori*.[2D,11D,22A+,26B-]

HP NEGATIVE → Reassure, as NPV of all tests is >95%.[16C] →

ASYMPTOMATIC post-HP treatment[2D,3A-,4A-] →

Only retest for HP if DU, GU, family history of cancer, MALToma, or if test was performed within two weeks of PPI, or four weeks of antibiotics.[21B+,27C] →

If *H. pylori* negative, treat as functional dyspepsia. Step down to lowest dose PPI or H$_2$A needed to control symptoms. Review annually, including PPI need.[2D,28D]

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TREATMENT REGIMENS FOR *HELICOBACTER PYLORI*

- ☐ Check antibiotic history as each additional course of clarithromycin, metronidazole or quinolone increases resistance risk.[11D,22A+,29B-,30A-,31A+,32A-] Stress the importance of compliance.[2A-,27C,32A-]

NO PENICILLIN ALLERGY

FIRST-LINE: 7 days, PPI twice daily[2A-,30A-,31A+]
PLUS amoxicillin 1g BD
PLUS either clarithromycin 500mg BD OR
metronidazole 400mg BD

ONGOING SYMPTOMS after first-line

SECOND-LINE: 7 days, PPI twice daily[2A-,30A-,31A+]
PLUS amoxicillin 1g BD
PLUS second antibiotic not used in first line, either clarithromycin 500mg BD OR metronidazole 400mg BD

**ONGOING SYMPTOMS after first-line
AND previous exposure to MZ and CLAR**

SECOND-LINE, 7 days, PPI twice daily[2A-,30A-,31A+]
PLUS amoxicillin 1g BD
PLUS second antibiotic, either tetracycline hydrochloride 500mg QDS OR levofloxacin 250mg BD[30A-,31A+,33A+,34A+]

PENICILLIN ALLERGY

FIRST-LINE: 7 days, PPI twice daily[2A-,30A+,31A+]
PLUS clarithromycin 500mg BD
PLUS metronidazole 400mg BD

**First-line with previous CLAR exposure
OR Second-line with previous levofloxacin exposure**

7 days, PPI twice daily[2A-,30A+,31A+]
PLUS bismuth subsalicylate 525mg QDS[35A+,36A+,37A+,38D]
OR tripotassium dicitratobismuthate 240mg QDS[39D]
PLUS tetracycline hydrochloride 500mg QDS[2A-]
PLUS metronidazole 400mg BD[2A-]

**ONGOING SYMPTOMS after first-line and NO
previous exposure to levofloxacin**

SECOND-LINE: 7 days, PPI twice daily[2A-,30A+,31A+,33A+]
PLUS metronidazole 400mg BD[2A-]
PLUS levofloxacin 250mg BD[31A+,33A+,34A+]

- ☐ PPI medication: lansoprazole 30mg BD, omeprazole 20-40mg BD, pantoprazole 40mg BD, esomeprazole 20mg BD, rabeprazole 20mg BD.[38D]
- ☐ If post gastro-duodenal bleed, start HP treatment only when patient can take oral medication.[40A+]
- ☐ If diarrhoea develops, consider *Clostridium difficile* and review need for treatment.
- ☐ Only offer longer duration or third-line eradication on advice from a specialist.[2D] Third line: 10 days of PPI twice daily, PLUS bismuth subsalicylate 525mg QDS, PLUS 2 antibiotics as above not previously used, OR rifabutin 150mg BD, OR furazolidone 200mg BD.[31A+,33A+,41A-,42A+,43D]

WHEN SHOULD I RETEST FOR *HELICOBACTER PYLORI*?

- ☐ As 64% of patients with functional dyspepsia will have persistent recurrent symptoms, do not routinely offer re-testing after eradication.[2D]

  - • if compliance poor, or high local resistance rates[11D,29B-]
  - • persistent symptoms, and HP test performed within two weeks of taking PPI, or within four weeks of taking antibiotics[19A+,20B+,21B+,22C]
  - • patients with an associated peptic ulcer, after resection of an early gastric carcinoma or MALT lymphoma[2D,11D,26C]
  - • patients requiring aspirin, where PPI is not co-prescribed[2D]
  - • patients with severe persistent or recurrent symptoms, particularly if not typical of GORD[11D,26C]

  DO NOT use serology for re-testing[2D,15A+,16C]

  - • UBT is most accurate[15A+,16C]
  - • SAT is an alternative[15A+,18A+]

  Wait at least four weeks (ideally eight weeks) after treatment.[11D,19A+] If acid suppression needed use H_2 antagonist.[39D]

  Use second-line treatment if UBT or SAT remains positive[2D]

WHAT SHOULD I DO IN ERADICATION FAILURE?

- ☐ Reassess need for eradication.[2D] In patients with GORD or non-ulcer dyspepsia, with no family history of cancer or peptic ulcer disease, a maintenance PPI may be appropriate.[2D,26C]

WHEN SHOULD I REFER FOR ENDOSCOPY, CULTURE AND SUSCEPTIBILITY TESTING?

- ☐ Patients in whom the choice of antibiotic is reduced due to hypersensitivity, known local high resistance rates, or previous use of clarithromycin, metronidazole, and a quinolone.[2A-,11D,28D]
- ☐ Patients who have received two courses of antibiotic treatment, and remain HP positive.[2D,11D,28D]
- ☐ For any advice, speak to your local microbiologist, or the *Helicobacter* Reference Laboratory.

GRADING OF GUIDANCE RECOMMENDATIONS

The strength of each recommendation is qualified by a letter in parenthesis. This is an altered version of the grading recommendation system used by SIGN.

STUDY DESIGN	RECOMMENDATION GRADE
Good recent systematic review and meta-analysis of studies	A+
One or more rigorous studies; randomised controlled trials	A-
One or more prospective studies	B+
One or more retrospective studies	B-
Non-analytic studies, eg case reports or case series	C
Formal combination of expert opinion	D

This guidance was originally produced in 2004 by the South West GP Microbiology Laboratory Use Group, in collaboration with the Association of Medical Microbiologists, general practitioners, nurses and specialists in the field. This guidance was reviewed and updated in 2016, with input from Professor Cliodna McNulty; Dr Philippa Moore; Dr Teh Li Chin; the British Society of Gastroenterology (BSG); the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI); the British Society for Antimicrobial Chemotherapy (BSAC); the British Infection Association (BIA); the Royal College of General Practitioners (RCGP); the Royal College of Nursing (RCN); general practitioners; specialists in the field; and patient representatives. Full consensus of the recommendations made was given by all guidance developers and reviewers prior to the dissemination of this guidance. All comments received have been reviewed and incorporated into the guidance, where appropriate. For detailed information regarding the comments provided and action taken, please email TARGETAntibiotics@phe.gov.uk. Public Health England works closely with the authors of the Clinical Knowledge Summaries.

If you would like to receive a copy of this guidance with the most recent changes highlighted, please email TARGETAntibiotics@phe.gov.uk.

For detailed information regarding the search strategies implemented and full literature search results, please email TARGETAntibiotics@phe.gov.uk.

References and rationale

1. National Institute for Health and Care Excellence (NICE). Suspected cancer: recognition and referral. 2015 Jun. Available from: https://www.nice.org.uk/guidance/ng12.

   RATIONALE: A NICE guideline indicating that patients presenting with symptoms suggestive of upper-gastrointestinal cancer should be referred to a specialist team. *Helicobacter pylori* status should not affect the decision to refer for suspected cancer. Patients aged 55 years or older, with recent onset, unexplained and persistent dyspepsia (over 4-6 weeks) should be referred urgently for endoscopy (within two weeks). Patients of any age with dyspepsia and any of the following should be referred urgently for endoscopy (within two weeks), or to a specialist: chronic gastrointestinal bleeding; dysphagia; progressive unintentional weight loss; persistent vomiting; iron-deficiency anaemia; epigastric mass; suspicious barium meal result. Patients of any age presenting with any of the following should be referred urgently to a specialist (within two weeks): dysphagia; unexplained abdominal pain and weight loss (with or without back pain); upper abdominal mass without dyspepsia; obstructive jaundice, depending on clinical state (consider urgent ultrasound, if available). Patients should be referred urgently (within two weeks) if presenting with any of the following: persistent vomiting and weight loss in the absence of dyspepsia; unexplained weight loss or iron-deficiency anaemia in the absence of dyspepsia; unexplained worsening of dyspepsia; known dysplasia, atrophic gastritis or intestinal metaplasia; peptic ulcer surgery over 20 years ago; AND Barrett's oesophagus.

2. National Institute for Health and Care Excellence (NICE). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. 2014 Sep. Available from: https://www.nice.org.uk/guidance/cg184.

   RATIONALE: A NICE guideline recommending that patients of any age with gastro-oesophageal symptoms that are unexplained or unresponsive to treatment should be referred to a specialist. Unexplained is defined as "a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations". Clinicians should offer *H. pylori* test and treat to patients with dyspepsia. Clinicians should leave a two week washout period after PPI use before testing for *H. pylori* with a urea breath test or stool antigen test. NICE recommend that patients with reflux-like symptoms should be treated in a similar way to those with dyspepsia, using full dose PPI for four weeks, before considering treatment for *H. pylori*. Clinicians should offer patients who need long-term management of dyspepsia symptoms an annual review of their condition, and should encourage them to try stepping down or stopping treatment (unless there is an underlying condition or co-medication that needs continued treatment). Clinicians should test for *H. pylori* using a carbon-[13]urea breath test or stool antigen test, or laboratory-based serology where performance has been locally validated. Clinicians should not use office-based serology tests for *H. pylori*, as their performance is routinely inadequate. Clinicians should discuss treatment adherence with the patient and should emphasise its importance. **First line treatment:** Clinicians should offer patients who test positive for *H. pylori* a seven day, twice daily course of treatment with a PPI, amoxicillin, and either

clarithromycin or metronidazole. Choose the treatment regimen with the lowest acquisition cost and take into account previous exposure to clarithromycin and metronidazole. All triple regimens have similar outcomes and are slightly better than quadruple regimens. Offer patients who are allergic to penicillin a seven day, twice daily course of treatment with a PPI, clarithromycin and metronidazole. Offer patients who are allergic to penicillin and who have had previous exposure to clarithromycin a seven day, twice daily course of treatment with a PPI, metronidazole and tetracycline.

Second line: Offer patients who still have symptoms after first-line eradication treatment a seven day, twice daily course of treatment with a PPI, amoxicillin and either clarithromycin or metronidazole (whichever was not used first-line). Offer patients who have had previous exposure to clarithromycin and metronidazole a seven day, twice daily course of treatment with a PPI, amoxicillin and a quinolone or tetracycline. Offer patients who are allergic to penicillin (and who have not had previous exposure to a quinolone) a seven day, twice daily course of treatment with a PPI, metronidazole and levofloxacin. Offer patients who are allergic to penicillin and who have had previous exposure to a quinolone a PPI, a bismuth salt (tripotassium dicitratobismuthate or bismuth subsalicylate), metronidazole and tetracycline. NICE document evidence from one study, stating that increasing the duration of PPI/amoxicillin/quinolones from seven to 10 days results in improved second-line *H. pylori* eradication when using standard or double dosing for the 10 day regimen. Evidence from other studies has shown that increasing the duration of a quadruple regimen from seven to 14 days does not improve second-line *H. pylori* eradication. Clinicians should consider referral for those patients who have *Helicobacter pylori*, which has not responded to second-line eradication therapy.

3. Gisbert JP, Calvet X. *Helicobacter pylori* "test-and-treat" strategy for management of dyspepsia: a comprehensive review. *Clin Transl Gastroenterol*. 2013 Mar; 4(32):1-17. Available from: http://www.nature.com/ctg/journal/v4/n3/pdf/ctg20133a.pdf.

   RATIONALE: A literature review analysing the results of randomised controlled trials across several areas of *Helicobacter pylori* investigation. The authors conclude that it is widely accepted that endoscopy should be reserved for patients with symptom onset over 45-55 years of age, those who have alarm symptoms, and those whose empirical antisecretory therapy or test and treat strategy fails. The test and treat strategy will cure most cases of underlying peptic ulcer disease, and will prevent most potential cases of gastroduodenal disease. In addition, a minority of infected patients with functional dyspepsia will gain symptomatic benefit. The test and treat strategy is reinforced by the accumulating data that supports the increasingly accepted idea that "the only good *Helicobacter pylori* is a dead *Helicobacter pylori*".

4. Jarbol DE, Kragstrup J, Stovring H, Havelund T, Schaffalitzky de Muckadell OB. Proton pump inhibitor or testing for *Helicobacter pylori* as the first step for patients presenting with dyspepsia? A cluster-randomized trial. *Am J Gastroenterol*. 2006 Jun; 101(6):1200-1208. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16771937.

   RATIONALE: A cluster-randomised trial in general practices in Denmark, comparing empirical antisecretory therapy (222 patients), test and eradicate for *H. pylori* (250 patients), or a combination of the two (250 patients) for the management of dyspepsia.

The prevalence of *H. pylori* infection was 24%. After one year, gastrointestinal symptom scores and quality of life scores had improved significantly and equally across the three groups ($p<0.001$), but no statistically significant differences were found within the groups. The mean use of endoscopies per patient after one year was higher in the PPI group (0.36 [95% CI 0.30 to 0.43]) than in the test and eradicate group (0.28 [95% CI 0.23 to 0.34]) or the combination group (0.22 [95% CI 0.17 to 0.27]; $p=0.02$). *H. pylori* positive patients receiving eradication therapy had more days without dyspeptic symptoms ($p<0.001$), used less antisecretory therapy ($p<0.01$), and were more satisfied ($p<0.001$), in comparison to *H. pylori* negative patients.

5. Moayyedi P. *Helicobacter pylori* test and treat strategy for young dyspeptic patients: new data. *Gut.* 2002 Apr; 50(4):47-50. Available from: http://gut.bmj.com/content/50/suppl_4/iv47.full.pdf+html.
   RATIONALE: A qualitative and semi-quantitative review of the data from four randomised controlled trials, comparing the *H. pylori* test and treat strategy with prompt endoscopy. Three trials measured dyspepsia symptom resolution, and found the *H. pylori* test and treat strategy to be as effective as prompt endoscopy. Quality of life was also similar across both groups, so conclusions were drawn that management decisions should be based on cost. The decision analysis model indicates that the *H. pylori* test and treat strategy is the cheapest and most cost-effective, costing US \$134 per patient per year, compared with US \$240 per patient per year for prompt endoscopy.

6. Delaney BC, Qume M, Moayyedi P, Logan RF, Ford AC, Elliott C et al. *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). *BMJ.* 2008 Mar; 22(336):651-654. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18310262.
   RATIONALE: A randomised controlled trial of 699 patients aged 18-65 who presented to their general practitioner with epigastric pain, heartburn, or both, without alarm symptoms for malignancy. This study compared the *H. pylori* urea breath test, plus one week of eradication treatment, if positive, to proton pump inhibitor therapy alone. At 12 months, there were no significant differences between the two groups in QALYs, cost, or dyspeptic symptoms. Minor reductions in costly resource use over the year in the test and treat group paid back the initial cost of testing. Therefore, test and treat and initial empirical acid suppression are equally cost-effective in the initial management of dyspepsia, when the prevalence of *H. pylori* infection is similar to the prevalence in this study (29%). As therapy costs are similar, general practitioners should discuss with patients at which point to consider *H. pylori* testing. At a lower prevalence (most areas of the UK) it is suggested that PPIs should be used before *H. pylori* test and treat, unless the chance of *H. pylori* infection is greater (older age; ethnicity; areas of high *H. pylori* prevalence).

7. Bauer S, Krumbiegel P, Richter M, Richter T, Roder S, Rolle-Kampczyk U et al. Influence of sociodemographic factors on *Helicobacter pylori* prevalence variability among school children in Leipzig, Germany. A long-term follow-up study. *Cent Eur J Public Health.* 2011 Mar; 19(1):42-45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21526656.

RATIONALE: This German study outlines overall *H. pylori* prevalence as 6.5%, having not significantly changed since 1998 (6.1%). Suggested risk factors for carriage are: foreign nationality of at least one parent; birth outside of Germany; low parental education and unemployment; two or more older siblings.

8. Miendje Deyi VY, Vanderpas J, Bontems P, Van den Borre C, De Koster E, Cadranel S et al. Marching cohort of *Helicobacter pylori* infection over two decades (1988-2007): combined effects of secular trend and population migration. *Epidemiol Infect.* 2011 Apr; 139(4):572-580. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20525410.

    RATIONALE: A long-term cohort study in Brussels involving 22,612 patients in whom a first culture of gastric biopsy (routinely performed in medical centres) yielded an interpretable result. The lowest infection rate was observed in Western European patients (n=11,238), with 36.2% and 15.2% infected subjects in 1988 and 2007, respectively, compared to 71.7% and 40% in North African patients (n=3,200).

9. Moujaber T, MacIntyre CR, Backhouse J, Gidding H, Quinn H, Gilbert GL. The seroepidemiology of *Helicobacter pylori* infection in Australia. *Int J Infect Dis.* 2008 Sep; 12(5):500-504. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18400542.

    RATIONALE: A randomised study of a representative sample of 2,413 sera, reporting a seroprevalence of 15.1% using *H. pylori*-specific ELISA for the presence of IgG antibodies. This study also discusses the varying prevalence of *H. pylori* across different population groups internationally.

10. McNulty CA, Lasseter G, Shaw I, Nichols T, D'Arcy S, Lawson AJ et al. Is *Helicobacter pylori* antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther.* 2012 May; 35(10):1221-1230. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22469191.

    RATIONALE: A 2009/2010 study of *Helicobacter pylori* antibiotic resistance surveillance in three centres across England and Wales. Biopsy specimens were taken from endoscopy patients in Gloucester, England and Bangor, Wales. Of 1,153 biopsy specimens in Gloucester, 11% were tested positive for *H. pylori* on culture or biopsy urease test, and 9% were tested positive by serology. Antibiotic resistance to amoxicillin, rifabutin and tetracycline remained very low, whereas each course of clarithromycin, metronidazole and levofloxacin was related to a 50% increase in resistance.

11. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F et al. Management of *Helicobacter pylori* infection – the Maastricht IV/Florence Consensus Report. *Gut.* 2012 Feb; 61:646-664. Available from: http://gut.bmj.com/content/61/5/646.full.pdf.

    RATIONALE: A consensus report providing expert opinion on the most appropriate management and diagnostic tests for *Helicobacter pylori*. The report advises that younger patients without alarm symptoms should be offered test and treat for *H. pylori* if local prevalence is over 20%, and also states that *H. pylori* eradication is most beneficial in patients with gastro-duodenal ulcer disease. Both *H. pylori* infection and NSAID use are independent risk factors for the development of peptic ulcer disease and associated bleeding. These conditions are uncommon in those who do not have either risk factor, but

there is an increased risk when both factors are present. In naïve users, it is clearly beneficial to eradicate *H. pylori*, but there is no clear benefit for those who are already long-term users. However, results from a meta-analysis showed that eradication seems less effective than treatment with a maintenance PPI for preventing NSAID-associated ulcers. Clinicians should test for *H. pylori* in patients with unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency. Two meta-analyses have supported the association between these conditions, with one illustrating a clear link between *H. pylori* infection and iron-deficiency anaemia, and the other showing that *H. pylori* eradication increases haemoglobin levels in patients with this condition. Systematic reviews have demonstrated that an overall platelet response has been recorded in more than 50% of patients successfully treated for *H. pylori* infection, and response rates are increasing in countries with a high prevalence of *H. pylori* infection in background populations. This report states that there is a negative association between the prevalence of *H. pylori* and GORD. The sequelae of GORD, such as Barrett's oesophagus and oesophageal adenocarcinoma, are less common in infected individuals, and eradication of *H. pylori* in populations of infected patients, on average, neither causes nor exacerbates symptoms of GORD. Therefore, the presence of GORD should not dissuade practitioners from *H. pylori* eradication treatment, where indicated. Long-term treatment with PPIs in *H. pylori* positive patients is associated with the development of corpus-predominant gastritis. This accelerates the process of losing specialised glands, leading to atrophic gastritis. Eradication of *H. pylori* in patients receiving long-term PPI treatment heals gastritis and prevents the progression to atrophic gastritis. However, there is no evidence that this reduces the risk of gastric cancer. Finally, this report emphasises that urea breath tests (UBTs) and stool helicobacter antigen tests (SATs) are the most accurate tests and should be used in preference to serology, unless the latter has been locally validated.

12. Ford AC, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients (Review). *Cochrane Database Syst Rev*. 2011 Apr; 1:1-121. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003840.pub4/pdf. RATIONALE: A Cochrane review examining duodenal ulcer healing in 3,910 patients across 34 trials. Findings indicated that *H. pylori* eradication therapy was superior to ulcer healing drugs (UHDs) (RR of ulcer persisting = 0.66, 95% CI 0.58 to 0.76) and no treatment (two trials, 207 patients, RR = 0.37, 95% CI 0.26 to 0.53). In gastric ulcer healing, no significant differences were detected between eradication therapy and UHDs (15 trials, 1,974 patients, RR = 1.23, 95% CI 0.90 to 1.68). In preventing duodenal ulcer recurrence, no significant differences were detected between eradication therapy and maintenance therapy with UHDs (4 trials, 319 patients, RR = 0.73, 95% CI 0.42 to 1.25), but eradication therapy was superior to no treatment (27 trials, 2,509 patients, RR = 0.20, 95% CI 0.15 to 0.26). In preventing gastric ulcer recurrence, eradication therapy was superior to no treatment (12 trials, 1,476 patients, RR = 0.31, 95% CI 0.22 to 0.45). Test and treat for *H. pylori* is therefore advised in patients with a past history of gastric ulcers.

13. Sykora J, Rowland M. *Helicobacter pylori* in pediatrics. *Helicobacter*. 2011 Sep; 16(1):59-64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21896087.

RATIONALE: A systematic review suggesting that upper gastrointestinal endoscopy is not appropriate for children with dyspeptic symptoms. Upper gastrointestinal endoscopy should be reserved for children with a family history of peptic ulcer disease and/or *H. pylori* infection, or children over ten years of age with symptoms persisting for more than six months, which are severe enough to affect daily activities.

14. Guarner J, Kalach N, Elitsur Y, Koletzko S. *Helicobacter pylori* diagnostic tests in children: review of the literature from 1999 to 2009. *Eur J Pediatr*. 2010 Jan; 169(1):15-25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19618211.

    RATIONALE: A systematic review concluding that SATs and UBTs have adequate sensitivity and specificity for the detection of *H. pylori* in children, but endoscopy is the gold standard.

15. Nocon M, Kuhlmann A, Leodolter A, Roll S, Vauth C, Willich SN et al. Efficacy and cost-effectiveness of the ^{13}C-urea breath test as the primary diagnostic investigation for the detection of *Helicobacter pylori* infection compared to invasive and non-invasive diagnostic tests. *GMS Health Technol Assess*. 2009 Oct; 21(5):1-12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21289901.

    RATIONALE: A systematic review of 30 studies (3,415 patients) directly comparing the ^{13}C-UBT and other non-invasive tests to biopsy-based tests as the gold standard for *H. pylori* testing. The ^{13}C-UBT showed higher sensitivity and specificity than IgG serology in 18 studies, and showed higher sensitivity and specificity than SATs in 13 studies (a 100% sensitive test correctly identifies all patients with *H. pylori*, and a 100% specific test correctly identifies all patients without *H. pylori*). Sensitivity and specificity higher than 90% was found in 84% of the studies for the ^{13}C-urea breath test. Sensitivity and specificity higher than 90% was found in 62% of the studies for the stool antigen test, and 56% sensitivity and 44% specificity for the IgG test. Nine health economic evaluations were included in this Health Technology Assessment (HTA) report. Test and treat strategies using the ^{13}C-UBT were more cost-effective than serology-based strategies in three of the nine, and was dominated by a test and treat strategy using the SAT in one of those three.

16. Vaira D, Vakil N. Blood, urine, stool, breath, money, and *Helicobacter pylori*. *Gut*. 2001 Mar; 48(3):287-289. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1760150/pdf/v048p00287.pdf.

    RATIONALE: A case report presenting data from eight studies, showing that the urea breath test has much higher accuracy (95% specificity and sensitivity) than the near patient serology test (71.1% sensitivity and 87.6% specificity) in detecting *H. pylori*.

17. Vakil N, Zullo A, Ricci C, Hassan C, Vaira D. Duplicate breath testing to confirm eradication of *Helicobacter pylori*: incremental benefit and cost in 419 patients. *Aliment Pharmacol Ther*. 2008 Dec; 1(28):1304-1308. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18774949.

    RATIONALE: A prospective study following 419 patients with documented *H. pylori* infection. Patients had two breath tests, one at four weeks, and the second at least eight weeks after completion of therapy. Following treatment, the results at one month were similar to the value obtained at the second breath test at two months. There were no

discordant results. This indicates that the urea breath test can be undertaken four weeks after treatment is completed.

18. Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: a systematic review and meta-analysis. *Am J Gastroenterol*. 2006 Aug; 101(8):1921-1930. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16780557.
RATIONALE: A systematic review of 22 studies (2,499 patients) showing *H. pylori* monoclonal stool antigen tests as having a sensitivity of 94% (95% CI, 93 to 95), and specificity of 97% (95% CI, 96 to 98), with LR+ and LR- being 24 (15 to 41) and 0.07 (0.04 to 0.12), respectively. Monoclonal tests were more sensitive than polyclonal tests (pooled sensitivity of 95% for monoclonal tests, and 83% for polyclonal tests). Post-treatment, the monoclonal stool antigen tests were evaluated in 957 patients, with a sensitivity of 93% (95% CI 89 to 96) and a specificity of 96% (95% CI 94 to 97), respectively. Pooled positive and negative LRs were 17 (12 to 23; non-heterogeneous results) and 0.1 (0.07 to 0.15; non-heterogeneous results).

19. Gisbert JP, Pajares JM. Stool antigen test for the diagnosis of *Helicobacter pylori* infection: a systematic review. *Helicobacter*. 2004 Aug; 9(4):347-368. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15270750.
RATIONALE: A systematic review evaluating all stool antigen test studies up to 2004. Findings indicate that post-antibiotic treatment tests are more accurate at four weeks post-treatment, than at two weeks, and eight weeks post-treatment, than at four weeks. This review found that proton-pump inhibitors affect the accuracy of stool antigen tests, and that when PPIs are started in *H. pylori* positive patients, SAT and UBT test values fall to negative figures at one week (in about 30% of patients), and revert to positive two weeks after treatment. This paper also states that sensitivity and/or specificity of SATs in patients with gastrointestinal bleeding is suboptimal. Studies of patients with upper gastrointestinal bleeding have produced very variable results. Negative UBTs in patients with upper gastrointestinal bleeding can be due to the interaction of blood with urea or *H. pylori* urease in the stomach. Blood in the stool may also lead to false negatives.

20. Mana F, Van Laer W, Bossuyt A, Urbain D. The early effect of proton pump inhibitor therapy on the accuracy of the ^{13}C-urea breath test. *Dig Liver Dis*. 2005 Jan; 37(1):28-32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15702856.
RATIONALE: A prospective study showing that the intake of proton pump inhibitors impairs the accuracy of the ^{13}C-urea breath test. 30 patients and 53 volunteers received a ^{13}C-urea breath test before starting PPI therapy, and every morning before the once-daily PPI dose, for ten days. 43% of *H. pylori* positive patients developed false negative breath tests in the first ten days, with false positive results occurring in 37.5% of *H. pylori* negative patients. False negative and false positive ^{13}C-urea breath tests are common in patients taking PPIs, occurring as soon as one day after starting treatment, and increasing with prolonged duration of treatment. The coefficient of reproducibility of the ^{13}C-urea breath test in patients receiving PPIs is not acceptable for clinical purpose, so the test should not be performed once PPI medication has been started.

21. Graham DY, Opekun AR, Hammoud F, Yamaoka Y, Reddy R, Osato MS et al. Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors. *Am J Gastroenterol*. 2003 May; 98(5):1005-1009. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12809820.

    RATIONALE: A prospective study in which the authors suggest the minimum of a three day delay between stopping PPI therapy and conducting a urea breath test, with the preference of a 14 day delay. In this study, 30 *H. pylori* infected volunteers received omeprazole 20mg twice daily for 13.5 days. UBTs with citric acid were conducted before PPI, after 6.5 days of PPI, and at 1, 2, 4, 7, and 14 days after completion of therapy. Positive UBTs were significantly reduced by day 6, but 33% of subjects developed transient negative UBTs. The UBT recovered in all but one subject by the fourth day post-PPI, and in all subjects by day 14, indicating that the UBT should be performed at 14 days post-treatment. PPI-induced negative UBT results were related to the anti-*Helicobacter pylori* effect of the PPI, as *H. pylori* density decreases with PPI therapy.

22. O'Connor A, Gisbert JP, McNamara D, O'Morain C. Treatment of *Helicobacter pylori* infection 2010. *Helicobacter*. 2010 Sep; 15(1):46-52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21054653.

    RATIONALE: A review of all previously published trials regarding the treatment of *H. pylori*. Eradication rates have been falling over the past ten years, and is below 80% in Southern European countries. Resistance to clarithromycin is the single most important factor when considering treatment failures, however resistance to clarithromycin remains low in most Northern European countries and in EU populations with low rates of ethnicity. This review discusses the importance of individualising *H. pylori* eradication treatment in order to maximise efficacy. This review emphasises the importance of: assessing previous antibiotic treatment for any other infection, as previous metronidazole, clarithromycin and quinolone use are all associated with increased resistance; reviewing national resistance rates; considering patient ethnicity. Poor compliance also has an impact on eradication rates. Compliance with *H. pylori* eradication therapy is a multifactorial process. Current evidence and published guidelines recommend complex and prolonged eradication regimens, using a number of antibiotics, and involving manipulation of gastric pH. It has been suggested that 10% of patients prescribed *H. pylori* eradication therapy will fail to take even 60% of medications. Improvements with respect to compliance are likely to lead to higher levels of eradication and lower rates of resistance. Finally, this review states that PPIs should be carefully chosen depending on the patient. Most PPIs are metabolised in the liver, with 18-27% of Europeans, compared to only 1-3% of Asians being rapid PPI metabolisers. Rabeprazole is not metabolised in the liver and, therefore, may be a good choice in Caucasians with treatment relapse.

23. Loy CT, Irwig LM, Katelaris PH, Talley NJ. Do commercial serological kits for *Helicobacter pylori* infection differ in accuracy? A meta-analysis. *Am J Gastroenterol*. 1996 Jun; 91(6):1138-1144. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8651160.

    RATIONALE: A meta-analysis of 21 laboratory-based studies comparing the accuracy of common commercial serological kits used for *Helicobacter pylori*. There was no significant

difference between the accuracies of different kits, and an overall sensitivity and specificity was recorded at 85% and 79%, respectively, both of which are low for a diagnostic test.

24. PennState Eberly College of Science. *Sensitivity, specificity, positive predictive value, and negative predictive value*. Available from:
https://onlinecourses.science.psu.edu/stat507/node/71 [Accessed: 15th April, 2016].
RATIONALE: A university publication, considering the importance of predictive values of diagnostic tests, and recognising the influence of these on the prevalence of disease. A

figure is included, which depicts the relationship between disease prevalence and predictive value in a test with 95% sensitivity and 95% specificity. Using the same test in a population with lower prevalence decreases positive predictive value. The positive predictive value is low in the majority of the population in the UK. Therefore, a positive serology should be confirmed with another test; either a urea breath test (UBT) or stool antigen test (SAT).
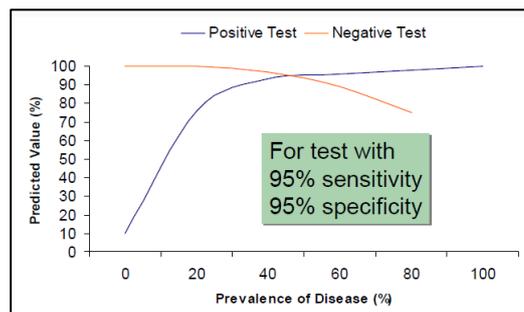
25. Laheij RJ, Straatman H, Jansen JB, Verbeek AL. Evaluation of commercially available *Helicobacter pylori* serology kits: a review. *J Clin Microbiol*. 1998 Oct; 36(10):2803-2809. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC105068/pdf/jm002803.pdf.
RATIONALE: A literature review providing a comparison of 36 laboratory-based serology kits in 26,812 patients. Median sensitivities and specificities were recorded at 92% (25% and 75% quartiles, 85% and 96%) and 83% (25% and 75% quartiles, 73% and 92%), respectively. Kits that measured IgG alone were more accurate than those using IgA, or a combination of IgM, IgG and IgA.

26. Ford AC, Moayyedi P. Whom should we "test and treat" for *Helicobacter pylori*? *BMJ*. 2014 May; 20(348):332-335. Available from:
http://www.bmj.com/content/bmj/348/bmj.g3320.full.pdf.
RATIONALE: A review article focusing on an area of practice where the management of *H. pylori* is contentious, together with outlining the principles of standard eradication therapy. The authors conclude that clinicians should continue to test and treat for *H. pylori* infection in patients presenting with symptoms of dyspepsia, those with peptic ulcer disease, and those with functional dyspepsia.

27. Braden B. Diagnosis of *Helicobacter pylori* infection. *BMJ*. 2012 Feb; 24(344):82-87. Available from: http://www.bmj.com/content/bmj/344/bmj.e828.full.pdf.
RATIONALE: A case report exploring how to test for *H. pylori* infection, which tests are most effective, and when clinicians should retest. The author suggests that retesting is appropriate for patients with an associated ulcer or MALT lymphoma, after resection of an early gastric cancer, or in those with persistent dyspeptic symptoms.

28. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol*. 2014 Feb; 12(2):177-186. Available from: http://www.cghjournal.org/article/S1542-3565(13)00773-8/pdf.

   RATIONALE: A review article providing the rationale for prescribing antibiotic regimens in treating *H. pylori*. Diagnostic and treatment pathways are provided in a step-wise progression, and success rates are outlined. Standard and alternative treatment regimens are discussed, and recommendations are provided for areas with high and low clarithromycin resistance. Salvage therapies (for patients where first line treatments have failed) are also detailed.

29. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut*. 2013 Jan; 62(1):34-42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22580412.

   RATIONALE: EU surveillance study, in which the authors state that, of the 2,204 patients included, *H. pylori* resistance rates for adults were 17.5% for clarithromycin, 14.1% for levofloxacin, and 34.9% for metronidazole. Resistance rates were significantly higher for clarithromycin and levofloxacin in Western/Central and Southern Europe (>20%) than in Northern European countries (<10%). Model fit improved for each additional year of antibiotic use accumulated, but the best fit was obtained for 2005. A significant association was found between outpatient quinolone use and the proportion of levofloxacin resistance (p=0.0013), and between the use of long-acting macrolides only and clarithromycin resistance (p=0.036). The authors conclude that in many countries, the high rate of clarithromycin resistance no longer allows its empirical use in standard anti-*H. pylori* regimens. The knowledge of outpatient antibiotic consumption may provide a simple tool to predict the susceptibility of *H. pylori* to quinolones and to macrolides, and may permit the alteration of treatment strategies.

30. Malfertheiner P, Bazzoli F, Delchier JC, Celinski K, Giguere M, Riviere M et al. *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. *Lancet*. 2011 Mar; 377(9769):905-913. Available from: http://www.sciencedirect.com/science/article/pii/S0140673611600202.

   RATIONALE: A randomised controlled trial, in which 339 patients across the UK, Germany, France, Ireland, Poland, and Spain were allocated to either 10 days omeprazole 20mg BD plus three capsules containing bismuth 140mg, metronidazole 125mg, and tetracycline hydrochloride 125mg QDS after meals, or seven days omeprazole 20mg BD plus 500mg amoxicillin and 500mg clarithromycin. According to intention to treat criteria, *H. pylori* eradication was successful in 92% of patients on quadruple therapy, and 69% of patients on triple therapy. In clarithromycin resistance, eradication was reduced to 8% of patients on triple therapy, but it did not influence quadruple therapy. Quadruple therapy is effective as a second-line treatment, and should be considered if there is a past history of clarithromycin use.

31. O'Connor A, Gisbert JP, McNamara D, O'Morain C. Treatment of *Helicobacter pylori* infection 2011. *Helicobacter*. 2011 Sep; 16(1):53-58. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1523-5378.2011.00881.x/pdf.

   RATIONALE: A review of all previously published trials regarding the treatment of *H. pylori*. Seven studies were cited describing the successful use of levofloxacin with amoxicillin or clarithromycin and a proton pump inhibitor as first-line treatment for *H. pylori* (85% eradication). Rifabutin 150mg BD with amoxicillin 1g BD achieved 79 to 85% eradication in patients who had failed other treatment regimens. A 14 day quadruple, bismuth-based treatment regimen using omeprazole, clarithromycin and amoxicillin attained an eradication rate of 94%.

32. Lee M, Kemp JA, Canning A, Egan C, Tataronis G, Farraye FA. A randomized controlled trial of an enhanced patient compliance program for *Helicobacter pylori* therapy. *Arch Intern Med*. 1999 Oct; 159(19):2312-2316. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10547171.

   RATIONALE: A randomised controlled trial assessing compliance with an enhanced compliance program (ECP) *H. pylori* therapy regimen. The authors conclude that although patients were able to complete 60% or more of a two week regimen, the ECP improved the percentage of *H. pylori* medications taken to almost 90%.

33. Gisbert JP, de la Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther*. 2006 Jan; 23(1):35-44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16393278.

   RATIONALE: A systematic review and meta-analysis of 149 studies demonstrating an 80% mean eradication rate with levofloxacin 250mg BD containing regimens. 10 day regimens were more effective than seven days, and side-effects were lower than with bismuth treatment. However, the authors conclude that this regimen should not be used if there has been previous use of a quinolone, as quinolone resistance develops easily.

34. Luther J, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of *Helicobacter pylori* infection: systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol*. 2010 Jan; 105(1):65-73. Available from: http://www.nature.com/ajg/journal/v105/n1/pdf/ajg2009508a.pdf.

   RATIONALE: A systematic review and meta-analysis of nine randomised controlled trials (n=1,679), which found that eradication rates for *H. pylori* were comparable between clarithromycin triple therapy (77%) and bismuth-containing quadruple therapy (78%). Most of the trials were of 7-10 days duration, with 10 days treatment exceeding the authors' baseline analysis (I^2 = 65.2%).

35. Dore MP, Lu H, Graham DY. Role of bismuth in improving *Helicobacter pylori* eradication with triple therapy. *Gut*. 2016 Feb; 1:1-9. Available from: http://gut.bmj.com/content/early/2016/02/04/gutjnl-2015-311019.full.pdf.

   RATIONALE: A literature review describing the increasing antibiotic resistance to *H. pylori* worldwide, and the added value of using bismuth in areas where resistance is high. This

review states that the addition of bismuth to form quadruple therapy can increase *H. pylori* eradication by 30-40% in populations with high resistance.

36. Sun Q, Liang X, Zheng Q, Liu W, Xiao S, Gu W, Lu H. High efficacy of 14-day triple therapy-based, bismuth-containing quadruple therapy for initial *Helicobacter pylori* eradication. *Helicobacter*. 2010 Jun; 15(3):233-238. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20557366.

    RATIONALE: A randomised controlled trial, in which a total of 160 patients with functional dyspepsia who were *H. pylori* positive were assigned to one of two groups. The treatment regimen was: omeprazole 20mg, amoxicillin 1g, clarithromycin 500mg, and bismuth potassium citrate 220mg, all twice daily. 80 patients received seven day quadruple therapy, and 80 patients received the same therapy for 14 days. Six weeks after treatment, *H. pylori* eradication was assessed by the ^{13}C-urea breath test. Minimum Inhibitory Concentrations (MICs) of clinical isolates of metronidazole, clarithromycin and amoxicillin were determined by the twofold agar dilution method. The authors explain that the results show that 14 day therapy leads to a significant increase in *H. pylori* eradication success, when compared to seven day therapy, according to the intention-to-treat analysis (93.7% vs. 80.0%; p=.01), and the per-protocol analysis (97.4% vs. 82.0%; p=.0016). The *H. pylori* resistance rates to metronidazole, clarithromycin and amoxicillin were recorded as 42.1%, 18.0%, and 0%, respectively. The authors conclude that 14 day therapy is significantly more effective in patients with clarithromycin-resistant strains of *H. pylori*. The addition of bismuth, and prolonging treatment duration, can overcome *H. pylori* resistance to clarithromycin, and decrease bacterial load. 14 day triple therapy-based, bismuth-containing quadruple therapy achieved an ITT success rate of 93%, and could be recommended as a first-line eradication regimen.

37. O'Connor A, Gisbert JP, O'Morain C, Ladas S. Treatment of *Helicobacter pylori* infection 2015. *Helicobacter*. 2015 Sep; 20(1):54-61. Available from: http://onlinelibrary.wiley.com/doi/10.1111/hel.12258/epdf.

    RATIONALE: A review of all previously published trials regarding the treatment of *H. pylori*. This review states that outcomes for standard triple therapy have been generally poor, and the most promising results have come from bismuth and non-bismuth containing quadruple therapies. The findings also indicate that levofloxacin-based therapies have performed well as both first- and second-line eradication regimens, and show promise when used in combination as a second-line treatment. However, issues regarding resistance and availability may limit the adoption of these agents in treatment protocols.

38. Chey WD, Wong BC, Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007 Aug; 102(8):1808-1825. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17608775.

    RATIONALE: An American College of Gastroenterology guideline, providing details of first-line regimens for *Helicobacter pylori* eradication. This guideline recommends that, for penicillin allergic patients, bismuth subsalicylate at a dose of 525mg QDS should be given alongside a PPI, tetracycline hydrochloride 500mg QDS, and metronidazole 250mg QDS.

This guideline also provides standard doses for a range of PPIs, including: lansoprazole 30mg; omeprazole 20mg; pantoprazole 40mg; rabeprazole 20mg; esomeprazole 40mg.

39. Drugs.com. *Helidac*. Available from: http://www.drugs.com/mtm/helidac.html [Accessed: 3rd June, 2016].

RATIONALE: The Helidac therapy pack consists of a 14 day course of either bismuth subsalicylate (Pepto Bismol[®]) QDS or tripotassium dicitratobismuthate (De-Noltab[®]), metronidazole 250mg QDS, and tetracycline hydrochloride 500mg QDS, taken in conjunction with an H_2 antagonist. *H. pylori* eradication rates with Helidac in patients with a history of duodenal ulcer disease are reported to be around 80%, and in patients with active duodenal ulcer disease are reported to be 77 to 82%. A proton pump inhibitor may be preferred to an H_2 antagonist for concomitant use with the Pepto Bismol[®] regimen.

40. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut*. 2017 Jan; 66(1):6-30. Available from: http://gut.bmj.com/content/gutjnl/66/1/6.full.pdf.

RATIONALE: A consensus report providing expert opinion on the most appropriate management and diagnostic tests for *Helicobacter pylori*. This report states that, when alarm symptoms are present (weight loss; dysphagia; overt gastrointestinal bleeding; abdominal mass; iron deficiency anaemia), an oesophago-gastro-duodenoscopy is needed. It is also stated that, if post-gastroduodenal bleed, *Helicobacter pylori* treatment should only be started when the patient can take oral medication.

41. Dojo M, Azuma T, Saito T, Ohtani M, Muramatsu A, Kuriyama M. Effects of CYP2C19 gene polymorphism on cure rates for *Helicobacter pylori* infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxicillin and clarithromycin in Japan. *Dig Liver Dis*. 2001 Nov; 33(8):671-675. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11785712.

RATIONALE: A randomised trial to investigate whether genetic polymorphism of CYP2C19 and selected proton pump inhibitors (omeprazole or rabeprazole) are associated with cure rates for *H. pylori* infection, when used in a triple therapy regimen. A total of 170 Helicobacter-positive patients with chronic gastritis were randomised to receive either omeprazole or rabeprazole, with amoxicillin and clarithromycin. Cure rates were not significantly different between the CYP2C19 genotypes. The authors conclude that triple therapy with proton pump inhibitor, amoxicillin and clarithromycin is sufficiently effective in the cure of *Helicobacter pylori* infection regardless of CYP2C19 status. It is also noted that rabeprazole may be worth consideration for patients in which other treatment regimens have failed, but not necessarily as first-line therapy.

42. Buzas GM, Jozan J. Nitrofuran-based regimens for the eradication of *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2007 Oct; 22(10):1571-1581. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1746.2007.05082.x/epdf.

RATIONALE: A systematic review and meta-analysis of 51 studies and 4,946 patients, examining furazolidone- and nitrofurantoin-based regimens in the eradication of infection. There have been some studies with small numbers of patients examining the

effectiveness of furazolidone with amoxicillin (60% eradication) and furazolidone with levofloxacin (83% eradication) in patients on rescue treatment. The overall eradication rate of third-line rescue therapies was 65.5%, but side-effects of the regimens containing furazolidone were more frequent than in standard therapies. (p=0.02). The authors conclude that primary triple regimens containing furazolidone are slightly less efficient than the standard primary combinations, and that it is the duration of treatment, not the dose, that has the largest influence on the treatment outcome.

43. Song M, Ang TL. Second and third line treatment options for *Helicobacter pylori* eradication. *World J Gastroenterol*. 2014 Feb; 20(6):1517-1528. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3925860/.

RATIONALE: A review article discussing the factors contributing to treatment failure, and reviewing the second- and third-line treatment strategies that have been investigated. This article suggests that antibiotic susceptibility testing should be conducted in the event of two treatment failures, as the choices of empirical antibiotics become much more restricted. Suggested antibiotics for third-line treatment include: rifabutin; rifaximin; levofloxacin; sitafloxacin. Rifabutin has very high bactericidal activity against *H. pylori* strains, and resistance in *H. pylori* isolates is low (1.3 to 2.4%). Two studies (n=434) found that eradication rates were higher for patients when using rifabutin as "rescue" therapy, after amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin have failed to eradicate *H. pylori*. One study (n=482) has shown that rifaximin might have a role in patients who have failed two eradication therapies; however, it does have poor systemic absorption. In levofloxacin-based third-line treatment, 68.38% eradication has been recorded in one study (n=119), where a sequential regimen of PPI and amoxicillin was used for the first five days, then PPI, levofloxacin, and tetracycline was used for the remaining five days. Sitafloxacin has superior activity against *H. pylori* with gyrA mutations, and two studies have shown better eradication rates as third-line therapy, compared to levofloxacin-based treatment (75%; 78.2%, respectively). The authors conclude that, in the event of treatment failure, the clinician should always check for poor patient compliance due to adverse reactions to the medications, or patient difficulties complying with the therapy regimen. Due to high resistance rates, an effort should be made before starting therapy to confirm if the patient has had several courses of antibiotics for other infections in the past.

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Dr Alastair Miller, Consultant Physicians, Royal Liverpool and Broadgreen University Hospitals NHS Trust

Layla Mohammadi, Lead Pharmacist – Antimicrobials, Lewisham and Greenwich NHS Trust

Dr Busi Mooka, Infectious Diseases Consultant, NHS Tayside

Dr Rohinton Mulla, Lead Consultant Medical Microbiologist, Luton and Dunstable Hospital NHS Foundation Trust

Dr Aaron Nagar, Consultant Microbiologist, Belfast Health and Social Care Trust

Dr John O'Donohue, Consultant Physician and Gastroenterologist, Lewisham Healthcare NHS Trust

Dr Ewan Olson, Consultant Microbiologist, NHS Lothian

Dr Tamsin Oswald, Consultant Microbiologist, Northumbria Healthcare NHS Foundation Trust

Elizabeth Ozogolu, Senior Prescribing Advisor, City and Hackney Clinical Commissioning Group

Sarah Partridge, Antimicrobial Pharmacist, Nottingham University Hospitals NHS Trust

Dr Terry Riordan, Consultant Medical Microbiologist, Royal Devon and Exeter Healthcare NHS Trust

Dr Andrew Stacey, Consultant Microbiologist, Royal Berkshire NHS Foundation Trust

Hazel Steele, Specialist Pharmacist – Antimicrobials (Primary Care), NHS Tayside

Dr Rebecca Tilley, Consultant Microbiologist (Antibiotic Lead), West Suffolk NHS Foundation Trust

Jane Usher, Biomedical Head of Serology/Virology, Public Health England

Dr Chloe Walsh, Microbiology Registrar, Leeds Teaching Hospitals NHS Trust

Rob Wise, Medicines Management Pharmacist, NHS Bassetlaw Clinical Commissioning Group

Primary Care Clinicians from Concord Medical Centre, Bristol

Primary Care Clinicians from Hanham Health Centre, Bristol

Members of the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

Members of the British Infection Association (BIA)

Members of the British Society for Antimicrobial Chemotherapy (BSAC)

Members of the British Society of Gastroenterology (BSG)

Members of the Public Health England (PHE) Standards Unit

Members of the Royal College of General Practitioners (RCGP)

Members of the Royal College of Nursing (RCN)

Abbreviations

^{13}**C** = ^{13}Carbon

BD = Twice daily

CI = Confidence interval

CLAR = Clarithromycin

CYP2C19 = Cytochrome P450 2C19

DU = Duodenal ulcer

ECP = Enhanced compliance programme

ELISA = Enzyme-linked immunosorbent assay

g = Gram

GORD = Gastro-oesophageal reflux disease

GU = Gastric ulcer

gyrA = DNA gyrase subunit A

H$_2$A = Histamine H$_2$-receptor antagonist

HP = *Helicobacter pylori*

HTA = Health technology assessment

IgA = Immunoglobulin A

IgG = Immunoglobulin G

IgM = Immunoglobulin M

ITT = Intention to treat

LR+ = Positive likelihood ratio

LR- = Negative likelihood ratio

LRs = Likelihood ratios

MALToma = Mucosa-associated lymphoid tissue lymphoma

MIC = Minimum inhibitory concentration

mg = Milligram

MZ = Metronidazole

NPV = Negative predictive value

NSAID = Non-steroidal anti-inflammatory drug

pH = Potential of hydrogen

PPI = Proton pump inhibitor

QALYs = Quality adjusted life years

QDS = Four times daily

RR = Relative risk

SAT = Stool antigen test

UBT = Urea breath test

UHD = Ulcer healing drug