The article explores how to test for *Helicobacter pylori* infection and when to check whether treatment has worked

A 32 year old nurse presents with intermittent discomfort in her upper abdomen for more than five months, particularly when fasting. She denies any weight loss, recurrent vomiting, dysphaiga, fever, or a change in bowel habits. There is no evidence of gastrointestinal bleeding. She takes no medications, including over the counter non-steroidal anti-inflammatory drugs. She does not smoke and drinks about 4 units of alcohol a week. Abdominal examination shows mild epigastric tenderness.

**What is the next investigation?**

Dyspepsia in patients younger than 55 years presenting without alarm symptoms does not require endoscopic investigation. Empirical treatment with a proton pump inhibitor or the “test and treat” strategy for *Helicobacter pylori* infection are recommended management strategies in this setting and are equally cost effective in relation to symptom control. *H pylori* infection is usually acquired during childhood, and the prevalence is high (70-90%) in Asia, Africa, South America, and eastern Europe and low in western Europe and North America (30%). Testing for the infection is recommended if the treatment is indicated to improve the clinical condition or outcome (table 1).

**Non-invasive tests**

Non-invasive tests include the $^{13}$C urea breath test and the $^{14}$C urea breath test, stool antigen tests, and antibody tests in serum, blood, urine, and saliva.

**Urea breath tests**

A urea breath test is the most accurate non-invasive test (table 2). The $^{13}$C test is preferable to the radioactive ($^{14}$C) test as it avoids any exposure to radiation. After the patient has drunk a citric acid solution containing $^{13}$C urea, the bacterial urease will hydrolyse the labelled urea to $^{13}$C carbon dioxide and ammonium. The increase in $^{13}$C labelled carbon dioxide in breath samples (taken before and 15-30 minutes after drinking the test solution) reflects the bacterial urease activity present on the gastric mucosa, and the intensity of the $^{13}$C signal in breath correlates with the density of the bacterial colonisation. The test should be done under fasting conditions, to optimise the contact of the test solution with the gastric mucosa. The $^{13}$C urea breath test is widely available in primary care as breath samples are easy to collect and can be sent by mail for analysis (if not directly measured using non-dispersive, isotope selective, infrared analysers that are simple to operate).

**Stool antigen test**

Testing for *H pylori* antigen in a random stool sample using an immunoassay is also suitable for primary diagnosis (table 2). In a meta-analysis, monoclonal stool antigen tests proved superior to polyclonal tests. Stool samples need refrigeration when stored before analysis. A new, rapid, office based, one step monoclonal immunoassay for detection of *H pylori* antigen in stool has shown promising results in pretreatment and post-treatment settings and provides results within 10 minutes. Further data and cost effectiveness analysis are needed before the one step test can be recommended for use in primary care. Disadvantages of faecal antigen tests include the aversion of patients and doctors to stool samples and the difficult logistics and the precautions needed in handling, storing, and disposing of faecal samples.

**Serological testing**

Serological testing is the cheapest and most widely available method of testing. However, avoid using it for primary diagnosis when the more accurate breath or stool tests are available because it indicates only previous exposure, not current *H pylori* infection. Generally, serological testing has a high negative predictive value, but its positive predictive value depends on the pretest probability of *H pylori* infection, which in turn depends on the patient’s age, the prevalence of infection in his or her country of origin, and his or her
socioeconomic status. Office based blood tests or antibody detection in urine or saliva are even less accurate and should not have a role in patient management.

Biopsy based tests
Refer for endoscopy any patients with new onset dyspepsia who are older than 55 years and patients of any age with alarm symptoms such as weight loss, dysphagia, persistent vomiting, iron deficient anaemia, or signs of gastrointestinal bleeding.

Rapid urease test
If an endoscopy is indicated, the rapid urease test from antral biopsies is the test of first choice as it provides a reliable and cheap method for identifying *H pylori* infection. The biopsy specimen is placed into a solution or gel containing urea and a pH indicator. If *H pylori* is present, the urease will convert the urea to ammonia, leading to an increase in the pH and a colour change on the pH indicator. A recent large study comprising 1000 patients reported excellent (>90%) sensitivity and specificity for a new generation, ultrafast rapid urease test, which allows reading after only one minute.18

Histology
Histology is more expensive but is also slightly more sensitive and specific than the rapid urease test and gives additional information on the type of gastritis, atrophy, intestinal metaplasia, and malignancy. If proton pump inhibitors have been taken, biopsies from the gastric body can improve the diagnostic yield. The organisms can be identified on conventional histological stains, such as Giemsa or haematoxylin and eosin; immunostaining increases sensitivity and specificity further, but its extra costs might be justified only in cases of assumed low colonisation density; it is not necessary for routine diagnostics.

Culture
Culturing of the organism from gastric biopsies is an insensitive but highly specific method, which is available only in specialised microbiology centres.15 Gastric biopsies for antimicrobial susceptibility testing are recommended when treatment has failed repeatedly.

Limiting factors
When the patient has acute bleeding or is taking proton pump inhibitors, *H* antagonists, or antibiotics, most diagnostic tests for *H pylori* infection (such as histology, the rapid urease test, the urea breath test, and the stool antigen test) can yield false negative results, as shown in systematic reviews and several studies.19–21 Proton pump inhibitors should therefore be stopped two weeks before, and antibiotics four weeks before, testing for *H pylori* infection.

The pH buffering effect of blood in the gastric lumen might impair the tests. In cases of upper gastrointestinal bleeding or in low colonisation density of *H pylori* (as in MALT lymphoma (mucosa associated lymphoid tissue lymphoma) and extensive mucosal atrophy) serological testing can be helpful as it indicates previous exposure to *H pylori*, although it does not confirm current infection. This diagnostic strategy is recommended by a consensus of the European Helicobacter Study Group. Alternatively, if tests were negative at the time of gastroduodenal haemorrhage, non-invasive tests conducted four to eight weeks after the bleeding event20 21 will avoid missing an *H pylori* infection.19

Therapy control (testing whether the treatment has worked)
Treatment for *H pylori* fails in about 20% of cases. Therefore, testing for eradication after treatment is advised in patients at risk of treatment failure but not generally in other patients. Do eradication testing, therefore, in those with an associated ulcer or MALT lymphoma; after resection of early gastric cancer; or in those with persistent dyspeptic symptoms. These recommendations are based largely on expert consensus agreement.4

For testing whether the treatment has worked, the non-invasive 13C urea breath test or the stool antigen test is recommended, unless repeat endoscopy is needed. Serological testing is unhelpful after treatment, as antibodies persist for months or even years. The urea breath test is simple to perform and also suitable in children. The current European consensus, based on recent comparative studies, regards it as more accurate than the faecal antigen test as a test for therapy control.4

Table 2  Common tests for diagnosis of *Helicobacter pylori* infection

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Indication</th>
<th>Comments</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea breath test*</td>
<td>Primary diagnosis, eradication control</td>
<td>Very accurate non-invasive test; practical, readily available</td>
<td>95</td>
<td>98</td>
<td>Leodolter et al7</td>
</tr>
<tr>
<td>Stool antigen*:</td>
<td>Primary diagnosis, eradication control</td>
<td>Rapidly available; requires refrigeration of samples</td>
<td>94</td>
<td>97</td>
<td>Gisbert et al11</td>
</tr>
<tr>
<td>Polyclonal</td>
<td>Primary diagnosis, eradication control</td>
<td>Readily available; requires refrigeration of samples</td>
<td>91</td>
<td>93</td>
<td>Gisbert et al11</td>
</tr>
<tr>
<td>Serological testing</td>
<td>Not after treatment</td>
<td>Widely available; inexpensive, good negative predictive values</td>
<td>85</td>
<td>79</td>
<td>Loy et al17</td>
</tr>
<tr>
<td>Office based blood test</td>
<td>Not advised</td>
<td>Low accuracy</td>
<td>71</td>
<td>88</td>
<td>Vaira et al19</td>
</tr>
<tr>
<td>Biopsy based diagnostic tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Histology</em></td>
<td>Additional information on gastritis, atrophy, dysplasia</td>
<td>Expensive; requires trained staff</td>
<td>93</td>
<td>99</td>
<td>Cutler et al16</td>
</tr>
<tr>
<td>Rapid urease test*</td>
<td>Primary diagnosis if endoscopy required</td>
<td>Inexpensive; rapid</td>
<td>90</td>
<td>95</td>
<td>Vaira et al19</td>
</tr>
<tr>
<td>Culture*</td>
<td>Antibiotic susceptibility testing</td>
<td>Excellent specificity, expensive; limited availability, slow growth</td>
<td>73</td>
<td>100</td>
<td>Grove et al15</td>
</tr>
</tbody>
</table>

*Proton pump inhibitors should be stopped two weeks, and antibiotics four weeks, before diagnostic tests are conducted.
Treatment failure usually results from non-compliance or antibiotic resistance, which varies with the country of origin of the patient and previous antibiotic treatment for other conditions. If treatment with the locally recommended second line rescue regimen fails repeatedly, referral for endoscopy is recommended so that biopsies can be obtained for susceptibility testing and culture guided treatment.

It is still not known whether molecular based methods using polymerase chain reaction in material from biopsies, stool, saliva, or string tests (in which a thread is swallowed, with one end kept outside the mouth, and pulled out again)\(^3\) or the direct visualisation of the organism on the gastric mucosa using endoscopy\(^4\) will ever have a role in diagnosing *H pylori* infection in clinical practice.

Outcome

On the basis of her positive \(^1^4\)C urea breath test result, the patient received treatment for *H pylori* infection (omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily for 10 days).\(^3\) Although her dyspepsia temporarily improved after treatment, the symptoms recurred three months later. A repeated \(^1^4\)C urea breath test indicated persistent *H pylori* infection. Second line treatment\(^2\)\(^5\) with omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and levofloxacin 500 mg twice daily for 10 days resulted in lasting symptom relief.

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Patient consent not required (patient anonymised, dead, or hypothetical).


Only a tonic

My surgical house job at a county hospital in Eire was coming to an end, and I was desperate to get an obstetric job next. I discovered there was going to be a senior house officer post at a nearby maternity hospital. So I asked the matron of my present hospital (a very kind and generous person) to telephone the maternity hospital and put in a good word for me.

On the telephone call, the only inquiry about me from the other side was, “Does he drink?” (I have to confess I loved the Irish beer.)

My matron immediately responded, “Good Lord, no he doesn’t.” I got the job.

At the maternity hospital, lunch was served for us two residents in the Doctors’ Parlour. On my first day I nearly fell off my chair when I saw a bottle of Guinness on the tray. I gasped and stammered, pointing towards the bottle: “But, but what….” Before I could finish the sentence, the maid retorted, “It is only a tonic.”

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Does taking probiotics routinely with antibiotics prevent antibiotic associated diarrhoea?

Christopher C Butler, Donna Duncan, Kerenza Hood

Diarrhoea develops in association with antibiotic treatment in 1% to 44% of cases, and ranges from mild episodes that resolve when antibiotics are stopped to serious complications such as toxic megacolon, bowel perforation, and death. Risk is increased with extremes of age, co-morbidity, oral broad spectrum antibiotics (particularly clindamycin, β-lactams, and third generation cephalosporins), prolonged antibiotic duration, previous antibiotic associated diarrhoea, and hospitalisation. Probiotics—live microorganisms that, when administered in adequate amounts, confer a health benefit on the host—are present in products available in shops as foodstuffs, and in formulations used for specific therapeutic purposes. Probiotics are thought to combat antibiotic associated diarrhoea through restoring resistance to colonisation by pathogenic bacteria after the normal colonic microflora have been damaged by antibiotics, by breaking down non-absorbable compounds into absorbable products, by interfering with pathogenic toxins, and by enhancing immunity. Effects of probiotics vary by strain owing to differing resistance to gastric acid and bile, ability to colonise mucosa, and susceptibility to antibiotics.

Probiotics carry theoretical risks, including infection beyond the gut and transfer of antibiotic resistant genes. However, so far, there have been no reports of bacteraemia or fungaemia attributable to the probiotics in trials included in published systematic reviews.

Lactobacillus bacteraemia is rare and has a low mortality rate. Cancer, diabetes, broad spectrum antibiotic therapy, organ transplantation, and abscess may be risk factors for lactobacillus bacteraemia. Twelve cases of lactobacillus bacteraemia have been reported in patients taking a probiotic and 24 cases of fungaemia associated with the probiotic Saccharomyces boulardii. However, many lactobacillus strains are human commensals and a review identified only five well documented published cases where the consumed probiotic strain was the same as a clinical isolate. Mild to moderate gastrointestinal side effects and rash are generally no more common than in patients on placebo probiotic.

Probiotics may therefore be an attractive option for preventing antibiotic associated diarrhoea because they are cheap (the cost of preventing one case in selected hospital patients may be as low as £50; £60, $79) and safe.

Is ongoing research likely to provide relevant evidence? We searched the Current Controlled Trials database (www.controlled-trials.com) for ongoing randomised controlled trials using the previously described search terms. Six placebo controlled trials are in progress examining the effect of probiotics in preventing antibiotic associated diarrhoea in hospitalised patients. Three (ISRCTN57305201, ISRCTN10768531, and ISRCTN19604441) are investigating the effect of a mixed probiotic, VSL#3, containing eight species of bacteria licensed for use in irritable bowel syndrome, with one recruiting exclusively from intensive care units (ISRCTN10768531). One trial (NCT01087892) is investigating the effect of Actimel, which contains three species (Lactobacillus casei DN 114 001, Lactobacillus bulgaricus, and Streptococcus thermophilus) and one (ISRCTN70017204) is investigating the effect of a probiotic that contains two strains of Lactobacillus acidophilus (National Collection of Industrial, Food and Marine Bacteria (NCIMB 30157 and 30156), Bifidobacterium bifidum (NCIMB 30153) and Bifidobacterium lactis (NCIMB 30172). One (ISRCTN86623192) is investigating the effect of S boulardii. These studies will provide information on probiotics to prevent antibiotic associated diarrhoea in a wider range of hospitalised patients and may be large enough to provide information on which subgroups of patients are at greatest risk and are most likely to benefit.

No randomised controlled trials have specifically assessed the use of probiotics with antibiotics in care homes. Robust data are lacking on levels of antibiotic use and on frequency and severity of associated diarrhoea this setting. Our Probiotics for Antibiotic Associated Diarrhoea
Systematic reviews of randomised placebo controlled trials (RCTs) and subsequent individual trials of probiotics to prevent antibiotic associated diarrhoea

<table>
<thead>
<tr>
<th>Reference (search date)</th>
<th>Number of studies and/or total number of participants, care setting</th>
<th>Intervention: organism in probiotic and daily dose (colony forming units)</th>
<th>Outcome (risk ratio) for antibiotic associated diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic reviews</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McFarland 2010(^a) (1976-2009)</td>
<td>10 RCTs, 1858 adults, 4 trials in hospitalised patients, 1 outpatient, 3 in patients receiving antibiotic treatment for H pylori infection</td>
<td>S boulardii, ranging from 4×10(^9) to 2×10(^10)</td>
<td>0.47 (95% CI 0.35 to 0.63)</td>
</tr>
<tr>
<td>Avadhani 2010(^b) (unclear)</td>
<td>8 RCTs, 1220 adults, inpatients</td>
<td>3 trials of S boulardii, L rhamnosus, range of doses</td>
<td>0.56 (95% CI 0.44 to 0.71)</td>
</tr>
<tr>
<td>McFarland 2006(^c) (1977-2005)</td>
<td>25 RCTs, 2810 children and adults, inpatients and outpatients including H pylori treatment</td>
<td>6 trials S boulardii, 6 trials L rhamnosus, range of doses, ranging from 1×10(^7) to 1×10(^11) (mean dose 3×10(^8))</td>
<td>Combined 0.67 (95% CI 0.31 to 0.80); S boulardii 0.37 (95% CI 0.26 to 0.52); L rhamnosus 0.31 (95% CI 0.13 to 0.72)</td>
</tr>
<tr>
<td>Kale-Pradham 2010(^d) (inception-May 2008)</td>
<td>10 RCTs, 1862 children and adults, inpatients and outpatients</td>
<td>Single agent lactobacillus, ranging from 2×10(^9) to 4×10(^10)</td>
<td>Combined 0.35 (95% CI 0.19 to 0.67); adults 0.24 (95% CI 0.08 to 0.75); children 0.49 (95% CI 0.18 to 1.08)</td>
</tr>
<tr>
<td>Sazawal 2006(^e) (inception-FEBRUARY 2006)</td>
<td>19 RCTs, children and adults, inpatients and outpatients</td>
<td>Single (S rhamnosus) and mixed, ranging from 1×7(^8) to 1×10(^10)</td>
<td>0.48 (95% CI 0.35 to 0.65)</td>
</tr>
<tr>
<td>Johnston 2007(^f) (inception to August 2006)</td>
<td>9 RCTs, 1946 children, inpatients and outpatients</td>
<td>2 RCTs lactobacillus GG, one S boulardii, 3 mixed, dose range unclear</td>
<td>0.44 (95% CI 0.25 to 0.77)</td>
</tr>
<tr>
<td><strong>Randomised controlled trials published after search dates of systematic reviews</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gao 2010(^g)</td>
<td>259 adults, inpatients, 744 of 1120 (66.5%) eligible participants were not recruited</td>
<td>Combination of L acidophilus and L casei in low (5× 10(^7)) or high (10×10(^9)) dose</td>
<td>High dose 0.34 (95% CI 0.20 to 0.60); low dose 0.64 (95% CI 0.42 to 0.97); 15.5% low dose, 28.2% high dose intervention, and 44.1% placebo treated patients developed diarrhoea</td>
</tr>
<tr>
<td>Lonnermark 2010(^h)</td>
<td>259 adults, inpatients and outpatients in a university hospital infectious diseases clinic</td>
<td>L plantarum, 1×10(^8)</td>
<td>1.25 (95% CI 0.40 to 3.92); 7.5% intervention and 6.0% treated placebo patients developed diarrhoea</td>
</tr>
<tr>
<td>Song 2010(^i)</td>
<td>214 adults, inpatients, 10 tertiary hospitals treated for a range of respiratory tract infections (mostly pneumonia)</td>
<td>L rhamnosus and L acidophilus, 2×10(^7)</td>
<td>0.54 (95% CI 0.17 to 1.74); 3.9% intervention and 7.2% placebo treated patients developed diarrhoea</td>
</tr>
<tr>
<td>Psaradellis 2010(^j)</td>
<td>437 adults, treated for a minimum of 12 hours in a hospital ward or emergency room in 8 centres</td>
<td>L acidophilus and L casei, 5×10(^7)</td>
<td>0.74 (95% CI 0.53 to 1.02); 21.8% intervention and 29.4% placebo treated patients developed diarrhoea</td>
</tr>
<tr>
<td>Merenstein 2009(^k)</td>
<td>125 children with upper respiratory tract infections aged 1-5, in primary care</td>
<td>Kefi fermented milk from grains containing Lactococcus lactis, Lactococcus plantarum, Lactobacillus rhamnosus, Lactobacillus casei, Lactococcus lactis subspecies diacetylactis, Leuconostoc cremoris, Bifidobacterium longum, Bifidobacterium breve, Lactobacillus acidophilus, and Saccharomyces florentinus; doses of organisms not given</td>
<td>0.82 (95% CI 0.54 to 1.43); 18.0% intervention and 21.9% placebo treated children developed diarrhoea</td>
</tr>
<tr>
<td>Szymanski 2008(^l)</td>
<td>78 children aged 5 months to 16 years with respiratory tract infections, inpatients and outpatients</td>
<td>B longum, L. rhamnosus, and L plantarum, twice daily at 10(^7)</td>
<td>0.50 (95% CI 0.06 to 3.50); 2.5% intervention and 5.3% placebo treated children developed diarrhoea</td>
</tr>
</tbody>
</table>

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(PAAD) Study (ISRCTN79548440) is in an observational phase to determine whether a trial of probiotics to prevent antibiotic associated diarrhoea is justified and feasible in care homes.

There is an absence or insufficiency of high quality evidence to support routine use of probiotics to prevent antibiotic associated diarrhoea in all people, regardless of age, comorbidity, and care setting. For example, few trials have been done in primary care,\(^h\) and we found none from intermediate and social care settings. We found no pragmatic, open implementation studies.

**What should we do in the light of uncertainty?**

Good evidence exists to support using probiotics with *S boulardii* and *Lactobacillus rhamnosus* GG (ATCC 53103)\(^c\)\(^e\)\(^f\) to prevent antibiotic associated diarrhoea, with emerging evidence for certain mixed strains that include *L casei* or *L acidophilus*.\(^h\) Probiotics also seem to be more effective at higher doses.\(^h\)\(^l\)\(^m\) However, because insufficient evidence exists to support routinely using probiotics for this purpose, and because of the low incidence and generally mild severity of antibiotic associated diarrhoea in otherwise healthy people, we recommend against routine use
of probiotics in all people taking antibiotics to prevent antibiotic associated diarrhea. Not all probiotics evaluated as part of clinical trials are commercially available in the United Kingdom. Nevertheless, probiotics are cheap and safe, so routine use with antibiotics is justified in frail patients in hospital and possibly in children. Those who have previously had antibiotic associated diarrhea should be offered probiotics when they are treated with antibiotics, regardless of setting, but probiotics should be avoided in people who are seriously immunocompromised. As probiotics seem more effective at higher doses, doses of at least 50 billion colony forming units should be used; probiotics should be taken for the duration of antibiotic treatment and continued for a week thereafter.

Evidence about the effectiveness of many strains is absent or insufficient. Head to head studies of probiotic strains are needed, as well as more studies to identify groups of patients at greatest risk and most likely to benefit, especially in the community and in intermediate care. Contributors DD and CB developed and conducted the searches and drafted the paper, which was revised by CB, DD, and KH. CB is guarantor. Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; The HTA has funded research involving probiotics for which all authors are grant holders; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; externally peer reviewed.


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ANSWERS TO ENDOGAMES, p 50 For long answers go to the Education channel on bmj.com

ANATOMY QUIZ
Anatomy of the dural venous sinuses
A: Inferior sagittal sinus
B: Superior sagittal sinus
C: Confluence of the sinuses
D: Transverse sinus
E: Sigmoid sinus

PICTURE QUIZ
A child with knee pain

1 Figure 1 is a “frog lateral” radiograph and it shows a widened physis and malalignment of the epiphysis and proximal femoral metaphyseal (fig 2), confirming the diagnosis of a left slipped upper femoral epiphysis.

2 Slipped upper femoral epiphysis may be classified according to the ability to bear weight (stable or unstable); chronologically in relation to the time of onset of symptoms; or radiographically, depending on the degree of displacement. Classification based on stability is the most useful in clinical practice and is also predictive of prognosis.

3 This rare condition can present with a limp or pain in the groin, thigh, or knee. The duration of symptoms can vary from days to months, or even years, depending on the stability of the slip.

4 The development of avascular necrosis and degenerative joint disease. Management aims to prevent these two complications.

5 Stable slips are best treated with fixation in situ at the time of presentation. This patient had an unstable slip and was therefore at risk of avascular necrosis. Surgery should be performed either within 24 hours or after one week of the onset of symptoms.