

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

Quick Reference Guide for Primary Care



For consultation and local adaptation



NICE cancer guidance advises that patients aged 55 years and older, with new unexplained & persistent (over 4-6 weeks) recent onset dyspepsia, should be referred urgently for endoscopy, to exclude cancer^{A 1,2}

WHEN TO TEST FOR HELICOBACTER^{A+ 2-5}

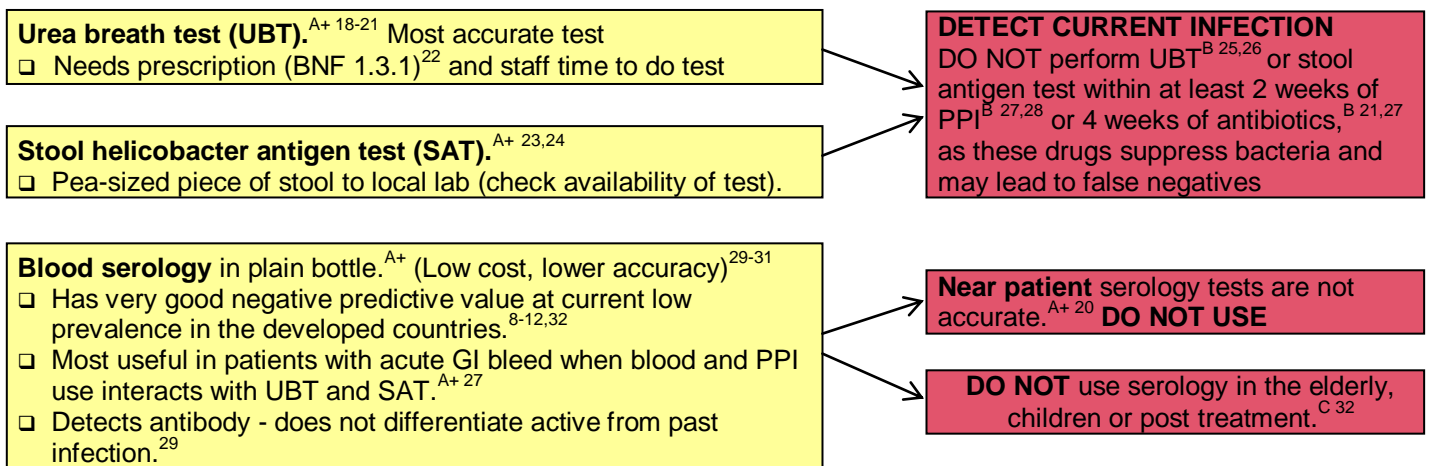
- ❑ Patients with uncomplicated dyspepsia unresponsive to lifestyle change, antacids, single course of PPI for 1 month^{2,3,6,7} and without alarm symptoms.^{A+1}
The prevalence of *H. pylori* in developed countries⁸⁻¹¹ is falling^{B+} and is lower than 15% in many areas in the UK;¹² therefore a trial of PPI should usually be prescribed before a *H. pylori* test unless chance of HP is higher than 20%^{13a} (i.e. ethnicity,^{9,10} older age, high risk area for HP) in which case the patient should have a test for HP first or in parallel with that of PPI.^D
- ❑ Patients with a past history of gastric ulcer or duodenal ulcer (DU) who have not previously been tested.^{A+ 13 b}
- ❑ Patients before starting or taking NSAIDs,^{A+ 14} especially if a prior history of gastro-duodenal ulcers.^{13c}
Both *H.pylori* and NSAIDs are independent risk factors for peptic ulcer, so eradication will not remove all risk.^{A 13c14}
- ❑ Unexplained iron-deficiency anaemia,^{A+} idiopathic thrombocytopenic purpura^A & vitamin B12 deficiency^{B 13d}

WHEN NOT TO TEST FOR HELICOBACTER^A

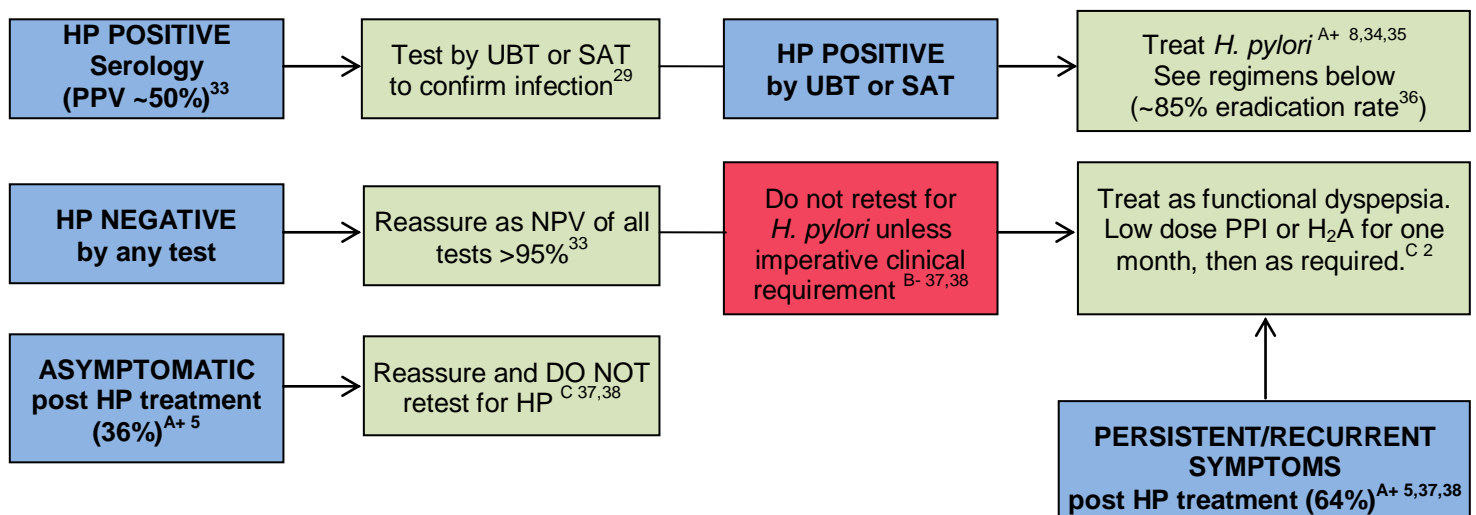
- ❑ Gastro-Oesophageal Reflux Disease^{A 2,13e}
- ❑ Children with functional dyspepsia.^{A+ 16,17}

WHICH NON-INVASIVE HELICOBACTER TEST IN UNCOMPLICATED DYSPEPSIA

UBT¹⁸ and stool antigen tests are the most accurate^{A+13f}



WHEN TO TREAT HELICOBACTER



TREATMENT REGIMENS¹³

- ❑ Check antibiotic history: Each course of clarithromycin, metronidazole or quinolone increases risk of resistance.^{B 12,39}
- ❑ Stress the importance of compliance to increase eradication rates.^{B+ 35,36 40}

First line 7 days twice daily^{A 36}

PPI e.g. lansoprazole 30mg,
PLUS two antibiotics:
amoxicillin 1g with
clarithromycin 500mg or
metronidazole 400mg
OR
clarithromycin 250mg
with metronidazole 400mg

Second line regimens^{A+} 14 days^{A- 36,41,42}

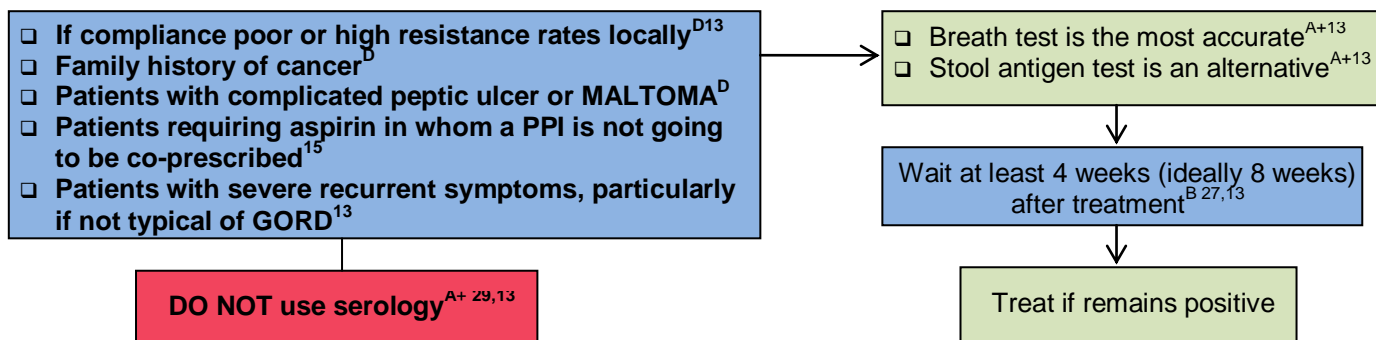
PPI BD PLUS
tripotassium dicitratobismuthate 240mg BD
PLUS 2 antibiotics:
tetracycline hydrochloride 500mg QDS or
metronidazole 400mg BD or } If not
clarithromycin^{A+ 42,43} 500mg BD } previously used
or amoxicillin 1g BD

Third line regimens on advice³⁶

14 days twice daily
PPI (consider rabeprazole in
Caucasians^B)^{44,45}
PLUS 2 antibiotics not previously used
Can consider using:
levofloxacin 250 mg BD^{A 46}
rifabutin 150mg BD^{B 42}
furazolidone 200mg BD^{B 47}

If diarrhoea develops, consider *Clostridium difficile* and review treatment need.

WHEN TO RETEST FOR HELICOBACTER



WHAT TO DO IN ERADICATION FAILURE^D

- ❑ Reassess need for eradication.
- ❑ In GORD, or NUD patients with no family history of cancer or PUD, maintenance PPI may be appropriate, after discussion with the patient.^D

WHEN TO REFER FOR HELICOBACTER CULTURE & SUSCEPTIBILITY TESTING AT ENDOSCOPY^{48,13}

- ❑ Patients in whom the choice of antibiotic is reduced due to hypersensitivity, local high resistance rates or previous use of both clarithromycin and metronidazole, and a quinolone.^{D13}
- ❑ Patients who have received two courses of antibiotic treatment and remain helicobacter positive.^{D13}
- ❑ For advice on gastric biopsy specimens and Dent's transport medium, contact HPA Centre for Infections, London.⁴⁹

Local adaptation:

- We would discourage major changes to the guidance but the Word format allows minor changes to suit local service delivery and sampling protocols.
- To create ownership agreement on the guidance locally, dissemination should be taken forward in close collaboration between primary care clinicians, laboratories and secondary care providers.

Grading of guidance recommendations

In the development of this guidance a full Medline search for recent articles since the last review in 2008 was undertaken, other searches were undertaken at the discretion of the experts and development team. The guidance has been reviewed by members of CKS, The BIA, BSAC, RCGP and The Department of Health Antimicrobial Resistance and Health Care Associated Infections Advisory Group.

Study design	Recommendation grade
Good recent systematic review of studies	A+
One or more rigorous studies, not combined	A-
One or more prospective studies	B+
One or more retrospective studies	B-
Formal combination of expert opinion	C
Informal opinion, other information	D

We welcome, in fact encourage, opinions on the advice given and future topics we should cover. We would be most appreciative if you could 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 Dr Clodna McNulty, Head, HPA Primary Care Unit, Microbiology Lab, Gloucestershire Royal Hospital, Great Western Rd, Gloucester GL1 3NN. clodna.mcnyulty@hpa.org.uk

References

1. NICE Clinical Guideline no. 27: Referral guidelines for suspected cancer. April 2011 <http://www.nice.org.uk/guidance/index.jsp?action=byID&r=true&o=10968> (Accessed 21st November 2011). *The NICE cancer guidance is based on all available evidence up to 2011 and indicates that a patient who presents with symptoms suggestive of upper gastrointestinal cancer should be referred to a team specialising in the management of upper gastrointestinal cancer. Helicobacter pylori status should not affect the decision to refer for suspected cancer.*
Refer urgently for endoscopy (currently within 2 weeks), patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone.
Refer urgently for endoscopy (currently within 2 weeks), or to a specialist, patients of any age with dyspepsia and any of the following: chronic gastrointestinal bleeding; dysphagia; progressive unintentional weight loss; persistent vomiting; iron deficiency anaemia; epigastric mass; suspicious barium meal result.
Refer urgently (currently within 2 weeks) patients presenting with: dysphagia; unexplained upper 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.
Consider urgent referral (currently within 2 weeks) for patients presenting with: 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 **AND:** -Barrett's oesophagus
(a) known dysplasia, atrophic gastritis or intestinal metaplasia
(b) peptic ulcer surgery over 20 years ago
2. NICE Clinical Guideline no. 17: Dyspepsia – management of dyspepsia in adults in primary care. Quick reference guide. August 2004 amended June 2005. <http://www.nice.org.uk/guidance/index.jsp?action=download&o=29458> (Accessed 4th November 2011).
Urgent referral: In June 2005 the NICE dyspepsia guidance was changed to be inline with the NICE cancer guidance and states: Routine endoscopic investigation of patients of any age, presenting with dyspepsia and without alarm signs, is not necessary. However, in patients aged 55 years and older with **unexplained** and **persistent** recent onset dyspepsia alone, an urgent referral for endoscopy should be made. **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 (if any). **Persistent** is defined as the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems.
Initial strategies: NICE dyspepsia guidance recommends that initial therapeutic strategies for dyspepsia are empirical treatment with a PPI or testing for and treating *H. pylori*. In 2005 there was insufficient evidence to guide which should be offered first. However, as the prevalence of *H. pylori* falls, the benefit of testing for *H. pylori* as a first line strategy falls in comparison to PPI.
Gastro-oesophageal reflux disease: NICE dyspepsia guidance recommends that un-investigated patients with reflux-like symptoms should be treated in a similar way to those with uninvestigated dyspepsia using full dose PPI for one or two months. As *H. pylori* is not usually associated with endoscopically-proven oesophagitis, *H. pylori* test and treat is not usually advised in these patients.
3. Ofman JJ, Rabeneck L. The effectiveness of endoscopy in the management of dyspepsia: a qualitative systematic review. *Am J Med* 1999;**106**:335-46. *This systematic review of 21 studies published between 1985 and 1998 found **NO** evidence that an initial course of empirical therapy with PPI rather than endoscopy adversely affects outcome. Decision analyses indicated that non-invasive *H. pylori* testing followed by anti-*H. pylori* therapy or empiric anti-secretory therapy is more cost-effective than initial endoscopy.*
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;**101**(6):1200-8. *This was a cluster-randomized trial in general practices in Denmark comparing: empirical antisecretory therapy (222 patients), test and for *H. pylori* (250), or a combination of the two (250) for management of dyspepsia. The prevalence of *H. pylori* infection was 24%. After 1 year gastrointestinal symptom scores and quality-of-life scores had improved significantly and equally in the three groups ($p < 0.001$), but no statistically significant differences were found among the groups. The mean use of endoscopies per patient after 1 year was higher in the PPI group (0.36 [95% CI 0.30-0.43]) than in the test-and-eradicate group (0.28 [95% CI 0.23-0.34]) and the combination group (0.22 [95% CI 0.17-0.27]), $p = 0.02$. *H. pylori*-positive patients given eradication therapy had more days without dyspeptic symptoms ($p < 0.001$), used less antisecretory therapy ($p < 0.01$), and were more satisfied ($p < 0.001$) than *H. pylori*-negative patients.*
5. Moayyedi P, Soo S, Deeks J, Forman D, Mason J, Innes M, Delaney B. Systematic review and economic evaluation of *Helicobacter pylori* eradication treatment for non-ulcer dyspepsia. *BMJ* 2000;**321**:649-64. *This is a systematic review of economic evaluation of *H. pylori* eradication in non-ulcer dyspepsia. The mean response rate to treatment in *H. pylori* positive NUD patients is 36% and the mean placebo response rate is 28%, thus 64% will have persistent or recurrent symptoms.*

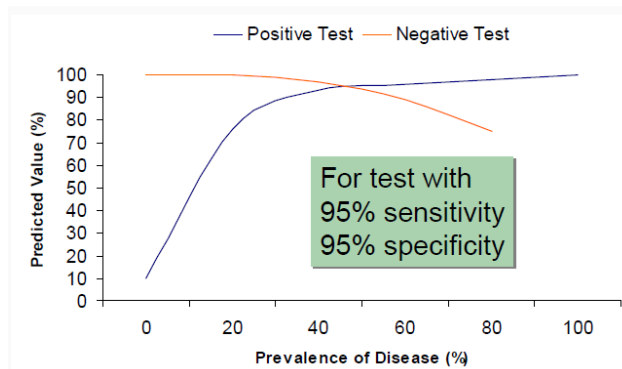
6. P Moayyedi. *Helicobacter pylori* test and treat strategy for young dyspeptic patients: new data. *Gut* 2002;**50**(Suppl IV):iv47–iv50. *In this review Moayyedi undertook a qualitative and semiquantitative review of the data in four randomised controlled trials comparing the H. pylori “test and treat” strategy with prompt endoscopy. Three trials measured dyspepsia symptom resolution and found the H. pylori test and treat strategy to be at least as effective as prompt endoscopy; quality of life was also similar in the two groups and, therefore, he concluded that management decisions should be based on costs. The decision analysis model indicates that the H. pylori test and treat strategy is the cheapest strategy, costing US\$134/patient/year compared with US\$240/patient/year for the prompt endoscopy strategy, using base case values. The H. pylori test and treat strategy is therefore the most cost-effective method for managing dyspepsia. The prompt endoscopy strategy only became cost-effective if endoscopy costs US\$160, the non-invasive test costs US\$80, and at a H. pylori prevalence of less than 20% (which in 2011 the latter is likely)*
7. Delaney BC, Qume M, Moayyedi P, Logan RFA, Ford AC, Elliott C, McNulty C, Wilson S, Hobbs FDR. *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;**336**:651-4. *This study of 699 patients aged 18-65 who presented to their general practitioner with epigastric pain, heartburn, or both without “alarm symptoms” for malignancy, compared H pylori urea breath test plus one week of eradication treatment if positive to proton pump inhibitor alone; at 12 months there were no significant differences between the two groups in QALYs, costs, 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. Thus test and treat and acid suppression are equally cost-effective in the initial management of dyspepsia when the prevalence of H. pylori infection is similar to this study at 29%. Empirical acid suppression is an appropriate initial strategy. As costs are similar overall, general practitioners should discuss with patients at which point to consider H. pylori testing. At a lower prevalence, as is now the case in most areas of the UK, expert opinion suggests that PPIs should be used before H. pylori test and treat unless chance of H. pylori infection is greater (older age, ethnicity, areas of high H. pylori).*
8. *Several seroprevalence studies have shown that H. pylori prevalence continues to fall in developed countries and now stands at between 6 and 15%: Germany 5.7% (Bauer); Belgium 15% (Miendje Deyi); Australia 15% (Moujaber). See references below.*
9. Bauer S, Krumbiegel P, Richter M, Richter T, Roder S, Rolle-Kampczyk U, Herbarth O Influence of sociodemographic factors on *Helicobacter pylori* prevalence variability among schoolchildren in Leipzig, Germany. A long-term follow-up study. *Central Eur J Pub Health*, 2011;**19**:1210-7778. *The overall H. pylori prevalence in this German study was 6.5% and had not significantly changed since 1998 and 2000 (6.1%, 5.7% respectively). Risk factors for carriage were foreign nationality of at least one parent, birth outside of Germany, low parental education and unemployment, and 2 or more older siblings.*
10. Miendje Deyi VY, Vanderpas J, Bontems P, Van den Borre C, De Koster E, Cadranel S, Burette A Marching cohort of *Helicobacter pylori* infection over two decades (1988-2007): combined effects of secular trend and population migration. *Epidemiology & Infection* 2011;**139**:572-80. *This study included 22,612 patients in whom a first culture of gastric biopsy (routinely performed in medical centres) yielded an interpretable result between 1988 and 2007 in Brussels. The lowest infection rate was observed in Western European patients (n=11,238) with respectively 36.2% and 15.2% infected subjects in 1988 and 2007, compared to 71.7% and 40% in North African patients (n=3200).*
11. 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;**12**:500-4. *This Australian study found a seroprevalence of 15.1% using H. pylori-specific ELISA for the presence of IgG antibodies in a representative sample of 2413 sera in 2002.*
12. McNulty C, Lasseter G, D’Arcy S, Lawson A, Shaw I, Glocker E. Is *Helicobacter pylori* antibiotic resistance surveillance needed and how can it be delivered? *Aliment Pharmacol Ther* 2012;**35**(10):1221-30. *In this 2009/10 study in three centres in England and Wales of Helicobacter pylori antibiotic resistance surveillance, biopsy specimens were taken from endoscopy patients in Gloucester, England and Bangor, Wales. Of 1153 biopsy specimens in Gloucester, 11% were positive for H. pylori on culture or biopsy urease test. Antibiotic resistance to amoxicillin, rifabutin and tetracycline remained very low. Each course of clarithromycin, metronidazole and levofloxacin was related to a 50% increase in resistance to that antibiotic. In the same centre, 19% (843/4461) were HP positive by serology.*
13. Malfertheiner P, Megraud F, O’Morain C A, Atherton J, Axon AT R, Bazzoli F, Franco Gensini G, Gisbert J P, Graham D Y, Rokkas T, El-Omar E M, Kuipers EJ, The European Helicobacter Study Group (EHSG). Management of Helicobacter pylori infections - the Maastricht IV/ Florence Consensus Report. *Gut* 2012;**61**:646e664. doi:10.1136/gutjnl-2012-302084
This consensus gives an excellent experts opinion of the most appropriate diagnostic tests and management of H.pylori. It particular the consensus report advises that
 - a. *test and treat for Helicobacter pylori in younger patients without alarm symptoms, should be used at a local H.pylori prevalence of over 20%.*
 - b. *H.pylori eradication is most beneficial in patients with gastro-duodenal ulcer disease.*
 - c. *Both H pylori infection and NSAID use are independent risk factors for the development of peptic ulcer disease and associated bleeding and these conditions are uncommon in those who do not have either risk factor. It has been shown that there is an increased risk when these factors are both present. In naive users it is clearly beneficial to eradicate H pylori. In those who are already long-term users there is no clear benefit. A meta-analysis showed,*

- however, that eradication seems less effective than treatment with a maintenance PPI for preventing NSAID-associated ulcers
- d. Clinicians should test for *H.pylori* in patients with unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura & vitamin B12 deficiency. The report references two separate meta-analyses in recent years that have supported this association 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 these patients. Similarly, for adults with ITP, Systematic reviews of past literature have shown an overall platelet response in more than 50% of the patients successfully treated for the infection and increased response rates in countries with a high prevalence of *H pylori* infection in background populations
 - e. This group examined the evidence and concluded that there is a negative association between the prevalence of *H. pylori* and GORD, Similarly, the sequelae of GORD, such as Barrett's oesophagus and oesophageal adenocarcinoma, are also less common in infected individuals. However, eradication of *H pylori* in populations of infected patients, on average, neither causes nor exacerbates 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 a corpus-predominant gastritis. This accelerates the process of loss of specialised glands, leading to atrophic gastritis.^A Eradication of *H pylori* in patients receiving long-term PPIs heals gastritis and prevents the progression to atrophic gastritis. However, there is no evidence that this reduces the risk of gastric cancer.^A
 - f. Urea breath Tests and stool antigen tests are the most accurate tests and should be used in preference to serology unless the latter has been locally validated.
14. Ford AC, Delaney B, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients. Cochrane Database of Systematic Reviews 2006, Issue 2.
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003840.pub4/pdf> (Accessed 20th December 2011). In this Cochrane review there were 34 trials examining duodenal ulcer healing in 3910 patients.
 - *H. pylori* eradication therapy was superior to ulcer healing drugs (UHD) (relative risk (RR) of ulcer persisting = 0.66, 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 UHD (15 trials, 1974 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 UHD (four trials, 319 patients, RR of ulcer recurring 0.73; 95% CI 0.42 to 1.25), but eradication therapy was superior to no treatment (27 trials 2509 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, 1476 patients, RR 0.31, 95% CI 0.22 to 0.45). Thus test and treat for *H. pylori* is advised in patients with a past history of peptic ulcer.
 15. Venerito M, Malfertheiner P. Interaction of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in gastric and duodenal ulcers. *Helicobacter* 2010;**15**:239-250. These authors reviewed studies of peptic ulcer prevention in NSAID use. Three studies examined the value of eradication of *H.pylori* in patients with no history of peptic ulceration in prevention of DU and GU. Eradication of HP before starting NSAIDs reduced the risk of NSAID induced GU and greatly reduced the risk of DU. Thus test and treat in these patients, especially if they are at greater risk of *H. pylori* (older, ethnicity), should be encouraged.
 16. Spee L A, Madderom MB, Pijpers M, van Leeuwen Y, Berger MY. Association between *Helicobacter pylori* and Gastrointestinal Symptoms in Children. *Pediatrics* 2010;**125**:e651-69.
<http://pediatrics.aappublications.org/content/125/3/e651.full.html> (Accessed 30th November 2011). Spee et al systematically reviewed the published evidence for an association between *H pylori* infection and GI symptoms in children searching Medline and Embase databases up to July 2009 to identify studies that evaluated the association between *H. pylori* and GI symptoms in children aged up to 18 years. They did not find any association between recurrent abdominal pain (RAP) and *H. pylori* infection in children. (Pooled ORs for the association between RAP and *H pylori* infection in children were 1.21 (95% CI: 0.82–1.78) in 12 case-control studies and 1.00 (95% CI: 0.76–1.31) in 7 cross-sectional studies. They found an association between unspecified abdominal pain (UAP) and *H. pylori* in hospitalised patients but NOT in primary care. Meta-analysis of the association between UAP and *H. pylori* infection in 6 hospital-based studies resulted in a pooled OR of 2.87 (95% CI: 1.62–5.09) but was not significant in 5 community-based studies OR 0.99 (95% CI:0.46–2.11).
 17. Sykora J & Rowland M. *Helicobacter pylori* in paediatrics. *Helicobacter* 2011;**16(Suppl 1)**:59-64. This 2011 review of the literature suggests that upper gastrointestinal endoscopy is not appropriate for children with dyspeptic symptoms but should be reserved for children with a family history of peptic ulcer and/or *H. pylori* infection, and children older than 10 years of age with symptoms persisting for more than six months and severe enough to affect activities of daily living.
 18. **The urea breath test** is considered the gold standard non-invasive test - see references below.
 19. Nocon M, Kuhlmann A, Leodolter A, Roll S, Vauth C, Willich SN et al. Efficacy and cost-effectiveness of the 13C-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 Technology Assessment* 2009;**5**:1861-8863. This systematic review examined 30 studies with 3,415 patients in total that directly compared the ¹³C-UBT and other non-invasive tests to biopsy-based tests as the gold standard. The ¹³C- UBT showed higher sensitivity and specificity than the IgG serology in 18 studies and stool antigen tests in 13 studies. (A 100% sensitive test correctly identifies all patients with helicobacter.

A 100% specific (spec) test correctly identifies all patients without helicobacter.) Sensitivity and specificity higher than 90% are found in 84% of the studies for the 13C-urea breath test. Sensitivity and specificity higher than 90% were found in 62% of the studies for the stool antigen test, for the IgG test in 56% (sensitivity) and 44% (specificity) of the studies. Nine health economic evaluations were included in this 2009 Health Technology Assessment (HTA) report. Test-and-treat using the C¹³ UBT was more cost-effective than the serology based strategy in three of six models and was dominated by a test-and-treat strategy using the stool antigen test in one of three models.

20. Vaira D, Vakil N. Blood, urine, stool, breath, money, and *Helicobacter pylori*. *GUT* 2001;**48**:287-9. Data from 8 studies showed urea breath test had much higher accuracy (95% specificity and sensitivity) than near patient serology tests which had overall sensitivity 71.1% and specificity 87.6%.
21. 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;**28**(11-12):1304-8. This study followed 419 patients with documented *Helicobacter pylori* infection who received eradication therapy and then had two breath tests, one 4 weeks and the second at least 8 weeks after the completion of treatment. Following treatment, the results at 1 month were similar to the value obtained at the second breath at 2 months and there were no discordant results.
22. British National Formulary No. 62 <http://bnf.org/bnf/bnf/62/73281.htm?q=Breath%20Test&t=search&ss=text&p=2> (Accessed 4th November 2011) It requires some staff time to supervise the test. A breath test is obtained before a radio-labelled urea tablet containing at least 75mg urea (obtained on prescription within the UK) is taken by the patient with citric acid or an orange drink to delay gastric emptying. A further breath test is taken 20-30 minutes after the urea tablet. Breath samples are then sent to a central laboratory. Full instructions on kit obtained when prescription cashed in.
23. **Stool antigen tests** detect antigens of *H. pylori* in stools using monoclonal antibodies and, therefore, are dependent on organisms being excreted in the faeces. They are not quite as accurate as the breath test but are almost as good and do not require practice staff time. Some laboratories do **NOT** provide this test as it is more expensive than serology. See evidence for test below.
24. Gisbert JP, de la Morena F, Abaira V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: A systematic review and meta-analysis. *Am J Gastroenterol* 2006;**101**:1921-30. Systematic review of 22 studies including 2,499 patients pre treatment showed HP monoclonal stool antigen tests had sensitivity 94% (95% CI 93–95%), and specificity 97% (CI 96–98) and LR+, and LR– were: 24 (15–41), and 0.07 (0.04–0.12). Monoclonal tests were more sensitive than the polyclonal tests (pooled sensitivity monoclonal technique 95% vs 83% with polyclonal tests). **Post treatment** the monoclonal stool antigen tests were evaluated in 957 patients with a sensitivity 93% (95% CI 89–96%), and specificity 96% (94%–97%), respectively. Pooled positive and negative LRs were, respectively, 17 (12–23; nonheterogeneous results) and 0.1 (0.07–0.15; nonheterogeneous results).
25. Mana F, Van Laer W, Bossuyt A, Urbain D. The early effect of proton pump inhibitor therapy on the accuracy of the 13C-urea breath test. *Dig Liver Dis* 2005;**37**(1):28-32. This study showed that the intake of proton pump inhibitors impairs the accuracy of the 13C-urea breath test. A 13C-urea breath test was performed before starting proton pump inhibitors therapy and every morning before the once-daily PPI dose for 10 days in 30 patients and 53 volunteers. 43% of the *H. pylori* positive patients developed false negative breath tests in the first 10 days. False positive results occurred in 37.5% of *H. pylori*-negative subjects in the first 10 days. False negative and false positive 13C-urea breath tests are common, occur as soon as after 1 day and increase with prolonged duration of treatment. The coefficient of reproducibility of the test in patients receiving proton pump inhibitors is not acceptable for clinical purpose and the test should **NOT** be performed once the medication has been started.
26. Graham DY, Opekum AR, Hammoud F, et al. Studies regarding the mechanism of false negative urea breath test with proton pump inhibitors. *Am J Gastroenterol* 2003;**98**:1005–9. The authors suggest that three days is likely to be the minimum delay from stopping PPI until one should perform a test for active infection, but a delay of 14 days is preferred. Thirty *H. pylori*-infected volunteers received omeprazole 20 mg b.i.d. for 13.5 days. UBTs with citric acid were done before, after 6.5 days of PPI, and 1, 2, 4, 7, and 14 days after therapy. Thirty subjects (mean age 42 yr) were enrolled. Positive UBTs were significantly reduced on day 6. (5 and 10 subjects (33%) 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. PPI-induced negative UBT results were related to the anti-*H. pylori* effect of the PPI as *H. pylori* density decreased with PPI therapy.
27. Gisbert JP, Pajares JM. Stool antigen test for the diagnosis of *Helicobacter pylori* infection: a systematic review. *Helicobacter* 2004;**9**:347–368. This systematic review evaluated all the stool antigen test studies up to 2004. **Studies, post antibiotic treatment**, indicate that tests are more accurate at 4 weeks than 2 weeks and 8 weeks rather than 4 weeks. **Proton-pump inhibitors** affected the accuracy of the stool antigen test. When PPIs are started in *H. pylori* positive patients, SATs and UBT test values fall and become negative at one week in about 30% of patients, and revert to positive 2 weeks after treatment. **Gastro-intestinal bleeding**: Sensitivity and/or specificity of SATs in patients with gastrointestinal bleeding were suboptimal. Studies of patients with upper GIT bleeding have produced very variable results. Negative UBTs in patients with upper GIT bleeding are probably due to the interaction of blood or its products with urea or HP urease in the stomach. Blood in the stool may also lead to false negatives.

28. El-Nujumi A, Halditch TE, Williams C, McColl KE. Current or recent proton pump inhibitor therapy markedly impairs the accuracy of the ¹⁴C urea breath test. *Eur J Gastroenterol Hepatol* 1998;**10**:759-64. *In this Scottish study in 20 H. pylori positive patients, suppression of results increased between 2 and 4 weeks and with higher dose of PPI. Most tests were positive 2 weeks after stopping PPI but about 20% still remained positive at this time.*
29. **Expert opinion about use of serology tests:** *As the prevalence of an infection falls, the positive predictive value of these tests falls and the negative predictive value increases (see reference 33). Using the specificity of 83% found in Laheij systematic review and the H. pylori prevalence of 10%, 62.5% of patients with a positive test are false positives. In contrast, at a prevalence of 10% the false negatives are very low at only 1% of tests. Thus we suggest that all patients with a positive serology test in a low prevalence population (15% or lower) go on to have a confirmatory urea breath test or stool antigen test to confirm if the patient has CURRENT infection, ensuring that the patient has been off PPIs for at least two weeks.*
30. 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;**91**:1138-44. *Meta-analysis of 21 laboratory based serology kits (studies published before 1995) – sensitivity 85% specificity 79%. There was no significant difference in the accuracy of different kits. This sensitivity and specificity is low for a diagnostic test.*
31. Laheij RJ, Straatman H, Jansen JB, Verbeek AL. Evaluation of commercially available *Helicobacter pylori* serology kits: a review. *J Clin Microbiol* 1998;**36**:2803-9. *A comparison of 36 laboratory based serology kits (up to 1997) in 26,812 patients – median sensitivity 92% (25 and 75% quartiles 85 and 96%) and specificity 83% (25 and 75% quartiles 73 and 92%). Kits that measured IgG alone were more accurate than those using IgA or a combination of IgM, IgG and IgA.*
32. 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;**169**:15-25. *This review concluded that SATs and UBTs have adequate sensitivity and specificity for detection of H. pylori in children but endoscopy is the gold standard.*
33. Mausner JS, Kramer S. Mausner and Bahn Epidemiology: an Introductory Text. Philadelphia, WB Saunders 1985 p221. *When considering predictive values of diagnostic or screening tests, recognize the influence of the prevalence of disease. The figure below 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. Conversely, lower prevalence results in increased negative predictive value. Thus the positive predictive value is low in the majority of the population in the UK and, therefore, a positive serology should be confirmed with another test: BUT or SAT.

34. **Triple treatment** with a PPI plus amoxicillin plus clarithromycin or metronidazole remains the first line treatment for *H. pylori* currently in the UK.
35. **Compliance:** *The importance of excellent compliance should be stressed with patients. Compliance issues are covered in reference 36 O'Connor 2010 treatment of H. pylori. Current treatment regimens are complex and, therefore, compliance is a problem and poor compliance lowers eradication and increases acquisition of resistance. Studies have shown that 10% of patients only take 60% of the medication. Compliance increased in studies where its importance was stressed.*
36. O'Connor A, Gisbert JP, McNamara D, O'Morain C. Treatment of *Helicobacter pylori* infection 2010. *Helicobacter* 2010;**15**(Supp1):46-52. *This review gives an annual update of all the trials published on the treatment of H. pylori. Eradication rates have been falling over the past 10 years and, in Southern European countries, is below 80%. Resistance to clarithromycin is the single most important factor in treatment failures. Resistance to clarithromycin remains low in most Northern European countries and in EU populations with low ethnicity. This review discusses individualisation of eradication treatment to maximise efficacy. This includes:*
- Assessing previous antibiotic treatment for any other infection – previous metronidazole, clarithromycin and quinolone use are all associated with increased resistance and, therefore, lower eradication with these agents.*
 - Reviewing national resistance rates - resistance to amoxicillin, rifabutin and tetracycline remain below 3% in most EU countries, including the UK (see ref 17).*

- (c) *Ethnicity – resistance in immigrants from countries with high clarithromycin, metronidazole and quinolone use is associated with greater resistance.*
- (d) *Compliance as discussed above.*
- (e) *PPI choice – most PPIs are metabolised in the liver. Some 18-27% of Europeans compared to only 1-3% of Asians are rapid metabolisers of PPIs. Rabeprazole is not metabolised in the liver and, therefore, may be a good choice in Caucasians with treatment relapse.*
37. *NICE dyspepsia guidance does not recommend retesting for H. pylori after treatment;^C this is based on economic modelling.*
38. Gene E, Calvet X, Azagra R. Diagnosis of *Helicobacter pylori* after triple therapy in uncomplicated duodenal ulcer: a cost-effective analysis. *Aliment Pharmacol Ther* 2000;**14**:433-42. *A decision tree was devised to compare different follow-up strategies post treatment in patients with uncomplicated DU. Testing for eradication (using UBT) after H. pylori treatment markedly increased cost with no clear improvement in results. This remained true for a wide range of eradication between 70 & 95%; specificity of UBT 70-90% and cost of the UBT. This scenario is likely to be even more cost-effective in NUD when less relapse will be due to H. pylori.*
39. Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut*. 2012 May 12. 10.1136/gutjnl-2012-302254 [Epub ahead of print]. *In this EU surveillance study resistance to clarithromycin in a country was related to clarithromycin use.*
40. Graham DY, Lew GM, Malaty HM et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. *Gastroenterol* 1992;**102**:493-6. *In this early study, when resistance rates were low, eradication of 96% was attained with compliance above 60% and 69% with compliance below 60%.*
41. Malferteiner P, Bazzoli F, Delchier J-C, Colinski 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;**377**:05-13. *In this study 339 patients across UK, Germany, Italy, France, Ireland, Poland, and Spain were allocated to either 10 days 20mg omeprazole BD plus 3 capsules containing 140mg Bismuth, 125mg metronidazole and 125 mg tetracycline hydrochloride four times per day after meals, or 7 days omeprazole 20mg BD, plus 500mg amoxicillin and 500mg clarithromycin. Eradication was successful in 92% on quadruple and 69% triple on intention to treat criteria. In clarithromycin resistance eradication was reduced to only 8% in triple therapy but it did not influence quadruple treatment. Quadruple treatment is effective as second line treatment, and should be considered if there is a past history of clarithromycin use.*
42. O'Connor A, Gisbert JP, McNamara, O'Morain C. Treatment of *Helicobacter pylori* infection 2011. *Helicobacter* 2011;**16(Suppl1)**:53-58. *This review gives an annual update of all the trials published on the treatment of H. pylori. In 2011 there were several studies describing the successful use of levofloxacin as first line treatment with amoxicillin or clarithromycin with a proton pump inhibitor, with 85% eradication. In 2010 there were four studies using rifabutin 150mg twice daily with amoxicillin 1g BD with 79-85% eradication in patients who had failed other treatment regimens. **Using clarithromycin in bismuth-based quadruple therapy:** This review also describes a study by Sun et al of a 14 day quadruple bismuth-based treatment using omeprazole, clarithromycin and amoxicillin, which attained 94% eradication.*
43. Sun Q, Liang X, Zheng Q et al. High efficacy of 14-day triple therapy-based bismuth-containing quadruple therapy for initial *Helicobacter pylori* eradication. *Helicobacter* 2010;**15**:233-238.
44. Sharara-Ala-I. Rabeprazole: the role of proton pump inhibitors in *Helicobacter pylori* eradication. *Expert Rev Ant Infect Ther* 2005;**3**:863-70. *Unlike other proton pump inhibitors, the metabolism of rabeprazole is primarily via a nonenzymatic reduction to the thioether derivative, and the cytochrome P450 isoenzyme 2C19 is only partly involved in its metabolism. The effect of genetic polymorphism in cytochrome P450 isoenzyme 2C19 on the pharmacokinetics and pharmacodynamics of rabeprazole is therefore limited. Caucasians are more likely to be fast metabolisers of PPIs and therefore in these patients who have failed treatment rabeprazole may be worth considering.*
45. 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;**33**:671-5. *To investigate whether genetic polymorphism of CYP2C19 and selected proton pump inhibitors (omeprazole or rabeprazole) were associated with cure rate for H. pylori infection using triple therapy with omeprazole or rabeprazole, amoxicillin, and clarithromycin. METHODS: A total of 170 Helicobacter pylori-positive patients with chronic gastritis were randomized to receive omeprazole or rabeprazole regimens. Cure rate were not significantly different between the CYP2C19 genotypes in both regimens. Rabeprazole may be worth considering in patients in which other regimens have failed, but not necessarily as first-line therapy.*
46. Gisbert JP, De La Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther* 2006;**23**:35–44. *This meta-analysis showed a mean eradication rate of 80% with levofloxacin 250mg BD containing regimens. 10 days were better than 7 days treatment.*

Side-effects were lower than with bismuth treatment; **however do not use this regimen if previous quinolone use as resistance develops quite easily (see refs 12 and 39).**

47. Buzas GM, Jozan J. Nitrofurantoin-based regimens for the eradication of *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2007;**22**:1571-81. *Furazolidone is a synthetic nitrofurantoin derivative but it is difficult to source in Europe. There have been some studies with small numbers of patients examining the effectiveness of furazolidone with amoxicillin (60% eradication) and levofloxacin (83% eradication) in patients on rescue treatment. This systematic review of 51 studies and 4,946 patients showed an overall eradication of 65%.*
48. **When to refer for culture and susceptibility:** *Expert opinion is that, as resistance is increasing, patients who have failed two courses of treatment should ideally be referred for endoscopy for culture and susceptibility testing, especially if they are allergic to amoxicillin, tetracycline or rifabutin, which have very low resistance rates. Patients should not receive PPI or antibiotics within at least four, and ideally eight, weeks of endoscopy.*
49. For advice contact the Diagnostic and Specialist Identification Unit, Gastrointestinal, Emerging and Zoonotic Infections, Health Protection Agency Centre for Infections, 61 Colindale Avenue, Colindale, London NW9 5EQ Tel: 020 8200 4400.