Management of Dyspepsia and Heartburn
Management of Dyspepsia and Heartburn
STATEMENT OF INTENT

Evidence-based best practice guidelines are produced to help health practitioners and consumers make decisions about health care in specific clinical circumstances. Research has shown that if properly developed, communicated and implemented, guidelines can improve care. The advice on dyspepsia and heartburn given in this guideline is based on epidemiological and other research evidence, supplemented where necessary by the consensus opinion of the expert development team based on their own experience.

While guidelines represent a statement of best practice based on the latest available evidence (at the time of publishing), they are not intended to replace the health practitioner’s judgment in each individual case.

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Where guidelines are modified for local circumstances, significant departures from the national guidelines should be fully documented and the reasons for the differences explicitly detailed.

2004 NZGG
Ka kohi te toi
Ka whai te maramatanga

(With the gathering of knowledge
Enlightenment will follow)
ENDORSED BY

Heart Foundation
The Heart of Our Nation

The Cardiac Society of Australia and New Zealand

The Royal Australasian College of Physicians
NEW ZEALAND

SUPPORTED BY

Royal Australasian College of Surgeons – New Zealand Branch.

The Royal New Zealand College of General Practitioners.
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PURPOSE

Dyspepsia and heartburn are very common symptoms. People with these symptoms frequently consult with general practitioners. Significant numbers of people are referred to specialists for advice and invasive procedures including oesophago-gastro-duodenoscopy (OGD). Furthermore, the dyspepsia and heartburn symptoms themselves, and the inconvenience resulting from them (including loss of work), carry important personal, social and financial costs. The treatment of dyspeptic symptoms in our current practice is often random, poorly advised and not evidence-based. The cost to the country (and not infrequently to people with dyspepsia and heartburn) needs to be rationalised so that those who are in most need achieve rapid and effective management.

The aim of this guideline is to promote up-to-date recommendations for the safe and efficient management of these individuals. The guideline is evidence-based and represents a distillation of a review of the extensive literature in the field.

The guideline is aimed particularly at primary health care providers, but also at medical and surgical specialists who are involved in the care of people with dyspepsia and heartburn. Pharmacists and nurse practitioners should also benefit from this information.

Good medical practice requires individual assessment of each person. This guideline is designed to guide management decisions, not to dictate a blanket policy.
ABOUT THE GUIDELINE

Guidelines promote effective health and disability services by collating and summarising the latest international studies and advising on their application in the New Zealand setting.

GUIDELINE DEVELOPMENT PROCESS

The Dyspepsia and GORD Working Party was formed in 1998 to develop guidelines for the management of dyspepsia in New Zealand. This was precipitated to some extent by PHARMAC indicating to Astra Pharmaceuticals NZ Ltd that availability of omeprazole to general practitioners be accompanied by firm guidelines on responsible use of the drug. The company invited two general practitioners and three gastroenterologists to investigate this issue. After consultation with Independent Practitioners Associations and the professional colleges of general practitioners, physicians and surgeons, this initial group decided that there was a need to revise and update the guidelines for dyspepsia and gastro-oesophageal reflux disease (GORD) that were published in 1995. Throughout the process the Working Party has expressed and maintained the need for the guideline process to be completely independent.

Since 1995, when the National Health Committee produced guidelines for dyspepsia,1 the evidence has changed considerably. At that time, treatment advice was that reflux and ulcer-like dyspepsia may respond better to acid inhibition while other types may respond better to motility agents. However, this has not been consistently supported by further studies.2 Prokinetics were seen as more effective for dyspepsia than acid inhibitors, and a review of the evidence concerning the precise indication for their use has been published.3 The role of Helicobacter pylori (H. pylori) eradication has been elaborated considerably. Test-and-treat or test-and-OGD strategies had not been considered. Since then, proton pump inhibitors (PPIs) have become available for prescription by general practitioners, resulting in widespread changes in treatment practices.

Other guidelines have been published recently, all giving variations on the themes of oesophago-gastro-duodenoscopy (OGD) versus empiric treatment versus test-and-treat, and advising OGD at ages 45 or 50 years.4,5,6,7,8,9,10 As well, there are a number of guidelines available on the Internet,11,12,13,14 and so increasingly doctors may be presented with a guideline by the person and asked to follow its recommendations. Providing specific advice for New Zealand conditions will help counter consumer pressure to follow inappropriate advice.
The Core Committee of the Dyspepsia and GORD Working Party established four regional committees, each including general practitioner, gastroenterology and surgical input, to develop the guidelines for specific areas: Dunedin/Christchurch for GORD; Wellington for undifferentiated dyspepsia and non-ulcer dyspepsia (NUD); Waikato/Rotorua/Bay of Plenty for NSAID-related dyspepsia; and Auckland for Helicobacter pylori and peptic ulcer.

The four regional working groups each established a systematic search of the literature. Each developed their evidence tables from which their recommendations were made. When the core committee convened they made a decision that the evidence tables would not be published nor would they include the level of evidence for each study in the guideline text. Rather, the committee would put its emphasis on producing a workbook style guideline with detailed references for those who wish to delve into the original research. Their drafts were developed between 1998 and 2001 by which time they had been submitted to the Core Committee for review. Decisions were made by consensus of the various groups, and eventually with the Core Committee. These were then collated and edited by members of the Core Committee and a professional editor/writer. The edited copies were returned to the four working groups to ensure they had maintained their original interpretation. Opportunity was given to update the information with the final drafts being returned in mid 2002. The final draft was again reviewed by the Core Committee and further corrections were made. The draft was then sent to the NZGG for circulation to reviewers as part of the AGREE process. The results of the AGREE review were circulated to the leaders of the Regional Working groups and members of the Core Committee. Most of the suggestions and comments made by reviewers were addressed before submitting the final version.

Flow diagrams were constructed from the recommendations agreed in the Guideline. They were discussed with representatives of the Best Practice Advocacy Centre Inc who reviewed the draft flow diagrams in association with some of their representatives and general practitioners.

Other dyspepsia guidelines published between 1998 and June 2003 were perused to ensure appropriate information was considered in developing the New Zealand version of the Guideline. As updates of Cochrane Reviews became available, they were also included in the review process to ensure new developments had been considered.

Guidelines and reviews considered in the Update include:

A. Cochrane reviews


B. Guidelines

Successful implementation of guidelines also requires adequate availability of information for all involved and adequate provision of health care resources. The guideline aims to ensure that people are referred appropriately and that those referred for OGD are those most likely to benefit from it. It is not envisaged that the guideline should greatly increase the demand for this procedure. However, current access to OGD is poor in certain parts of the country and this will need to be addressed by the Ministry of Health. Discussions with district health boards may need to follow.

DESIRED OUTCOMES

These remain similar to those expressed in the previous guidelines published by the National Advisory Committee in 1994. These are as follows:

Clinical
1. Relieve symptoms.
2. Cure ulcers.
4. Prevent recurrence of peptic ulcer disease.
5. Prevent complications.
6. Minimise side effects.
7. Ensure the early identification of complications especially where those might require surgery.
8. Stimulate early investigation and diagnosis of serious pathology, including cancer.
9. Appreciate the role of surgery where this is demonstrated to present a cost-effective option.
10. Reduce the mortality from peptic ulcer disease.

Resources and equity
1. Promote the cost-effective use of health resources.
2. Ensure appropriate and acceptable diagnostic and treatment services.
3. Ensure equitable access to investigations and treatment.
4. Promote reduction in surgical intervention where cost-effective medical alternatives exist.

Public health
1. Improve public knowledge, especially as to what constitutes normality and what may be required in diagnosis and treatment.
2. Improve knowledge of all health care practitioners.
3. Reduce the impact of conditions producing dyspepsia on socio-economic wellbeing.
4. Reduce the incidence of new peptic ulcer disease by appropriate education and public health measures.

THE DYSPEPSIA AND GORD WORKING PARTY

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DECLARATIONS OF COMPETING INTERESTS

No current competing interests were reported by any member of the guideline development team.

ACKNOWLEDGEMENTS

The Working Party would like to thank AstraZeneca for providing the original seeding grant and Janssen-Cilag who added a supplementary grant.

Thanks go to Mary Trewby and Stewart Wells for editing the guideline, and Reywa Brown, Pers Howe and Annie Bourvis who provided secretarial assistance. Thanks also to Julie Knight for developing and reviewing the flow diagrams.

UPDATING THE GUIDELINE

A committee will need to be formed to ensure the guideline is updated at regular intervals. A period of three years is suggested; this will need to be negotiated with the New Zealand Guidelines Group and those nominated for the committee (see Chapter 8: Evaluation).

In the next update, information on nutrition and diet, as well as alternative and complimentary remedies (e.g., slippery elm) may be added if appropriate information is published on these topics.
FUNDING

Funding for this guideline was initiated by an independent grant from Astra Pharmaceuticals NZ Ltd, which also provided secretarial assistance. A second major grant was received from the Health Funding Authority, and supportive grants from Janssen-Cilag Pty Ltd and PHARMAC. The New Zealand Guidelines Group took over administration of funds from the Royal Australasian College of Physicians.

EVIDENCE AND RECOMMENDATION GRADING
SYSTEM USED FOR THIS GUIDELINE

Groups developing the guideline conducted literature searches, including current computer searches (Medline, EMBASE) and surveys of review publications (Cochrane Library, Bandolier). There are a number of systems for grading the evidence. The method adopted for this guideline is shown below.

<table>
<thead>
<tr>
<th>LEVELS OF EVIDENCE</th>
<th>Ia</th>
<th>Ib</th>
<th>IIa</th>
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<th>IV</th>
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<td>Evidence obtained from meta-analysis of randomised controlled trials (RCTs)</td>
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<td>Evidence obtained from at least one randomised controlled trial</td>
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<td>Evidence obtained from at least one well-designed controlled study without</td>
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<td>Evidence obtained from well-designed descriptive studies, such as comparative</td>
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<td>Evidence obtained from expert committee reports or opinions, and/or clinical</td>
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<td>experiences of respected authorities</td>
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</table>
The guideline recommendations have been graded to reflect the quality of the evidence, based on the quality of the studies supporting the claims made.

**GRADES OF RECOMMENDATION**

<table>
<thead>
<tr>
<th>Evidence levels Ia &amp; Ib</th>
<th>Requires at least one RCT as part of the body of literature of overall good quality and consistency addressing specific recommendation</th>
<th>A</th>
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<tr>
<td>Evidence levels IIa, IIb &amp; III</td>
<td>Requires availability of well-conducted studies but no RCTs addressing specific recommendation</td>
<td>B</td>
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<td>Evidence level IV</td>
<td>Requires evidence obtained from expert committee reports or opinions, and/or clinical experiences of respected authorities Indicates absence of directly applicable clinical studies of good quality</td>
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**GOOD PRACTICE POINT**

Recommended best practice based on the clinical experience of the Dyspepsia and GORD Working Party
INTRODUCTION

Dyspepsia is a key but not a specific symptom indicating upper gastrointestinal (GI) malfunction or disease. Only a minority of people with dyspepsia have specific abnormalities (eg, erosive oesophagitis, peptic ulcer or cancer). The challenge of this guideline is to present an approach that helps the doctor to choose which people to treat empirically and whom to investigate (when and how), and to guide management of specific diagnoses.

This guideline is designed to be a practical, working document. The first encounter between the person with dyspepsia and the practitioner starts with the undifferentiated symptoms of dyspepsia or heartburn. The choice is then between empiric management and investigation. Alarm signals are clearly defined to channel the individual for early investigation. Individuals with heartburn often have GORD (about 75%) and respond well to appropriate treatment. Others require more information, exercising both the art and science of medical practice, and guidance is given here to the management of this group.

For those in whom investigation has established a specific diagnosis, there are now treatments that, although having the common features of acid inhibition, differ widely in their details and application. There is now good evidence for optimum but different regimens for the main diagnostic groups: GORD, H. pylori-related peptic ulcers and gastric cancer. Problems related to NSAID use have a separate origin and often run a different clinical course, which must be recognised and treated specifically. GORD, H. pylori-related peptic ulcers, and NSAID-induced problems are addressed in separate sections in the guideline, while gastric cancer is discussed, where appropriate, in the relevant sections.

A large group of individuals remain with non-ulcer or functional dyspepsia. Management approaches for these individuals are varied and have a high placebo response rate. Broad management issues are covered separately for this group.

NSAIDs, particularly aspirin, have a very useful part to play in the treatment of a variety of non-gastrointestinal conditions (eg, arthritis, and prevention of ischaemic heart disease and stroke). Individual evaluation of the risks and benefits is required, preferably by the medical practitioner responsible for that person’s care, although team consultation with other practitioners involved may be necessary. Risk factors for GI complications are defined, and potential adverse effects of NSAIDs are described. Where there is an increased risk of NSAID-induced GI complications, or any adverse effects, NSAID treatment may be able to be stopped. However, if he benefit of continued treatment outweighs the risks, treatment can be continued, providing appropriate steps are taken as described in this Guideline, to minimise the degree of risk. An alternative medication could also be considered. While this Guideline provides evidence-based advice on best management, it cannot replace the art of medicine required in the care of individuals.
SUMMARY AND RECOMMENDATIONS

KEY MESSAGES

Initial Evaluation
- Identify risk factors for organic pathology. If there are alarm signals, or if age >50 years at first presentation, refer for oesophago-gastro-duodenoscopy (OGD).
- If there is any heartburn, manage as GORD.
- If a NSAID is being used, evaluate risk of GI complications, as well as potential benefit (eg, from aspirin use for prevention of cardiovascular events and stroke).

Undifferentiated Dyspepsia
- If prevalence of \textit{H. pylori} >30%, treat empirically (domperidone or H$_2$RA for 4 – 12 weeks) OR test for \textit{H. pylori} and treat if positive. If there is no response to test-and-treat, or if prevalence of \textit{H. pylori} <30%, treat empirically. If there is no response to either strategy, refer for OGD.

GORD
- Commence empiric step-down therapy, and adjust according to response.
- If there is no response or early recurrence after cessation of treatment, refer for OGD, and manage according to the severity (Grade) of GORD.

\textit{H. pylori} Management
- Test for \textit{H. pylori} in those with past history of peptic ulcer, family history of gastric cancer, or where the prevalence of \textit{H. pylori} is >30%. Urea breath test is recommended. Serology can be used where the prevalence of \textit{H. pylori} is >30%. Faecal antigen test is also recommended, and is becoming increasingly available in New Zealand. If testing is positive, treat with triple therapy.
- Check eradication of \textit{H. pylori} in those with a peptic ulcer complication, important comorbidity factors, symptom recurrence or those living in isolated areas. Re-treat if testing is positive.

Peptic Ulcer
- If peptic ulcer is identified, test for \textit{H. pylori}, treat if positive, and start a PPI or H$_2$RA. Treat gastric ulcers for 8 – 12 weeks, and check healing with OGD. Treat duodenal ulcers for 4 – 8 weeks (not essential if \textit{H. pylori} eradicated and no complications).

NSAID Use
- If there is no dyspepsia, consider a safer alternative, or a less toxic NSAID (eg, ibuprofen). If continued use is required, and there is increased risk of GI complications, consider a PPI or misoprostol, or possibly a COX-2 inhibitor (providing patient not on aspirin).
- If there is dyspepsia and increased risk of GI complications, refer for OGD. Eradicate \textit{H. pylori} if positive at OGD.
- If there is dyspepsia and no increase in risk, stop NSAID, use a safer alternative, reduce the dose, or use a less toxic NSAID. If symptoms continue, refer for OGD. Eradicate \textit{H. pylori} if positive at OGD.
- If an ulcer is identified, and continued NSAID use is required, treat with a PPI, and consider use of a COX-2 inhibitor as an alternative.
### RECOMMENDATIONS

#### UNDIFFERENTIATED DYSPEPSIA

Initial management of undifferentiated dyspepsia

<table>
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<tr>
<th><strong>RECOMMENDATIONS</strong></th>
<th><strong>GRADE</strong></th>
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<td>If there are any alarm signals, or if the person is aged &gt;50 years at first presentation, refer for OGD.</td>
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#### Empiric therapy

- For people with heartburn, manage as GORD (see recommendations for GORD).
- For people with dyspepsia but no heartburn (reflux) symptoms, either:
  - treat initially with domperidone or H₂RAs OR if aged <50 years and in an area of high (>30%) *H. pylori* prevalence
  - test-and-treat* for *H. pylori*.

---

* Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

---

* Although data regarding the prevalence of *H. pylori* infection in New Zealand are patchy, the following statements can be made:
  - rates in the South Island are well below 30%
  - rates tend to be >30% in adult Maori, Pacific peoples, native populations in Asia, and those with lower socio-economic status
  - rates in adults living in Auckland have generally been found to be >30%.

#### GOOD PRACTICE POINTS

- Review lifestyle factors (eg, diet, weight, smoking, alcohol).
- If alarm signals indicate organic disease, refer to specialist for OGD.
- If there is heartburn and dyspepsia, treat as GORD in the first instance.
- Review person’s intake of all medications, especially NSAIDs.
- Commence empiric therapy in those without alarm signals or heartburn.
- If there is concurrent use of NSAIDs, evaluate for risk of GI complications, and consider alternative strategies if risk is increased. (See Chapter 5: NSAIDs and GI Complications.)

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Recommended best practice based on the clinical experience of the Guideline Development Team.
Management of recurring undifferentiated dyspepsia

**RECOMMENDATIONS**

If there is failure to respond to treatment in 4 – 12 weeks, refer for OGD.  

If previous dyspepsia symptoms recur 1 – 6 months after cessation of treatment, re-evaluate person for alarm signals, taking into account timing of relapse and severity of symptoms.  

If previous dyspepsia symptoms recur after 6 months with no alarm signals, repeat empiric therapy.  

If symptoms recur after test-and-treat, refer for OGD.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

Management of functional dyspepsia

**RECOMMENDATIONS**

Provide reassurance regarding the absence of organic pathology.  

Encourage lifestyle changes: diet, weight control, smoking cessation, and alcohol moderation.  

Consider drug therapy in the following order:  
1. prokinetics (domperidone) NNT 2.8 (NNT based on total prokinetics studied)  
2. H$_2$RAs NNT=5.9  
3. PPIs NNT=11.1.

Test-and-treat people aged <50 years with dyspeptic symptoms (excluding heartburn) and no alarm signals who originate from areas of high *H. pylori* prevalence (>30%).  

Consider *H. pylori* eradication in others.

**GOOD PRACTICE POINT**

Check patient:  
- does not have heartburn  
- is not taking NSAIDs  
- has normal blood tests (FBC, ESR, CRP)  
- has normal OGD.

Recommended best practice based on the clinical experience of the Guideline Development Team.
GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

GORD symptoms

RECOMMENDATIONS

Consider GORD in people with:

- heartburn (burning sensation radiating from the epigastrium towards the neck)
- non-cardiac chest pain, asthma, chronic cough, hoarseness of voice and erosion of teeth

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

Initial management with empiric therapy

RECOMMENDATIONS

If the person’s symptoms are suggestive of GORD, treat with a step-down drug regimen, usually in 4 – 8 week steps:

Step 1. full-dose PPI (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg) daily
Step 2. half-dose PPI
Step 3. H₂RA (famotidine 20 – 40 mg, ranitidine 150 – 300 mg) twice daily
Step 4. antacids/alginate.

If there is no response to full dose PPI therapy, double the dose.

Continue treatment for at least 3 – 6 months.

If the person fails to respond, or if symptoms recur within 1 month after end of treatment, consider OGD rather than long-term empiric therapy.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

GOOD PRACTICE POINT

Exclude people with alarm signals from empiric therapy, and refer for OGD.

Recommended best practice based on the clinical experience of the Guideline Development Team.
### Treatment of GORD diagnosed after OGD

#### RECOMMENDATIONS

**People with grades 0, A and B**
- Treat with a step-down drug regimen (see Algorithm 3: Heartburn +/- Dyspepsia: Empiric Therapy).
- If symptoms recur at stepped-down dosage, continue on lowest effective dose; intermittent therapy may control symptoms.

**People with grades C and D**
- Treat with ongoing continuous full-dose PPI treatment.

Consider surgery as an alternative to long-term drug treatment if:
- age <50 years
- age 50 years and over and there is no comorbidity
- there is inability or unwillingness to take medications
- there is inadequate control with medical therapy.

If high-dose PPI treatment fails, re-evaluate symptoms and consider 24-hour pH telemetry.

In people with Barrett’s oesophagus or unresolved complications (grade D), re-evaluate with OGD if necessary.

**Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.**
HELICOBACTER PYLORI AND PEPTIC ULCERATION

Initial diagnostic investigation for *H. pylori*

**RECOMMENDATIONS**

Test-and-treat for *H. pylori* in those:
- who originate from areas of high (>30%) *H. pylori* prevalence
- with present or past history of peptic ulcer
- with Mucosa-associated lymphoid tissue lymphoma
- with a family history of gastric cancer.

Recommended diagnostic tests
- Urea breath test (UBT) is the recommended non-invasive test. Stop treatment (other than antacids) for 2 weeks prior to UBT.
- Although UBT and faecal antigen tests are also valid options, serology (validated with sensitivity and specificity of at least 90%) is recommended where the prevalence of *H. pylori* is high (>30%).
- Faecal antigen test is also recommended, although it is not yet universally available in New Zealand. Omeprazole can interfere with the result.
- If OGD is being performed for investigation of dyspepsia, consider testing with the rapid urea test, histology or culture.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

Initial treatment of *H. pylori*

**RECOMMENDATIONS**

Give triple therapy: regimens containing PPI, clarithromycin, and amoxycillin or metronidazole, have consistently high eradication rates after one week.

Substitute metronidazole for amoxycillin in penicillin-allergic individuals.

Emphasise to the person that successful eradication depends on compliance with treatment regimen.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
**H. pylori treatment failure**

**RECOMMENDATIONS**

For initial treatment failure, use either of the following for 1 week:
- an alternative triple therapy regimen (PPI plus two of the following: clarithromycin, amoxicillin, metronidazole, tinidazole, tetracycline and bismuth), **OR**
- quadruple therapy (standard triple therapy plus bismuth).

Repeated treatment failure:
- review compliance factors and consider testing for bacterial resistance
- consider retreatment for 2 weeks.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

**Confirmation of H. pylori eradication**

**RECOMMENDATIONS**

Confirm eradication of *H. pylori* in those with a peptic ulcer complication, important comorbidity factors, symptom recurrence or residence in isolated areas.

Recommended tests
- UBT is the recommended non-invasive test (serology should not be used because it takes 6 – 12 months to become negative).
- *H. pylori* stool antigen may be used for confirmation of eradication at least 4 weeks after stopping treatment. Omeprazole can interfere with result.
- For people having OGD to check for healing of gastric ulcer, confirm eradication by histology.

Timing of tests
- Perform at least one month after completion of eradication regimen
- For people taking PPIs, perform at least one week after cessation of PPI.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
Management of *H. pylori*-negative peptic ulcers

**RECOMMENDATIONS**

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<tbody>
<tr>
<td>Treat duodenal ulcers with ( \text{H}_2 \text{RAs} ) or PPIs for 4 – 8 weeks.</td>
<td>A</td>
</tr>
<tr>
<td>Treat gastric ulcers with PPIs or ( \text{H}_2 \text{RAs} ) for 8 – 12 weeks and confirm healing with OGD.</td>
<td>A</td>
</tr>
<tr>
<td>Use maintenance treatment with ( \text{H}_2 \text{RA} ) or PPI if:</td>
<td>C</td>
</tr>
<tr>
<td>• ulcer recurrences are frequent (eg, more than once per 12 months) or severe</td>
<td></td>
</tr>
<tr>
<td>• there is a previous peptic ulcer complication</td>
<td></td>
</tr>
<tr>
<td>• there are comorbid factors that might make any complications life-threatening.</td>
<td></td>
</tr>
</tbody>
</table>

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

**NSAIDS AND GI COMPLICATIONS**

Individuals at increased risk of NSAID-induced GI complications

**RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begin treatment with either of the following:</td>
<td>A</td>
</tr>
<tr>
<td>• misoprostol at doses of 200 mcg/day. Increase dose over two weeks as tolerated, to a maximal dose of 800 mcg/day</td>
<td></td>
</tr>
<tr>
<td>• standard doses of PPI once daily.</td>
<td></td>
</tr>
<tr>
<td>Eradicate <em>H. pylori</em>, if testing is positive.</td>
<td>A</td>
</tr>
</tbody>
</table>

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
Treatment of NSAID-related dyspepsia

**RECOMMENDATIONS**

- Review person’s history for risk factors.  
  
- Stop NSAID if possible.  
  
- In person with symptoms and risk factors, refer for OGD.  
  
- If ongoing symptom relief is needed:  
  - continue NSAID with co-prescription of PPI or misoprostol OR  
  - replace NSAID with COX-2 selective inhibitor.  
  
- Eradicate *H. pylori* if testing is positive.  

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

Management of NSAID-induced Peptic Ulcer

**RECOMMENDATIONS**

- If NSAID can be stopped, treat with an H$_2$RA (ranitidine 150 mg twice daily or famotidine 20 mg twice daily) or PPI (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) for 8 weeks for duodenal ulcers and 12 weeks for gastric ulcers.  
  
- If NSAID needed:  
  - treat with PPI for 8 weeks for duodenal ulcer and 12 weeks for gastric ulcer; if unsuccessful increase dose. Ongoing maintenance treatment is advised (as for individuals at increased risk of NSAID-induced GI complications)  
  - consider replacement of NSAID with COX-2 selective inhibitor.  
  
- Eradicate *H. pylori* if testing is positive.  
  
- Refer individuals with complications (ie, bleeding, perforations, obstruction) to specialist.  
  
- Check healing of gastric ulcer with OGD.  

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
ALGORITHM 1
DYSPEPSIA and/or HEARTBURN: Initial Evaluation

**NO**

? Age >50 years at first presentation

NO

? Heartburn (with/without dyspepsia)

NO

? NSAID use

NO

See Undifferentiated Dyspepsia (Algorithm 2)

YES

See NSAIDs & GI Complications (Algorithm 3)

YES

OGD

NO

Full clinical assessment

YES

? Alarm signals*

NO

See GORD (Algorithm 3)

*Alarm Signals
People with alarm signals must be referred for OGD investigation. Alarm signals, which increase the likelihood of significant organic disease, include the following:
- family history of gastric cancer (onset <50 years)
- severe or persistent dyspeptic symptoms
- previous peptic ulcer disease, particularly if complicated
- ingestion of NSAIDs in those at risk (see Algorithm 5: NSAID and GI Complications)
- unexplained weight loss
- gastrointestinal bleeding (haematemesis or melaena)
- anaemia
- dysphagia (difficulty swallowing)
- coughing spells or nocturnal aspiration
- protracted vomiting or persistent regurgitation of food
- palpable abdominal mass.

NB: All symptoms should be regarded as more serious in people who are aged >50 years when presenting for the first time. Gastric cancer tends to occur a decade earlier in people of Maori, Pacific Island or Asian origin.
ALGORITHM 2
UNDIFFERENTIATED DYSPEPSIA

UNDIFFERENTIATED DYSPEPSIA:
Initial Evaluation (See Algorithm 1)

? High H. pylori prevalence (>30%)

NO

Empiric therapy (4 – 12 weeks)
• Lifestyle factors
• Antacids
• Drug therapy
  1. Domperidone
  2. H₂RA
  3. PPI

NO

? Response in 4 – 12 weeks

NO

? Recurrence

NO

? Alarm signals (Algorithm 1)

YES

OGD

YES

OGD

YES

Manage as Functional Dyspepsia
• Provide reassurance
• Encourage lifestyle changes
• Consider drug therapy
  1. Domperidone
  2. H₂RA
  3. PPI

NO

? Organic pathology

YES

? Recurrence

YES

Appropriate care

NO

No Further Action

* The recommendation of the Working Party is to test-and-treat for H. pylori where the prevalence in the population under 50 years of age is >30%. In populations where prevalence is <30%, benefit of the test-and-treat approach is variable. Although data regarding the prevalence of H. pylori infection in New Zealand are patchy, the following statements can be made:
  • rates in the South Island are well below 30%
  • rates tend to be >30% in adult Maori, Pacific peoples, native populations in Asia, and those with lower socio-economic status
  • rates in adults living in Auckland have generally been found to be >30%.
ALGORITHM 3
GORD

HEARTBURN (+/- Dyspepsia): Initial Evaluation
(See Algorithm 1)

Empiric Therapy
- Lifestyle factors
- Step-down medication
  (4 – 12 weeks for each step)
  - Step 1: PPI full dose
  - Step 2: PPI half dose
  - Step 3: H2RA twice daily
  - Step 4: Antacid/alginate
  - As necessary treatment

? Response

YES
Continue step-down treatment

? Recurrence

NO
Severe and/or frequent

• OGD
• Grade GORD

NO
Mild and/or infrequent

Symptomatic treatment at lowest effective medication dose (if any)

? Severity

NO
No further action

YES
Step-down PPI

Grade 0, A or B

Full dose, long-term PPI

Grade C or D

Complicated (eg, stricture, Barrett’s oesophagus)

Gastro follow-up

Note: Surgery is an alternative for selected people
ALGORITHM 4
PEPTIC ULCER

? NSAID use

NO

? H. pylori positive

NO

PPI or H2RA

Gastric Ulcer
• Treat for 8 – 12 weeks
• Confirm healing with OGD and biopsy

Duodenal ulcer
• Treat for 4 – 8 weeks
Note: If H. pylori treated, and there are no complications, acid suppression is not essential

? Complication or comorbidity

NO

Symptomatic follow-up

YES

Ensure H. pylori eradication (urea breath test, or faecal antigen test if no OGD)
**Algorithm 5**

**NSAIDS AND GI COMPLICATIONS**

1. **NSAID use**
   - NO
   - YES
     - Initial Evaluation (See Algorithm 1)
       - ? Increased risk*
         - NO
         - YES
           - ? Safer alternative
             - NO
             - YES
               - ? Response
                 - NO
                 - YES
                   - Use lowest effective dose
                     - NO
                     - YES
                       - Prophylactic co-therapy
                         - PPI
                         - Misoprostol
                       - YES
                         - Consider COX-2 agent in selected high-risk people if NOT on aspirin
                         - Note cost/effect profile
                       - NO
                       - YES
                         - ? Increased risk*
                           - NO
                           - YES
                             - ? Response
                               - NO
                               - YES
                                 - ? Lower dose or less toxic NSAID eg, ibuprofen
                                   - NO
                                   - YES
                                     - ? Safer alternative
                                       - NO
                                       - YES
                                         - ? Response
                                           - NO
                                           - YES
                                             - OGD
                                             - YES
                                               - Eradicate H. pylori if testing is positive
                                                 - NO
                                                 - YES
                                                   - ? Ulcer
                                                     - NO
                                                     - YES
                                                       - Co-therapy
\* Increased risk of GI complications:
- Age <65 years and 2 risk factors
- Age >65 years and 1 risk factor

**Risk factors**
- History of peptic ulcer
- History of GI bleeding
- Significant co-morbidity
- Previous NSAID gastropathy
- Concomitant use of:
  - corticosteroids
  - anticoagulants
  - bisphosphonates
- High dose NSAID (includes NSAID and aspirin)

---

Second-line intervention

**NB:** Cost/adverse effect profile of all medications
The word ‘dyspepsia’ comes from the Greek ‘dys’ meaning ‘bad’ and ‘pepsia’ meaning ‘digestion’. Dyspepsia is a common symptom complex with epigastric pain and other associated features. Dyspepsia may have an organic cause such as peptic ulcer, but is more frequently associated with normal or near-normal findings on gastroscopy (ie, functional or non-ulcer dyspepsia).

In Britain it has been estimated that more money is spent on drugs for dyspepsia than on any other treatment for a symptom. It is likely a similar situation exists in New Zealand. About 25% of people with dyspepsia in Britain consult their general practitioner for the problem; the remainder either use no medication or self-medicate. Self-medication is common amongst people with dyspepsia.

Management of dyspepsia is variable, and a number of possible strategies have been recommended in different guidelines. This evidence-based guideline attempts to provide a framework that is appropriate for New Zealand conditions.

**WHAT IS DYSPEPSIA?**

Dyspepsia, or indigestion, is a common symptom complex, defined as pain or discomfort centred in the upper abdomen (epigastrium). Dyspepsia may have a number of associated symptoms, including fullness after meals, bloating, belching, early satiety, anorexia, nausea and vomiting. Heartburn, retrosternal pain and acid regurgitation, although commonly included with dyspepsia, relate more to lower oesophageal dysfunction, which is treated separately in this guideline. Heartburn is also linked with some dyspepsia subgroups and with cardiac disease. Some people may have both symptom complexes.

Symptoms of dyspepsia may be episodic, recurrent or chronic. Many but not all symptoms are related to food. Symptoms connected with the process of defaecation are excluded from a definition of dyspepsia as they relate more to bowel function in the lower part of the GI tract. However, a number of people will have both dyspepsia and lower abdominal symptoms.

Dyspepsia is not a diagnosis. It is a symptom complex associated with upper gastrointestinal (GI) tract conditions (eg, peptic ulcer or gastric cancer), other upper abdominal pathology (eg, gallstones), or disorders related to other systems (eg, cardiovascular). People with dyspeptic symptoms and no demonstrable organic cause, are said to have functional dyspepsia.
Attempts have been made to link particular symptoms with specific pathological entities. Heartburn—defined as a burning sensation starting in the epigastrium and radiating towards the neck—is classified as a reflux-like symptom. Heartburn is the most reproducible and sensitive indicator of gastro-oesophageal reflux disease (GORD) with a specificity (the probability of correctly excluding those without the disease) of about 75%, but it may also be linked with some dyspepsia subgroups and with cardiac disease. Heartburn may also indicate potentially more serious oesophageal disorders.

Dyspepsia has been sub-classified into ulcer-like (localised epigastric pain, either aggravated or relieved by meals and relieved by antacids) and dysmotility-like (fullness after meals, bloating, belching, early satiety, anorexia, nausea and vomiting). Although these sub-categories have some use in directing initial approaches to empiric treatments for non-ulcer dyspepsia, and are still favoured by some, the sensitivity and specificity of these are very poor in predicting specific organic conditions.

Table 1.1: Dyspepsia sub-groups

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux-like</td>
<td>Heartburn - acid regurgitation</td>
</tr>
<tr>
<td>Ulcer-like</td>
<td>Upper abdominal pain predominant with three or more of:</td>
</tr>
<tr>
<td></td>
<td>• epigastric pain or discomfort</td>
</tr>
<tr>
<td></td>
<td>• pain relieved by food</td>
</tr>
<tr>
<td></td>
<td>• pain relieved by antacids or ulcer-reducing drugs</td>
</tr>
<tr>
<td></td>
<td>• pain occurring before meals or when hungry</td>
</tr>
<tr>
<td></td>
<td>• pain that at times wakens the person from sleep</td>
</tr>
<tr>
<td></td>
<td>• periodic pain with remission and relapse</td>
</tr>
<tr>
<td>Dysmotility-like</td>
<td>Upper abdominal discomfort characterised by three or more of:</td>
</tr>
<tr>
<td></td>
<td>• early satiety</td>
</tr>
<tr>
<td></td>
<td>• post-prandial fullness</td>
</tr>
<tr>
<td></td>
<td>• nausea</td>
</tr>
<tr>
<td></td>
<td>• retching and/or vomiting</td>
</tr>
<tr>
<td></td>
<td>• bloating in upper abdomen not accompanied by visible distension</td>
</tr>
<tr>
<td></td>
<td>• upper abdominal discomfort often aggravated by food.</td>
</tr>
<tr>
<td>Unspecified (non-specific)</td>
<td>Dyspepsia that cannot be classified into the other groups</td>
</tr>
</tbody>
</table>
ALARM SIGNALS

The following features increase the likelihood of significant organic disease:

- family history of gastric cancer (onset age <50 years)
- severe or persistent dyspeptic symptoms
- previous peptic ulcer disease, particularly if complicated
- ingestion of NSAIDs, particularly in those at risk
- unexplained weight loss
- GI bleeding
- anaemia
- dysphagia (difficulty swallowing)
- coughing spells or nocturnal aspiration
- protracted vomiting
- palpable abdominal mass.

NB: All symptoms should be regarded as more serious in people who are aged >50 years when presenting for the first time. Gastric cancer tends to occur a decade earlier in people of Maori, Pacific Island or Asian origin.

Although classification into various subtypes of dyspepsia is generally unreliable, there is reasonable evidence that the majority of people presenting with heartburn have gastro-oesophageal reflux disease (GORD). However, there is significant overlap between dyspepsia and reflux symptoms. In a New Zealand study, Haque et al showed that 56% of those with non-specific dyspepsia symptoms also have GORD symptoms, with the reverse in 63%. In such cases, the initial focus should logically be directed towards the reflux symptoms, which have a much greater sensitivity and specificity for a more specific diagnosis (GORD), and which often respond to treatment for this.

The literature on dyspepsia very often fails to differentiate between heartburn (as defined) and dyspepsia (non-specific and including heartburn), and conclusions drawn on natural history and effect of treatment have become confused because of this. In this guideline, heartburn (as defined) will be regarded as an initial indicator of GORD (see Chapter 3: Gastro-oesophageal Reflux Disease).
HOW COMMON IS DYSPEPSIA?

Dyspepsia is very common in the population at large, with a prevalence of between 23 and 41% in OECD countries, with much of the variation appearing to be due to differences in definitions of relevant symptoms and their duration.\(^8\)\(^9\) Significantly, most of those suffering from dyspepsia do not seek medical advice for their symptoms, often accepting them as a natural consequence of their diet or lifestyle. This is reflected in the widespread consumption of readily available over-the-counter antacids.

Haque et al received an 81.7% response rate to a questionnaire sent to 1000 randomly selected adults in the Wellington region.\(^7\) Respondents were asked about symptoms of heartburn and abdominal pain, and whether they ‘kept getting’ symptoms. They were also asked to rate symptoms as ‘mild’ (can be ignored), ‘moderate’ (can’t be ignored but not affecting lifestyle) or ‘severe’ (affecting lifestyle). Defining ‘significant’ as occurring more than monthly or with severity greater than mild, the researchers found that 34% of respondents reported significant symptoms of dyspepsia (defined as occurring more than monthly or with severity greater than mild) and 30% had significant heartburn. In all, 45% of respondents had one or both symptoms. Of those with GORD symptoms, 70% took over-the-counter medication and only 17% had consulted their general practitioner for this problem in the previous year.

Estimates of the number of new dyspepsia sufferers per year are difficult to gauge, but it has been estimated that 5 – 10% of the adult population who did not previously have dyspepsia will develop the symptom in any one year.\(^10\)

Dyspepsia can occur at any age but in older age groups it is more likely to be associated with organic diseases such as peptic ulcers (ie, gastric and duodenal ulcers) and cancer. Nonsteroidal anti-inflammatory drugs (NSAIDs), which are significantly associated with dyspepsia and peptic ulceration, are more often prescribed in older people (aged >65 years) and complications are more common in this group. It should be remembered that aspirin is a NSAID which has a significant effect on the GI tract even at low dosage, and is widely prescribed in the older age group (See chapter 5: NSAIDs and GI Complications).

Although ethnicity may have implications for disease patterns, no accurate figures are available relating to dyspepsia in New Zealand. However, \(H.\, pylori\) infection, which is linked to peptic ulceration (see Chapter 4: Helicobacter pylori and Peptic Ulceration), is more prevalent among Maori and Pacific Island people.\(^11\) A dominant genetic disorder that predisposes members of a Maori family group to develop gastric cancer at a young age has been identified.
POPULATION SEEKING MEDICAL ADVICE

Besides the severity and persistence of dyspepsia, many other factors (including psychosocial issues) are important in determining who seeks medical consultation, although these factors are not well understood. Studies such as a postal survey conducted by Jones et al. have shown that only about 25% of people with dyspepsia actually seek medical advice. Nevertheless, because dyspepsia symptoms are so common, this accounts for between 3 and 10% of the adult population and for between 2 and 7% of visits to general practitioners.

One British study estimated that 4 to 5% of general practice consultations are for dyspepsia. Results obtained by McAvoy et al in the New Zealand-based WaiMedCa study showed that 6.4% of general practice consults were for digestive problems (both upper and lower GI symptoms) and resulted in a higher referral rate for secondary investigation (12% of consults) compared with consultations relating to other systems.

QUALITY OF LIFE WITH DYSPEPSIA

A number of studies have shown an association between dyspepsia and reduced quality of life. In general, people with functional dyspepsia score higher on measures of anxiety, neuroticism, depression and hypochondriasis compared with healthy controls. These personality profiles are similar to people with other pain syndromes, both organic and functional in nature. Haug et al compared 100 people with functional dyspepsia, 100 with duodenal ulcer, and 100 controls, and found that those with functional dyspepsia had more anxiety and depression, and a lower general level of functioning than people in the other two groups. In addition, those with functional dyspepsia had more frequent dyspepsia symptoms and longer duration of symptoms than those with duodenal ulcer. However, it was more difficult to recruit people with functional dyspepsia, which may have biased this group towards those with more severe symptoms.

Interestingly, quality-of-life scores (as judged by total symptoms) improve with improvement of dyspepsia, suggesting that anxiety and stress-related symptoms may be the result of dyspepsia rather than its cause.

The quality of life of people with GORD has been shown to be similar to that of people with severe angina pectoris.
CAUSES OF DYSPEPSIA

The causes of dyspepsia are shown in Table 1.2. The prevalence figures given are derived from the small minority of people who are referred to gastroenterologists for investigation and definitive diagnosis. It can be reasonably assumed that more people with functional dyspepsia will be treated at the general practice level and that those with organic disorders will be more likely to be referred to specialists. However, reliable data to support this are not available.

**Table 1.2: Causes of dyspepsia diagnosed by OGD**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Auckland n = 399</th>
<th>Dunedin n = 500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>43.9</td>
<td>47.4*</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>29.1</td>
<td>28.4</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>4.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>4.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>9.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Cancer: stomach oesophagus</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Other</td>
<td>9.3</td>
<td>10.4</td>
</tr>
</tbody>
</table>

* Includes gastritis hiatal hernia (isolated finding)

**Sources:**
- Dunedin data: Barbezat GO. Unpublished data. First 500 endoscopies of 2001; total 106.8%, as some with >1 diagnosis.

Gastro-oesophageal Reflux Disease (GORD)

This condition is common in OECD countries but rare in the rest of the world. It encompasses a broad range of clinical disorders, from simple acid reflux without inflammation of the oesophagus to severe oesophagitis and its complications. Besides typical heartburn and acid regurgitation symptoms, people may present with atypical chest pain, and respiratory and throat symptoms (e.g., cough, asthma, hoarseness).

Unfortunately, there is a poor correlation between endoscopically demonstrable oesophageal inflammation and the severity of symptoms, as at least half the people with symptomatic gastro-oesophageal reflux will have a normal OGD. It has been demonstrated that it is exceedingly rare for OGD-negative and minor grades of oesophagitis to progress to the severe complicated forms. Treatment is aimed not only at relieving symptoms but at treating or preventing inflammatory changes and complications in the more severe grades.
Peptic ulcer

Gastric ulcer

By definition, a gastric ulcer occurs in the stomach and implies a break in the gastric lining that extends through the muscularis mucosa. The development of a gastric ulcer requires the presence of acid and pepsin, and in about 60 – 70% of cases, is also associated with the presence of the bacterium *H. pylori*. Most other gastric ulcers can be attributed to the ingestion of NSAIDs, including aspirin.

Dyspepsia, nausea and vomiting are characteristic symptoms associated with gastric ulcer, particularly when dyspepsia occurs soon after the ingestion of meals. However, these symptoms have very poor sensitivity and specificity for gastroscopically confirmed gastric ulcer. Complications (especially bleeding but also perforation and obstruction) can be life-threatening, particularly in older people in whom comorbidity complicates medical management. Asymptomatic individuals (particularly those taking NSAIDs) who present for the first time with complications (eg, bleeding and perforations) may have peptic ulcers.

Gastric ulcers must be differentiated from malignant ulcers with which they may occasionally coexist. Having a gastric ulcer increases the risk of gastric malignancy. Ordinary gastric ulcers do not appear to progress into cancers. However, because gastric cancers can masquerade as, or coexist with, gastric ulcers, healing of gastric ulcers should be checked endoscopically and histologically. Most gastric ulcers can be treated medically, and surgery is usually reserved for a minority of those with complications.

Duodenal ulcer

These usually occur in the first 2 – 3 cm of the duodenum, just distal to the stomach, where the small intestine is exposed to gastric acid. The presence of acid is essential to the development of the ulcers, and about 95% of duodenal ulcers are also associated with the presence of *H. pylori*. In recent years, the proportion of *H. pylori*-positive duodenal ulcers appears to be declining in OECD countries. This has been associated with a decreased prevalence of *H. pylori* infection and possibly increased ingestion of NSAIDs.

Duodenal ulcers can occur at any age, but are more frequent from the late 30s onwards, generally occurring two decades earlier than in people who have gastric ulcers. Individuals typically experience food-related dyspeptic symptoms (pain that occurs a few hours after a meal, is relieved by the ingestion of food or antacids, and/or may interrupt sleep). However, duodenal ulcers often occur in the absence of typical symptoms.

The commonest complication is bleeding. Upper GI haemorrhage has an incidence of 100 per 100,000 in the USA and Britain; peptic ulcers are the commonest cause of this bleeding in both countries. A small proportion of duodenal ulcers may perforate, or heal with scarring (resulting in upper GI obstruction), although both of these complications are now extremely rare.

Duodenal ulcers are not precancerous; indeed, gastric cancers are less common in people with duodenal ulcers. The vast majority of duodenal ulcers (over 95%) can be healed
with appropriate medical treatment, including acid inhibition and *H. pylori* eradication. Ulcer recurrence is common (up to 88% by 1 year), unless *H. pylori* is eradicated. Recurrence after *H. pylori* eradication is rare.\(^{37}\)

**Cancer**

**Gastric cancer**

Cancer of the stomach accounts for a small minority of people with dyspepsia (1 – 2% of OGDs). It is uncommon in the European population in New Zealand and is extremely rare below the 46 to 55 age group. However, it is more prevalent among certain ethnic groups, including Maori, Pacific and East Asian people.\(^ {38}\) One Maori family cohort with a genetic predisposition to gastric cancer has been identified; these individuals can present at a very young age (from adolescence onwards).\(^ {39}\)

*H. pylori* has been shown to be a carcinogen (see pages 52 – 53). In the early stage of gastric cancer, dyspepsia may be the only symptom. In later stages, presenting symptoms include weight loss, anaemia, early satiety and, in some cases, pyloric obstruction. Because gastric cancers can masquerade as, or coexist with, gastric ulcers, healing of gastric ulcers should always be checked endoscopically and histologically.

Cure of gastric cancer usually depends on early diagnosis and appropriate surgical intervention. The cure rate is generally poor, with recent figures varying from 5 to 30% in most OECD countries, although better results have been obtained where surgical resection has been possible.\(^ {40}\) Different forms of early gastric cancers may exist in Japan, making interpretation of research studies difficult.\(^ {41}\)

**Gastric lymphomas**

Other gastric malignant conditions include lymphomas. Some lymphomas involving the stomach are related to *H. pylori* infection (mucosa-associated lymphoid tissue, or MALT lymphoma) and can now be treated medically (see Chapter 4: *Helicobacter pylori* and *peptic ulceration*). Overall, gastric lymphomas are less common than cancers (about 10% of gastric malignancies) but have better survival rates (often 40 – 50%).\(^ {42}\)

**Oesophageal cancer**

Although some people with oesophageal cancer will present with symptoms of reflux or dyspepsia, most will have dysphagia as their presenting symptom. This will not be pursued further in this guideline.

**Non-Ulcer Dyspepsia (NUD)**

Other common organic causes of dyspepsia include symptomatic cholelithiasis (ie, gallstones) and ingestion of drugs (eg, NSAIDs, aspirin, iron, digoxin, theophylline, antibiotics, and potassium). Less common causes include gastric dysmotility (eg, with diabetic gastroparesis), chronic mesenteric ischaemia, chronic pancreatitis, pancreatic malignancy, gastric surgery, lower GI tract disorders, partial small bowel obstruction, Crohn’s disease, coeliac disease, liver cancer, and malabsorption syndromes. Non-gastrointestinal causes
include cardiac pain, metabolic disturbances, collagen vascular disorders and abdominal wall syndromes.\textsuperscript{43,44}

Although conditions such as cholecystitis with gallstones, lactose intolerance, pancreatitis and achalasia of the oesophagus usually present with their own, often typical, constellation of symptoms, many people with these conditions present in a non-specific way with dyspepsia. Certain aspects of the person’s history or examination may offer clues for a correct diagnosis, and where necessary be confirmed by the appropriate choice of investigations.

**Functional dyspepsia**

This term includes all defined cases of dyspepsia in which ulceration, GORD, malignancy and other defined conditions have been excluded. ‘Functional’ dyspepsia is defined as dyspepsia of at least several weeks’ duration for which no focal or structural lesion(s) can be found using upper OGD, and which cannot be explained by any other obvious structural or biochemical abnormalities on ultrasound examination or screening blood tests.\textsuperscript{45} This large group of conditions includes common, sometimes stress-related, GI symptoms and disorders of gastric motility with delayed stomach emptying.\textsuperscript{46}

The pathogenesis of functional dyspepsia has been the subject of considerable study, but remains unclear. If defined pathology can be demonstrated for any identifiable subgroup, by definition this cannot be functional dyspepsia.

**RANGE OF MANAGEMENT OPTIONS**

The range of management options is great, particularly if it is accepted that dyspepsia has a wide variety of causes.\textsuperscript{2,47,48,49,50} In addition, many people with dyspepsia will decide that their symptoms are minor or transient enough to ignore, or they will prefer to treat themselves with proprietary antacids or over-the-counter acid inhibitors rather than consult general practitioners. A wide variety of psychosocial factors often affect this decision.

When consulted, the general practitioner must decide whether the person requires reassurance only, empiric treatment, simple investigation, or referral to a gastroenterologist for definitive diagnosis. Appropriate treatment includes the care of the whole person. It is an opportunity to review personal and lifestyle factors (eg, diet, weight control, smoking, alcohol abuse, drug use) and, in a number of cases, this may be all that is required. Most people can be treated by simple medical means with satisfactory outcomes. However, symptomatic recurrence is common, so that repeated courses and sometimes continuous medication may be required.

Once a definitive diagnosis has been made, further follow-up can be defined more precisely. However, for functional dyspepsia, follow-up is often dictated by symptoms. Long-term continuing medication for functional dyspepsia is discouraged. Care needs to be exercised to achieve a balance between not ‘overmedicalising’ and offering rational long-term follow-up when necessary.
The biggest concern for clinicians and those being treated, is probably cancer, specifically, not missing it, and the desire to diagnose any cancer at an early stage. Five-year survival rates are significantly better for stage II gastric cancer (70%) than for stage IV (10–30%).

MEDICAL AND ECONOMIC IMPACTS OF DYSPEPSIA

The common occurrence of dyspepsia makes it an important social and economic condition. Besides discomfort, pain and suffering, dyspepsia is responsible for a significant proportion of absenteeism. It also has a significant impact on the workload of general practitioners and the related costs of primary care (2 – 7% of visits). Specialist investigations, particularly OGD, are costly and require a sophisticated degree of training and facilities to offer people the required diagnosis and management advice. There is considerable pressure on all public hospital endoscopy waiting lists. Although it is tempting to pursue an accurate diagnosis in everyone with dyspepsia, this is neither feasible nor necessary. Careful selection of people, investigation and treatment is essential. This guideline aims to provide recommendations to achieve this.

The proportion of people with dyspepsia referred on for OGD in New Zealand is not known. There is wide variation in access to OGD among regions and in people’s ability to pay for private OGD. Current recommendations are that people with dyspepsia aged 50 years and over and those with alarm signals (see Chapter 2: Undifferentiated Dyspepsia) need referral. However, strict adherence to this age recommendation would undoubtedly put further pressure on OGD services, and clinical judgment is important. Hopefully, appropriate referral will optimise use of OGD.

The cost of medical therapy is significant. According to PHARMAC’s 2002 Annual Report, the cost of prescribed pharmaceutical agents in the treatment of dyspepsia has risen yearly to $44 million (excluding GST), equating with nearly 700,000 prescriptions. However, because the price of pharmaceuticals is so changeable, it is difficult to usefully model the costs of specific treatments. For example, the costs of H$_2$ Receptor Antagonists (H$_2$RAs) and proton-pump inhibitors (PPIs) were initially high but have declined considerably in the last few years. Overseas studies are usually based on completely different price structures and thus have limited, if any, application here. Therefore, great care is required to ensure careful and rational choice of medication to derive most benefit from the health dollar. In many cases, there are treatment alternatives and the cheaper option can often be chosen if there is reasonable evidence for equal outcome. Clinical complexity related to diagnosis and management presents an even greater challenge.

H. pylori eradication has revolutionised the approach to ordinary peptic ulcers, virtually eliminating the need for maintenance treatment. Although a test-and-treat strategy (see Chapter 4: Helicobacter pylori and Peptic Ulceration) has been shown to reduce costs of investigations where H. pylori prevalence is reasonably high, where prevalence is low (eg, in certain areas of the South Island), the cost effectiveness of this approach has still to be evaluated. The role of H. pylori eradication with respect to functional dyspepsia, and perhaps the long-term prevention of gastric cancer, remains controversial.
UNDIFFERENTIATED DYSPEPSIA

OVERVIEW

• Undifferentiated dyspepsia represents a poorly defined group of disorders.
• Alarm signals indicate a higher likelihood of organic disease.
• NSAID use is associated with dyspepsia and peptic ulcer.
• Only about one-quarter of those reporting dyspeptic symptoms seek medical advice. Many of these have self-medicated with antacids and H₂RAs before presentation.
• Treatment responses of those with dyspepsia are different from those with heartburn (75% of whom have GORD). People with heartburn respond best to PPIs, while those with undifferentiated dyspepsia respond better to prokinetic agents and H₂RAs, than PPIs.
• The test-and-treat strategy for *H. pylori* infection has been shown to be effective in areas of moderate to high (>30%) *H. pylori* prevalence. There is no evidence of efficacy for this strategy in areas of low *H. pylori* prevalence.
• Reassurance is an important part of initial therapy.
• Recurrence is common.
INITIAL MANAGEMENT OF UNDIFFERENTIATED DYSPEPSIA

RECOMMENDATIONS

If there are any alarm signals, or if the person is aged >50 years at first presentation, refer for OGD.

Empiric therapy

• For people with heartburn, manage as GORD (see recommendations for GORD).

• For people with dyspepsia but no heartburn (reflux) symptoms, either:
  – treat initially with domperidone or H₂RAs OR if aged <50 years and in an area of high (>30%) H. pylori prevalence

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

* Although data regarding the prevalence of H. pylori infection in New Zealand are patchy, the following statements can be made:
  • rates in the South Island are well below 30%
  • rates tend to be >30% in adult Maori, Pacific peoples, native populations in Asia, and those with lower socio-economic status
  • rates in adults living in Auckland have generally been found to be >30%.

GOOD PRACTICE POINTS

Review lifestyle factors (eg, diet, weight, smoking, alcohol).

If alarm signals indicate organic disease, refer to specialist for OGD.

If there is heartburn and dyspepsia, treat as GORD in the first instance.

Review person’s intake of all medications, especially NSAIDs.

Commence empiric therapy in those without alarm signals or heartburn.

If there is concurrent use of NSAIDs, evaluate for risk of GI complications, and consider alternative strategies if risk is increased. (See Chapter 5: NSAIDs and GI Complications.)

Recommended best practice based on the clinical experience of the Guideline Development Team.
MANAGEMENT OF RECURRING UNDIFFERENTIATED DYSPEPSIA

RECOMMENDATIONS

If there is failure to respond to treatment in 4 – 12 weeks, refer for OGD.  

If previous dyspepsia symptoms recur 1 – 6 months after cessation of treatment, re-evaluate person for alarm signals, taking into account timing of relapse and severity of symptoms.  

If previous dyspepsia symptoms recur after 6 months with no alarm signals, repeat empiric therapy.  

If symptoms recur after test-and-treat, refer for OGD.  

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

MANAGEMENT OF FUNCTIONAL DYSPEPSIA

RECOMMENDATIONS

Provide reassurance regarding the absence of organic pathology.  

Encourage lifestyle changes: diet, weight control, smoking cessation, and alcohol moderation.  

Consider drug therapy in the following order: 
1. prokinetics (domperidone) NNT 2.8 (NNT based on total prokinetics studied)  
2. H2RAs NNT=5.9  
3. PPIs NNT=11.1.  

Test-and-treat people aged <50 years with dyspeptic symptoms (excluding heartburn) and no alarm signals who originate from areas of high H. pylori prevalence (>30%).  

Consider H. pylori eradication in others.  

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

GOOD PRACTICE POINT

Check patient:
• does not have heartburn  
• is not taking NSAIDs  
• has normal blood tests (FBC, ESR, CRP)  
• has normal OGD.  

Recommended best practice based on the clinical experience of the Guideline Development Team.
PROBLEMS ASSOCIATED WITH STUDIES OF DYSPEPSIA

There are a number of problems associated with clinical trials of therapy for dyspepsia, and this is reflected in the number of poor quality trials in the literature. Clinical trials in secondary and tertiary care centres are usually performed on carefully selected people with defined specific diagnoses, usually supported by endoscopic evidence. Treatment groups are thus generally similar and the information provided not necessarily directly relevant to people presenting to general practitioners. Furthermore, individuals who have been referred to secondary and tertiary care centres from primary care may well represent those who fail to respond to simple initial therapy (e.g., H₂RAs or antacids, and now often also PPIs). On the other hand, it could also be argued that if these difficult cases respond to treatment, less severe cases are more likely to respond.

Further issues:

- The placebo effect is very high (mean 56%; range 5 – 90%),\(^1\) which means that any gains from medication are difficult to measure. The placebo effect is generally so consistent that any study with a placebo effect lower than 20% should be interpreted with caution, unless the outcome is complete resolution of symptoms.
- Many trials have inadequate controls.
- Crossover trials are likely to be inaccurate because the duration of benefit may continue for some time beyond the 2 – 4 weeks of treatment.
- Many different definitions of dyspepsia have been used — for instance, some studies include people with predominantly reflux symptoms while others do not.
- Some studies use a washout period with antacid treatment prior to the study proper and exclude any responders, which may reduce the true placebo response rate.
- Some studies have used treatment phases as short as two weeks which may not allow the full benefits of treatment to be seen.
- Few studies have looked at long-term management.
- Most medication studies have been in the secondary health care setting where the person’s characteristics are potentially different from those of people seen in the primary health care setting.
- Different endpoints for benefit are used, from complete resolution of symptoms to reduction in symptom scores, for which different scoring systems have been developed.

AGA MANAGEMENT OPTIONS

The American Gastroenterological Association (AGA) position statement,\(^2\) published in 1998, considered four major options for the management of new-onset dyspepsia.

1. Empiric medical therapy (antisecretory or prokinetic), with any subsequent investigation reserved for treatment failures.
2. Immediate diagnostic evaluation in all cases, preferably with OGD.

3. Testing for *H. pylori* and following up all positive cases with OGD to look for peptic ulcer or cancer.

4. Testing for *H. pylori* and treating all positive cases with potentially ulcer-curing antibacterial therapy.

The conclusion in the accompanying review by Talley is particularly pertinent:

‘The decision to choose empiric therapy, *H. pylori* testing, or initial endoscopy should be based not only on cost, but also on other considerations such as patient and physician attitudes toward uncertainty, the ethics of not identifying a curable disease such as peptic ulcer or cancer, patient satisfaction, institutional or societal forces to restrain the use of diagnostic procedures, and the background prevalence of disease. Guidelines may therefore reasonably endorse any of these management approaches depending on the weight of circumstances in different regions.’

Although other approaches could be suggested, the recommendations of the AGA were endorsed by a working party of the World Congresses of Gastroenterology in 1998.

**COCHRANE REVIEW OF INITIAL MANAGEMENT STRATEGIES**

The recent Cochrane review by Delaney *et al* evaluated the four initial management strategies recommended by the AGA by assessing randomised controlled trials (RCTs) of dyspeptic people presenting in primary care, while a further group of RCTs which treated *H. pylori* without prior testing was also included. A key factor to note concerning this review is that it was restricted to studies of people presenting in primary care. The reasons for excluding studies of people in secondary care were not given, but presumably were based on the assumption that those people were a selected group who may not have responded to initial treatments, and therefore were not representative of the population with dyspepsia who present to general practitioners. It should also be noted that this Cochrane report’s definition of ‘dyspepsia’ included both dyspepsia and heartburn. Unpublished papers and research still under way were examined, as well as published papers. Only 10 trials reporting 12 comparisons met the search criteria. No eligible trials were identified for *H. pylori* testing and OGD of those that tested positive, or *H. pylori* testing and treating of those that tested positive, were identified.

These RCTs showed that PPIs were more effective than both placebo and alginate/antacid, and *H$_2$*RAs. However, the inclusion of people with reflux makes the results difficult to interpret. Those with reflux clearly responded more effectively to more potent acid inhibition. In the heterogenous group, *H$_2$*RAs were no better than alginate/antacid, but the low numbers studied resulted in low statistical power. In one study, PPIs were found to be of similar efficacy to cisapride. From this, it could be postulated that PPIs were more effective in those with reflux while cisapride was more effective in those with functional dyspepsia (as shown in studies where both groups have been differentiated by prior investigation).
Although these studies do not directly address the strategy of empiric medical therapy, they provide the most relevant information on likely response rates for people presenting in primary care. The Cochrane review authors commented that there are no long-term treatment trials. This is an important deficiency because dyspepsia is a chronic relapsing condition, and that intermittent use of medication may be effective. PPIs seem more effective in the treatment of reflux symptoms in the non-differentiated group, but between 5 and 6 individuals would have to be treated for one to gain some benefit. For the symptom of heartburn, the number needed to treat (NNT) for PPIs to gain advantage over antacids and H₂RAs was 3.5 and 3.1, respectively. The effect on those with no reflux symptoms is less clear.

The effectiveness and cost implications of early investigation versus acid inhibition were examined in four trials. No difference was shown in global improvement, and the economic data were also inconclusive. However, several studies are currently under way examining these management strategies and it is hoped they will clarify these issues.

COCHRANE REVIEWS OF PHARMACOLOGICAL INTERVENTIONS

In the Cochrane review by Soo et al, on pharmacological intervention in non-ulcer dyspepsia (NUD), trials with people presenting primarily with heartburn were specifically excluded. The authors felt this would lead to a ‘purer’ cohort with NUD. Their review clearly showed a treatment preference for prokinetic agents, with the important proviso that the results could have been influenced by publication selection bias. Compared with placebo, H₂RAs were shown to be significantly more effective, and PPIs and bismuth salts only marginally superior. This is compatible with results reflecting the exclusion of individuals with heartburn. This review was based on trials of people referred to hospital clinics, and not on presentation to primary care.

Table 2.1: Response to treatment of non-ulcer dyspepsia (heartburn excluded)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative Risk Reduction (RRR)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokinetics</td>
<td>50%</td>
<td>2.8</td>
</tr>
<tr>
<td>H₂RAs</td>
<td>30%</td>
<td>5.9</td>
</tr>
<tr>
<td>PPIs*</td>
<td>12%</td>
<td>11.1</td>
</tr>
<tr>
<td>Bismuth salts*</td>
<td>40%</td>
<td>4.2</td>
</tr>
<tr>
<td>Antacids</td>
<td>no benefit</td>
<td>—</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>no benefit</td>
<td>—</td>
</tr>
</tbody>
</table>

* PPI results mostly from one trial
# Bismuth salts marginally statistically significant, wide CI

The proportion of people presenting with dyspepsia who have peptic ulcer is relatively small when judged by disease incidence, but important with respect to potential for complications. These individuals would respond better symptomatically to acid inhibition and therefore it would be reasonable to treat these people with $H_2$RAs or PPIs. Bismuth salts are no longer favoured as a sole treatment but can be used as part of $H. pylori$ eradication therapy. Clues to peptic ulcer may include night pain, complications (revealed by a number of alarm signals), NSAID use and $H. pylori$ infection.

**COCHRANE REVIEW OF THE TEST-AND-TREAT STRATEGY**

The Cochrane review by Moayyedi et al, examined studies of $H. pylori$ eradication in the management of NUD. In theory, the test-and-treat approach should capture people with peptic ulcers and lead to appropriate treatment in those with ulcers. The outcomes were improvements in individual or global dyspepsia symptom scores and quality-of-life scores. The trials with PPIs in the eradication combination showed a small but significant improvement where dyspepsia cure was defined as no symptoms or mild symptoms not interfering with daily activities at one year after treatment. Relative risk reduction was 7% (95% CI 1 – 12%), with an NNT of 19 to cure one extra case. A follow-up paper included 12 trials and gave similar results, with a relative risk reduction of 9% (95% CI 4 – 14%) and an NNT of 15 for every dyspepsia cure.

These results are underlined by the comprehensive meta-analysis by Laine et al, which concluded that there was little support for the use of $H. pylori$ eradication therapy in people with NUD (see Table 3.5).

**RESULTS OF OTHER STUDIES**

Finny et al conducted a meta-analysis of published studies of antisecretory and prokinetic agents. The inclusion and exclusion criteria were rigorous: only 18 of 150 trials retrieved were analysed. No studies involving a PPI were included. On an intention-to-treat analysis, the difference in success rates for the treatments compared with placebo are shown in Table 2.2.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Success rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>14 (95% CI 3 – 24)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>33 (95% CI 23 – 43)</td>
</tr>
<tr>
<td>Cisapride</td>
<td>36 (95% CI 28 – 44)</td>
</tr>
<tr>
<td>Domperidone</td>
<td>35 (95% CI 24 – 46)</td>
</tr>
</tbody>
</table>

In a meta-analysis, Veldhuyzen van Zanten et al showed that cisapride produced a global improvement of functional dyspepsia symptoms (as assessed by the investigator or individual with dyspepsia; odds ratio (OR) 2.9, 95% CI 1.5 – 5.8). The corresponding figure for domperidone, based on a smaller number of individuals (n=211), was OR 7.0 (95% CI 3.6 – 16), which clearly demonstrates its efficacy as a prokinetic agent. Cisapride also improved epigastric pain (OR 0.19, 95% CI 0.05 – 0.7), early satiety (OR 0.32, 95% CI 0.1 – 0.7) and nausea (OR 0.26, 95% CI 0.1 – 0.5).

Cisapride is no longer a first-line treatment for dyspepsia because of the risk of cardiac arrhythmias which is very rare but can prove fatal. Cisapride requires specialist recommendation in New Zealand.

In an open trial in general practice, Heyse et al showed that at six months, after a four-week course of cisapride, there was a 27% relapse rate in people previously ‘cured’ (as judged by symptom control) at the end of the treatment period. Of those who relapsed, 88% responded well to a repeat treatment. Despite the obvious limitations of an open trial, this result raises the possibility that repeat courses of therapy on demand, rather than continuous therapy, may well be beneficial.

This conclusion is further supported by Farup, who was involved in an RCT comparing those who responded to acid inhibition therapy with those who did not. A multi-crossover design was used to identify people who consistently responded to ranitidine compared with placebo. This group of responders was then entered into a double-blind parallel study with placebo, and their responses compared with those of the non-responders from the initial study. Responders again improved significantly with ranitidine, while non-responders showed no benefit.

In practice, intermittent therapy may be what people choose anyway, as noted in the study by Hungin et al, who analysed the prescribing patterns for PPIs over a calendar year. It was found that of 299 individuals on long-term PPIs for a variety of reasons, including dyspepsia and reflux, 21% requested sufficient prescriptions for the entire year, 44% requested enough for less than 9 months total, and 20% requested more than 1 year’s worth.

Although one study showed that smoking and aspirin were both independent risk factors for dyspepsia (smoking OR 2.1, 95% CI 1.3 – 3.6; aspirin OR 2.2, 95% CI 1.3 – 3.7) among 592 healthy blood donors, other studies, including the Wellington survey, did not support the association with smoking. To date, there are no consistent data showing alcohol consumption levels affect the prevalence of dyspepsia.
INITIAL MANAGEMENT OF UNDIFFERENTIATED DYSPEPSIA

The initial management of a person presenting for the first time with dyspepsia needs to focus on two initial questions.

1. Is there a significant underlying pathology that needs to be treated?
2. Why has the person presented with this problem at this time?

The organic causes of dyspepsia are described in Chapter 1: Background. Specific alarm signals are indicative of specific pathology. Heartburn as a primary presenting complaint gives at least a 75% chance of the person having GORD. Symptoms may be associated with recent medication intake, particularly NSAIDs and aspirin, and the person’s drug history should be reviewed. Less common causes of dyspepsia may have other features on history or examination that indicate their presence.

ALARM SIGNALS

The following features increase the likelihood of significant organic disease:

• family history of gastric cancer (onset age <50 years)
• severe or persistent dyspeptic symptoms
• previous peptic ulcer disease, particularly if complicated
• ingestion of NSAIDs in those at risk
• unexplained weight loss
• GI bleeding
• anaemia
• dysphagia (difficulty swallowing)
• coughing spells or nocturnal aspiration
• protracted vomiting
• palpable abdominal mass.

NB: All symptoms should be regarded as more serious in people who are aged >50 years when presenting for the first time. Gastric cancer tends to occur a decade earlier in people of Maori, Pacific Island and Asian origin.

Besides addressing these issues, the fears that precipitate the initial visit for dyspepsia should also be elicited, and hopefully allayed. One of the intriguing features of dyspepsia is why only about one-quarter of people with dyspepsia consult their general practitioner for the problem. Lydeard and Jones compared a group of 69 consulters with a group of 66 non-consulters identified by postal questionnaire, and found no differences in the frequency or duration of symptoms between consulters and non-consulters (7 – 10 years). Consulters tended to be older (55.4 vs 48.6 years), had more severe symptoms (p<0.05), and had greater concerns that their symptoms may be indicators of underlying serious or potentially...
fatal disorders (74% vs 17%, p<0.001). They had specific concerns about cancer of the stomach, cancer generally, and heart disease. These underlying fears need to be addressed in the evaluation of the person with dyspepsia. The person needs to feel that his or her symptoms are being considered seriously, in the context of a full history and examination. In cases where there are no indications of organic disease, reassurance is an important part of initial therapy.

The level of initial investigation undertaken will depend on both the individual and the doctor, the level of uncertainty each is comfortable with, the age of the person, and other local factors such as availability of services and rates of *H. pylori* in the community. The Patient Information Sheet about dyspepsia, giving background information including risks associated with age, may help allay the person’s fears (see Appendix C). However, this has not been tested in the management of dyspepsia, and the available background data are much more limited than for cardiovascular risk.

When the person requests treatment, once alarm signals of organic causes have been ruled out and an initial decision has been made not to investigate by OGD, two strategies appear by default: empiric treatment with further investigation of treatment failures, and an *H. pylori* test followed by OGD or eradication. In areas and groups with low levels of *H. pylori*, the empiric therapy strategy is reasonable on the grounds that peptic ulcer is unlikely.

**PEOPLE WITH ALARM SIGNALS**

**OGD investigation**

There is little doubt that OGD is the investigation of choice where a positive diagnosis needs to be made in a person presenting with dyspepsia. It has greater sensitivity and specificity than barium meal examinations (previously, the main method of investigation) and allows biopsy of abnormalities and other interventions for complications (eg, sclerotherapy for bleeding). Refinements in endoscopic technology, modern sedation and/or regional anaesthesia, and credentialing to ensure appropriate training and skill maintenance of endoscopists, have all contributed to OGD being regarded as the ‘gold standard’ for the diagnosis of upper GI disorders. The change in emphasis from barium meal to OGD took place over the 1980s. The challenge, in a world of limited resources, is to use this relatively expensive test judiciously.

Most guidelines have regarded the age of 45 years as the cut-off point above which individuals should be investigated when presenting initially with upper GI symptoms. In this guideline, we recommend 50 years as the age above which risks of missing pathology increase significantly. There is much evidence to support this. In the British studies by Sue-Ling et al, only 2.8% of gastric cancers presented earlier than 50 years of age. Hallissey et al found that only one of 57 individuals with gastric cancer was aged less than 55 years. In the guideline on the management of dyspepsia presented as a working party report to the World Congresses of Gastroenterology in 1998, Talley et al recommended a cut-off
of age 50 years. In addition, Delaney et al have produced evidence that initial OGD in people aged 50 years and over is a cost-effective measure in primary care in Britain.

However, each case needs to be judged not only on biological age but also on past history and ethnicity. Maori and Pacific people have an incidence of gastric cancer that is up to five times higher than European New Zealanders, and their cancers often occur 10 years earlier, as do those of people from East Asia. New Zealand cancer registrations for 1998 show that stomach cancer accounts for 3% of cancer deaths in women and 5% in men. Maori are at higher risk, with twice the risk for Maori men compared with non-Maori men, and five times the risk for Maori women compared with non-Maori women. Of the 411 people diagnosed with stomach cancer in 1998, 63 (15%) were aged <55 years, and of these, 16 (25%) were Maori. Family history is an important factor. A Maori family cohort with a genetic predisposition to cancer has been identified, in which the youngest documented person was aged 14 years.

A family history of early gastric cancer warrants investigation of dyspepsia by OGD at any age of presentation. Bodger et al make the reasonable observation that knowledge of the characteristics of people consulting with dyspepsia in primary care should be an important factor in determining the case mix and complexity relative to age in that area.

A further recommendation is that all people with alarm signals should be referred for OGD, primarily to diagnose organic diseases, including gastric cancer. There are now good data to show that most people with gastric cancer below the age of 55 years have alarm signals. For example, the British review by Christie et al found that of 319 individuals with gastric cancer, 25 presented under the age of 55; of these 25, 24 had one or more suspicious signals, and only one (4%) presented with uncomplicated dyspepsia.

The value of OGD in the management of dyspepsia was recently examined by Ofman and Rabeneck, who undertook a systematic review of the literature in an attempt to find out whether OGD results in improved outcomes for people with dyspepsia, a reduction in the use of subsequent medical resources, and/or improved medical decision-making. They also investigated whether it was cost effective. Twenty-one studies met the inclusion criteria, although they were limited by several factors, including the use of varying tools to measure people’s response and the difficulties of comparing studies that did not include H. pylori status with those that did. One RCT showed higher patient satisfaction and lower costs with initial OGD compared with empiric therapy, but no difference in symptoms or quality of life at one year. The other studies failed to clearly answer the questions posed, by failing to show any significant differences.

**Barium meal examination**

This was previously the main method of investigating dyspepsia. It may still be superior to OGD in the investigation of upper GI motility disorders, particularly in the act of deglutition and in the oesophagus. Otherwise, it should be regarded as a screening investigation if OGD is not available or in certain selected cases (eg, dysphagia with normal OGD, or where OGD has failed or is unacceptable to the person). There is evidence that barium meal examination prior to referral for OGD increases the cost of investigation with no additional benefit.
Barium meal examination has a number of disadvantages. Minor abnormalities, (particularly if confined to the epithelial layer) may be missed, biopsies cannot be taken, \textit{H. pylori} status is not clarified, and, if the result is normal and symptoms are serious or persistent, OGD will still be required.

**PEOPLE WITHOUT ALARM SIGNALS**

**Empiric therapy**

Many people will have already tried antacids prior to seeing their general practitioner, and some will have also tried \textit{H},\textsubscript{2}RAs, which are available over the counter. Obviously, taking a medication history is important, and a decision would need to be made about whether the dose of \textit{H},\textsubscript{2}RA that the person had taken could be regarded as a trial of empiric therapy. Although the dosages recommended on over-the-counter \textit{H},\textsubscript{2}RAs are usually half that prescribed by doctors, RCTs have demonstrated their efficacy in heartburn.\textsuperscript{33,34,35}

Placebo response is very common in the treatment of dyspeptic disorders, especially functional dyspepsia where it often achieves a 60 to 80% response.\textsuperscript{36} The reasons for this are the subject of much speculation, and include a number of psychological factors, which convert those with minor non-specific events into people presenting with worrying symptoms. However, the placebo healing rate for endoscopically confirmed peptic ulcers is also very variable. There are good data showing some reaching 60%,\textsuperscript{37} although most are usually between 30 and 50%. A person’s confidence in both their therapist and the type of treatment seem to play an important part in the placebo response.

The evidence is not clear on which class of medication (prokinetic, \textit{H},\textsubscript{2}RA or PPI) would be most appropriate for empiric treatment of all people, including those with dyspepsia and reflux. All show some benefit over placebo but different reviews give different levels of benefit for each. Given that dyspepsia is a symptom that may be present intermittently for many years, it would be fiscally prudent to choose a relatively cheap option such as an \textit{H},\textsubscript{2}RA or prokinetic (eg, domperidone) initially, and assess the response. The Cochrane review by Soo et al, which specifically excluded people with reflux, supports this strategy, emphasising the benefits of prokinetic agents or \textit{H},\textsubscript{2}RAs over PPIs.\textsuperscript{5} However, the Cochrane review by Delaney et al, which included patients with dyspepsia and/or heartburn, showed the most benefit for treatment with PPIs.

After exclusion of alarm signals, it is our recommendation that people be divided into those with predominantly heartburn symptoms and those with dyspepsia without symptoms of heartburn.

**People with heartburn/reflux**

Of people with heartburn, as defined in this guideline, there is now reasonable evidence that about 75% will have GORD.\textsuperscript{16,17,18} Therefore, logically, empiric treatment should be directed as for GORD in these individuals. A step-down or step-up regimen can be followed, bearing in mind the person’s previous response to self-medication (see Chapter 3: Gastro-oesophageal Reflux Disease).
People with dyspepsia

Empiric treatment for the remainder of people with dyspepsia will be with either prokinetic agents or acid inhibition. As most of these people have functional dyspepsia, prokinetic agents may have some benefit. Cisapride (10 mg taken before meals and bedtime) has most evidence in its support, but recently, identification of rare but serious cardiological side effects have dampened enthusiasm for its use. Risks and benefits have to be weighed up in each individual in the light of individual cardiac history and status. A small number of people worldwide have had cardiac arrest on cisapride. Contraindications include concomitant use of potent CYP3A4 inhibitors (eg, azole antifungals, macrolides, HIV protease inhibitors), QT prolongation or conditions leading to QT prolongation (eg, bradycardia, hypokalaemia, medication prolonging QT interval) and family history of congenital long QT syndrome. Furthermore, currently cisapride is not funded and prescribing is restricted to specialists.

Domperidone (in the same dose) has also been shown to be helpful. Metoclopramide is less favoured because of its potential extrapyramidal adverse effects, and because no eligible studies were found in the Cochrane review by Soo et al to support its use.

Among acid inhibitors, H$_2$RAs are the obvious first choice owing to their reasonable efficacy, low incidence of adverse effects, and low cost. PPIs are not recommended as first-choice agents for people with non-specific dyspepsia where heartburn has been excluded, as they are no more effective than H$_2$RAs and are more costly.

Most studies on therapy have looked at continuous treatment for four weeks before determining effectiveness, but there are no good data comparing longer or shorter treatment periods or intermittent therapy (which is the de facto choice of many people). However, given the preponderance of the four-week trial, it seems reasonable to treat for at least four weeks before deciding whether or not therapy has been effective.

There is no recommended duration of a trial of therapy, but three to six months is reasonable if there has been a satisfactory improvement.

MANAGEMENT OF RECURRING UNDIFFERENTIATED DYSEPSIA

‘Treatment failure’ is difficult to define, and no specific evidence could be found about this. Therefore, for the purposes of this guideline, people are defined as treatment failures if they have reported:

1. no improvement or a worsening of symptoms at the end of a four-week trial or
2. a rapid return of symptoms within a month of cessation of treatment.

It should be noted that good or complete resolution of symptoms, but recurrence after six months, is consistent with the expected natural history of functional dyspepsia.
People who report only a small improvement, or a recurrence in less than six months, will need re-evaluating on an individual basis.

People who do not respond to treatment need further evaluation, most often by OGD. Recurrences after six months or so are expected, given the natural history of the problem, and empiric treatment may be repeated. Some individuals may need regular treatment, but for others, symptoms may be controlled with intermittent treatment. The physician should be alert for the development of alarm signals that will require different management.

Studies quoted in Talley et al., suggest 65 – 85% of people with functional dyspepsia will still have symptoms after 1 to 3 years. A 10-year follow-up study by Lindell et al. showed 64% reporting dyspeptic symptoms in the previous year. Notably, there was no increase in numbers of people with peptic ulcer during this 10-year period compared with the general population of a similar age, and no cases of stomach or oesophageal cancer (in 240 for whom records were available from the original sample of 271). Over 60% had had further upper GI investigation, with a low yield of significant pathology.

One concern is that delay in referral for OGD will lead to a worse outlook for individuals who are eventually diagnosed with gastric cancer (which could occur in a management regime of empiric therapy with further investigation restricted to non-responders). However, Martin et al. examined delays in diagnosis of gastric cancer and found no relationship between duration of symptoms and stage of tumour. Furthermore, most people with gastric cancer have some alarm signals.

THE TEST-AND-TREAT STRATEGY: H. PYLORI ERADICATION IN FUNCTIONAL DYSPEPSIA

The role of H. pylori in peptic ulceration and undifferentiated and functional dyspepsia is discussed fully in Chapter 4: Helicobacter pylori and Peptic Ulceration. In summary, one of the options in the management of primary-presenting dyspepsia is to test for H. pylori and treat those who are positive. This enables most people with peptic ulcers to be treated, assuming the possibility of NSAID-related ulcers being excluded on the history. H. pylori is also a risk factor for gastric cancer, while ethnic groups with higher prevalence of H. pylori also have a higher incidence of gastric cancer. Treating H. pylori without investigation in these individuals may delay the diagnosis of a tumour, particularly if they have a family history of gastric cancer. Generally, the test-and-treat approach has been shown to be cost-effective, and to reduce the demand for OGD where the prevalence of H. pylori in the population below the age of 50 years is reasonably high (at least 30%). In areas where the prevalence of H. pylori is low in the same population (eg, in the Dunedin and Christchurch areas, where prevalence at 21 years is 4.1 and 17.5% average in those under 50), benefit has not been shown. In these circumstances, empiric drug treatments are favoured.
MANAGEMENT OF FUNCTIONAL DYSPEPSIA

Functional dyspepsia has been defined as dyspepsia of at least several weeks duration for which no focal or structural lesion(s) can be found using OGD, and which cannot be explained by any other obvious structural or biochemical abnormality on screening blood tests or abdominal ultrasound examination where appropriate. It is the commonest ‘cause’ of dyspepsia.

People with this diagnosis should be treated as for those with undifferentiated dyspepsia, provided they meet all the following criteria:

1. no heartburn
2. no NSAID use
3. normal blood tests (eg, FBC, ESR, CRP)
4. no evidence of an abnormality to explain their symptoms on OGD.

Reassurance concerning the absence of severe organic pathology (particularly stomach cancer) is important for many patients. Their presentation may be a good opportunity to review lifestyle factors, including diet, weight control, smoking cessation and moderation of alcohol intake (although there is little direct trial evidence to support their efficacy in this context).

DRUG THERAPY

As presented above in Tables 2.1 and 2.2, these patients respond best to prokinetic agents (of which domperidone is the best current choice), followed by H₂RAs, and least reliably with PPIs (given the important proviso that patients with heartburn have been excluded). In many people, symptomatic treatment with antacids may be all that is required.

In people with proven functional dyspepsia (where organic pathology has been excluded), the results from H. pylori eradication are controversial. Current data indicate that from 1 in 15 to 1 in 20 may benefit from such eradication, while one meta-analysis found no benefit at all (see Chapter 4: Helicobacter pylori and Peptic Ulceration).
GASTRO-OESOPHAGEAL REFUX DISEASE

OVERVIEW

- Gastro-oesophageal reflux disease (GORD) is a common condition presenting with classic symptoms such as heartburn and acid regurgitation (burning feeling rising from the epigastrium into the chest and up towards the neck), and sometimes with atypical symptoms such as unexplained chest pain, asthma, cough and hoarseness of the voice.
- GORD is present in 75% of those with heartburn.
- Severity of symptoms does not necessarily correlate with endoscopic findings as approximately 50% of people with heartburn have no endoscopic evidence of inflammation (Grade 0).
- Symptomatic response and healing are more rapid and complete with PPIs than with H₂RAs.
- PPIs are most effective when taken with a glass of water 15 to 30 minutes before breakfast.
- PPIs and H₂RAs, given to relieve heartburn, can mask signs of inflammation at OGD. When referring for OGD, symptoms can be relieved with antacids or alginates for at least one month prior to the procedure.
- The role of OGD is to establish whether any inflammation is present, determine the degree of inflammation (absent – Grade 0, A – D for severity) and identify any complications (eg, Barrett’s oesophagus).
- Grades 0 – B rarely progress to higher grades.
- Long-term treatment of grades C and D with PPIs reduces the risk of complications.
- In routine management, pH telemetry is of limited value, but can be used when diagnostic problems arise and in those who fail to respond to high-dose PPI therapy.
- Laparoscopic fundoplication is an alternative treatment for people who fail to respond to medical therapy or who require long-term treatment for effective control of symptoms. It is more suitable for younger people without comorbidity.
GORD SYMPTOMS

RECOMMENDATIONS

Consider GORD in people with:

- heartburn (burning sensation radiating from the epigastrium towards the neck)
- non-cardiac chest pain, asthma, chronic cough, hoarseness of voice and erosion of teeth.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

INITIAL MANAGEMENT WITH EMPIRIC THERAPY

RECOMMENDATIONS

If the person’s symptoms are suggestive of GORD, treat with a step-down drug regimen, usually in 4 – 8 week steps:

Step 1. full-dose PPI (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg) daily
Step 2. half-dose PPI
Step 3. H₂RA (famotidine 20 – 40 mg, ranitidine 150 – 300 mg) twice daily
Step 4. antacids/alginate.

If there is no response to full dose PPI therapy, double the dose.

Continue treatment for at least 3 – 6 months.

If the person fails to respond, or symptoms recur within 1 month after end of treatment, consider OGD rather than long-term empiric therapy.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

GOOD PRACTICE POINT

Exclude people with alarm signals from empiric therapy, and refer for OGD.

Recommended best practice based on the clinical experience of the Guideline Development Team.
TREATMENT OF GORD DIAGNOSED AFTER OGD

RECOMMENDATIONS

People with grades 0, A and B
- Treat with a step-down drug regimen (see Algorithm 3: Heartburn +/- Dyspepsia: Empiric Therapy).
- If symptoms recur at stepped-down dosage, continue on lowest effective dose; intermittent therapy may control symptoms.

People with grades C and D
- Treat with ongoing continuous full-dose PPI treatment.

Consider surgery as an alternative to long-term drug treatment if:
- age <50 years
- age 50 years and over and there is no comorbidity
- there is inability or unwillingness to take medications
- there is inadequate control with medical therapy.

If high-dose PPI treatment fails, re-evaluate symptoms and consider 24-hour pH telemetry.

In people with Barrett’s oesophagus or unresolved complications (grade D), re-evaluate with OGD if necessary.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

INTRODUCTION

GORD is a common condition presenting with classic symptoms such as heartburn and acid regurgitation (burning feeling rising from the epigastrium into the chest and up towards the neck), and sometimes with atypical symptoms such as unexplained chest pain, asthma, cough, and hoarseness of the voice.1-3 Prevalence and incidence may vary significantly among different ethnic groups.4-6 The effect on quality of life has been found to be similar to that of severe angina pectoris.7,8

Frequent transient, spontaneous, lower oesophageal sphincter relaxation (TSLOSR) appears to be the primary abnormality in GORD.9 Contrary to previous assumptions, the mere presence of a hiatus hernia rarely accounts for symptoms, although recent evidence suggests that the perturbed anatomy associated with a hiatus hernia is more likely to result in reflux of acid into the lower oesophagus and this is associated with exacerbation of symptoms.10

The prevalence of GORD in New Zealand is similar to that in other OECD countries.5,11 At OGD, oesophagitis is demonstrated in about 50% of people presenting with typical GORD symptoms. In people with typical symptoms but no signs of oesophagitis at OGD
(defined as grade-0 GORD), a different sensitivity to acid at the level of the oesophageal epithelium has been suggested. The severity of reflux symptoms does not necessarily correlate with endoscopic findings.

A survey of prevalence of oesophagitis in people in the Otago area has shown a steady rise of nearly 10% (22 – 31%) in people presenting for their first upper diagnostic OGD from 1991 to 1999, and this appears to be a world-wide trend. Cancer of the lower oesophagus is also on the rise in the industrialised world, particularly associated with Barrett’s oesophagus, which appears to link oesophagitis with adenocarcinoma of the oesophagus.

SYMPTOMS CONSISTENT WITH GORD

Heartburn (as defined above) is considered to be the most common symptom of GORD, occurring in 75% of people presenting with this symptom. It may be more noticeable when bending forwards or after meals. Heartburn frequently occurs in the absence of definite OGD-proven oesophagitis. Significant impairment of health-related well-being may occur when people experience heartburn on two or more days per week and this frequently interferes with daily activities.

Other symptoms that are sometimes related to the presence of GORD include non-cardiac chest pain, chronic hoarseness, asthma, chronic cough, and erosion of teeth. Effective treatment of reflux can be extremely successful in alleviating these symptoms.

GORD, as determined by OGD and pH studies, can also occur in the absence of any symptoms. The person’s presentation, particularly the perceived severity and significance of symptoms, may be influenced by her or his fear of severe organic disease (particularly cancer and heart disease).

ALARM SIGNALS

- Weight loss
- Persistent regurgitation of food or vomiting
- Dysphagia
- Symptoms of GI bleeding (haematemesis or melaena).

People aged 50 years and over who are presenting for the first time have a higher incidence of organic disease.
AIMS OF MANAGEMENT

In a review Bell et al demonstrated that, although GORD is related to a motor dysfunction allowing gastric content to enter the oesophagus, the severity of disease is correlated with the degree and duration of oesophageal acid exposure. The primary aim of treatment is to protect the lower oesophagus from exposure to acid.

In people with more severe grades of GORD, the intra-oesophageal pH was <4 for 36% of the time as opposed to 5% of the time in people with mild GORD. Furthermore, most individuals with mild disease experience oesophageal acid exposure during the day, mostly in the post-prandial period, related to TSLOS R. In contrast, individuals with more severe grades of GORD experience reflux both by day and by night.

The acid inhibition obtained with conventional doses of H$_2$RAs cannot overcome the integrated stimuli experienced during the ingestion of food. The efficacy of these drugs is therefore suboptimal in controlling the acid exposure of the oesophagus related to TSLOS R. In contrast, PPIs offer good acid control over prolonged periods, especially during the day after a pre-breakfast dose. Using data from people with duodenal ulcer, Bell et al showed that PPIs controlled gastric acid secretion (pH >4.0) for significantly longer periods than H$_2$RAs (see Table 3.1).

Table 3.1: Control of gastric acid secretion with PPIs and H$_2$RAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of intra-gastric pH &gt;4.0 (% of the day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 60 mg/d</td>
<td>88</td>
</tr>
<tr>
<td>Omeprazole 30 mg/d</td>
<td>80</td>
</tr>
<tr>
<td>Omeprazole 10 mg/d</td>
<td>63</td>
</tr>
<tr>
<td>Ranitidine 300 mg nocte</td>
<td>37</td>
</tr>
<tr>
<td>Ranitidine 150 mg nocte</td>
<td>34</td>
</tr>
<tr>
<td>Famotidine 40 mg nocte</td>
<td>37</td>
</tr>
</tbody>
</table>


In the Bell study, there was a correlation coefficient of 0.87 (p<0.05) between the healing rate of erosive oesophagitis at eight weeks and the duration in hours that the intra-gastric pH was maintained above pH 4.0 with any particular class of drug. These correlations, based on indirect observations, have been confirmed by a later meta-analysis by Chiba et al. These authors analysed results of treatment of endoscopically observed erosive oesophagitis in 7635 individuals; oesophagitis was indicated as grade 2 in 61.8%, grade 3 in 31.7%, and grade 4 in 6.5%. Endoscopically observed healing rates were far superior with PPIs than with H$_2$RAs (see Table 3.2).
Table 3.2: Healing rates with various treatments for erosive oesophagitis (meta-analysis, irrespective of drug dose or treatment duration)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% healed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>83.6 ± 11.4</td>
<td>79.1 – 88.1</td>
</tr>
<tr>
<td>H₂RA</td>
<td>51.9 ± 17.1</td>
<td>46.9 – 56.9</td>
</tr>
<tr>
<td>Cisapride</td>
<td>37.9 ± 4.5</td>
<td>not stated*</td>
</tr>
<tr>
<td>Placebo</td>
<td>28.2 ± 15.6</td>
<td>19.2 – 37.2</td>
</tr>
</tbody>
</table>


In addition, Chiba et al also demonstrated that healing rates at two weeks were higher with those treated with PPIs than at 12 weeks with H₂RAs (see Table 3.3).

Table 3.3: Healing rates and symptomatic response of erosive oesophagitis with PPIs and H₂RAs

<table>
<thead>
<tr>
<th></th>
<th>Totally healed (%)</th>
<th>Symptom free - no heartburn (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 weeks 4 weeks 6 weeks 8 weeks 12 weeks</td>
<td>1 – 2 weeks 3 – 4 weeks 6 – 8 weeks</td>
</tr>
<tr>
<td>PPIs</td>
<td>64 69 90 84 92</td>
<td>69 88 93</td>
</tr>
<tr>
<td>H₂RAs</td>
<td>31 38 39 52 61</td>
<td>34 42 58</td>
</tr>
<tr>
<td>Placebo</td>
<td>8 16 18 24 34</td>
<td></td>
</tr>
</tbody>
</table>


Although symptom control is more difficult to interpret in a meta-analysis, these results reflected those of healing of inflammation. Overall, at 4 – 12-week endpoints, 77.4% (± 10.4%) of those treated with PPIs were heartburn-free compared with 47.6% (± 15.5%) on H₂RAs (p<0.0001). There were more symptom-free individuals at 1 – 2 weeks with PPIs than at 6 – 8 weeks with H₂RAs.
INITIAL MANAGEMENT: EMPIRIC THERAPY

The presence of alarm symptoms should result in urgent referral for OGD. People with persistent heartburn and no alarm features may be further evaluated with a simple questionnaire (Appendix A). Although this has been shown to substantially facilitate the diagnosis of GORD, it is seldom used in clinical practice.

Treatment should provide sufficient control of symptoms and should also increase health-related quality of life. This is achieved in the majority of people irrespective of GORD grade. Although the traditional lifestyle measures usually recommended to people with GORD, such as raising the head of the bed, decreasing fat intake (to reduce body weight and to prevent delayed gastric emptying), cessation of smoking, moderation of alcohol intake, and avoiding tight clothing, may have some place in overall management, there are no systematic studies on these treatments, and published data are based on disputable methodology.

Over-the-counter medication (antacids, alginate, H₂RAs) provides effective symptom relief in approximately 20% of people.

A trial of empiric therapy is justified in people aged <50 years presenting with typical GORD symptoms in the absence of alarm signals. In ascending order of potency and efficacy, the choice of drugs available includes: antacid/alginate, H₂RAs (single then double dose, both twice daily); prokinetics; PPIs (half, standard, double doses) and combinations of PPIs and H₂RAs or prokinetic agents (see Appendix B). Prokinetics (e.g., domperidone and ciapride) are comparable in efficacy with H₂RAs, but cisapride is no longer favoured because of rare but potentially serious adverse effects. It also requires specialist recommendation in New Zealand.

In the Cochrane review, van Pinxteren et al analysed the results of 14 studies involving 4764 individuals in short-term (2 – 12 weeks) RCTs of individuals treated with PPIs, H₂RAs or prokinetic agents. These people did not have any endoscopic information involved in their selection. The endpoints of the studies were often difficult to assess, but were defined as relief of heartburn to no more than one day of mild heartburn per week. The results showed that PPIs were significantly superior to H₂RAs in controlling symptoms.

Table 3.4: Remission of heartburn with empiric treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPIs</td>
<td>0.35</td>
<td>0.26 – 0.46</td>
</tr>
<tr>
<td>H₂RAs</td>
<td>0.77</td>
<td>0.60 – 0.99</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>0.86</td>
<td>0.73 – 1.01</td>
</tr>
</tbody>
</table>

Many studies have demonstrated that PPIs provide more symptom relief and better healing than the other treatments.\textsuperscript{30,31,36-38} Bate et al have even used rapid response to PPI treatment as a diagnostic test for GORD;\textsuperscript{36} good response to PPI empiric therapy has a sensitivity of 80% and specificity of 40% for the diagnosis of GORD.

‘STEP-DOWN’ AND ‘STEP-UP’ TREATMENT OPTIONS

There is a choice between the so-called ‘step-down’ and ‘step-up’ treatment regimens. The step-down approach, starting with a standard dose of PPI (taken 15 – 30 minutes before breakfast with water) and then gradually stepping down to less potent drugs, is recommended. Advantages of such an approach include rapid pain relief, ease and efficiency of prescribing, and avoidance of over-investigation and its costs.\textsuperscript{39} Disadvantages are that initial drug cost is higher and there is the possibility of some individuals being over-treated if an appropriate step-down procedure is not followed.

The main advantage of a step-up regimen is that it avoids initial over-treatment and costs. However, disadvantages include unnecessary ongoing symptoms in about half of those being treated, wasting of doctors’ and individuals’ time for repeat visits over a prolonged period, over-investigation for persistent symptoms, and judgment of the endpoint of treatment by improvement only, rather than complete response.

PPIs are usually started in conventional doses of omeprazole 20 mg, lansoprazole 30 mg and pantoprazole 40 mg daily 15 – 30 minutes before breakfast with a glass of water. An evening dose (before a meal) can also be considered in some cases. \( \text{H}_2 \text{RAs} \) are usually prescribed in standard doses twice daily (ranitidine 150–300 mg, and famotidine 20–40 mg).

<table>
<thead>
<tr>
<th>Table 3.5: Step-down regimen</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PPIs</th>
<th>( \text{H}_2 \text{RAs} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>omeprazole 20 mg or lansoprazole 30 mg or pantoprazole 40 mg</td>
<td>ranitidine 300 mg twice daily or famotidine 40 mg twice daily</td>
</tr>
<tr>
<td>Step 2</td>
<td>omeprazole 10 mg</td>
<td>lansoprazole 15 mg</td>
</tr>
<tr>
<td>Step 3</td>
<td>ranitidine 300 mg twice daily or famotidine 40 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td>ranitidine 150 mg twice daily or famotidine 20 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Step 5</td>
<td>antacids/alginates</td>
<td></td>
</tr>
</tbody>
</table>

The initial treatment trial should cover at least 2 – 4 weeks, but the dosage may be continued for 6 – 8 weeks in total before step-down is attempted, according to symptom control.\textsuperscript{7,33}
Eventual withdrawal of medication is recommended after 3 – 6 months, as approximately 20% of people may not experience recurrence of symptoms.\textsuperscript{12}

If the symptoms persist or recur after three months of high-dose empiric treatment, the person should be referred for OGD.

**OESOPHAGO-GASTRO-DUODENOSCOPY INVESTIGATION**

The role of OGD is to rule out significant pathology in the upper GI tract (such as cancer of the oesophagus and stomach) and to verify objective signs of GORD and its degree of severity. As the incidence of cancer is extremely low in younger people but increases with age, the person’s age becomes a risk factor for cancer, and the age of 50 years should be considered as a guide for referral for OGD. In addition, all people with alarm signals (see Chapter 2: Undifferentiated Dyspepsia) should be investigated with OGD.

Findings at OGD should not be used as the definitive criteria for the primary diagnosis of GORD. As at least 50% of people with symptomatic GORD do not have inflammatory damage at OGD, the procedure is not a sensitive tool for diagnosis. In meta-analyses, both Galmiche et al and Carlson et al have demonstrated a poor correlation between symptoms and disease severity in GORD.\textsuperscript{9,40}

At OGD, oesophagitis is characterised by ‘breaks’ (erosions) in the oesophageal epithelium. However, so-called ‘minor changes’ (erythema, oedema, friability) are not considered to have any diagnostic significance.\textsuperscript{11,12} The appearance of these mucosal breaks on inspection at OGD is usually defined using the Los Angeles classifications (see Table 3.6).\textsuperscript{14,41} Grades 0 to B indicate that complications are most unlikely to develop,\textsuperscript{6,9,42} while stricture and bleeding are almost always confined to people with grades C and D. The older Savary-Miller classification (see Table 3.7) of oesophagitis is still used by many endoscopists. It has similar gradings of oesophagitis (I to IV), although grade II is roughly equivalent to the Los Angeles classification C. People with a history of heartburn (2 or more times a week for over 6 months) and normal OGD are considered to have grade 0 GORD.\textsuperscript{11,12}

**Table 3.6: Los Angeles endoscopic classifications of oesophagitis**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal endoscopic findings</td>
</tr>
<tr>
<td>A</td>
<td>One or more mucosal breaks confined to the mucosal folds, each no longer than 5 mm</td>
</tr>
<tr>
<td>B</td>
<td>At least 1 mucosal break more than 5 mm long confined to the mucosal folds but not continuous between the tops of 2 mucosal folds</td>
</tr>
<tr>
<td>C</td>
<td>At least 1 mucosal break continuous between the tops of 2 or more mucosal folds but not circumferential</td>
</tr>
<tr>
<td>D</td>
<td>Circumferential mucosal break</td>
</tr>
</tbody>
</table>

Table 3.7: Savary-Miller endoscopic classification of oesophagitis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>One or more supravestibular, non-confluent mucosal lesions accompanied by erythema, exudate, or superficial erosion</td>
</tr>
<tr>
<td>II</td>
<td>Erosive and exudative mucosal lesions are confluent but do not cover the entire circumference of the oesophagus</td>
</tr>
<tr>
<td>III</td>
<td>Erosive and exudative lesions cover the entire circumference of the mucous membrane leading to inflammatory infiltration of the wall without stricture</td>
</tr>
<tr>
<td>IV</td>
<td>Appearance of chronic mucosal lesions (ulcers, fibrosis of walls, stricture, short oesophagus, scarring without columnar epithelium)</td>
</tr>
</tbody>
</table>


Histological examination of a normal-looking oesophageal mucosa rarely provides further information about the diagnosis and is therefore not currently recommended in routine management.\(^{11,12}\) *H. pylori* plays no role in GORD and eradication is not recommended for this indication.\(^{11,20,43,44}\) As noted earlier, treatment is aimed at acid control and not primarily at hiatus hernia if this is present.

**H. pylori and GORD**

*H. pylori* has no known role in the cause or direct treatment of GORD, and eradication is not recommended for this indication alone.\(^{11,20,43,44}\)

A number of studies have indicated that eradication of *H. pylori* infection may increase the incidence of GORD in people with duodenal ulcers,\(^{60,61}\) although this finding has not been found consistently.\(^{62,63}\) Some have observed that oesophagitis in *H. pylori*-positive patients, heals more rapidly with a PPI than in those who are *H. pylori*-negative,\(^{64}\) and that *H. pylori* infection may increase the efficacy of PPIs in reducing acid secretion.\(^{65}\) However, Moayyedi et al.,\(^{66}\) have shown in a randomised control trial that *H. pylori* eradication does not exacerbate reflux symptoms in GORD.

Another consideration involving *H. pylori* eradication in GORD is whether this results in significant gastric atrophy, with a potential to develop intestinal metaplasia and possibly gastric cancer after prolonged therapy. There is some evidence to support this progression,\(^ {67}\) although this remains controversial owing to other studies not supporting the findings.\(^ {68}\) In a prospective study, Sung et al.,\(^ {69}\) showed that gastric inflammation and atrophy could be reduced one year after *H. pylori* eradication compared to those with continuing infection. This confirms the findings of a previous study.\(^ {70}\) Longer study periods are clearly required. The topic of GORD and *H. pylori* has recently been reviewed by Vakil.\(^ {71}\)
At present the definitive information has not progressed beyond the advice given by Moayyedi et al who stated:

‘The decision as to whether H. pylori eradication therapy should be offered to infected GORD patients rests on the individual beliefs of clinicians about the risks of developing corpus atrophy and intestinal metaplasia during prolonged acid suppression.’

TREATMENT OF GORD DIAGNOSED AFTER OGD

For most people with a positive GORD diagnosis, treatment is aimed primarily at symptom control.11,12

Many RCTs have been conducted with various cohorts of people with GORD. Many have been based in general practice and have included a wide range of grades of oesophagitis, reflecting those in general populations. The results of these are summarised in Tables 3.2 and 3.8.

In their guideline review, DeVault et al analysed the results of 33 RCTs involving over 3000 individuals with GORD.12 They found that symptomatic relief could be expected with 27% of placebo-treated, 60% of H2RA-treated and 83% of PPI-treated individuals; oesophagitis had healed in 24, 50 and 78% of these groups respectively. Using economic modelling, Bate et al showed that use of PPIs is more cost effective than H2RAs because of greater efficacy and lower relapse rate. However, the findings of this British study depend on local drug prices, which are now outdated and do not apply to New Zealand.36

GRADE 0 AND MINOR GRADES A AND B

In the Cochrane review, van Pinxteren et al analysed the results of 10 studies involving 2638 individuals in short-term (2 – 6 weeks) RCTs of individuals treated with PPIs, H2RAs or prokinetic agents with Grade 0 GORD.22 The endpoints of the studies were sometimes difficult to clarify but defined as relief of heartburn to no more than one day of mild heartburn per week. The results showed that PPIs were significantly superior to H2RAs in controlling symptoms (PPI; RR 0.68, 95% CI 0.53 – 0.88: H2RA; RR 0.84, 95% CI 0.74 – 0.95). It may be noted that these results are less favourable than those obtained with empiric treatment (see Table 3.4). This might indicate that although clearly helpful, the diagnosis of grade 0 is still empiric and imperfect. Therapy for the more precisely defined grades of erosive oesophagitis seems more successful (see Table 3.3).
Table 3.8: Symptom response to treatment of low-grade GORD

<table>
<thead>
<tr>
<th>Treatment (no. of individuals)</th>
<th>Duration of treatment (weeks)</th>
<th>Symptom remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OM 20 mg once daily (330)</td>
<td>4</td>
<td>61</td>
</tr>
<tr>
<td>OM 10 mg once daily (338)</td>
<td>4</td>
<td>49</td>
</tr>
<tr>
<td>RAN 150 mg twice daily (326)</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td><strong>Venables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OM 10 mg once daily (242)</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>Placebo (253)</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td><strong>Carlsson</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OM 20 mg once daily (87)</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>OM 10 mg once daily (86)</td>
<td>4</td>
<td>49</td>
</tr>
<tr>
<td>Placebo (88)</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td><strong>Erosive GORD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OM 20 mg once daily (138)</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>OM 10 mg once daily (139)</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
* Heartburn prominent, acute study, both Grade 0 (68.2%) and erosive oesophagitis
# Heartburn prominent, maintenance of above study with only Grade 0
+ Carlsson-Dent questionnaire positive for GORD, 48.5% Grade 0

Abbreviations: OM = omeprazole; RAN = ranitidine


Grades 0, A and B rarely progress to higher grades. In a retrospective analysis of nearly 4000 individuals, Rejeb et al found that peptic strictures were very rare in the minor grades of oesophagitis, and they suggested that symptomatic treatment is all that is necessary in such cases.

In grades 0 to B, a step-down regimen should be tried, going down to the lowest dose of acid inhibition (if any) required to control symptoms, as on-demand treatment has demonstrated good symptom control without increase of GORD grade.

The Management of Dyspepsia and Heartburn
GRADES C AND D

Many studies of individuals with various grades of oesophagitis have been undertaken. The meta-analysis by Chiba et al has already been quoted (see Table 3.3). Although most of the individuals (61.8%) were the equivalent of grade B, 31% were grade C and only 6.5% were grade D. Some correlation exists between higher grades of GORD (C and D) and more severe symptoms. Those with these grades of oesophagitis demonstrated at OGD require long-term treatment with PPIs. Indeed, some individuals with grades C and D (5 – 10%) may need full-dose repeated twice-daily maintenance treatment. In a New Zealand study of 69 individuals with oesophageal strictures, Barbezat et al showed that long-term PPI use reduced the risk of stricture recurrence. Long-term treatment with PPIs has been demonstrated to be safe for over 10 years. There is no need for re-OGD in most individuals with well-controlled symptoms. Where there is suboptimal, or no response to treatment, alternative PPIs can be tried as differences in metabolic pathways may be responsible.

For those people who are on high-dose treatment and who do not become asymptomatic, 24-hour pH telemetry should be considered. Repeat OGD may also be an option. The success of pooled 1-year GORD relapses in people with proven erosive oesophagitis (grades B to D) is shown in Table 3.9.

Table 3.9: Relapse rate of GORD with long-term treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of trials</th>
<th>No. of people with GORD</th>
<th>1 – year relapse (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 20 mg/d</td>
<td>6</td>
<td>433</td>
<td>21</td>
<td>18 – 26</td>
</tr>
<tr>
<td>Omeprazole 10 mg/d</td>
<td>3</td>
<td>323</td>
<td>40</td>
<td>35 – 46</td>
</tr>
<tr>
<td>H₂RA all doses</td>
<td>5</td>
<td>301</td>
<td>63</td>
<td>58 – 69</td>
</tr>
<tr>
<td>Placebo</td>
<td>4</td>
<td>297</td>
<td>82</td>
<td>77 – 86</td>
</tr>
</tbody>
</table>


BARRETT’S OESOPHAGUS

This is defined as the presence of specialised intestinal epithelium in the lower oesophagus. Barrett’s oesophagus should be investigated in specialist centres (some with surveillance OGD). The biological age of the person and comorbidity will determine frequency of surveillance, generally at 3 to 5-year intervals if the histology does not show any dysplasia, while surveillance is usually stopped at about age 70 years. Protocols for managing epithelial dysplasia in people with Barrett’s oesophagus are beyond the scope of this guideline. Long-term treatment with PPIs appears reasonable in people with Barrett’s oesophagus as this condition represents a complication of severe GORD (Grade D). OGD surveillance of coincidental (normal macroscopic appearance) short-segment Barrett’s
oesophagus and intestinal metaplasia in the area of the gastric cardia is not recommended currently.\textsuperscript{14,17,49} New treatment modalities, such as photodynamic eradication or argon plasma coagulation of intestinal metaplasia of the oesophagus, are currently being developed and trialled.\textsuperscript{11,50}

**FURTHER INVESTIGATION**

**24-HOUR PH TELEMETRY**

This measures intra-oesophageal pH at two sites using a fine tube introduced via the nose into the distal oesophagus. The pH is recorded electronically and can be reproduced on a graph using an appropriate computer programme. The 24-hour pH profile in the distal oesophagus can be related to pain events marked by the person, who continues normal daily activities while the tube is *in situ*.

Interpretation of 24-hour pH telemetry is difficult without a definitive test for the diagnosis of GORD. It is most reliable in individuals with typical symptoms (where it is least needed), but may be of considerable benefit when it is clearly positive in individuals with atypical symptoms. A negative test does not necessarily exclude GORD. Previously, measurement of 24-hour oesophageal acidity was considered the gold standard for differentiating individuals with grade-0 GORD from individuals with other problems. However, in their technical review of clinical oesophageal pH recordings, Kahrilas and Quigley found that only about 50\% of grade 0 GORD individuals had abnormal acid reflux, and that some individuals appear to be much more sensitive to normal acid exposure of the lower oesophagus.\textsuperscript{51} Thus, measurement of oesophageal acidity reaches a high sensitivity in a selected group (those with typical GORD symptoms), but does not reach the sensitivity in the overall population that was initially expected.

Currently, 24-hour pH telemetry should be used to investigate high-dosage treatment failures or to assess individuals with grade-0 GORD prior to considering surgery (usually combined with manometry).\textsuperscript{51}

People with GORD (all grades) not responding to high-dosage twice-daily PPIs and with signs of ‘acid break-through’ (particularly at night) demonstrated on pH telemetry while on medication, need the maximum twice-daily dose of PPIs, as well as nocturnal H\textsubscript{2}RA.\textsuperscript{11,12} In a controlled trial, Peghini et al showed that a bedtime H\textsubscript{2}RA was more effective than a bedtime PPI on residual nocturnal acid secretion in individuals receiving twice-daily PPIs.\textsuperscript{52} Additional prokinetic agents can be recommended for those with symptoms suggesting acid-volume reflux (regurgitation).\textsuperscript{11}
**SURGERY**

Anti-reflux surgery offers an alternative to medical therapy. Surgery should not be performed without a definitive diagnosis of GORD; 24-hour pH telemetry is advised in individuals with grade 0 GORD. Analysis of outcomes is difficult as results are operator-dependent and the most successful tend to be those included in published literature.

Open fundoplication was the standard procedure but this has now been largely superseded by the laparoscopic technique. Although a learning curve has been clearly defined with this procedure, results for experienced surgeons are comparable between open and laparoscopic surgical approaches. The laparoscopic approach offers reduced hospital stay (2 – 5 vs 8 – 9 days) and time off work (21.3 vs 38.2 days).

A Scandinavian study using open fundoplication showed surgery and medical therapy with omeprazole to be equally effective if the dose of PPI is adjusted according to symptoms, as described in the current Guideline. Costs of surgery versus medical therapy are difficult to evaluate because of the different cost structures in various countries. The ‘up-front’ cost of surgery (and its complications) must be compared with life-long use of PPI, although the cost of medical therapy is likely to decrease significantly with time. Surgical therapy is likely to be more cost effective in younger compared with older people, while the reverse is true for medical therapy. The age at which the costs are equivalent depends on the local cost of surgery versus medication. Risks of surgery increase with age, particularly with any comorbidity.

Laparoscopic fundoplication has been recognised as a significant therapeutic advance. The choice of surgery over drug therapy should be made after evaluation of risks and benefits of both modes of therapy, and is usually made on the basis of a person’s age, factors relating to compliance and acceptance of long-term drug therapy, cost, convenience and, of course, a person’s preference. Surgery has the potential to cure GORD but it is important that the diagnosis is confirmed by OGD and/or pH telemetry. Oesophageal manometry is useful to exclude achalasia and other forms of oesophageal dysmotility.

Bowrey and Peters have published a review of laparoscopic oesophageal surgery which elaborates on the current status of laparoscopic compared with open anti-reflux surgery. The Nissen fundoplication is the current favoured method with the Toupet partial fundoplication reserved for some cases. The choice of surgical technique is beyond the scope of this guideline.

Complications occur in 8% (2 – 13%) of people following laparoscopic fundoplication, with a 2% (1 – 10%) conversion rate to an open procedure. Complications include perforation of a hollow viscus, bleeding, vessel thrombosis, pneumothorax, pneumomediastinum and, very rarely, death.

Post-operatively, dysphagia is common (about 10%) but typically resolves within three months (7% at 3 months, 5% at 6 months, 2% at 12 months, with some even improving between 1 and 2 years). Inability to burp or vomit, increased flatulence, and discomfort are problems for a number of people.
Reflux (heartburn) and regurgitation are relieved in more than 90% assessed in follow up over three years. Notably, atypical symptoms (cough, asthma, laryngitis) are only relieved in two-thirds of people. As with medical therapy, surgery is more successful in the typical, well-defined erosive oesophagitis. Surgery does not avoid the cancer risk or the need for continued surveillance in people with Barrett’s oesophagus.

The decision to perform surgery should take into account the following factors.

1. The disease severity, in terms of symptoms and OGD findings, is predictive of the long-term prognosis on medical therapy; GORD grades 0, A and B have a good complication-free long-term prognosis, whereas complications may occur in grades C and D.

2. The recognised complications of uncontrolled reflux are stricturing, ulceration and intestinal metaplasia. Good drug treatment compliance is essential if these are to be avoided in people with severe GORD.

3. Surgery is more cost effective, and safer, in people of young biological age.

4. Comorbidity, such as cardio-pulmonary disease, increases the risk of surgery. This is more common in people aged 60 years and over.

5. Post-operatively, dietary restrictions may be necessary and flatulence and inability to vomit may be problems. Although dysphagia is usually self-limiting (within a few months), this can be a longer-term problem.

6. Previous abdominal surgery can make laparoscopic surgery difficult.

7. The morbidity of surgery must be compared with the known side effects of medical therapy. Although long-term PPI is considered safe, most long-term studies only extend to about 15 years.

8. The experience of the surgeon with this particular operation is a critical factor in the long-term success.
OVERVIEW

- The role of *H. pylori* has been demonstrated in the pathogenesis of gastric and duodenal ulcers, as a co-factor in the development of gastric cancer and in increasing the risks of peptic ulcer in people taking NSAIDs.

- *H. pylori* eradication is effective in healing peptic ulcers, and also very significantly reduces ulcer recurrence (rare) and complications.

- Most peptic ulcers (especially gastric ulcers) not related to *H. pylori* occur in those taking NSAIDs.

- Prevalence of *H. pylori* infection is very variable among various population groups in New Zealand.

- A test-and-treat strategy for *H. pylori* had been shown to be safe and to reduce the number and cost of OGDs when applied to dyspeptic individuals aged less than 50 years with no alarm signals in areas of moderate to high *H. pylori* prevalence (>30%).

- Testing for *H. pylori* implies an intention to treat if positive. Blind testing of all dyspeptic individuals or treating them empirically for *H. pylori* without testing is not recommended.

- UBT is the most reliable non-invasive test. Laboratory serology is less reliable, and finger-prick serology least reliable, especially in areas of low *H. pylori* prevalence. The faecal antigen test is also recommended, and is becoming increasingly available in New Zealand.

- Triple therapy is the most successful initial treatment for *H. pylori* eradication, with compliance and the absence of bacterial resistance being the two most important factors determining success of treatment.
### INITIAL DIAGNOSTIC INVESTIGATION FOR *H. pylori*

**RECOMMENDATIONS**

Test-and-treat for *H. pylori* in those:
- who originate from areas of high (>30%) *H. pylori* prevalence
- with present or past history of peptic ulcer
- with Mucosa-associated lymphoid tissue lymphoma
- with a family history of gastric cancer.

Recommended diagnostic tests
- Urea breath test (UBT) is the recommended non-invasive test. Stop treatment (other than antacids) for 2 weeks prior to UBT.
- Although UBT and faecal antigen tests are also valid options, serology (validated with sensitivity and specificity of at least 90%) is recommended where the prevalence of *H. pylori* is high (>30%).
- Faecal antigen test is also recommended, although it is not yet universally available in New Zealand. Omeprazole can interfere with the result.
- If OGD is being performed for investigation of dyspepsia, consider testing with the rapid urea test, histology or culture.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

### INITIAL TREATMENT OF *H. pylori*

**RECOMMENDATIONS**

Give triple therapy: regimens containing PPI, clarithromycin, and amoxicillin or metronidazole, have consistently high eradication rates after one week.

Substitute metronidazole for amoxicillin in penicillin-allergic individuals.

Emphasise to the person that successful eradication depends on compliance with treatment regimen.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
H. PYLORI TREATMENT FAILURE

RECOMMENDATIONS

For initial treatment failure, use either of the following for 1 week:
• an alternative triple therapy regimen (PPI plus two of the following: clarithromycin, amoxicillin, metronidazole, tinidazole, tetracycline and bismuth), OR
• quadruple therapy (standard triple therapy plus bismuth).

Repeated treatment failure:
• review compliance factors and consider testing for bacterial resistance
• consider retreatment for 2 weeks.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

CONFIRMATION OF H. PYLORI ERADICATION

RECOMMENDATIONS

Confirm eradication of H. pylori in those with a peptic ulcer complication, important comorbidity factors, symptom recurrence or residence in isolated areas.

Recommended tests
• UBT is the recommended non-invasive test (serology should not be used because it takes 6 – 12 months to become negative).
• H. pylori stool antigen may be used for confirmation of eradication at least 4 weeks after stopping treatment. Omeprazole can interfere with result.
• For people having OGD to check for healing of gastric ulcer, confirm eradication by histology.

Timing of tests
• Perform at least one month after completion of eradication regimen
• For people taking PPIs, perform at least one week after cessation of PPI.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
Management of H. pylori-negative Peptic Ulcers

Recommendations

- Treat duodenal ulcers with H$_2$RAs or PPIs for 4 – 8 weeks.  
  - Grade A

- Treat gastric ulcers with PPIs or H$_2$RAs for 8 – 12 weeks and confirm healing with OGD.  
  - Grade A

- Use maintenance treatment with H$_2$RA or PPI if:
  - ulcer recurrences are frequent (eg, more than once per 12 months) or severe
  - previous peptic ulcer complication
  - there are comorbid factors that might make any complications life-threatening.  
  - Grade C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

Introduction

The presence of spiral organisms in the stomach was first recorded in 1896 and subsequent publications attempted to link these with the aetiology of peptic ulceration. However, it was not until 1983 that these ‘unidentified curved bacilli’ on gastric epithelium were linked to active chronic gastritis and eventually to peptic ulceration.\(^1\)\(^5\) This discovery has not only resulted in major advances in the understanding of GI microbiology and its pathophysiological links but also ushered in an era of major change in the approach to peptic ulceration treatment. For the first time peptic ulcers are being cured, rather than simply held in check by control of acid secretion.

The vast majority of gastric infection with H. pylori (originally known as Campylobacter pyloridis) is acquired in childhood. It produces gastritis, which is asymptomatic in most cases, although about one in six may develop a peptic ulcer. About 95% of people with duodenal ulcers and 70% with gastric ulcers have been shown to be infected with H. pylori.\(^6\) However, in recent studies this proportion has been found to be decreasing in OECD countries and this has been related largely to the use of NSAIDs, which is the other main independent cause of peptic ulceration.\(^7\)\(^8\)

The other important link between H. pylori and GI pathology is with gastric cancer. Although an important carcinogen, H. pylori is only one of multiple factors involved in the pathogenesis of gastric cancer, which is a truly heterogeneous disease.\(^2\) The other link with H. pylori and malignancy concerns the very rare mucosa-associated lymphoid tissue (MALT) lymphoma, which, in many cases, has been cured by eradication of H. pylori.

The link between NUD and H. pylori is still highly controversial,\(^9\)\(^,\)\(^10\) as is its relation with a number of other non-gastrointestinal disorders.\(^11\) Although there is still some controversy on the issue, H. pylori does not appear to play a significant role in the cause of GORD.
PREVALENCE OF *H. PYLORI* INFECTION

The mode of transmission of *H. pylori* infection of the gastric mucosa is uncertain, but there is evidence for spread person-to-person via oral-oral or faecal-oral routes. Living conditions are more important than genetic factors in transmission of infection: the incidence of infection is inversely proportional to socio-economic status and lower household income, and particularly with consequent overcrowding.\(^{12-16}\) Childhood is the period of major risk for acquisition of *H. pylori* infection. The prevalence of infection increases with increasing age, due to a cohort effect.\(^ {13-15,17}\)

The infection incidence rates vary around the world, and within New Zealand. It is more prevalent in poorer regions. Decreasing incidence in OECD countries is believed to be due to improved hygiene, improved childhood nutrition, smaller family sizes, larger time intervals between children, and possibly an increase in consumption of antimicrobials.\(^ {18}\)

Detailed data relating to prevalence around New Zealand are limited, but Dunedin and Christchurch population-based studies suggest that prevalence in the central and southern South Island is similarly low. The following figures are currently available:

**Auckland**

A study by Fraser *et al* showed that rates of sero-positivity vary according to age and ethnicity, and that the incidence of infection was not significantly associated with gender, smoking or alcohol intake.\(^ {19}\)

| Table 4.1: Rates of *H. pylori* sero-positivity in Auckland, by age and ethnicity |
|-------------------------------------|-----------------|-----------------|
| Age group                          | 11 – 12 years   | 40 – 65 years   |
| European                           | 7               | 35.8            |
| Maori                              | 21              | 57.4            |
| Pacific people                     | 48              | 73.2            |


**Wellington**

In an unpublished study, 22% of all people presenting for OGD in the Wellington/Hutt area were found to be sero-positive.\(^ {20}\)

**Dunedin**

Fawcett *et al*, in a longitudinal study, reported that spontaneous reversion of *H. pylori* sero-prevalence may occur in childhood and adolescence, and that sero-conversion was rare after age 11. The sero-prevalence of this cohort was significantly lower than that of most
populations of about the same ages in other countries: 6.6% at age 11, and 4.1% at 21 years. Of those aged <50 years with dyspepsia referred to Dunedin Hospital for OGD, 17.5% were infected with H. pylori compared with 31.8% of those aged 50 years and over, while the overall infection rate was 26.8%.

Christchurch

Collett et al found that of 1064 people randomly chosen in the community and tested for H. pylori sero-positivity, 25.9% of males and 22.6% of females tested positive. The mean was 24%, and prevalence in those ages 20 – 29 years was 4.2%. On multivariate analysis, ethnicity, low income and smoking over 20 cigarettes per day were all independent predictors of H. pylori sero-positivity. Prevalence of infection increased significantly with age.

H. PYLORI AND DISEASE

Numerous toxigenic factors, such as the production of cytokines associated with H. pylori may be responsible for pathogenic effects. However, not all of those infected with H. pylori develop disease, and most people remain asymptomatic. As yet, it is unclear why this should be the case.

A number of possible virulence factors for H. pylori have been identified, including the cytotoxin-associated gene (cagA). None of the postulated virulence factors, including cagA, have disease specificity and it is impossible to predict the ultimate outcome of H. pylori infection in an individual.

Susceptibility to infection with H. pylori, as well as the different patterns of disease in response to this infection, appears to be dependent on interaction between environmental (including diet) and genetic factors (both of the host and of the strain of H. pylori). High acid secretors have predominantly antral infection (and are more susceptible to duodenal ulcer), while low acid secretors have a body-dominant gastritis (and a greater predisposition to gastric ulcer, gastric atrophy, intestinal metaplasia and cancer). This is the subject of intense current research.

The first recognisable pathology is a chronic active gastritis that affects the body and/or antrum. In approximately half the cases, the gastritis slowly (over years to decades) progresses to atrophic gastritis with intestinal metaplasia. There is an approximately one in six lifetime risk of a peptic ulcer with H. pylori infection. The odds ratios have been reported in various studies as:

- 4.0 (95% CI 1.1 – 14.2) for duodenal ulcer
- 3.8 (95% CI 1.4 – 10.2) for duodenal ulcer
- 5.0 (95% CI 0.6 – 45) for duodenal ulcer
- 3.2 (95% CI 1.6 – 6.5) for gastric ulcer
- 3.8 (95% CI 1.4 – 10.1) for all peptic ulcers.
The odds ratio for developing gastric cancer with *H. pylori* infection has been estimated as 1.9 – 4.9. MALT lymphoma may develop as a very rare complication of *H. pylori* infection.\(^\text{33,34}\)

**PEPTIC ULCERS**

The proportion of peptic ulcer disease attributed to *H. pylori* infection varies from population to population, and is directly proportional to the incidence of *H. pylori* infection.\(^\text{35}\)

As the prevalence of *H. pylori* infection is falling in OECD countries, so is the proportion of *H. pylori*-related duodenal ulcers.\(^\text{7,18,36,37}\) Between 90 and 95% of duodenal ulcers are associated with *H. pylori* infection, while the rest are mainly NSAID related.\(^\text{1,2,4}\) Eradication of *H. pylori* heals between 95 and 98% of associated duodenal ulcers compared with 85 – 95% with acid suppression alone.\(^\text{38,39}\)

*H. pylori* infection is associated with 70 – 80% of gastric ulcers.\(^\text{2,4,40}\) Studies have shown that approximately 85% of gastric ulcers heal with eradication of associated *H. pylori* infection compared with approximately 60% with acid inhibition alone in those with persistent *H. pylori* infection.\(^\text{38,41,42}\) *H. pylori*-negative gastric ulcers are commonly caused by NSAID use, but up to 11% may have no discernible cause.\(^\text{43}\) The proportion of *H. pylori*-negative gastric ulcers in a population is inversely proportionate to the prevalence of *H. pylori* infection.\(^\text{35}\)

**Recurrence**

According to a meta-analysis by Hopkins *et al*, after eradication of associated *H. pylori* infection, duodenal ulcer recurrence at one to four years is about 6% (95% CI 4 – 9) compared with a median recurrence of about 67% (95% CI 63 – 72) with persistent infection. The recurrence rate of gastric ulcers after eradication at one to four years is approximately 4% (95% CI 1 – 10) and approximately 59% (95% CI 49 – 69) at one to four years if *H. pylori* infection persists.\(^\text{38}\)

**Upper GI bleeding from peptic ulceration**

For people with upper GI bleeding from peptic ulcers, eradication of *H. pylori* infection leads to a reduction in ulcer recurrence and thus a reduction in re-bleeding. A number of studies have shown that without *H. pylori* eradication, 27 – 37% of those with upper GI bleeds from peptic ulcers will suffer a re-bleed annually but with eradication of *H. pylori*, the risk is virtually zero (see Table 4.2).\(^\text{42,44-48}\)
Table 4.2: *H. pylori* eradication vs no maintenance therapy for recurrence of peptic ulcer bleeding

<table>
<thead>
<tr>
<th>Nature of study</th>
<th>Re-bleed with <em>H. pylori</em> eradication</th>
<th>Re-bleed with no therapy</th>
<th>Follow up (months)</th>
<th>ARR (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>3.4% (1/29 individuals re-infected)</td>
<td>50% (2/4)</td>
<td>12</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>Cohort</td>
<td>0% (0/21)</td>
<td>81.8% (9/11)</td>
<td>48</td>
<td>82</td>
<td>1</td>
</tr>
<tr>
<td>RCT</td>
<td>0% (0/17)</td>
<td>28.6% (4/14)</td>
<td>12</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>RCT</td>
<td>0% (0/29)</td>
<td>27.3% (6/22)</td>
<td>12</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>RCT</td>
<td>0% (0/42)</td>
<td>37.5% (9/24)</td>
<td>12</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>RCT</td>
<td>0% (0/6)</td>
<td>33% (5/15)</td>
<td>12</td>
<td>33</td>
<td>3</td>
</tr>
</tbody>
</table>

There have been three trials comparing eradication of *H. pylori* and ranitidine maintenance therapy in recurrence of bleeding from a peptic ulcer. They show that eradication therapy is superior to maintenance therapy (see Table 4.3). 49,50,51

Table 4.3: *H. pylori* eradication vs ranitidine maintenance therapy for recurrence of peptic ulcer bleeding

<table>
<thead>
<tr>
<th>Nature of study</th>
<th>Re-bleed with <em>H. pylori</em> eradication</th>
<th>Re-bleed with maintenance ranitidine 150 mg daily</th>
<th>Follow up (months)</th>
<th>ARR (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-RCT Santander, 199649</td>
<td>2.3% (2/84) (both individuals re-infected)</td>
<td>12.1% (5/41)</td>
<td>12</td>
<td>9.8</td>
<td>10</td>
</tr>
<tr>
<td>RCT Reimann, 199750</td>
<td>4.2% (2/47) (both individuals on NSAIDs)</td>
<td>8.3% (4/48)</td>
<td>24</td>
<td>4.1</td>
<td>25</td>
</tr>
<tr>
<td>RCT Sung, 199751</td>
<td>(0/97)</td>
<td>3% (3/99)</td>
<td>12</td>
<td>3</td>
<td>33</td>
</tr>
</tbody>
</table>
NSAID therapy

Although *H. pylori* infection and NSAID use are independent risk factors for peptic ulceration and GI bleeding, data on whether or not they are interactive have been conflicting. Chan et al demonstrated a decrease in peptic ulcer disease with *H. pylori* eradication in previously well individuals who required NSAID therapy for musculoskeletal pain (7 vs 26%), suggesting that elimination of *H. pylori* before starting NSAID therapy might decrease the development of ulcers. Aalykke et al found that if *H. pylori* infection was present, there was an 80% increase in NSAID-associated bleeding peptic ulcers.

However, other studies of long-term NSAID users found no significant differences in peptic ulcer bleeding or healing with *H. pylori* eradication.

Some trials have suggested that eradication of *H. pylori* infection in long-term NSAID users might impair the healing of gastric ulcers. For instance, Stack et al found that those infected with cagA-positive strains of *H. pylori* have decreased risk of bleeding from peptic ulcers when taking NSAIDs. Santolaria et al also found *H. pylori* infection to be a protective factor against bleeding gastric ulcers. It is postulated that *H. pylori*-induced stimulation of gastric mucosal prostaglandin production protected against the intrinsic toxicity of the NSAID, acting through reduction in gastric mucosal prostaglandin synthesis.

A recent meta-analysis by Huang et al has shown that both *H. pylori* infection and NSAID use independently and significantly increase the risk of peptic ulcer and bleeding from ulcers. Synergism was demonstrated between the development of peptic ulcer and ulcer bleeding, and *H. pylori* infection and NSAID use. In all NSAID takers (1625 in 16 studies), peptic ulcers were found in 41.7% of those who were *H. pylori*-positive compared with 25.9% of those who were negative (OR 2.12, 95% CI 1.68 – 2.67). In five controlled studies, NSAID takers had more peptic ulcers than controls (35.8 vs 8.3%), irrespective of *H. pylori* infection. The risk of ulcer in *H. pylori*-infected NSAID takers compared with subjects who were *H. pylori*-negative and non-NSAID takers was 61.1 (95% CI 9.98 – 373). For those with *H. pylori* infection, use of NSAIDs increased the risk of peptic ulcer 3.55-fold. *H. pylori* infection and NSAID use increased the risk of ulcer bleeding 1.79-fold and 4.85-fold respectively, but this risk was increased to 6.13 when both factors were present.

In a prospective controlled trial, Chan et al showed that screening and treatment for *H. pylori* infection significantly reduced the risk of ulcers in individuals starting NSAID treatment. However, it should be stressed that the study was performed in a cohort (Hong Kong) with 61% prevalence of *H. pylori*, thus making screening more productive. The 6-month probability of ulcer was 12.1% (95% CI 3.1 – 21.1) in the eradication group and 34.4% (95% CI 21.1 – 47.7) in the placebo group (p=0.0085). Complications were recorded in 4.2% (95% CI 1.3 – 9.7) and 27.1% (95% CI 4.7 – 39.5) of individuals respectively (p=0.0026).

At present, the consensus advice is to treat *H. pylori* if it is present, especially in people with duodenal ulcers. This is supported by the study by Huang et al indicating synergism for the development of peptic ulcers and ulcer bleeding between *H. pylori* and NSAID use. Further studies are awaited to guide recommendations in this area.
Gastric cancer

*H. pylori* is now recognised as a class I carcinogen by the World Health Organization. Progression from *H. pylori* infection to gastric adenocarcinoma appears to be dependent on the interaction between environmental and genetic factors (both of the host and the strain of *H. pylori*), and is currently the topic of intense research.\(^{25,26,28,29}\) However, not all gastric cancers are associated with *H. pylori* infection. When adjusting for the prevalence of *H. pylori* infection in a population, as well as for the sensitivity and specificity of particular tests, it appears that between 35% (OECD countries) and 68% (non-OECD countries) of gastric cancers are attributable to *H. pylori* infection.\(^{35}\)

Overall, New Zealand has a low-to-moderate incidence of gastric cancer, although some areas, such as South Auckland and the east coast of the North Island, do have high rates. Males have a greater incidence of gastric cancer than females, and Maori and Pacific peoples incidence rates are higher than those for European New Zealanders.\(^{19,63}\)

**Table 4.4: Rates of gastric carcinoma in New Zealand, by gender and ethnicity**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Rate per 100 000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>European</td>
<td>8</td>
</tr>
<tr>
<td>Maori</td>
<td>24</td>
</tr>
<tr>
<td>Pacific peoples</td>
<td>40</td>
</tr>
</tbody>
</table>

*Source:* Fraser *et al.* 1996\(^{19}\) and Tukuitonga *et al.* 1992.\(^{63}\)

The prognosis for survival is generally poor. It is currently recommended that *H. pylori* infection be treated following resection of early gastric cancer where the prognosis is a little more favourable.\(^{39,64}\) Uemera found that 0% (0/65) of individuals developed recurrence of gastric cancer following endoscopic resection and *H. pylori* eradication compared with 9% (6/67) recurrence rate following endoscopic resection and no *H. pylori* eradication.\(^{64}\) However, different forms of early gastric cancer may exist in Japan, making interpretation of their research studies difficult. There is no evidence that eradication of *H. pylori* infection reverses atrophic gastritis and prevents the development of gastric adenocarcinoma. It is not known at what point the progression to gastric cancer might be reversed with eradication of *H. pylori*, and currently there are no established predictors for the development of gastric cancer.\(^{25,39}\) However, in a further Japanese study, Uemera *et al.* showed that people with *H. pylori* and gastric ulcer, severe gastric atrophy, corpus predominant gastritis or intestinal metaplasia were at increased risk of developing gastric cancer. Those with *H. pylori*, NUD and hyperplastic polyps were also found to be at increased risk, but those with duodenal ulcers were not.\(^{65}\)
Malt Lymphoma of the Stomach

In most cases, MALT (mucosa-associated lymphoid tissue) lymphoma of the stomach has been found in association with *H. pylori* infection. Of those, eradication of *H. pylori* has been reported to lead to complete remission of this malignancy in about 75% of people.

WHO SHOULD BE INVESTIGATED?

Testing implies an intention to treat if the test is positive. Ideally, only people who could benefit from treatment should be investigated for *H. pylori*. Routine testing of all dyspeptic individuals cannot be advocated. At the opposite extreme, blind treatment for *H. pylori* in dyspeptic individuals who have not been tested is also unacceptable. In addition, people presenting primarily with heartburn do not warrant testing for *H. pylori*. The prevalence of *H. pylori* in the local situation will also determine the predictive value of a positive test and could well influence the decision to test.

Most benefit is gained by treating individuals with peptic ulcer. The prevalence of peptic ulceration in the community should be considered in the decision whether to test for *H. pylori*. In people with NSAID-related peptic ulcer, benefits may be gained by treating *H. pylori* if present. Most people with dyspepsia have NUD, and the benefit of testing these people is uncertain. People with the rare MALT lymphoma should be tested for *H. pylori*. Although evidence is largely circumstantial, *H. pylori* eradication, and therefore testing, might be justified in people with a family history of gastric cancer.

FUNCTIONAL DYSPEPSIA

Most people with dyspepsia have non-ulcer or functional dyspepsia. There is still considerable controversy as to whether these individuals benefit from *H. pylori* eradication, and a number of studies have been performed to investigate this (see Table 4.5). Recent meta-analyses, including the Cochrane review by Moayyedi et al, showed some, but minor, benefit of *H. pylori* eradication among these individuals. The Cochrane review indicated that the NNT to cure one case of dyspepsia was 19. However, a more recent meta-analysis by Laine et al, showed that there was considerable heterogeneity among the studies, and their conclusion was that there was no benefit from treating such people. It is interesting that the McColl study, which is included in both meta-analyses and shows most success in the treatment of functional dyspepsia by *H. pylori* eradication, was from Glasgow where the prevalence of peptic ulcer is particularly high. Some of these results may have been skewed by covert treatment of peptic ulcer.
Table 4.5: Response of non-ulcer dyspepsia to *H. pylori* medications

<table>
<thead>
<tr>
<th>Research</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moayyedi et al⁹</td>
<td>0.91</td>
<td>0.86 – 0.96</td>
</tr>
<tr>
<td>Laine et al¹⁰</td>
<td>All data</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia defined</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td>Cure of <em>H. pylori</em></td>
<td>1.17</td>
</tr>
</tbody>
</table>

**DIAGNOSING *H. PYLORI***

It should be noted that a positive diagnostic test indicates simply that the person is infected with *H. pylori* and does not necessarily equate with the cause of presenting symptoms.

Serology is the simplest and cheapest, but least reliable, test. The finger-prick, whole-blood tests are easier and convenient but have the lowest sensitivity and specificity (about 80%).⁷⁰ Laboratory tests on whole blood using more refined techniques are more accurate, with sensitivity and specificity often about 90% and, in some well validated studies, up to 96%.⁷¹ *H. pylori* serology should be validated locally,¹⁹ as it is more accurate in areas of moderate to high prevalence (>30%) of *H. pylori* infection (higher positive and negative predictive values),⁸³ but unreliable (lower positive and negative predictive values) in areas of low prevalence (<30%) such as the South Island.⁷² It cannot be used to confirm eradication because antibody titres decline slowly and variably after eradication, and may persist at detectable levels for six months to years.

Stool tests (*H. pylori* stool antigen [HpSA]) can also be very accurate, and are becoming increasingly available in New Zealand. They have a sensitivity and specificity of 93.1% and 92.8% respectively, and play a useful role in primary diagnosis.⁹⁷ There is still some debate as to usefulness for confirmation of eradication; some have found it useful, but at least 4 weeks must be allowed after completion of treatment.⁹⁸ Omeprazole can interfere with results.⁹⁹

The UBT, usually using ¹³C (which is non-radioactive), is the most reliable non-invasive test. It may be used both for diagnosis of presence of infection and confirmation of eradication. If instructions are followed carefully, sensitivity and specificity are about 98%.³⁹,⁷³ However, this test costs three to five times more than serology. It should be noted that ingestion of antibiotics or bismuth within four weeks or proton pump inhibitors within one week of testing can invalidate results.⁷⁴

Other tests for *H. pylori* rely on samples taken at OGD. The procedure is performed primarily to diagnose the cause of the symptoms, and *H. pylori* tests are now often added as an adjunct to this. These include the rapid urea (CLO) test, which depends upon the property of *H. pylori* to digest urea and release bicarbonate and has a sensitivity and specificity of
about 90 – 95%. The yield is improved if multiple biopsies are taken from the body and the antrum, although ingestion of PPIs, antimicrobials and bismuth compounds may reduce sensitivity. Histology has similar success, and this can be increased by using special stains. Culture of the organism is not performed routinely, but may be useful where bacterial resistance presents a therapeutic challenge. The bacterium requires prolonged incubation (96 hours) and although sensitivity can be as low as 70%, specificity is 100%.

Table 4.6: Diagnostic tests for *H. pylori* infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Non-endoscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>whole blood</td>
<td>70 – 85</td>
<td>75 – 90</td>
</tr>
<tr>
<td>serum</td>
<td>86 – 94</td>
<td>75 – 90</td>
</tr>
<tr>
<td>ELISA (enzyme-linked immunosorbent assay)</td>
<td>86 – 94</td>
<td>80 – 95</td>
</tr>
<tr>
<td>Stool antigen</td>
<td>88 – 98</td>
<td>89 – 98</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>90 – 96</td>
<td>88 – 98</td>
</tr>
<tr>
<td><strong>II. Endoscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urease</td>
<td>90 – 95</td>
<td>95 – 100</td>
</tr>
<tr>
<td>Histology</td>
<td>90 – 95</td>
<td>95 – 100</td>
</tr>
<tr>
<td>Culture</td>
<td>60 – 95</td>
<td>100</td>
</tr>
</tbody>
</table>


**INITIAL TREATMENT OF *H. PYLORI***

This relies on triple therapy. Combinations of two antibiotics plus another drug are usually required, the choice depending on a number of factors, including penicillin allergy and drug resistance. In a comprehensive meta-analysis, Laheij *et al* found that regimens containing a PPI and clarithromycin have been shown to be the most effective. Although bismuth is still an effective compound, its popularity has declined because of the greater reliability and shorter course of treatment required with other drugs. Ranitidine bismuth citrate is a drug combining ranitidine and bismuth in a novel molecule, but this was not available in New Zealand at the time of writing.

Dual therapy has been discredited and is not recommended.
Most modern drug regimens are given for one week. Compliance (which is essential and needs to be stressed to the person), and bacterial resistance are the two most important factors determining success of the treatment.\textsuperscript{24}

The most effective treatment is to eliminate the bacterium with a first-hit regimen. If this fails, an alternative triple therapy regimen, or quadruple therapy including bismuth, can be given.

\textbf{THE TEST-AND-TREAT STRATEGY FOR UNDIFFERENTIATED PEOPLE}

The gold standard for investigation of dyspepsia and diagnosis of \textit{H. pylori} infection is OGD and rapid urease test, histology or culture. Traditionally, many individuals suffering from dyspepsia have been referred by their general practitioner for OGD. However, in individuals with dyspepsia who are aged $<50$ years with no alarm signals, there is a very low incidence of serious organic disease beyond \textit{H. pylori}-related peptic ulcers.\textsuperscript{71}

In areas of moderate-to-high prevalence of \textit{H. pylori} infection ($>30\%$) and high incidence of symptomatic peptic ulceration, the test-and-treat strategy may be used.\textsuperscript{39} In this approach, a non-invasive test for the presence of \textit{H. pylori} infection is offered to the dyspeptic person who is aged $<50$ years with no alarm signals. If the test is positive, eradication therapy is offered to the person. The positive and negative predictive values of such testing are higher in areas of high prevalence of \textit{H. pylori} infection, and lower in areas of low prevalence.\textsuperscript{76,77} Thus, this method is most useful in an area of moderate-to-high prevalence of \textit{H. pylori} infection.\textsuperscript{78,79}

The test-and-treat strategy should not be relied on in areas of low prevalence ($<30\%$).\textsuperscript{72} In some areas in OECD countries with decreasing incidence of \textit{H. pylori} infection, there have been increasing reports of \textit{H. pylori}-negative peptic ulcers.\textsuperscript{7} For example, Xia \textit{et al} in Sydney, Australia, found using a 96%-sensitive validated serology test for peptic ulcer disease in those aged $<45$ years, that 42% were sero-positive, but 17% of peptic ulcers might have been missed in this group by applying a test-and-treat strategy.\textsuperscript{71}

\textbf{ERADICATION THERAPY}

\textit{H. pylori} may be difficult to eradicate. The gastric lumen is a hostile environment for antimicrobial therapy because the bacteria reside within the mucus, and some may be attached to epithelial cells. Therefore the drugs need to penetrate the thick mucus and also need to be active at a low pH. In addition, there is ongoing gastric motility.\textsuperscript{24}

Therapy has evolved over the last decade, and there have been hundreds of trials investigating eradication rates of various regimens, including several large, international, multicentre RCTs\textsuperscript{37,80-86} (see Tables 4.7 and 4.8). In \textit{H. pylori} eradication, seemingly identical regimens often behave differently for unclear reasons. Interpretation of many clinical trials is confounded by lack of pre-treatment antibiotic susceptibility testing. Antimicrobial
resistance in the place where the study is performed has a significant impact on eradication rates, as does compliance with triple therapy regimens. Thus, there are problems in applying the tool of meta-analysis to eradication of *H. pylori* using data from different regimens.²⁴

**Table 4.7: Comparison of eradication therapies**

<table>
<thead>
<tr>
<th>Nature of study</th>
<th>Therapy</th>
<th>Mean eradication rate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Huang et al</strong> ⁸⁰</td>
<td>PAC</td>
<td>ITT: 86.6 (81 – 89.3) PP: 89.5 (86.9 – 92)</td>
</tr>
<tr>
<td>Meta-analysis: 82 studies; 6123 individuals</td>
<td>PMC</td>
<td>PP: 90.8 (87 – 94.5)</td>
</tr>
<tr>
<td><strong>Schmid et al</strong> ⁸¹</td>
<td>OAC</td>
<td>82</td>
</tr>
<tr>
<td>74 RCTs: 4769 individuals</td>
<td>OAI</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>OCI</td>
<td>83</td>
</tr>
<tr>
<td><strong>Penston et al</strong> ⁸²</td>
<td>PMC</td>
<td>81 – 93 (77 – 99)</td>
</tr>
<tr>
<td>‘Objective literature review’: 352 studies; 536 different treatment arms</td>
<td>PAC</td>
<td>86 (79 – 93)</td>
</tr>
</tbody>
</table>

**Abbreviations**: P = proton pump inhibitor, A = amoxycillin, C = clarithromycin, M = metronidazole, O = omeprazole, I = imidazole, ITT = intention to treat analysis, PP = protocol analysis.

The most effective therapy, which requires a combination of drugs, is PPI-based triple therapy, in which a PPI (omeprazole or pantoprazole or lansoprazole) is used in combination with two antimicrobials. Best results are obtained if one of these is clarithromycin and the other either amoxycillin or metronidazole (see Table 4.7).
Table 4.8: *H. pylori* eradication therapies

<table>
<thead>
<tr>
<th>Nature of study</th>
<th>OAC eradication rates % (95% CI)</th>
<th>OMC eradication rates % (95% CI)</th>
<th>OAM eradication rates % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT: MACH 1&lt;sup&gt;83&lt;/sup&gt; Multicentre trial, 43 centres in Canada &amp; Europe (n=787 with duodenal ulcer and <em>H. pylori</em> infection)</td>
<td>OAC250 79.5 (72.2 – 86.8)* 85.1 (78.3 – 91.8)*</td>
<td>OMC250 89.7 (84.3 – 95.2)* 94.3 (89.9 – 98.7)*</td>
<td>OAM250 75.8 (68.3 – 83.3)* 81.6 (74.5 – 88.7)*</td>
</tr>
<tr>
<td></td>
<td>OAC500 90.6 (85.3 – 95.9)* 98 (95.4 – 100)*</td>
<td>OMC500 85.5 (79.3 – 91.7)* 92.5 (87.4 – 97.5)*</td>
<td></td>
</tr>
<tr>
<td>RCT: MACH 2&lt;sup&gt;84&lt;/sup&gt; Multicentre trial, 47 centres in Europe (n=539 with duodenal ulcer &amp; <em>H. pylori</em> infection)</td>
<td>94 (88 – 97)* 95 (90 – 99) #</td>
<td>87(79 – 92)* 91(84 – 95) #</td>
<td></td>
</tr>
<tr>
<td>RCT: GU-MACH&lt;sup&gt;85&lt;/sup&gt; Multicentre trial, 18 centres in Europe (n=160 with gastric ulcer &amp; <em>H. pylori</em> infection)</td>
<td>79 (65 – 90)* 83 (68 – 93)*</td>
<td>86(73 – 94)* 93(80 – 98) *</td>
<td></td>
</tr>
<tr>
<td>RCT: DU-MACH&lt;sup&gt;86&lt;/sup&gt; Multicentre trial, 15 centres in Canada (n=149 with duodenal ulcer &amp; <em>H. pylori</em> infection)</td>
<td>78* 87*</td>
<td>85* 92*</td>
<td></td>
</tr>
<tr>
<td>RCT: HERO&lt;sup&gt;37&lt;/sup&gt; Multicentre trial, Australia &amp; NZ (n=220 with duodenal ulcer &amp; <em>H. pylori</em> infection)</td>
<td>82(74 – 89)* 85(76 – 91) #</td>
<td>58(49 – 67)* 63(52 – 72) #</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Mean eradication rates for OMC were 95% for sensitive strains and 76% for resistant strains
* Intention-to-treat; # protocol analysis

**Abbreviations:** A = amoxycillin, C = clarithromycin, M = metronidazole, O = omeprazole, I = imidazole

Effective therapies identified were OAC (omeprazole-amoxycillin-clarithromycin) and OMC (omeprazole-metronidazole-clarithromycin) with mean eradication rates around 85 – 95%. OAM (omeprazole-amoxycillin-metronidazole) was found to be less effective with mean eradication rates of around 60 – 80%. It does not appear necessary to continue acid inhibition beyond eradication therapy for uncomplicated duodenal ulcers.\(^8^7\)

**ANTIMICROBIAL RESISTANCE**

The major obstacle to effective therapy is the presence of antimicrobial resistance.

**Clarithromycin resistance**

This generally results in complete loss of any anti-*H. pylori* effect (all-or-none).\(^2^4\) Two New Zealand studies have found low rates of resistance: clarithromycin-resistant isolates comprised 7% (18/257) of *H. pylori* strains in an audit in Auckland,\(^8^8\) and 0% (0/50) in Dunedin.\(^8^9\)

**Metronidazole resistance**

Metronidazole resistance exhibits a continuous spectrum of minimal inhibitory concentrations *in vitro*, which suggests that there may be more than one mechanism causing resistance. However, *in vitro* resistance does not always predict *in vivo* results. Increasing the dose generally improves the results of therapy in metronidazole-resistant strains. Bayerdorffer et al have found that primary metronidazole resistance may be partially overcome with high-dose metronidazole (eg, 800 mg twice daily).\(^9^0\) However, higher doses need to be balanced against the risk of more severe adverse effects. There appears to be a synergistic effect with the combination of clarithromycin and metronidazole, and the addition of clarithromycin to metronidazole may partially overcome metronidazole resistance.\(^2^4\)

Eradication rates vary between metronidazole-resistant and metronidazole-sensitive strains.\(^3^7,8^3,9^0,9^1\) Primary metronidazole resistance has a significant negative impact on eradication rates with OAM.

**Table 4.9: Eradication rates for metronidazole-resistant and metronidazole-sensitive strains**

<table>
<thead>
<tr>
<th>Study</th>
<th>OMC Metronidazole-resistant rate (%)</th>
<th>OAM Metronidazole-resistant rate (%)</th>
<th>OMC Metronidazole-sensitive rate (%)</th>
<th>OAM Metronidazole-sensitive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lind T et al(^8^4)</td>
<td>76</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katelaris PH et al(^3^7)</td>
<td>80</td>
<td>45</td>
<td>95</td>
<td>79</td>
</tr>
<tr>
<td>Houben MH et al(^9^1)</td>
<td>82</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayerdorffer E et al(^9^0)</td>
<td></td>
<td>60</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>
An audit of 665 individuals treated in Auckland over five years found that metronidazole resistance significantly affected *H. pylori* eradication for regimens containing metronidazole without clarithromycin. An audit of 665 individuals treated in Auckland over five years found that metronidazole resistance significantly affected *H. pylori* eradication for regimens containing metronidazole without clarithromycin. Eradication with metronidazole without clarithromycin was achieved in 90% of metronidazole-sensitive strains and 55% of resistant strains. In contrast, eradication with metronidazole combined with clarithromycin was achieved in 86% of metronidazole-sensitive strains and 78% of resistant strains. The authors commented that the clinical implication of the rising rate of metronidazole resistance in New Zealand is that treatments not containing clarithromycin are becoming ineffective.

### Table 4.10: Metronidazole resistance rates of *H. pylori* in Auckland

<table>
<thead>
<tr>
<th>Year</th>
<th>Metronidazole resistance rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993 – 4</td>
<td>12% (4/32)</td>
</tr>
<tr>
<td>1995</td>
<td>34% (37/110)</td>
</tr>
<tr>
<td>1996</td>
<td>31% (27/87)</td>
</tr>
<tr>
<td>1997 – 8</td>
<td>44% (16/36)</td>
</tr>
</tbody>
</table>

**Source:** Fraser et al. 1999.

### Table 4.11: Metronidazole resistance according to ethnicity in Auckland

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Metronidazole resistance rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>32% (32/100)</td>
</tr>
<tr>
<td>Maori</td>
<td>25% (13/51)</td>
</tr>
<tr>
<td>Pacific peoples</td>
<td>25% (16/64)</td>
</tr>
<tr>
<td>Other</td>
<td>46% (23/50)</td>
</tr>
</tbody>
</table>

**Source:** Fraser et al. 1999.

An audit in Dunedin showed that 20% of strains (10/50) were found to be metronidazole-resistant.

**RANITIDINE BISMUTH CITRATE**

Ranitidine bismuth citrate is a new chemical entity, which incorporates bismuth into the ranitidine molecule, but is not available in New Zealand. It appears to act synergistically in combination with other antimicrobials against metronidazole- and clarithromycin-resistant strains.
ADVERSE REACTIONS ASSOCIATED WITH ERADICATION THERAPY

Adverse effects were very common with traditional bismuth-containing regimens (up to 40%), but only led to discontinuation of therapy in 4 – 5% of those taking part in clinical trials (likely to be greater in routine clinical use).\(^8^2\)

Modern PPI-containing regimens still have a high incidence of adverse effects (as for the antibiotics above), but withdrawal of treatment because of drug-related effects is only recorded as 0 – 2% in various trials.\(^8^2,^8^3\) One reason for the differences might be because these current regimens are given for one week with twice-daily doses, as opposed to the two weeks and three- or four-times daily doses for traditional treatments.

Adverse effects include:

- diarrhoea and candidiasis (amoxycillin)
- metallic taste, nausea, diarrhoea and disulfiram-like reaction to alcohol (metronidazole)
- metallic taste, diarrhoea, nausea and headache (clarithromycin)
- nausea, diarrhoea and photosensitivity (tetracycline)
- black stools and discolouration of the tongue (bismuth)
- pseudomembranous colitis (antibiotics)
- sensitivity reactions, including anaphylaxis.

WHICH THERAPY SHOULD BE SELECTED?

In selecting which antibiotic regimen is the best for each person, the following should be taken into consideration:

- ethnicity of person and (past and present) geographical area of residence (possible metronidazole resistance)\(^8^8\)
- previous failed eradication therapy (possible metronidazole resistance)
- medication allergies or sensitivities
- ease of administration of the selected regimen (ie, fewer tablets over shorter duration provides greater compliance)
- possible side-effect profile of the selected regimen
- cost to the person.
IF INITIAL TREATMENT FAILS

An alternative triple therapy regimen can be used in the first instance. If triple therapy should fail to achieve eradication, quadruple therapy is recommended for seven days.\textsuperscript{39,92} Some have indicated a preference for two weeks’ treatment.\textsuperscript{92,93}

- PPI (omeprazole 20 mg or lansoprazole 30 mg or pantoprazole 40 mg twice daily)
- Tetracycline HCl 500 mg qid
- Metronidazole 400 mg twice daily (or tds or qid)\textsuperscript{24}
- Colloidal bismuth subcitrate 120 mg qid

An alternative is standard triple therapy with PPI, clarithromycin, amoxycillin or metronidazole plus colloidal bismuth subcitrate.

Testing for antibiotic sensitivities is recommended with failure of two or more regimens (if treatment compliance has been assured).\textsuperscript{39}

CONFIRMATION OF ERADICATION

There are no randomised controlled trials comparing outcomes with and without confirmation of eradication after triple therapy.

Lam et al and Graham et al recommend confirmation of cure of \textit{H. pylori} infection with UBT.\textsuperscript{24,39} However, a decision analysis performed by Gene et al concluded that in healthy people with uncomplicated duodenal ulcer, post-treatment UBT after \textit{H. pylori} eradication therapy markedly increased costs, with no significant improvement in outcomes.\textsuperscript{94} The authors suggested that post-therapy urea breath testing should be reserved for those with symptom recurrence, complicated duodenal ulcers, comorbidity and gastric ulcers. Those living in places where treatment facilities are difficult to access might also be considered for confirmation of eradication.

MANAGEMENT OF \textit{H. PYLORI}-NEGATIVE PEPTIC ULCERS

For \textit{H. pylori}-negative peptic ulcers that are associated with NSAID use, see Chapter 5: NSAIDs and GI Complications.

For \textit{H. pylori}-negative peptic ulcers not associated with NSAID use, acid suppression is associated directly with healing of both duodenal and gastric ulcers.

Burget et al reported the findings of a workshop investigating duodenal ulcers healing relative to gastric acid suppression.\textsuperscript{95} In their meta-analysis, 19 drug regimens used in 22 studies provided data on duodenal ulcers healing at various endoscopic endpoints and compared these with data on acid suppression. There was a highly significant correlation.
(r=0.9814) between healing and the degree of acid suppression, the duration of acid suppression over 24 hours and the total duration of therapy. Acid suppression beyond pH 3 was not found to increase ulcer healing, indicating that a longer duration of antisecretory effect and/or a longer duration of therapy was more important than potency.

Most regimens suppressing gastric acid accelerate duodenal ulcer healing. PPIs are more effective than H$_2$RAs, which in turn are more effective than simple antacids (the speed of ulcer healing and symptom control is related to degree and duration of acid suppression). Excessive acid suppression (beyond pH 3) is unnecessary.

In a similar type of meta-analysis, Howden and Hunt analysed the results of 74 double-blind trials where the healing of gastric ulcers was studied endoscopically using various drug regimens. Information on gastric acid suppression was derived from a separate review of 10 published studies on the suppression of gastric acid secretion with the various antisecretory drug regimens used in the ulcer healing studies. There was a significant correlation between acid suppression over 24 hours and ulcer healing after two, four and eight weeks. The benefit of PPIs on ulcer healing was most marked at weeks two and three, but by week eight, the differences in healing rates were less marked.

| Table 4.12: Endoscopic healing of gastric ulcers with PPIs and H$_2$RAs |
|-----------------------------|-----------------------------|-----------------------------|
|                            | Week 2                     | Week 4                     | Week 8                     |
| PPI                        | 41 – 43%                   | 73 – 80%                   | 89 – 96%                   |
| H$_2$RA                    | 21 – 32%                   | 50 – 66%                   | 82 – 91%                   |


**MAINTENANCE TREATMENT**

As already indicated, ulcer recurrence is very frequent after completion of a course of acid suppression alone. Where there is symptom recurrence, negative *H. pylori* status should be checked and a careful review made of the person’s history, and all medication intake (both prescribed and over-the-counter). If no predisposing cause is identified, maintenance treatment should be considered. Maintenance treatment is also necessary in people who have significant comorbidity, or who have had a complication from their peptic ulcer.

Standard dose PPI is regarded as omeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg daily. Standard dose H$_2$RA is regarded as ranitidine 150 mg twice daily, or 300 mg nocte, and famotidine 20 mg twice daily or 40 mg nocte.
NSAIDS AND GI COMPLICATIONS

OVERVIEW

- NSAID ingestion is associated with GI mucosal damage: stomach > duodenum > distal intestine.
- GI intolerance to NSAID is a systemic effect which occurs whether the drug is taken orally, parenterally or rectally.
- NSAID-related complications (haemorrhage, ulceration, perforation) can occur in otherwise asymptomatic individuals.
- The efficacy and toxicity of individual NSAIDs vary greatly, as anti-inflammatory activity and adverse effects are both dose-related.
- Strategies, such as drug choice and protective co-therapies, should be used to minimise the risk of adverse effects of NSAIDs.
- Low-dose aspirin produces significant inhibition of gastric mucosal prostaglandins even when taken as an enteric coated tablet.
- COX-2 selective agents lose their specificity when prescribed with aspirin.
- Although COX-2 agents have less GI adverse effects that other NSAIDs, total withdrawal from drug trials because of all adverse effects are similar to non-selective NSAIDs.
- Co-prescription of COX-2 agents and PPI or misoprostol is not recommended because there is no evidence of benefit.
- Risk factors for NSAID-associated adverse upper GI events include the use of NSAID (includes aspirin, and COX-2 inhibitors plus aspirin) plus the following:
  - aged 65 years and over
  - history of peptic ulcer
  - history of upper GI bleeding
  - concomitant disease, especially coronary heart disease
  - increased frailty such as substantial arthritis-related disorder
    (osteoarthritis [OA] is a milder disease than rheumatoid arthritis [RA], requires lower doses of NSAIDs and use of oral prednisone is rare)
  - previous NSAID gastropathy
  - concomitant use of corticosteroids
  - concomitant use of anticoagulants
  - concomitant use of bisphosphonates
  - high doses of NSAID (includes NSAID + aspirin)
  - H. pylori infection.
- Increased-risk patients are:
  - aged less than 65 years with 2 risk factors
  - aged 65 years and over with 1 risk factor.
NSAIDS AND GI COMPLICATIONS

RECOMMENDATIONS

Begin treatment with either of the following:
- misoprostol at doses of 200 mcg/day. Increase dose over two weeks as tolerated, to a maximal dose of 800 mcg/day
- standard doses of PPI once daily.

Eradicate *H. pylori*, if testing is positive.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

TREATMENT OF NSAID-RELATED DYSPEPSIA

RECOMMENDATIONS

Review person’s history for risk factors.

Stop NSAID if possible.

In person with symptoms and risk factors, refer for OGD.

If ongoing symptom relief is needed:
- continue NSAID with co-prescription of PPI or misoprostol OR
- replace NSAID with COX-2 selective inhibitor.

Eradicate *H. pylori* if testing is positive.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.

MANAGEMENT OF NSAID-INDUCED PEPTIC ULCER

RECOMMENDATIONS

If NSAID can be stopped, treat with an *H₂RA* (ranitidine 150 mg twice daily or famotidine 20 mg twice daily) or PPI (omeprazole 20 mg, lansoprazole 30 mg or pantoprazole 40 mg) for 8 weeks for duodenal ulcers and 12 weeks for gastric ulcers.

If NSAID needed:
- treat with PPI for 8 weeks for duodenal ulcer and 12 weeks for gastric ulcer; if unsuccessful increase dose. Ongoing maintenance treatment is advised (as for individuals at increased risk of NSAID-induced GI complications)
- consider replacement of NSAID with COX-2 selective inhibitor.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
INTRODUCTION

NSAIDs, which can be purchased without prescription, are pharmacological agents very commonly used for the relief of pain, and as anti-inflammatory compounds to reduce inflammation in arthritis. Another property of NSAIDs (especially aspirin) is to reduce platelet stickiness and the risk of thrombosis, particularly in the coronary and cerebral vasculature, via the mechanism of inhibition of prostaglandins.

Unfortunately, prostaglandins are an important component of systems responsible for maintaining normal GI mucosal function. NSAIDs inhibit cyclooxygenase (COX) enzymes, which are required to convert arachidonic acid to prostaglandins. There are two COX isoforms: COX-1 maintains normal GI mucosal function, and COX-2 is induced and related to inflammation. Analgesic and anti-inflammatory activity is related to COX-2 inhibition. The action of COX enzymes on platelets is mediated via COX-1. Most NSAIDs (including aspirin) inhibit both COX-1 and COX-2 isoforms. Since the mid-1990s, drugs have become available (the coxib group) that are COX-2 selective, and therefore have less adverse effects in the GI tract. However, taking COX-2 selective NSAIDs with aspirin negates the selective effect.

NSAIDs act primarily by the systemic route, although local concentrations can be increased even further when the drugs are taken orally. People are at risk of adverse effects whether the drugs are taken orally, parenterally or as suppositories. Gastric mucosal prostaglandins have been shown to be reduced by 60% with doses of aspirin as low as 10 mg per day.¹

THE RISKS OF NSAIDS

There are generally three levels of adverse effects with NSAIDs. The first includes dyspepsia symptoms, the second, the development of intestinal mucosal abnormalities including peptic ulceration, and the third, ulcer complications (predominantly bleeding and perforation). Unfortunately, ulcers and/or their complications are not necessarily preceded by dyspepsia and not infrequently complications occur in otherwise asymptomatic individuals.

In 2000, PHARMAC paid subsidies of $732,232 on NSAIDs prescriptions in New Zealand, and $818,127 the previous year.² Based on 1999 British NSAID-incidence figures,³

**RECOMMENDATIONS Continued…**

Eradicate *H. pylori* if testing is positive.  
Refer individuals with complications (ie, bleeding, perforations, obstruction) to specialist.  
Check healing of gastric ulcer with OGD.

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations - refer to page xv for grading details.
New Zealand could expect an estimated 556 NSAID-related hospital admissions and 120 NSAID-related deaths per year. This is only taking into account NSAIDs that are prescribed and not those sold over-the-counter. Recently, a wide variety of non-selective NSAIDs have been released for sale without prescription and specific enquiry needs to be made concerning such possible exposure when taking a drug history from people with dyspepsia.

Case-control or cohort studies have shown an incidence of such events as ulcers, bleeding and perforations of 2 – 4% in those who take NSAIDs for a year, and OGD studies have shown the prevalence of peptic ulcers is 20 – 30% among regular users.

Users of NSAIDs are at approximately three times greater relative risk of severe GI adverse events than non-users. The absolute risk of serious GI complications is low: approximately 1 – 2% of all individuals exposed to NSAID therapy. The vast majority of people (81%) who had a serious GI complication had no prior GI symptoms. The analgesic effects of NSAIDs may mask the pain or dyspepsia that are generally associated with other peptic ulcers.

**NSAID-INDUCED ULCERS**

NSAID-induced ulcers may develop in otherwise histologically normal mucosa and are likely to be associated with other damage, such as erosions and mucosal haemorrhage. In contrast, *H. pylori*-related ulcers are associated with acute or chronic inflammation and the presence of *H. pylori* organisms. NSAID-induced ulcers are more likely to be gastric than duodenal and are often asymptomatic until complications occur.

NSAID-related peptic ulcers and their complications are more common in people infected with *H. pylori* (see Chapter 4: *Helicobacter Pylori and Peptic Ulceration*).

The spectrum of NSAID-related gastroduodenal injury includes a combination of subepithelial haemorrhages, erosions and ulcerations, often referred to as NSAID gastropathy. The distinction between erosions and ulcerations depends on pathological definitions: ulcers are defined as lesions that penetrate to the level of the submucosa, and erosions as lesions confined to the mucosa. For practical purposes, an OGD definition that is based on a subjective assessment of size, shape and depth of the lesion is used. Erosions are likely to be small and superficial, while ulcers tend to be larger (>5 mm in diameter) and deeper.

The clinical significance of OGD findings remains unclear. It has been suggested that an ulcer complication cannot occur without the presence of an ulcer. However, in up to 50% of serious GI haemorrhage cases, an active ulcer cannot be seen with OGD.

In the Cochrane review on ulcer disease and NSAIDs, Rostom et al showed that endoscopically verified ulcers can be documented in up to 40% of chronic NSAID users, but it is estimated that as many as 85% of these never become clinically apparent. Conversely, common side effects, such as nausea and dyspepsia, correlate poorly with...
serious adverse GI events. Serious complications (mostly bleeding or perforation) are less common. Silverstein et al indicated an incidence of 2% per year of haemorrhage, perforation or death in an average patient population. In the Rostom review, the relative risk of upper GI haemorrhage or perforation varied from 4.7 in hospital-based case control studies to 2.0 in cohort studies. In a study of 235 consecutive individuals presenting with serious GI complications, Armstrong et al found that 60% were taking NSAIDs and 80% of all ulcer deaths were related to NSAIDs.

IDENTIFYING INCREASED-RISK INDIVIDUALS

The following characteristics have been described in predicting the risk of adverse upper GI events in those taking NSAIDs: use of NSAID (includes aspirin, and COX-2 inhibitors plus aspirin) plus any of the following:

- aged 65 years and over
- history of peptic ulcer
- history of upper GI bleeding
- concomitant disease, especially coronary heart disease
- increased frailty such as substantial arthritis-related disorder (Note: OA is a milder disease than RA, requires lower doses of NSAID and use of prednisone is rare)
- previous NSAID gastropathy
- concomitant use of corticosteroids
- concomitant use of anticoagulants
- concomitant use of bisphosphonates
- high doses of NSAID (includes NSAID + aspirin)
- H. pylori infection

Increased-risk individuals

- Aged less than 65 years with 2 risk factors
- Aged 65 years and over with 1 risk factor.

Note: High dose is the maximum tolerated dose as opposed to standard maintenance dose (eg, ibuprofen: initially 1200 – 1800 mg daily, maintenance 600 – 1200 mg daily, maximum 2400 mg daily; 2400 mg is considered a ‘high-dose’).

The age at which NSAID complications begin to increase significantly cannot be pinpointed with any accuracy. There is an increase in peptic ulcers and their complications after the age of 60 years, even in individuals not taking NSAIDs. This is increased further in people on NSAIDs, and the increase rises with advancing age.

In a meta-analysis, Gabriel et al found that people taking NSAIDs aged >60 years had a relative risk for GI complications of 5.52 (95% CI 4.63-6.60) whereas those aged <60 years had a much reduced relative risk of 1.65 (95% CI 1.08-2.53) compared with non-users. MacDonald described a progressive increase in risk with advancing age: 1.53 at
60–69 years, 2.85 at 70–79 years, 5.36 at 80–89 years, and 3.04 at 90 and over.\textsuperscript{20} This was confirmed in a meta-analysis by Kurata.\textsuperscript{13} The reasons for this are uncertain, but more comorbidity and use of other drugs may be related. It is a matter of clinical judgment as to when a person is regarded as being ‘at increased risk’. The age of 65 years has been chosen as a clear level for most, although it is accepted that some will be at risk at an advanced age.

Previously, reports suggested that the risks with continuous use of NSAIDs diminish over time, but a recent study by Singh et al indicates that the risk of GI toxicity and haemorrhage remains constant with continuous exposure over an extended period of observation, as the human body does not adapt sufficiently to the insult that occurs.\textsuperscript{4,9,20} It has also been shown that the GI toxicity may continue for some time after treatment stops. One observational study by MacDonald reported toxicity continues for at least a year after last exposure.\textsuperscript{20} However, this appears to be a controversial area.

**MINIMISING THE RISKS**

Choosing to use a NSAID carries an implication of potential risk. Eccles has made a useful checklist that is helpful in minimising these risks when prescribing NSAIDs.\textsuperscript{21}

- Is there a safer alternative drug (eg, paracetamol)?\textsuperscript{21}
- Has the person been informed of potential adverse effects and what to do should they occur?\textsuperscript{21}
- How long does the treatment need to continue? Regular review of the person’s risk status is needed.\textsuperscript{21}
- If a NSAID is selected, does it have a low or high risk of adverse effects relative to other NSAIDs?\textsuperscript{20,23}
- What is the lowest effective dose for this person?\textsuperscript{22}
- Has the person had dyspepsia with NSAID use? If so, is gastro-protection required?
- Is the person in the high-risk group for adverse effects? If so, is gastro-protection required?\textsuperscript{21}
- If dyspepsia occurs, could this be an indication of a potential complication (eg, GI bleeding)?
- Is the person on aspirin? If so:
  - is the dose greater than 150 mg/day for antiplatelet effect?
  - has the additive effect of aspirin and any other NSAID been considered?
  - is the person on a COX-2 selective drug which loses its selectivity in the presence of aspirin?
- What is the cost of the NSAID being prescribed? Is there a more economical option available to achieve the same result?
- If the person were \textit{H. pylori}-positive, has this been eradicated?
The choice of which NSAID to use is important. Henry et al conducted a collaborative meta-analysis of variability of risks of GI complications for a range of NSAIDs using ibuprofen as a reference. They found that ibuprofen is associated with the lowest relative risk of severe GI toxicity, but that there is a positive dose-toxicity relationship with all NSAIDs. The authors suggest that it cannot be assumed that the apparent advantage of ibuprofen exists when the dosage is increased beyond 1600 mg daily. Unfortunately, NSAIDs with a greater relative risk of adverse effects are often required for adequate symptom control.

### Table 5.1: Gastrointestinal toxicity of NSAIDs, with ibuprofen as reference

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Pooled RR</th>
<th>95% CI for pooled RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>1.6</td>
<td>1.0 – 2.5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.6</td>
<td>1.3 – 2.0</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.8</td>
<td>1.4 – 2.3</td>
</tr>
<tr>
<td>Sulindac</td>
<td>2.1</td>
<td>1.6 – 2.7</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>2.2</td>
<td>1.2 – 4.1</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2.2</td>
<td>1.7 – 2.9</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2.4</td>
<td>1.9 – 3.1</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>3.8</td>
<td>2.7 – 5.2</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>3.8</td>
<td>2.7 – 6.4</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>9.2</td>
<td>4.0 – 21.0</td>
</tr>
</tbody>
</table>

**Note:** Doses used were those prescribed in the 12 studies using 14 drugs assessed in this meta-analysis.


The incidence of untoward events and the degree of anti-inflammatory activity for aspirin and non-aspirin NSAIDs are both dose-related. Many studies have reported that decreasing the daily dose of aspirin also decreases the risk of GI complications. Nevertheless, any dose of aspirin has the potential to induce gastric lesions and GI complications, even in normal healthy subjects. Adverse effects of aspirin and other NSAIDs are additive.

### COX-2 SELECTIVE NSAIDS

The prediction that COX-2 selective agents would have fewer adverse effects on the GI tract than non-selective NSAIDs has generally been supported in the literature. In the Bombardier review a meta-analysis by Langman et al was conducted of perforations, ulcers and bleeds (PUBs) of all rofecoxib RCTs: 5435 individuals (mean age 63, range 38 – 94 years) were included. PUBs over 4 months were identical for rofecoxib and placebo groups but the cumulative incidence of PUBs over 12 months for rofecoxib was half that...
found for non-selective NSAIDs (RR 0.51) (see Table 5.2). Similarly, combined data from studies by Simon, Laurie and Hawkey showed minimal difference in incidence of endoscopic ulcers under 6 mm in 1156 individuals with OA or RA after 12 weeks of treatment with celecoxib (6%) and placebo (6.6%), while the incidence was 24% in individuals taking non-selective NSAIDs.

There have been further large studies confirming these findings. The CLASS study published by Silverstein et al\textsuperscript{26} showed that celecoxib resulted in a lower incidence of symptomatic ulcers and ulcer complications combined than patients on ibuprofen or diclofenac over a 6-month period. Patients in this study were permitted to take aspirin, and in those who took aspirin with celecoxib (21%), the incidence of ulcers was the same as in those taking non-selective NSAIDs. The CLASS study triggered much controversy in that it was subsequently discovered that the 12 months’ results originally planned in the protocol had very different results. Almost all of the ulcer complications that had occurred during the second six months were in patients taking celecoxib with the favourable result being negated completely. Details of this, including references to FDA material on the internet, have been published.\textsuperscript{31} Notably, patients in the study had similar rates of myocardial events in both selective and non-selective COX-inhibition groups. An editorial accompanying the original paper suggested that although COX-2 selective NSAIDs appeared to be ‘new and improved’, they were certainly less than perfect.\textsuperscript{32}

The VIGOR study compared the efficacy and safety of rofecoxib and naproxen in 8076 patients over 1 year.\textsuperscript{33} Those taking rofecoxib had significantly fewer GI events than those on naproxen (2.1 vs 4.5 per 100 patient years, RR 0.5, 95% CI 0.3-0.6, p<0.001). Combined GI complications were also less in the rofecoxib group (0.6 vs 1.4 per 100 patient years, RR 0.4, 95% CI 0.2 – 0.8, p=0.005). In this study, patients were not permitted to take aspirin. The incidence of myocardial infarction was lower in the naproxen group than those on rofecoxib (0.1 vs 0.4%, RR 0.2, 95% CI 0.1 – 0.7). The overall mortality rate as well as that from cardiovascular causes was similar in both treatment groups.

In a short-term (3 month) meta-analysis involving 15,187 patients, Deeks et al showed that celecoxib was effective in controlling symptoms in patients with OA or RA with a significant reduction in GI adverse effects compared to those on non-selective NSAIDs.\textsuperscript{34} However, the protection from celecoxib was reduced significantly in patients also on aspirin. There was no significant difference between celecoxib and NSAIDs in the incidence of withdrawal for all adverse events.

Mamdani et al published an observational cohort study of upper GI haemorrhage in elderly patients (over age 66 years) given selective COX-2 inhibitors (rofecoxib n=14,583, celecoxib n=18,908) or conventional anti-inflammatory drugs (n=5391).\textsuperscript{35} Results were compared with a group of patients receiving diclofenac plus misoprostol (n=5087) and a randomised selective control cohort not exposed to NSAIDs (n=100,000). Follow up was over 3 – 6 months. Those taking celecoxib were the only group not to show a higher rate of GI bleeding (controls 1.0, celecoxib 1.0, 95% CI 0.7 – 1.6). All the other groups showed various rates of increased risk: rofecoxib 1.9 (95% CI 1.38 – 2.8), diclofenac plus misoprostol 3.0 (95% CI 1.7 – 5.6) and non-selective NSAIDs 4.0 (95% CI 2.3 – 6.9).
The gastro-duodenal adverse effects of NSAIDs can be minimised by the simultaneous ingestion of a PPI at least for the prevention of the development of peptic ulcers. In an RCT, Chan et al investigated the efficacy of diclofenac and omeprazole compared to celecoxib in preventing re-bleeding of peptic ulcers in patients with arthritis. Interestingly, the probability of recurrent bleeding over 6 months for those on celecoxib was 4.9% (95% CI 3.1 – 6.7%) and 6.4% (95% CI 4.3 – 8.4%) for those on the PPI-NSAID combination, which was not statistically significant. Real adverse events were recorded in 24.3% of patients on celecoxib and 30.8% of those on combination therapy. These complications are therefore common in this particular group of patients. This prompted an editorial suggesting that Pandora’s box had been opened and that a false sense of security engendered by the COX-2 agents might have been exposed.

ADVERSE EFFECTS OF COX-2 AGENTS

Adverse events of COX-2 selective agents include epigastric discomfort (5.6%), heartburn (5%), nausea (2-8%) and diarrhoea (4-12%). These rates do not differ from ordinary NSAIDs. Renal function may also be affected adversely including fluid retention. Rash, bronchospasm and rarely angio-oedema have been recorded. Interaction between rofecoxib and warfarin has been reported, and although this was originally thought not to be of clinical relevance, reports have been received of very significant interactions of both rofecoxib and celecoxib with warfarin, especially in patients aged 60 years and over. Hepatotoxicity has also been recorded following ingestion of celecoxib and rofecoxib. In a post-marketing survey, celecoxib was associated with oedema in 2.1% of patients, hypertension in 0.8% and exacerbation of pre-existing hypertension in 0.6%, a profile similar to that seen with non-selective NSAIDs. Similarly, rofecoxib was associated with peripheral oedema in 3.8%.

The question of predisposition to myocardial infarction in patients on the COX-2 agents was raised in the VIGOR study (0.4% with rofecoxib vs 0.1% with naproxen over 9 months). This could be a result of loss of anti-platelet activity with COX-2 selective drugs but other mechanisms have been postulated. The CLASS study did not show any such effect but 21% of patients were taking aspirin while the benefits of the COX-2 agents over 12 months is still in some dispute. Subsequent studies recorded no increase in thromboembolic events with either celecoxib or rofecoxib. The debate about the safety of COX-2 agents is continuing and more studies are in progress.

WHEN SHOULD WE USE COX-2 AGENTS?

The answer to this question is still being developed, but a number of important factors should be considered before prescribing these drugs.

- COX-2 agents are most beneficial in high-risk patients (see Table 5.3), and of disputable cost/benefit in patients with a low risk profile.
- Overall adverse effect profile in non-GI areas are at least similar to other NSAIDs.
- Selective COX-2 effect is largely negated by simultaneous use of aspirin, and care needs to be exercised in patients at risk of myocardial events who need aspirin.
• COX-2 agents do not offer significant protection against upper GI haemorrhage in patients who have bled previously from a peptic ulcer.
• COX-2 agents are not yet funded in New Zealand and cost up to ten times more than nonselective NSAIDs.
• Alternative protection against NSAID-adverse effects is available in the form of co-prescription of PPI or misoprostol with the NSAID.

To date there is no evidence to support the co-prescription of gastro-protective agents (PPI or misoprostol) with COX-2 selective drugs in at-risk individuals.

Table 5.2a: Adverse effects of COX-2 selective agents: Celecoxib

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Outcome</th>
<th>Celecoxib</th>
<th>Other NSAIDs*</th>
<th>RR</th>
<th>p value</th>
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<tbody>
<tr>
<td>Patients not on aspirin</td>
<td>Upper GI ulcer complications; annualized incidence rate (%)</td>
<td>0.44</td>
<td>1.27</td>
<td>0.35</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Upper GI ulcer complications + symptomatic ulcers; annualized incidence rate (%)</td>
<td>1.40</td>
<td>2.91</td>
<td>0.48</td>
<td>0.02</td>
</tr>
<tr>
<td>Patients on aspirin</td>
<td>Upper GI ulcer complications; annualized incidence rate (%)</td>
<td>2.01</td>
<td>2.12</td>
<td>0.95</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Upper GI ulcer complications + symptomatic ulcers; annualized incidence rate (%)</td>
<td>4.70</td>
<td>6.00</td>
<td>0.78</td>
<td>0.49</td>
</tr>
<tr>
<td>All patients</td>
<td>Withdrawals due to adverse effects (%)</td>
<td>18.4</td>
<td>20.6</td>
<td>0.89</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Study properties: Multicentre (US), double-blind, RCT; n = 8059, with either OA or RA, 20% on aspirin, 6 month follow-up

* Other NSAIDs were ibuprofen and diclofenac

ns = not significant

Note: For a critique of these data, see Juni P, Rutjes AWS, Dieppe PA. Are selective COX 2 inhibitors superior to traditional nonsteroidal anti-inflammatory drugs? Adequate analysis of the CLASS trial indicates this may not be the case. BMJ 2002;324:1287-8.

Table 5.2b: Adverse effects of COX-2 selective agents: Rofecoxib

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rofecoxib</th>
<th>Naproxen</th>
<th>RR(95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed GI events/100 patient-years</td>
<td>2.1</td>
<td>4.5</td>
<td>0.5 (0.3-0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulcer complications/100 patient-years</td>
<td>0.6</td>
<td>1.4</td>
<td>0.4 (0.2-0.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Discontinuation due to an adverse event (%)</td>
<td>16.4</td>
<td>16.1</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Mortality rate (%)</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiovascular death (%)</td>
<td>0.2</td>
<td>0.2</td>
<td>1.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Study properties: International, multicentre RCT; n = 8076 patients with RA, aged >50 years, or >40 years if on long-term glucocorticoid therapy, 9 month follow-up

ns = not significant


Table 5.3: Benefit of rofecoxib vs naprosyn by risk group

<table>
<thead>
<tr>
<th>Risk rate</th>
<th>Factors</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Prior event</td>
<td>10 – 12</td>
</tr>
<tr>
<td></td>
<td>Age &gt;75 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe RA</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Age 65 – 75 years</td>
<td>17 – 33</td>
</tr>
<tr>
<td></td>
<td>Baseline steroid use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No baseline NSAID use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H₂RA use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RA &gt;25 years</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>No risk factors</td>
<td>42 – 106</td>
</tr>
</tbody>
</table>

Source: Laine et al. Gastroenterology 2002; 123: 1006-1012 (8076 patients with RA from 301 centres in 22 countries; aspirin users excluded). 48

INCREASED-RISK INDIVIDUALS ON NSAIDS

Co-prescription of cytoprotective agents to increased-risk individuals is recommended for those aged <65 years with one additional risk factor, or those aged <65 years with two or more risk factors. It is not cost-effective to co-prescribe to all those on NSAIDs.

The results of the Cochrane meta-analysis by Rostom et al demonstrated that misoprostol, PPIs and double doses of H₂RAs are effective at reducing the risk of both endoscopically verified gastric and NSAID-induced duodenal ulcers. 10
PPIs significantly reduced the risk of both duodenal and gastric ulcers, with results being similar for both primary and secondary prophylaxis trials. Although NSAID-induced ulcers are effectively prevented by co-prescription of PPIs, evidence is only available to demonstrate a reduction in peptic ulcer complications with low-dose aspirin.38

Table 5.4: Reducing risk of NSAID-induced ulcer disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duodenal ulcer</th>
<th>Gastric ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced risk (95% CI)</td>
<td>Reduced risk (95% CI)</td>
</tr>
<tr>
<td>Misoprostol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg/day</td>
<td>0.22 (0.09 – 0.53)</td>
<td>0.18</td>
</tr>
<tr>
<td>400 mg/day</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>pooled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2RA std dose</td>
<td>0.24 (0.1 – 0.57)</td>
<td>0.73 (0.5 – 1.09)</td>
</tr>
<tr>
<td>H2RA twice daily</td>
<td>0.26 (0.11 – 0.65)</td>
<td>0.44 (0.26 – 0.74)</td>
</tr>
<tr>
<td>PPI</td>
<td>0.19 (0.09 – 0.40)</td>
<td>0.37 (0.27 – 0.51)</td>
</tr>
</tbody>
</table>

**Notes:** Meta-analysis of 33 RCTs; adults requiring >3 wk duration NSAID drugs; primary and secondary studies included; clinically important GI outcomes, GI symptoms, endoscopic ulcers recorded.


Overall, it has been found that H2RAs and PPIs are better tolerated than misoprostol, and reduce NSAID-related dyspeptic symptoms. However, PPIs are recommended over H2RAs. No economic or therapeutic advantages have been shown in using double doses of H2RAs, rather than standard doses of PPIs which provide more potent and reliable acid inhibition (see Table 3.1). Furthermore, although the meta-analysis by Koch demonstrates that H2RAs in standard doses afford some protection against NSAID-related duodenal ulcers, they are not effective in preventing gastric ulcers. As these are more commonly related to NSAID use than duodenal ulcers, standard doses of H2RAs cannot be recommended for the prevention of NSAID-related GI toxicity.

Misoprostol is the only prophylactic agent to date that has been evaluated in a true clinical outcome trial with NSAIDs in standard dose. The PPI lansoprazole has been shown to prevent recurrences of ulcer complications from long-term low-dose aspirin use.28

Misoprostol 800 mcg/day is more effective at reducing gastric ulcers than 400 mcg/day. Although it is associated with statistically significant adverse effects, which are more common at higher doses, the evidence for the effectiveness of low doses (400 mcg/day) in the reduction of clinical ulcer complications is controversial.29 Diarrhoea (in 9 – 13% of individuals) and abdominal cramps may limit compliance with misoprostol but these are often transient and may be reduced by starting with a low dose. Additionally, misoprostol is an abortifacient, and must be used cautiously by women of child-bearing age.29
PEOPLE WITH NSAID-RELATED DYSPEPSIA

Symptoms of dyspepsia, nausea and abdominal pain correlate poorly with the occurrence of NSAID-induced ulcer complications such as bleeding.\(^1\) The ability of NSAIDs to alter or mask the symptoms of GI damage is particularly dangerous in those aged >65 years since it may cause them to present late with a serious complication.\(^2\)

Ongoing use of prophylactic medications may also suppress early warning symptoms that would otherwise lead the physician to discontinue or change NSAIDs.\(^2\) Suppression of symptoms by the NSAID itself or a prophylactic agent may also encourage the use of higher doses of NSAIDs for longer periods, ultimately resulting in more severe GI complications.

Omeprazole co-prescription is associated with significantly less NSAID-induced dyspeptic symptoms.\(^2\) A quality-of-life evaluation showed that individuals receiving omeprazole have significantly greater improvement in scores on the Gastrointestinal Symptom Rating Scale than those receiving misoprostol.\(^5\) Despite the effectiveness of misoprostol in preventing gastroduodenal ulcers, it was not associated with any improvement in dyspeptic symptoms in these studies. Because PPIs represent a suitable means of preventing the development of peptic ulcers associated with the use of NSAIDs, they appear to provide a safe and effective form of therapy for NSAID-associated dyspepsia.\(^9\)

PEOPLE WITH NSAID-INDUCED PEPTIC ULCERS

Treatment with conventional doses of H\(_2\)RAs for 6 to 12 weeks results in healing of approximately 75% of gastric ulcers and 87% of duodenal ulcers, despite the continued use of NSAIDS. However, healing is delayed and is largely dependent on the initial size of the ulcer.\(^9\)

The ASTRONAUT study by Yeomans et al found higher rates of healing of all types of lesions (gastric ulcer, duodenal ulcer, erosions) in omeprazole compared with ranitidine-treated groups (more improvement of overall symptoms at four weeks).\(^30\) The success in healing is 80% with omeprazole 20 mg, 79% with omeprazole 40 mg, and 63% with ranitidine 150 mg twice daily. Overall, there is a higher likelihood of successful treatment of duodenal than of gastric ulcers. The authors concluded that omeprazole 20 mg was superior to ranitidine with respect to healing and preventing peptic ulcers and erosions, as well as for controlling dyspeptic symptoms.

The OMNIUM study by Hawkey et al found that rates of treatment success of NSAID-induced ulcers with continuous use were similar for all treatment groups (omeprazole 20 mg, omeprazole 40 mg, misoprostol 200 mg qid).\(^5\) Omeprazole 20 mg was shown to be better than misoprostol in treating gastric ulcers, and misoprostol was better at healing erosions. The authors concluded that the success rates were similar with omeprazole and misoprostol during the healing phase but that omeprazole was better tolerated. The omeprazole 40 mg dose offered no additional healing benefit over that afforded by 20 mg dose, but gave better symptom control.
Table 5.5: Treatments for NSAID-induced ulcers in people who continue to take NSAIDs

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase I (4 – 8 weeks)</th>
<th>Phase II (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healing (%)</td>
<td>Adverse effects (%)</td>
</tr>
<tr>
<td>Yeomans20+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Omeprazole 40 mg</td>
<td>79</td>
<td>38</td>
</tr>
<tr>
<td>Ranitidine 150 mg twice daily</td>
<td>63</td>
<td>40</td>
</tr>
<tr>
<td>Hawkey29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>76</td>
<td>48</td>
</tr>
<tr>
<td>Omeprazole 40 mg</td>
<td>75</td>
<td>46</td>
</tr>
<tr>
<td>Misoprostol 200 mcg qid</td>
<td>71</td>
<td>59</td>
</tr>
</tbody>
</table>

Notes:
* RCT, double-blind, in two phases; 93 centres in 14 countries (Europe, Scandinavia, North America); n=935, aged 18 – 85 years, at OGD had ulcer >3 mm or more than 10 erosions in stomach or duodenum
# RCT, double-blind, in two phases; 73 centres in 15 countries (Europe, Scandinavia, Canada); n=541, aged 18 – 85 years, at OGD had ulcer >3 mm or more than 10 erosions in stomach or duodenum

Although omeprazole has been shown to heal both gastric and duodenal ulcers irrespective of continued NSAID use, caution should be exercised in extrapolating these results to people presenting with NSAID-induced upper GI haemorrhage because safety and efficacy have not been assessed in this situation.29

Fewer people remaining on NSAIDs relapse on misoprostol than on omeprazole or placebo, once ulcers or erosions are healed.29

The appropriate choice of therapy for secondary prophylaxis against NSAID-related ulcer recurrence among chronic NSAID users is problematic. Currently, the only agent with proven efficacy for the primary prevention of NSAID ulcers is misoprostol, which is also the only agent that has been of proven benefit in the primary prevention of NSAID-induced clinical events.11 However, although there is an absence of evidence for the effectiveness of PPIs protecting against clinically important primary GI events (bleeding, perforation, pyloric stenosis), omeprazole has been found to be successful in healing NSAID-induced gastric and duodenal ulcers and lesions. It is reasonable to expect that peptic ulcer complications would also be prevented.

Those people who are positive for H. pylori, should have it eradicated.

The cost-effectiveness of PPIs for the primary or secondary prophylaxis against NSAID induced upper GI toxicity has not been clearly established.29 Adverse effects with misoprostol have distracted significantly from routine use of this drug, and its use is also restricted to specialists.
THE GUIDELINE IN GENERAL PRACTICE

The development of this guideline is in part a response to a recognised need to update general practitioners on current best-practice management of individuals with dyspepsia and GORD and to reduce uncertainty about who should be offered specific investigative procedures.

Since the National Health Committee produced guidelines for dyspepsia in 1995, the evidence has changed considerably. At that time, treatment advice was that reflux and ulcer-like dyspepsia may respond better to acid inhibition and other types to motility agents; however, this has not been consistently supported by further studies. Prokinetics were seen as more effective for dyspepsia than acid inhibitors and a review of the evidence concerning the precise indication for their use has been published. Acid suppression is much more successful in treating GORD. The role of *H. pylori* eradication has been elaborated considerably. Test-and-treat or test-and-OGD strategies had not been considered. Since then PPIs have become available for prescription by general practitioners resulting in widespread changes in treatment practices, especially for GORD.

Management of NSAID-related problems has been clarified considerably. Co-therapy with misoprostol or PPI offers significant (but not perfect) protection from upper GI adverse events. The availability of selective COX-2 inhibitors has also been helpful but their introduction has not provided a complete answer, as other adverse effects have been significant and their benefit is largely negated by aspirin. Cost of COX-2 agents is also a problem. Identification of groups at particular risk is an important factor in choosing medication for patients requiring any NSAID. It is the high-risk older patient who may benefit from COX-2 agents.

Emphasis should be placed on this work being a guideline and not a protocol for treatment. It does not replace the art of medicine. For example, the Committee deliberated at length concerning the age above which investigations were recommended as a first choice for the management of people with dyspepsia – age 45, 50 or 55 years. Our final recommendation was to point out that age greater than 50 years is an indicator of a greater likelihood of organic disease, but that each person still needs to be assessed on his or her clinical merits after a full history and examination. The Guideline is not a substitute for that. There are many areas, particularly in functional dyspepsia, where knowledge is incomplete and uncertain to say the least. It is not possible to make fixed recommendations in such circumstances.
It is anticipated that the summary of key messages and recommendations will be the document medical practitioners, pharmacists and other health professionals will use most (if not exclusively) on a day-to-day basis. It is hoped that some will have their interest and curiosity stimulated to venture into the main text and references to inform themselves of the underlying evidence and information. There is occasional repetition in the text, usually illustrating important points which may apply to more than one area. It was our conscious decision to leave those as they were, hopefully to make individual sections more readable in their own right.
IMPLEMENTATION

OVERVIEW

The aim of this guideline is to ensure that from their first encounter with a health care practitioner, individuals with dyspepsia and heartburn are treated promptly and efficiently. Most individuals should be treated by their general practitioner and guidance is given concerning individuals requiring referral for specialist investigation or consultation. Judicious choice of effective primary treatment and accurate selection for investigation and specialist care should optimise the use of limited resources required for appropriate care.

The choice available includes:

• empiric treatment
• testing and treating for *H. pylori* where appropriate
• referral for OGD in selected cases
• definitive treatment where a specific diagnosis has been made
• referral for urgent consultation and management when alarm signals are present.

Information is provided to help primary care practitioners match the appropriate choice to the person’s specific presentation.

Recommendations also need to be matched with the availability of treatments (mostly drugs), investigations (*H. pylori* investigation, OGD) and their availability in various parts of New Zealand. It is appreciated that availability of investigative and specialist services varies considerably from one part of the country to the other. Recognition needs to be given where availability of services and medications do not meet the recommended standards as interpreted from the evidence-based literature.
SPECIFIC IMPLEMENTATION STRATEGIES

The Working Party has aimed to ensure that the recommendations made are practical and can be implemented in the New Zealand setting. The guideline is intended to be discussed and used as a dynamic document, not only for the person’s care but also for development and improvement of the provision of care in both rural and urban areas in New Zealand.

ENDORSEMENT

Endorsement by stakeholder organisations is essential to the successful implementation of the guideline. At the start of the project, a number of professional groups gave their approval and endorsed committee members to represent their views. An advanced draft of the guideline was sent to the relevant organisations for their comment to ensure all views have been considered. All resulting comments and suggestions were reviewed by the Working Party.

PUBLICATION OF THE FULL GUIDELINE

The full guideline and the summary document will be available in an electronic form on the New Zealand Guidelines Group website at http://www.nzgg.org.nz. There will be no charge for downloading these documents.

Publication of a printed copy requires funding and this will be negotiated with the New Zealand Guidelines Group.

QUICK REFERENCE CLINICAL FORMAT

The summary document incorporates the main recommendations of the guideline. Flow charts have been added. Full text is available for reference.

DISSEMINATION

Wide dissemination of the quick reference summary guideline is planned in order to reach all health care practitioners who treat people with dyspepsia and heartburn. Further groups may also benefit from referral to the guideline for academic, educational or commercial purposes.

Health Care Practitioners

• General health care practitioners
• General physicians and surgeons
• Gastroenterologists
• Pharmacists
Care Facilities

- Accident and emergency departments
- Geriatric units
- After-hours clinics
- Hospital wards

Provider Organisations and Professional Bodies

- Primary Health Organisations
- Independent Practitioners Associations (IPAs)
- Academic lecturers, curriculum planners involved in medical training
- Medical colleges
- Professional bodies
- PHARMAC

Other Agencies

- Health insurers
- Support groups
- Community health agencies and interest groups

Commercial Organisations

- Providers of medications discussed or recommended in the guideline

Development of Performance Indicators

- Primary Health Organisations are to be encouraged to identify appropriate clinical indicators eg, average daily dose of PPIs

EVENTS, PRESENTATION AND TRAINING

The guideline should be presented to health care practitioners to familiarise them with the recommendations. They should be presented at major meetings or small education groups included in postgraduate medical education. This process has already been initiated during the development phase of the guideline. It is anticipated that members of the Working Party will play a key part in disseminating the information to their peers.

National Level

- Formal endorsement and presentation at general practitioner and specialty and subspecialty conferences
- Educational seminars and workshops for practitioners and IPAs
- Specific educational initiatives for particular interest groups, including general practitioners and pharmacists eg, develop a toolkit for pharmacy facilitators and other speakers such as Powerpoint for Primary Health Organisations
• Liaison with bodies controlling funding and resources to ensure that district health board policies and facilities become compatible with the recommendations made
• Corrective measures need to be taken to ensure that rural areas have access to appropriate investigation and treatment. Representatives of rural communities need to be included in the discussion process
• Key recommendations may be promoted by groups such as Best Practice Advocacy NZ
• Conferences:
  – The Combined NZ Rural General Practice Network & Rural Nurse National Network Conference, April
  – College of General Practitioners’ Conference, July, Wellington
  – General practitioner CME Meeting, July
  – National Gastroenterology Conference, November

Local Level
• Local CME activities can include this guideline as part of their programmes
• Local general practitioners and specialists should meet to discuss specifically referral patterns, priorities and access to investigations and treatments
• IPA pharmacists can play a very important role in prescriber education and in monitoring and reviewing prescribing habits

Publicity
The guideline needs to be publicised in the media, including the local medical press. This has already been initiated via certain professional group meetings (eg, general practitioners, gastroenterologists, pharmacists). Publicity needs to encompass:
• journals and health professional publications, including the New Zealand Medical Journal, New Zealand Nursing Journal and NZ Doctor
• a well-publicised formal launch of the guideline and a planned seminar programme. This should inform health care practitioners, not only of the contents of the guideline but what is anticipated concerning dissemination and discussion, as stated above
• public education to ensure that there is widespread and realistic understanding of the guideline
• radio and television interviews, which can be conducted by members of the Working Party. Care needs to be taken to ensure that public expectation and reality are well balanced.

ACCESS TO OESOPHAGO-GASTRO-DUODENOSCOPY

The guideline aims to ensure that people are referred appropriately and that those referred for OGD are those most likely to benefit from it. It is not envisaged that the guideline should greatly increase the demand for this procedure. However, current access to OGD is poor in certain parts of the country and this will need to be addressed by the Ministry of Health. Discussions with district health boards may need to follow.
EVALUATION

People experiencing dyspepsia and heartburn have an interest in the quality of care and management of dyspepsia and heartburn. This places a responsibility on service providers to collect information relevant to the management of dyspepsia and heartburn.

Evaluation can occur at many different levels, including the following:

- **OGD Providers**
  Numbers of referrals, quality of referrals

- **General Practitioners**
  Access to the guideline, use and practicality of the guideline, efficacy of recommendations
  Monitoring or auditing of:
  - use of PPIs and other treatments recommended in this guideline
  - use of medications, especially the step-down process with acid lowering agents
  - use of maintenance therapy
  - *H. pylori* eradication regimens.
  - numbers of patients referred for investigation (especially OGD).

- **OGD Providers**
  Recommendations for treatment could be audited in OGD reports
  (eg, stepdown or maintenance treatment and/or *H. pylori* eradication regimens should be explicit)

- **Primary Care Organisations (IPAs, PHOs, Māori & Pacific Health Care Providers)**
  Measurement of practice patterns, referral patterns, national pharmaceutical budgets, investigation budgets

- **IPA Pharmacy Facilitators**
  Prescribing by general practitioners - may be able to link with General Practitioners to monitor or audit drug regimens as suggested above

- **PHARMAC**
  Prescribing patterns at the national level
• **District Health Boards**
  – Drugs for GI ulcer and other gastric conditions should be monitored
  – Information on access to OGD services should be recorded
  – Recommendations for treatment in patient discharge letters and in procedure (OGD) reports could be monitored or audited
  – The appropriateness of stepdown or maintenance regimens should be explicit
  – Numbers of patients referred for OGD should be monitored.

Ideally, a formal evaluation of the implementation of the Guideline recommendations could be undertaken after one year. This should yield information on:

• practical usefulness
• acceptability of recommendations to:
  – patients
  – medical practitioners
  – pharmacists
  – other health care professionals.
• areas where expansion is required
• areas needing updating of information
• difficulties or improvements with access to procedures or treatments
• cost savings or changes in costs of treatments.

During this year, a Group should be nominated to take up the recommendations of the evaluation and prepare an updated Guideline in 2007.
APPENDICES

A. Questionnaire for People with Gastro-oesophageal Reflux Disease
B. Recommended Medication for Heartburn and/or Dyspepsia
C. Patient Information Sheet: I Have Dyspepsia (Indigestion) – What Does This Mean?
APPENDIX A

QUESTIONNAIRE FOR PEOPLE WITH GASTRO-OESOPHAGEAL REFLUX DISEASE

This standardised questionnaire for people with gastro-oesophageal reflux disease (GORD) has proved valuable in the diagnosis of ‘acid-reflux disease’ in the clinical trial setting.¹

1. Which one of these four statements BEST DESCRIBES the main discomfort you get in your stomach or chest?
   - □ A burning feeling rising from your stomach or lower chest up towards your neck
   - □ Feelings of sickness or nausea
   - □ Pain in the middle of your chest when you swallow
   - □ None of the above, please describe below:

2. Having chosen one of the above, please now chose which one of the next three statements BEST DESCRIBES the timing of your main discomfort?
   - □ Any time, not made better or worse by taking food
   - □ Most often within 2 hours of taking food
   - □ Always at a particular time of day or night without any relationship to food

3. How do the following affect your main discomfort?

<table>
<thead>
<tr>
<th></th>
<th>Worsens</th>
<th>Improves</th>
<th>No effect/unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larger than usual meal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food rich in fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongly flavoured or spicy food</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Which one of the following **BEST DESCRIBES** the effect of indigestion medicines on your main discomfort?
- ☐ No benefit
- ☐ Definite relief within 15 minutes
- ☐ Definite relief after 15 minutes
- ☐ Not applicable (I don’t take indigestion medicine)

5. Which one of the following **BEST DESCRIBES** the effect of lying flat, stooping or bending on your main discomfort?
- ☐ No effect
- ☐ Brings it on or makes it worse
- ☐ Gives relief
- ☐ Don’t know

6. Which one of the following **BEST DESCRIBES** the effect of lifting or straining (or any other activity that makes you breathe heavily) on your main discomfort?
- ☐ No effect
- ☐ Brings it on or makes it worse
- ☐ Gives relief
- ☐ Don’t know or this does not apply to me

7. If food or acid tasting liquid returns to your throat or mouth what effect does it have on your main discomfort?
- ☐ No effect
- ☐ Brings it on or makes it worse
- ☐ Gives relief
- ☐ Don’t know or this does not apply to me
APPENDIX B

RECOMMENDED MEDICATION FOR HEARTBURN AND/OR DYSPEPSIA

Antacids/algines may be used for symptomatic control. Doses will vary.

**Proton pump inhibitors**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half dose</th>
<th>Standard dose</th>
<th>Double dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>15 mg/day</td>
<td>30 mg/day</td>
<td>60 mg/day OR 30 mg BD</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>10 mg/day</td>
<td>20 mg/day</td>
<td>40 mg/day OR 20 mg BD</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20 mg/day</td>
<td>40 mg/day</td>
<td>80 mg/day OR 40 mg BD</td>
</tr>
</tbody>
</table>

**H₂-receptor antagonists**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Peptic ulcer</th>
<th>GORD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg nocte OR 20 mg BD</td>
<td>20 mg nocte</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>300 mg nocte OR 150 mg BD</td>
<td>150 – 300 mg nocte</td>
</tr>
</tbody>
</table>

**Prokinetic agents**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domperidone</td>
<td>10 mg 3 – 4 times daily</td>
<td>Dose can be increased (to double) after 2 weeks</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg TDS</td>
<td>Metoclopramide is less favoured:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• potential extrapyramidal adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• no eligible studies were found to support its use.</td>
</tr>
</tbody>
</table>

**H. pylori eradication therapy**

**Initial therapy**

<table>
<thead>
<tr>
<th>Triple therapy (7 days)</th>
<th>Option 1</th>
<th>Option 2 (penicillin allergy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• PPI (standard dose) BD</td>
<td>• PPI (standard dose) BD</td>
</tr>
<tr>
<td></td>
<td>• Clarithromycin 500 mg BD</td>
<td>• Clarithromycin 500 mg BD</td>
</tr>
<tr>
<td></td>
<td>• Amoxicillin 1000 mg BD</td>
<td>• Metronidazole 400 mg BD</td>
</tr>
</tbody>
</table>

**Initial treatment failure**

| Triple therapy (7 days) | • PPI (standard dose) BD PLUS 2 of the following: |
|                        | • Clarithromycin 500 mg BD |
|                        | • Amoxicillin 1000 mg BD |
|                        | • Metronidazole 400 mg BD |
|                        | • Tetracycline 500 mg QID |
|                        | • Colloidal bismuth 120 mg QID |

**Repeated treatment failure**

<table>
<thead>
<tr>
<th>Quadruple therapy (7 days)</th>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• PPI (standard dose) BD</td>
<td>• PPI (standard dose) BD</td>
<td>• PPI (standard dose) BD</td>
</tr>
<tr>
<td></td>
<td>• Clarithromycin 500 mg BD</td>
<td>• Clarithromycin 500 mg BD</td>
<td>• Tetracycline 500 mg QID</td>
</tr>
<tr>
<td></td>
<td>• Amoxicillin 1000 mg BD</td>
<td>• Metronidazole 400 mg BD</td>
<td>• Metronidazole 400 mg BD</td>
</tr>
<tr>
<td></td>
<td>• Colloidal bismuth 120 mg QID</td>
<td>• Colloidal bismuth 120 mg QID</td>
<td>• Colloidal bismuth 120 mg QID</td>
</tr>
</tbody>
</table>

**Note:** Some advocate treatment for 14 days for repeated treatment failure

March 2004
I HAVE DYSPEPSIA (INDIGESTION) – WHAT DOES THIS MEAN?

WHAT IS DYSPEPSIA?

Dyspepsia is a general term defined as a pain or discomfort in the upper abdomen. In some people it is also felt as bloating, nausea and premature fullness after eating.

Heartburn is defined as a burning sensation radiating from the upper abdomen towards the throat. This is a different symptom from simple dyspepsia: it can be there on its own or with dyspepsia. People aged 65 years and over taking NSAIDs are at particular risk of upper gastrointestinal complications if they have other medical conditions, especially heart or lung disorders.

WHAT CAUSES DYSPEPSIA AND HEARTBURN?

About 70% of people with dyspepsia do not have any evidence for any serious stomach or bowel disorder (so-called functional dyspepsia [FD]). FD is believed to be related to an increased sensitivity of the stomach and bowel to normal digestive processes. Some may have a disorder of gut motility. Others may simply have had a dietary indiscretion (eg, alcohol excess). Some medications, particularly non-steroidal anti-inflammatory drugs (NSAIDS), may cause dyspepsia.

A minority of people with dyspepsia may have a peptic ulcer (gastric or duodenal). Very few will have other significant conditions. These usually present with additional features which can be identified by your doctor.

Heartburn is typical of reflux of acid from the stomach into the oesophagus (gullet). This is known as gastro-oesophageal reflux disease (GORD). This is caused by the valve at the lower end of the oesophagus permitting acid and food to come back into the oesophagus; the acid produces the burning.

WHAT SHOULD I DO ABOUT DYSPEPSIA?

Sometimes attention to simple lifestyle factors is all that is required to bring relief (eg, moderate alcohol intake, stop smoking, avoid rich/fatty foods, lose weight if applicable). Most people self-medicate (at least initially) with antacids or acid lowering medications which are available in pharmacies and supermarkets. If symptoms are severe or persistent for more than a few weeks, consult your doctor.
Symptoms that should always be assessed by your doctor include:
• unexplained weight loss
• food blocking when swallowing
• vomiting of blood or coffee ground-like material
• passage of black bowel motions
• when symptoms are associated with taking NSAIDS.

All symptoms should be regarded as more serious in people who are aged greater than 50 years when presenting for the first time, and those with a family history of stomach cancer presenting below the age of 50 years.

WHAT CAN MY DOCTOR DO?

He/she will assess your symptoms in the light of your medical history and decide an appropriate management strategy. This may include:

1. Giving lifestyle advice: attention to diet, eating habits, weight, smoking, alcohol intake, and psychosocial stresses. Some people taking medications which can cause dyspepsia, especially NSAIDS, will have their medicines reviewed.

2. Prescribing simple antacids or acid lowering medications for a short course of treatment.

3. Test for the bacteria Helicobactor pylori. This germ may be linked to peptic ulceration and can be detected by simple tests. Testing for H. pylori and treating people who have a positive test can be useful in areas and groups where the germ is common, (eg, South and West Auckland, Maori, Polynesian and Asian populations). Blood tests are inexpensive, but have variable reliability. Faeces tests are very good, and the breath test is the most reliable but unfortunately the most expensive. H. pylori needs to be treated (with an acid lowering agent and two antibiotics for one week) if the test is positive. Instructions for treatment must be followed closely to avoid the bacteria losing their sensitivity to antibiotics.

4. Motility modifying agents include domperidone (Motilium) or metoclopramide (Maxalon).

5. Prescribing acid lowering agents. These include ranitidine (eg, Zantac) and famotidine (eg, Pepsidine) which are mild in their effect and omeprazole (Losec) or pantoprazole (Somac) which are very potent. These will be prescribed initially for a defined period (eg, one month). These are the drugs of choice in heartburn but may also be effective in some people with dyspepsia.
6. Ordering investigations. In some circumstances your doctor will consider it important to do some tests to help him or her make a more definitive diagnosis. This may initially be simple blood tests. You may also be referred for a procedure (called oesophago-gastro-duodenoscopy [OGD]) which can check the appearance of your oesophagus, stomach and duodenum. A slim tube is passed through the mouth by a specially trained medical team. The discomfort of this procedure is minimised by using sedation and/or a throat spray to anaesthetise the back of your throat. A barium meal x-ray is an alternative, but it is less sensitive and less specific in diagnosis and may not avoid your having an OGD anyway.

HOW LONG WILL I NEED TO TAKE MEDICATIONS?

In most cases, short-term treatment is sufficient.

If treatment needs to be prolonged to control symptoms (continuous over 3 months), it may be better to come to a definitive diagnosis (with endoscopy).

Once a diagnosis is established, most people can be treated with one of the above described medications using the lowest dose which controls the symptoms. Many people will be able to stop their medications altogether.

A minority of people will have ulcers and require *H. pylori* eradication. A small minority will be advised to stay on long-term potent acid suppression (eg, those with severe GORD, complicated ulcers who do not have *H. pylori*, and those on NSAIDS who cannot change to other medications).
### GLOSSARY & ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse events</td>
</tr>
<tr>
<td>ARI</td>
<td>Absolute Risk Increase</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute Risk Reduction</td>
</tr>
<tr>
<td>CagA</td>
<td>Cytotoxin-associated gene</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CME</td>
<td>Continuing medical education</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclo-oxygenase</td>
</tr>
<tr>
<td>COX-1</td>
<td>Cyclo-oxygenase-1 inhibitor</td>
</tr>
<tr>
<td>COX-2</td>
<td>Cyclo-oxygenase-2 inhibitor</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FBC</td>
<td>Full blood count</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GORD</td>
<td>Gastro-Oesophageal Reflux Disease</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>H₂RA</td>
<td>Histamine type 2 Receptor Antagonist</td>
</tr>
<tr>
<td>IPA</td>
<td>Independent Practitioners Association</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
</tr>
<tr>
<td>NNH</td>
<td>Numbers needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>NUD</td>
<td>Non-ulcer dyspepsia</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>OGD</td>
<td>Oesophago-gastro-duodenoscopy</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
</tbody>
</table>

**AE (Adverse Events)**

The adverse event rate in the placebo group (P) minus the adverse event rate in the active treatment group (A). \( \text{ARR} = P - A \). 

**CagA (Cytotoxin-associated gene)**

**CI (Confidence interval)**

**CME (Continuing medical education)**

**CRP (C-reactive protein)**

**COX (Cyclo-oxygenase)**

**COX-1 (Cyclo-oxygenase-1 inhibitor)**

**COX-2 (Cyclo-oxygenase-2 inhibitor)**

**ESR (Erythrocyte sedimentation rate)**

**FBC (Full blood count)**

**GI (Gastrointestinal)**

**GORD (Gastro-Oesophageal Reflux Disease)**

**H. pylori (Helicobacter pylori)**

**H₂RA (Histamine type 2 Receptor Antagonist)**

**IPA (Independent Practitioners Association)**

**ITT (Intention to treat)**

**NNH (Numbers needed to harm)**

**NNT (Number needed to treat)**

**NSAID (Non-Steroidal Anti-Inflammatory Drug)**

**NUD (Non-ulcer dyspepsia)**

**OA (Osteoarthritis)**

**OGD (Oesophago-gastro-duodenoscopy)**

**OR (Odds ratio)**

The ratio of the probability of occurrence of an event to that of non-occurrence.
PHARMAC  Pharmaceutical Management Agency
The government’s drug-purchasing agency.

PP  Per protocol

PPI  Proton Pump Inhibitors

PUB  Perforation, Ulceration, Bleeding

RA  Rheumatoid arthritis

RCT  Randomised controlled trial

RR  Relative risk
The ratio of the risk of disease or death among those exposed to the risk among the unexposed (also called the ‘risk ratio’). If the RR > 1.0 this suggests the exposure is harmful (the risk of disease or death is higher in the exposed group). If the RR < 1.0 this suggests the exposure is protective.

RRR  Relative Risk Reduction
The adverse event rate in the placebo group (P) minus the adverse event rate in the active treatment group (A), divided by the adverse event rate in the placebo group. RRR = (P-A) / P. The RRR gives the proportion of adverse events occurring without treatment, which could be avoided by active treatment.

TSLOSR  Transient, spontaneous, lower oesophageal sphincter relaxation

UBT  Urea breath test
REFERENCES

ABOUT THE GUIDELINE


CHAPTER 1: BACKGROUND


CHAPTER 2: UNDIFFERENTIATED DYSPEPSIA


20. Patient Information Sheet - See Appendix C.


CHAPTER 3: GORD


3. Irwin RS, Zawachi JK. Accurately diagnosing and successfully treating chronic cough due to gastroesophageal reflux disease can be difficult. \textit{Am J Gastroenterol} 1999;94:3095–8.


CHAPTER 4: *H. PYLORI* AND PEPTIC ULCERATION


20. Personal communication, J Wyeth, Department of Gastroenterology, Wellington Hospital.


22. Personal communication, M Schlup, Department of Gastroenterology, Dunedin Hospital.


89. Personal communication, G Barbezat, Department of Gastroenterology, Dunedin Hospital.


CHAPTER 5: NSAID-INDUCED GI COMPLICATIONS


APPENDIX A: QUESTIONNAIRE FOR PEOPLE WITH GORD

Management of
Dyspepsia and
Heartburn