Appendix J: Content from NICE clinical guideline 17 [2004] that has been deleted

The table shows content from 2004 that NICE proposes to delete in the 2014 update. The right-hand column explains the reason for the deletion.

Content in 2004 guideline	Comment
Summary – overview section There are three main changes between this and previous guidelines: • Management of symptoms in primary care is appropriate for most patients rather than routinely seeking a pathological diagnosis. • Alarm signals and signs are the major determinant of the need for endoscopy, not age on its own. • Long term care should emphasise patient empowerment, for example by promoting 'on demand' use of the lowest effective dose of PPI. **Using this guideline** This document is intended to be relevant to the primary care team, including pharmacists, general practitioners, nurses, practice nurses and other primary healthcare professionals who have direct contact with patients. It does not consider dyspepsia during pregnancy or the hospital setting but provides criteria for referral to secondary care. To promote continuity of care, it is important that clinicians initiating treatment in secondary care are aware of the recommendations of this guideline. Inevitably, parts of this document are technical but we have tried as much as possible to make this document accessible to patients, carers of patients and the public. The Summary (pages 1-21) can be used as a standalone document by those wanting to access the recommendations, supporting evidence and management flowcharts. A table of contents for the full guideline is found on page 23. A description of the methods used to develop the guideline is found on page 28. The evidence review used in the guideline development process begins on page 41.	This section is superseded by the Overview, Summary and Methods sections of the Update.

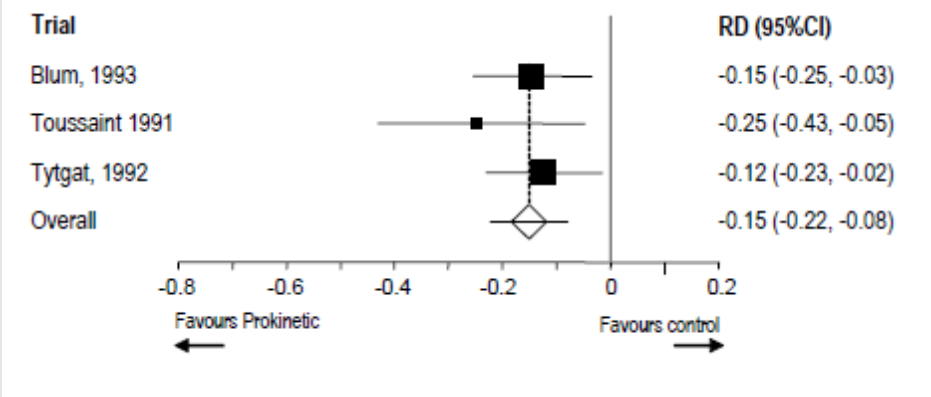
Content in 2004 guideline	Comment
This full version of the guideline is available to download free-of-charge from the National Electronic Library for Health website (http://www.nelh.nhs.uk/). A printed copy of this document can be purchased from the Centre for Health Services Research, University of Newcastle. The Institute makes available three summary versions developed from this document on its website (http://www.nice.org.uk/): a patient version, a healthcare professional version and a quick reference guide. **Using recommendations and supporting evidence** The guideline development group have worked to understand and reflect the overall benefits, tolerability, harms, costs, feasibility and fairness of alternative patterns of care, as the evidence allows. However, healthcare professionals need to apply their general medical knowledge and clinical judgement when applying recommendations which may not be appropriate in all circumstances. Decisions to adopt any particular recommendation are made in the light of individual patients' views and circumstances as well as available resources. To enable patients to participate in the process of decision making to the extent that they are able and willing, clinicians need to be able to communicate information provided in this guideline. To this end, recommendations are often supported by evidence statements which provide summary information to help clinicians and patients discuss care options. Recommendations about drug treatment assume that clinicians will take account both of the response of individual patients and of the indications, contra-indications and cautions listed in the British National Formulary (BNF) or Summary of Product Characteristics (see http://www.medicines.org.uk; within the Electronic Medicines Compendium).	
Referral guidance for endoscopy at presentation – overview section This follows since upper gastrointestinal malignancy is uncommon in patients with dyspepsia, especially below the age of 55 years, and when it is found, it is often associated with a poor prognosis. Dysphagia (difficulty swallowing) and weight loss are the most reliable 'alarm features' at primary care level, although only a small minority of patients with these symptoms will actually have malignancy. Given the prevalence of dyspepsia, the costs of investigation for such a small yield in potentially curable cancers and the risk of harm from the investigation, a policy of prompt endoscopy in patients without alarm symptoms is not currently justifiable. As 'cure' is so rarely achieved 'prevention' strategies using H. pylori 'test and treat' in dyspeptic patients, population screening for H. pylori and surveillance programmes for Barrett's metaplasia may offer an alternative. Further research is needed in these areas before such a programme can be recommended. The summary of the available evidence and group discussions was used to develop a flowchart showing referral criteria and subsequent management (Figure 12).	As this section will be superseded by NICE clinical guideline (CG27) update it was agreed that it should be removed and replaced by a cross-reference to CG27 and the update.

Content in 2004 guideline	Comment
Referral guidance for endoscopy at presentation – alarm signs & symptoms section A number of signs and symptoms are reported as indications for urgent or emergency endoscopy [161], although different commentators place different emphases on these. The consensus view of the group on indications for referral is summarized in Box 3. While it is recognised certain patients are at higher risk of malignancy or ulceration (gastric surgery, unmodified NSAID use and older patients) this was not seen as an indication for routine referral. However, in high risk patients, when symptoms persist, it may become appropriate to refer to a specialist for a second opinion. Dyspepsia; alarm signs and symptoms – patient with dyspepsia Immediate (same day) referral is indicated for: - significant gastro-intestinal bleeding Urgent referral (within 2 weeks) is indicated at any age for: - progressive dysphagia - unintentional weight loss - epigastric mass - suspicious barium meal - iron deficiency anaemia - persistent vomiting If treatment is unsuccessful, consider referring patients over 55 years old, for: - previous gastric ulcer - previous gastric surgery - pernicious anaemia - NSAID use - family history of gastric cancer A key issue is whether to investigate all patients presenting with dyspepsia above a certain age threshold, or only those with alarm features. Alarm features are present in 10% of patients presenting with dyspepsia in primary care [162]. Since cancers of the upper gastrointestinal tract are rare, this means that the positive predictive value of alarm symptoms is low and the negative predictive value high. Upper gastrointestinal (GI) malignancy tends not to	As this section will be superseded by NICE clinical guideline (CG27) update it was agreed that it should be removed and replaced by a cross-reference to CG27 and the update.

Content in 2004 guideline	Comment
present as an alarm sign until late in the disease process with a poor prognosis (often inoperable, less than 10% survival at 5 years) while cancer detected early has good prognosis (with surgery about 80% survival at 5 years). Thus there has been interest in screening all patients with dyspepsia. A large cohort study of rapid access endoscopy in the West Midlands [163] suggested that prompt investigation could increase detection of early stage cancers, but the study was uncontrolled and did not measure survival in the screened patients. Evidence for the value of age and alarm symptoms in selecting patients for endoscopy comes from three types of study, retrospective studies of symptoms in patients found to have cancer, retrospective studies of findings and symptoms in patients undergoing endoscopy, and prospective studies of patients presenting in primary care. A difficulty is that very large numbers of patients are needed in prospective studies to identify adequate number of cancers (yet alone operable cancers) to evaluate potential referral rules. However, retrospective studies may introduce recall bias and artificially inflate the importance of alarm symptoms by using a highly selected population. Three studies have examined retrospective cohorts of patients in whom upper GI cancers were detected. Two studies found that cancer was rarely detected in patients under the age of 55 years without alarm symptoms, and when found the cancer was usually inoperable. In the first study in Gloucester of 319 cases of upper GI cancer, 25 were in patients under the age of 55 years and only one of these patients presented without alarm features [164]. In the second study in Glasgow, 169 patients under the age of 55 years, with upper GI cancer were studied, only five had presented without alarm features, and all these also had inoperable disease [165]. The Glasgow study estimated the rate of presentation of malignancy in patients less than 55 years without alarm symptoms at 1 per million population per year. Data from the USA have shown similar findings [166]. All of these studies have limited value, since patients were not referred until they had developed the signs of late disease, earlier investigation may have permitted surgery. A large dataset of endoscopic findings in 7004 patients under the age of 45 years in Canada [167] identified 3,634 (52%) patients investigated without alarm features: 3 cancers were found and of which 2 were resectable. This gave an incidence of resectable cancer in patients under 45 years with simple dyspepsia of less than one per 1000. Two studies in primary care populations provide more applicable evidence. In a Dutch study, a prospective referral guide was used to select patients for endoscopy on the basis of persistent symptoms or alarm and symptoms [168]. A scoring system was used to evaluate the predictive value of symptoms for malignancy in 861 referred patients. Logistic regression showed that the presence of weight loss (OR: 4.4), dysphagia (OR: 6.1), male sex (OR: 1.4) and smoking (OR: 2.6) were the only independent factors increasing the likelihood of malignancy. Nocturnal dyspepsia (OR: 0.3), daytime heartburn (OR: 0.2) and a history of dyspepsia longer than a year (OR: 0.4) featured a lower-than- average likelihood of malignancy. A Danish	

Content in 2004 guideline	Comment
study collected symptoms, using a structured questionnaire, from consecutive patients presenting with dyspepsia in general practice. Patients were managed according to the GP's usual care, and followed up three years later [162]. In a cohort of 2,479 patients with 13 upper GI cancers, only 1.5% of patients with dysphagia and 1.5% of those with weight loss had upper GI malignancy. A similar rate of colorectal cancers and upper GI cancer was diagnosed in dyspeptic patients with weight loss. Published guidance for the prompt investigation of patients with suspected malignancy [169] fast tracks patients with dysphagia, dyspepsia with weight loss, anaemia or vomiting at any age and those over 55 years of age with onset within a year of continuous symptoms of epigastric pain, family history of malignancy in more than two first degree relatives, Barrett's oesophagus, pernicious anaemia, peptic ulcer surgery more than 20 years ago, known dysplasia, atrophic gastritis, intestinal metaplasia, jaundice or upper abdominal mass. However, a recent study has examined the predictive value of symptoms and signs for gastric and oesophageal cancers among a prospective cohort of 1,852 patients with dyspepsia referred for rapid upper GI endoscopy by GPs, under the UK cancer guidance. The mean age was 59; 63% were over 55 years of age and the prevalence of cancer was 3.8% (70 cases). The odds ratio for cancer was OR: 3.1 (95%CI: 5.2 to 1.8) with dysphagia, OR: 2.6 (95%CI: 4.4 to 1.5) with weight loss, predictive of cancer. The existing criteria of age more than 55 years, with new onset or continuous epigastric pain was found to be negatively associated with cancer, OR: 0.1 (95%CI: 0.01 to 0.75). A decision rule of dysphagia or significant weight loss at any age plus age greater than 55 with alarm symptoms would have detected 99.8% of the cancers found in the cohort [170]. As gastric cancer is rare in dyspeptic patients an RCT to evaluate different referral thresholds is infeasible. Simulation modeling can be used to extrapolate from existing knowledge to explore different referral rules. A Discrete Event Simulation of the management of dyspepsia in primary care [171] was adapted to compare the cost per life year saved by prompt endoscopy-based management and an H. pylori 'test and treat' strategy for patients above different age thresholds [172]. The model suggested that up to age 60 years test and treat was likely to save more life years and be cheaper than endoscopy. Even above age 60 the gain in life years was very marginal, and endoscopy based management was not cost-effective.	
Interventions for univestigated dyspepsia – evidence review (pharmacological therapy) PPI vs. cisapride Lewin et al [182,183] found no difference in the proportion of symptom-free patients at 52 weeks when comparing omeprazole with cisapride in 164 patients, Risk Ratio: 0.95 (95%CI: 0.80 to 1.13). Treatment was provided for 8 weeks and assessments were made at 8, 14 and 52 weeks. None of the assessments	Cisapride has been suspended in the UK since the publication of CG17

Content in 2004 guideline	Comment
showed a significant difference. Symptom scores similarly revealed no difference between treatments.	
Interventions for GORD - acute healing of oesophagitis section Prokinetic agents One RCT with 101 patients compared prokinetic therapy with placebo [223]. This trial found that cisapride was more effective at healing oesophagitis than placebo: the risk ratio for patients healed was 0.79 (95%CI: 0.63 to 0.99). The average healing rate in the placebo group was 21% and cisapride treatment resulted in an absolute increase of 17% (95%CI: 0.01% to 33%), a number needed to treat of 6.0 (95%CI: 3.0 to 127).	Evidence reviewed for original guideline was only for Cisapride not Domperidone or Metoclopramine. Cisapride has been suspended in the UK since the publication of CG17.
Interventions for GORD - acute healing of oesophagitis section Doubling the dose of Proton Pump Inhibitors Two studies evaluated healing rates by severity of oesophagitis [278,285] suggested high dose PPI resulted in an absolute increase of 10-20% healing in Los Angeles (LA) grade C and D patients. This was a post-hoc subgroup analysis and results should be treated with caution. Nevertheless it may be appropriate to increase the dose of PPI if LA grade C and D patients fail to respond to full doses of PPI. Severe oesophagitis represents only approximately 5% of all gastro-oesophageal reflux disease and it is therefore not appropriate to increase the dose of PPI beyond full doses unless there is endoscopic evidence of LA grade C or D oesophagitis.	Superseded by review question on *what is the clinical effectiveness of PPIs in patients with severe erosive reflux disease (page x)*
Interventions for GORD - maintenance therapy for oesophagitis section Summary of strategies for patients not responding to initial PPI therapy If the patient has severe LA grade C or D oesophagitis the dose of PPI may need to increased if patients' symptoms do not resolve.	Superseded by review question on *what is the clinical effectiveness of PPIs in patients with severe erosive reflux disease (page x)*
Interventions for GORD - maintenance therapy for oesophagitis section Prokinetic agents Three trials with 666 participants compared cisapride with placebo, with between 24 weeks and one year follow-up respectively [296,297,298]. Cisapride was effective in reducing relapse of oesophagitis when compared with placebo: the risk ratio for patients relapsing was 0.71 (95%CI: 0.53 to 0.96; Q: p=0.102, size: n/a). The average relapse rate in control groups was 56% and cisapride treatment resulted in an absolute reduction of 15% (95%CI: 8% to 22%; Q: p=0.529, size: n/a), a number needed to treat of 6.6 (95%CI: 4.5 to 12.6) (Figure 13). Cisapride is not available in the UK and no other prokinetic agents have been studied. Meta-analysis of randomised placebo-controlled trials of prokinetics to prevent relapse in healed	Evidence reviewed for original guideline was only for Cisapride not Domperidone or Metoclopramine. Cisapride has been suspended in the UK since the publication of CG17.

Content in 2004 guideline	Comment
oesophagitis  	
Interventions for GORD – surgery section An alternative approach for patients who require long-term medication is to undergo anti-reflux surgery. A systematic review was retrieved and updated comparing medical and surgical treatment for long term management of gastro-oesophageal reflux disease [347]. Five RCTs were identified that compared open anti-reflux surgery with medical therapy in patients with GORD. Outcomes assessed were heterogeneous and insufficient data was given to report the relative risk of healing or relapse following surgery. Three of these trials compared open anti-reflux surgery with antacids and/or H2RAs and all reported that surgery was the superior intervention. Two further Scandinavian and American RCTs compared open surgery with PPI treatment [348,349]. In the Scandinavian study [348] 155 patients were randomized to receive omeprazole 20 mg once daily and 144 to receive open anti-reflux surgery with three years of follow up. At three years 111/133 (83%) of the omeprazole patients were in remission from oesophagitis compared with 103/119 (87%) of the surgery patients (Risk Ratio: 0.96: 95%CI: 0.87 to 1.07). The US study [349] also found no statistical difference between medical therapy (including a PPI if necessary) and open Nissen fundoplication after a mean of 10 years follow-up. The mean endoscopic score was 1.89 (SD: 1.15) for the 63 patients in the medical group and 1.80 (SD: 0.95) for the 20 patients in the surgical group (p=0.76). One RCT randomized 47 patients to laparoscopic Nissen fundoplication and 43 patients to PPI therapy with	Superseded by review question on the *effectiveness of fundoplication vs medical management (page X)*

Content in 2004 guideline	Comment
three month follow-up [350]. The mean DeMeester acid reflux score was 13 in the surgery arm compared with 14 in the medical arm and was reported as not statistically significant although no p- value was provided. Two RCTs compared laparoscopic and open Nissen fundoplication [351,352]. A Dutch study randomized 69 patients to Open Nissen fundoplication and 79 patients to laparoscopic surgery and followed up patients at three months [351]. In the open surgery group 45/46 (98%) were in remission at the end of follow-up compared to 55/57 (96%) in the laparoscopic surgery group (Risk Ratio: 1.01, 95%CI: 0.95 to 1.08). There was a statistically significant increase in dysphagia in the laparoscopic group: 7/57 (12%) compared to the open surgery group: 0/46 (0%); Risk Ratio: 1.14, 95%CI: 1.03 to 1.26). A Finnish study [352] randomized 21 patients to laparoscopic and 20 patients to open Nissen fundoplication. Remission from oesophagitis was seen in 21/21 (100%) of the laparoscopic and 18/20 (90%) of the open surgery group (Risk Ratio = 1.11; 95%CI = 0.96 to 1.29). There is a small (0.1 to 0.5%) but important post-operative mortality associated with anti-reflux surgery [349].	
Interventions for GORD – overview section H. pylori eradication is appropriate for peptic ulcer disease, non-ulcer dyspepsia and as part of a H. pylori test and treat strategy in uninvestigated dyspepsia. Current evidence demonstrates that a number of approaches to eradication are effective and that in the clinical context there is scope to exercise appropriate judgement. Twice daily PPI, metronidazole, clarithromycin 250 mg (PMC250) or PPI, amoxicillin, clarithromycin 500 mg (PAC500) are both recommended as first line strategies. It has been argued that the use of PAC500 allows more options for second line therapy. However, this assertion is not based on RCT evidence and is unlikely to be clinically important in a 'test and treat' strategy for the management of dyspepsia and when H. pylori eradication is being used to treat non- ulcer dyspepsia. The benefits of H. pylori eradication in these situations are relatively minor [394,395]. For this reason it is also preferable to use one-week regimens for H. pylori test and treat and in therapy for non-ulcer dyspepsia. When treating MALT lymphoma, eradication carries a more important advantage and there is a case to increase duration of therapy to fourteen days. The possibility that rabeprazole may be more effective in this regimen deserves further consideration but the consensus view of the group is that currently any PPI should be recommended for H. pylori eradication. At the time of writing, work is ongoing on a Cochrane Collaboration systematic review of all eradication therapies [396], consequently this section builds on and updates published reviews	Superseded by review question on *the pharmacological management for eradication of H pylori in patients with confirmed infection (page X)*

Content in 2004 guideline	Comment
Interventions for GORD • Selecting an eradication therapy Eradication of the bacterium H. pylori has been evaluated using a number of short courses (one or two weeks) of one of more antibiotics together with an acid suppressant, usually a PPI. Quadruple therapy with a PPI, bismuth salts, tetracycline and metronidazole have been shown to be effective but therapy involving up to 17 tablets a day is not thought practical as a first line therapy. Published reviews have shown that PPI dual therapy is inadequately effective as triple therapy [408]. Consequently current treatments involve a triple therapy consisting of a PPI and two antibiotics from: amoxicillin, clarithromycin or a 5-nitroimidazole. Findings from four randomised controlled trials demonstrate that PPI, amoxicillin and metronidazole is less effective than either of the two PPI triple therapies that contain clarithromycin (Figure 53) [409,410,411,412]. Ranitidine bismuth citrate triple therapy regimens are as effective as their PPI counterparts in eradicating H. pylori [413], but the latter are more widely used and form the basis of this review. The optimum dosage of the drugs used in PPI based clarithromycin triple therapies is reviewed to identify the optimum regimen(s). Strategies that might improve on these therapies using existing antibiotics are also explored. • Optimum PPI used in a clarithromycin-based therapy ○ Optimum PPI dose The dose of PPI used in amoxicillin dual therapy is influential with increasing acid suppression leading to greater efficacy [414]. The effect of dose of PPI in clarithromycin-based triple therapies was explored drawing on the findings of a published review [415]. Twelve randomised controlled trials (RCTs) [416,417,418,419,420,421,422,423,424,425] with 2,186 patients evaluated full versus double dose PPI in clarithromycin and amoxicillin (PAC) regimens. The pooled eradication rate was 78.5% in the single dose arms compared with 85.4% in the double dose arms (risk difference = 6%; 95%CI = 2% to 11%) (Figure 54). Double dose PPI therapy is therefore an optimal component of PAC regimens (number needed to treat = 17; 95%CI = 9 to 50). Three RCTs [426,427,428] in 378 patients evaluated single versus double dose PPI in clarithromycin and metronidazole (PCM) regimens. Single dose PPI therapy achieved a pooled eradication rate of 84.3%	Superseded by review question on *the pharmacological management for eradication of H pylori in patients with confirmed infection (page X)*

Content in 2004 guideline	Comment
compared with 86.0% for double dose PPI therapy. There was no statistically significant difference between the two doses of PPI in PCM regimens (RD: 1.3%, 95%CI: -5.9% to 8.5%) (Figure 55). The number of patients evaluated in PCM trials was less than PAC trials and therefore the power of this meta-analysis is limited. These data suggest single dose PPI therapy may be sufficient for PCM triple therapy. ○ Optimum PPI A meta-analysis of 10 RCTs, evaluating a total of 1,348 patients, performed in 2001 [429] showed that there was no significant difference between omeprazole and lansoprazole-based triple therapies of seven days or more. Five further RCTs were identified [425,430,431,432,433] evaluating 934 patients that compared the equivalent doses of rabeprazole and omeprazole in PAC regimens. The pooled eradication rate was 76.8% in the omeprazole and 83.7% in the rabeprazole groups. The meta-analysis of these trials suggests that rabeprazole is superior to omeprazole (risk difference: 6.9%; 95%CI: 1.8% to 11.9%) NNT: 16 (95%CI: 9 to 65) (Figure 56). With regard to the use of rabeprazole in PCM regimens there was only one trial comparing it to an omeprazole-containing regimen and this showed no significant difference between the two [431]. ○ Optimum Dose of Clarithromycin The optimum dose of clarithromycin in triple therapy was addressed by a systematic review in 1999 [434]. Four trials, evaluating 385 patients, compared clarithromycin 250mg to 500mg in a PAC regimen. Meta-analysis found that the higher dose of clarithromycin was optimal with a pooled eradication rate of 79.8% in the PAC250 arms and 89.6% in the PAC500 arms (RD: 10%, 95%CI: 3% to 17%; NNT: 10, 95%CI: 6 to 33) (28). Similarly, 4 trials evaluating 642 patients compared 250mg and 500mg clarithromycin in a PCM regimen. Doubling the dose of clarithromycin had no statistically significant effect on eradication rates, with a pooled eradication rate of 87.4% with clarithromycin 250mg and 88.9% with clarithromycin 500 mg (RD: 2%, 95%CI: -6% to 10%) (28). A dose of 250mg should therefore be recommended for PCM as this is cheaper and uses less antibiotic without any apparent loss of efficacy. ○ Optimum Regimen On current evidence, the optimum PAC regimen taken for seven days contains PPI, clarithromycin 500mg and amoxicillin 1g all given twice daily, whereas the optimum PCM regimen contains PPI, clarithromycin 250mg and metronidazole 400mg all given twice daily. The evidence for using PPIs once daily for PCM is	

Content in 2004 guideline	Comment
based on relatively few patients in trials and there are no trials comparing a PCM regimen PPI once daily and a PAC regimen with PPI twice daily. There are, however, a number of trials that compared PMC using clarithromycin 250mg (PMC250) with PAC using clarithromycin 500mg (PAC500). A published systematic review [429] comparing these two optimal regimens was updated, providing 10 trials [411,435,436,437,438,439,440,441,442,443] and 1805 patients. Pooled eradication rates for PAC500 and PMC250 were 82.0% and for 82.6% respectively. There was no statistically significant difference in eradication rates (RD: 0%, 95%CI: -4% to 4%) (Figure 57). The finding that there is no difference in efficacy between optimal PAC and PMC regimens is unexpected, as three meta-analyses have suggested that PMC is approximately 20% less effective against metronidazole resistant strains of H. pylori [444,445,446]. It is unlikely that all trials had a low prevalence of resistant strains and the number of patients evaluated gives the power to detect even small differences in efficacy between the two regimens (Relative Risk Reduction: 95%CI +/- 4% of 0%). Furthermore there was not statistically significant heterogeneity although trials were from different countries with varying rates of H. pylori metronidazole resistance. Possible explanations are that PMC may be more effective than PAC in metronidazole sensitive H. pylori strains or that the impact of metronidazole resistance may not be as marked as observational studies suggest. ○ Choosing the optimum regimen. PMC250 is as effective as PAC500 and is less expensive. PMC250 therefore appears to be the most cost-effective regimen although adverse events and the potential impact on the efficacy of second line therapy should also be considered. Microbiologists are concerned about the increase of clarithromycin resistant H. pylori. It has been suggested that GPs should not use clarithromycin or metronidazole if the patient has received this for any infection in the past year, as monotherapy with these agents very readily leads to resistance. At a level of 33% metronidazole resistance, H. pylori treatment efficacy is reduced by 38%. At a level of 10% clarithromycin resistance, H. pylori treatment efficacy is reduced by 55% [447, 448, 449]. In Mid-Essex, where culture and sensitivity testing has been routine for many years, 39% of isolates are resistant to one or more antibiotics. Of strains resistant to clarithromycin, 58% are also resistant to metronidazole. This may present important problems where GPs treat without knowledge of antibiotic resistance. Treatment failure may be due to poor predictive value of serological testing and/or ineffective antibiotics due to resistance. Further inappropriate tests and treatment could further confound the problem. The value of establishing a number of surveillance centres (microbiology laboratories and gastroenterology units) should be explored, where culture and sensitivity testing could be regularly monitored and UK treatment regimens advised accordingly.	

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Metronidazole can be associated with an antabuse reaction so alcohol must be avoided whilst taking this regimen. Metronidazole is very rarely associated with peripheral neuropathy, when used in a one- week duration regimen. Amoxycillin on the other hand is commonly associated with minor allergic reactions and very rarely can cause severe anaphylaxis. Amoxycillin is also the commonest antibiotic associated with Clostridium difficile pseudomembranous colitis, which has been described after H.pylori eradication therapy [450]. Metronidazole is used to treat Clostridium difficile and this adverse event should in theory be less common with PMC250 than PAC500. PAC500 has sometimes been recommended as the optimum first line therapy over PMC250 on account of potential metronidazole resistance and since second line therapy may be compromised by using an initial regimen containing both clarithromycin and metronidazole [451]. Whilst the guideline does not recommend routine re-testing of patients receiving H. pylori eradication, a subset of patients will require second line therapy for treatment failure. There are inadequate data on the optimum second line therapy but quadruple therapy such as a PPI, once daily DeNol 120 mg qds, tetracycline 500 mg qds and metronidazole 400mg tds for one week is sometimes recommended [452,453]. If patients take PAC500 first line they will not have been exposed to any of these antibiotics, which should maximise the chances of H. pylori cure. Patients given PMC250 are likely to harbour metronidazole resistant strains if therapy has failed [454] and this may compromise second line treatment with quadruple therapy. Studies have suggested however that metronidazole resistance has no [455] or only a modest impact on quadruple therapy success [456]. Any benefit in terms of overall H. pylori eradication using PAC500 is likely to be small. Nevertheless the impact of increasing the prevalence of antibiotic resistant H. pylori in the community is difficult to quantify and depends on the predominant mode of transmission of the infection. If H. pylori is transmitted predominantly from child to child, then any antibiotic resistance that develops in an adult patient is unlikely to be transferred. If on the other hand predominant transmission is from adult to child then there is a theoretical risk that use of PMC250 may select H. pylori that become have resistant to both antibiotics and this may make eradication more difficult for future generations. Given this balance of effects the group concluded PMC250 and PAC500 are both valid alternative first line therapies. ○ Optimum Duration of Treatment It is plausible that increasing the duration of therapy could improve eradication efficacy. US guidelines recommend 10 days of therapy, while European guidelines advocate 7 days.	

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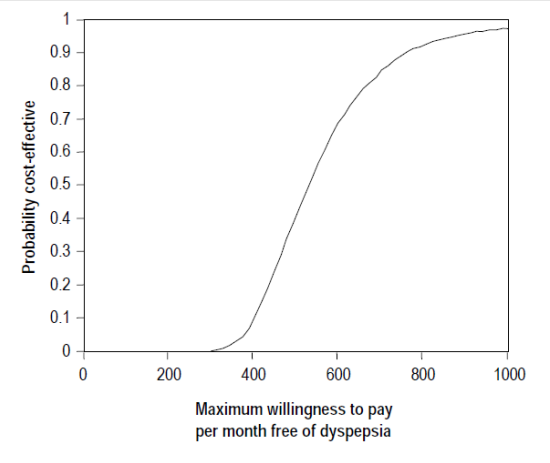
A previous systematic review [457] addressing the question of optimum duration of treatment was updated. There was a statistically non-significant trend of greater eradication for 10 compared to 7 day therapy. Twelve trials, evaluating 1592 patients, compared 7 and 14 day PPI triple therapy [458,459,460,461,462,463,464,465,466]. Seven days therapy was significantly less likely to cure H. pylori with a pooled eradication rate of 67.8% compared with 77.2% with 14 day therapy (RD: 9%, 95%CI: 5% to 14%; NNT: 11, 95%CI: 7 to 20) (Figure 58). These data combine PAC and PMC regimen; longer duration therapy remained statistically significantly more effective for each regimen when considered separately. Current evidence shows that increasing the length of therapy from one to two weeks improves eradication rates.	
***Helicobacter pylori* testing and eradication** Cost-effectiveness analysis of two week and one week *H.pylori* eradication Increasing the length of therapy from one to two weeks improves the eradication rate by 9% (95%CI = 5 to 14%). A simple model was constructed to evaluate whether increasing the length of therapy was cost-effective in duodenal ulcer disease. This was based on the model presented on page 131 (Figure 1) with the ranitidine arm replaced with an arm that treated patients with H. pylori eradication for two weeks. Meta-regression of the duodenal ulcer systematic review data suggested that two weeks of therapy increased the eradication rate and reduced the ulcer relapse rate. The data suggest that a 9% increase in eradication rate with the two week regimen will translate to risk ratio for relapse of 0.85 (95%CI: 0.78 to 0.93). Patients taking one week therapy incur an average cost of £54.70 per year for 10.39 months free from dyspepsia. Patients taking two week therapy incur an average cost of £71.10 per year for 10.42 months free from dyspepsia. The two week regimen costs an extra £16.30 for an extra 0.03 months freedom from dyspepsia over one year, which is an incremental cost-effectiveness ratio of £523 per month free from dyspepsia. Figure 59 displays the uncertainty in the data and suggests that the willingness to pay for an extra month free from dyspepsia needs to be £880 for a two week therapy strategy to be cost-effective with 95% confidence. Although the benefits of H. pylori eradication are likely to last longer than one year, the two-week regimen appears to be prohibitively expensive. The incremental cost-effectiveness ratio is likely to be even less favourable for gastric ulcer, non-ulcer dyspepsia and as part of a test and treat strategy. For this reason it is preferable to use a one-week regimen except in the case of MALT lymphoma, where the increased efficacy of the two-week regimen will reduce the need for chemotherapy and/or gastric resection. The possibility that rabeprazole may be more effective in this regimen requires further investigation but the consensus view of the group is that currently any PPI should be recommended for H. pylori eradication.	Superseded by review question on *the pharmacological management for eradication of H pylori in patients with confirmed infection (page X)*

Content in 2004 guideline	Comment
Cost effectiveness acceptability curve for two versus one week of H. pylori eradication therapy for duodenal ulcer  	

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