Barrett’s oesophagus affects 2% of the adult population in the West, which makes it one of the most common premalignant lesions after colorectal polyps. Conversion to oesophageal adenocarcinoma is the most important complication of the condition, with a lifetime risk of 5% in men and 3% in women. Several large trials investigating surveillance (Barrett’s Oesophagus Surveillance Study (BOSS)), chemoprevention (the Aspirin Esomeprazole Chemoprevention Trial (AspECT)), genetic stratification (EARly Genetics and Lifeourse Epidemiology (EAGLE) consortium), and endotherapy for high risk individuals are under way to determine the best way to prevent progression to adenocarcinoma. There are now several endoscopic alternatives to the long established technique of radical surgical oesophagectomy for treating high grade dysplasia and early mucosal cancer, which avoid the mortality and morbidity of surgery. Recently consensus on optimal management of the condition was reached after a National Institute of Health and Clinical Excellence (NICE) review. It is recommended that clinicians, after discussion within the multidisciplinary team, consider offering endoscopic ablative therapy as an alternative to oesophagectomy for patients with high grade dysplasia and intramucosal cancer.

A diagnosis of Barrett’s oesophagus has important ramifications for the patient because of the uncertainty of prognosis, possible anxiety about cancer in the future, the need for repeated endoscopy in a surveillance programme, and the costs of drugs and repeated investigations. We review evidence from epidemiological studies, observational studies, and randomised trials, and draw on expert opinion to discuss the importance of early recognition and optimal treatment of Barrett’s oesophagus.

What is Barrett’s oesophagus and who gets it?

Barrett’s oesophagus is a change in the lining of the oesophagus from normal stratified (multilayered) squamous mucosa to single layered, inflamed, premalignant, mucin secreting mucosa with variable degrees of goblet cell differentiation, termed intestinal metaplasia. Barrett’s oesophagus develops in 5% of people with gastro-oesophageal reflux disease, which affects as many as 30% of adults in the Western world. Evidence from one case series suggests that at least 60% of patients with Barrett’s oesophagus develop the disease as a result of chronic reflux, although other forms of mucosal inflammation in the lower oesophagus (such as from damage by chemotherapy, non-steroidal anti-inflammatory drugs, and viral infections) could be linked to the condition.

Community studies have estimated the prevalence of Barrett’s oesophagus to be just under 2% among adults in the West, which corresponds with approximately one million cases in the United Kingdom and four million in the United States. It is especially prevalent in middle aged to older men of Anglo-Saxon origin. The annual incidence of Barrett’s oesophagus in the adult population is probably around 0.1% (1 new case a year for every 1000 people)—approximately 60 000 new cases in the UK and 240 000 in the US a year—but evidence from case series suggests that the global rate of diagnosis of Barrett’s oesophagus is increasing by 2% a year. This high rate may be in part because of increased endoscopic recognition, but it probably reflects a true increased incidence.

What is the natural history of the condition?

Complete resolution of Barrett’s oesophagus rarely occurs except in very small segments, despite early reports suggesting otherwise. However, it is not uncommon to see modest shrinkage of the segment length in patients treated with acid suppression. The majority of cases stay constant, neither progressing to oesophageal adenocarcinoma nor regressing.
Summary points

Barrett’s oesophagus usually occurs as a consequence of chronic gastro-oesophageal reflux disease

The incidence of Barrett’s oesophagus is increasing: the condition is present in 2% of the adult population in the West

The incidence of oesophageal adenocarcinoma related to Barrett’s oesophagus is also increasing. In the United Kingdom, especially Scotland, oesophageal adenocarcinoma rates are higher than anywhere else in the world

Patients detected with early cancer related to Barrett’s oesophagus might have surgically or endoscopically curable disease. Endoscopic therapy is recommended as an alternative to oesophagectomy for patients with dysplasia

The value of protocol based endoscopic surveillance to detect early cancer is yet to be established and is the subject of a major randomised clinical trial.

Other cancer prevention strategies being tested are chemoprevention of Barrett’s oesophagus by aspirin in the 2513 patient AspECT trial and genome-wide identification of inherited risk factors in the 4500 patient EAGLE consortium study

Sources and selection criteria

We searched Medline using the keywords “Barrett’s oesophagus,” “epidemiology,” “high grade dysplasia,” “medical therapy,” “surgery,” “histology,” and “endoscopic ablation,” and found 12 000 relevant articles. We also searched the Cochrane central register of controlled trials and the BMJ Clinical Evidence database. We went through the reference lists of articles identified from the Medline search to identify further relevant papers. Observational studies, epidemiological studies, and randomised controlled trials were extracted, and expert opinion was sought in areas where no trials existed. In addition, we consulted national and international guidelines on the management of Barrett’s oesophagus, including guidelines from the British Society of Gastroenterology and the American College of Gastroenterology.

Two of the authors (JJ and HB) served on the National Institute for Health and Clinical Excellence review board for the management of dysplastic Barrett’s oesophagus, which allowed us to do an extensive data search and seek independent advice on the robustness of the evidence available. All four authors are members of the consensus panel for the BAReit’s Dysplasia and Cancer Taskforce (BAD CAT), which is composed of approximately 100 individuals and endorsed by 14 international societies. Although this taskforce has not completed its deliberations, the four authors exploited a small part of this resource to compile sections of this review.

Conditions associated with the development of Barrett’s oesophagus

Chronic oesophageal reflux (>60% of cases)
Congenital retardation syndromes (1%)
Non-steroidal anti-inflammatory drugs (1%)
Chemotherapy (<1%)
Viral oesophagitis (<1%)

Conditions associated with the development of Barrett’s oesophagus

Case series have indicated that the risk of patients with Barrett’s oesophagus developing oesophageal adenocarcinoma is small in absolute terms (~5% lifetime risk in men and ~3% in women). A recent decision analysis has suggested that in secondary referral centres this risk could be higher at 14% lifetime risk—a 30-100-fold higher risk of adenocarcinoma of the oesophagus compared with the general population’s risk of 0.1%. The rates of oesophageal adenocarcinoma related to Barrett’s oesophagus in west Scotland are the highest in the world (16 per 100 000 population) compared with lower rates in eastern Europe, Africa, and Asia. Once a patient is in a surveillance programme, the risk of developing oesophageal adenocarcinoma varies from 0.4% a year in the US to 1% a year in the UK.

How does Barrett’s oesophagus progress to adenocarcinoma of the oesophagus?

Figure 1 illustrates the stages of progression of Barrett’s oesophagus, from oesophagitis through metaplasia and dysplasia to adenocarcinoma. The sequence is thought to involve damage to stem cells deep in the oesophageal mucosa, an increase in number of abnormal but non-malignant cells, development of precancerous (dysplastic) cells, and, finally, progression to invasive cancer.

The steps of progression to cancer all involve genetic (damage to the DNA in cells) and epigenetic (reversible alterations to cell function) changes. For example, the development of metaplasia is associated with alterations in genes controlling stem cells, and progression to dysplasia is reflected by loss of heterozygosity or methylation of the adenomatous polyposis coli (APC) gene. Further progression entails loss of expression or mutations in P16 and P53, which decrease their function. However, none of these biological alterations can yet replace conventional histology for diagnosis and staging, because their exact relation with clinical progression has not been robustly tested in large randomised clinical trials.

What influences the risk of developing adenocarcinoma?

The major factors associated with progression to cancer are: male gender; white ethnicity; length of Barrett’s segment in centimetres, as seen during endoscopy (higher risk for length greater than 8 cm); diet poor in vegetables and fruit and high in fats; cigarette smoking; and obesity.

Case-control studies have shown that symptoms of gastro-oesophageal reflux disease are associated with a significant increase in the risk of developing cancer (odds ratio 40±15), but also that as many as 40% of those with adenocarcinoma do not report a history of reflux symptoms.

How is Barrett’s oesophagus diagnosed?

Current evidence based guidelines on the management of dyspepsia from the National Institute for Health and Clinical Excellence advise that patients with long term symptoms of reflux (more than 5-10 years) should be referred for screening endoscopy to check for Barrett’s oesophagus or its complications. On endoscopy, if the distal oesophagus looks pink or crimson in colour and is clearly distinguishable from the appearance of a hiatal hernia (fig 2), using accepted criteria...
such as the Prague endoscopic criteria, 17 then mucosal biopsies should be performed and the samples examined histopathologically. Biopsy samples are graded as “diagnostic of Barrett’s oesophagus,” “corroborative of Barrett’s oesophagus,” “consistent with Barrett’s oesophagus,” or “Barrett’s oesophagus not present.” The first three classifications should qualify the patient for entry into an endoscopic surveillance programme. 18

The exact protocol for surveillance programmes varies, but they conventionally consist of biennial endoscopies (that is, every two years) with random circumferential biopsies, ideally four quadrants every 2 cm for flat mucosa and additional targeted biopsies for any areas that appear abnormal on endoscopy. The vast majority of patients will be assessed according to this protocol unless dysplasia is found, when more frequent intervals of endoscopy a few months apart coupled with more intensive endoscopic pinch biopsies should be used. Alternatively, those who are no longer fit for any intervention may be discharged. However, age alone should not be the sole criterion for removing patients from surveillance, because even octogenarians can cope easily with endoscopy. 9 16 20 21 22

**Does surveillance prevent the development of adenocarcinoma?**

Data from several medium sized case series suggest that patients with Barrett’s oesophagus enrolled in surveillance programmes have cancer detected at an earlier (and hence more curable) stage than patients not in a surveillance programme who present with symptoms of oesophageal cancer. 19 20 Other evidence suggests that most patients with cancer related to Barrett’s oesophagus do not benefit from surveillance endoscopy. 23 24 BOSS is a randomised trial aimed at identifying both the objective value of endoscopic surveillance and the best protocol. Data from the 2500 patient trial will be used to explore the benefits, in terms of preventing oesophageal cancer, of a regular two year upper gastrointestinal endoscopic surveillance programme versus endoscopy at time of need. 25 Without evidence from randomised trials such as the BOSS trial to guide surveillance, current empirical random biopsy protocols may be suboptimal. In addition, several audits have shown that many specialists do not adhere to international surveillance guidelines. 22 24

The cost effectiveness of surveillance is still highly uncertain in the absence of real cost estimates from randomised controlled trials such as BOSS. Costs have been estimated to be about £40 000 (£50 000; $60 000) per cancer diagnosed for less than one quality adjusted life year (QALY) gained. 25 26 The cost effectiveness is arguably better in the US. Although the country has a lower incidence of oesophageal adenocarcinoma than in the UK, endoscopic surveillance is undertaken less often (three yearly in the US v two yearly in the UK). In addition, in the US endoscopic surveillance is undertaken only in patients with proven intestinal metaplasia on biopsy, because such patients are threefold more likely to develop cancer than those without proven intestinal metaplasia. 2 17 24 26

Surveillance related prevention of oesophageal adenocarcinoma, even if optimised, might not dramatically increase the longevity of patients because Barrett’s oesophagus has also been associated with an increased risk of other potentially fatal conditions. For example, Barrett’s oesophagus might be associated with an increased morbidity from aspiration, which increase the risk of ischaemic heart disease and bronchopneumonia, respectively. 26 The principal concern for health systems is how to manage patients at greatest risk of oesophageal cancer and distinguish them from those who are more likely to die of other causes.

**What treatments can prevent progression of Barrett’s oesophagus to adenocarcinoma?**

Case series have suggested that as many as 10% of patients with Barrett’s oesophagus develop high grade dysplasia in their lifetime. 1 Cohort studies have shown that such patients have an increased risk of progression to adenocarcinoma compared with those who have non-dysplastic Barrett’s oesophagus (30-55% in 8 years). 28 Data from several case control series indicate that management of multifocal areas of high grade dysplasia can be technically difficult and may require multiple interventions. 19 20 Expert consensus indicates that because of their increased risk of cancer, such patients warrant intervention with either several sessions of endoscopic ablation therapy or, in exceptional cases, oesophagectomy. 4 5 18 Arguably these patients represent a bigger burden to healthcare providers than those with cancer 4.

**Proton pump inhibitors**

A recent large randomised controlled trial found that early effective therapy for gastro-oesophageal reflux disease with proton pump inhibitors both manages symptoms effectively and heals oesophageal ulceration. 27 These findings have given rise to a strategy whereby acid suppressant drugs such as proton pump inhibitors are used not only to heal and maintain healing of oesophagitis but also for “chemoprevention” in patients with Barrett’s oesophagus. Proton pump inhibitor therapy for Barrett’s oesophagus has been shown to be well tolerated and safe in both case-control studies and randomised controlled trials. 28 They do not seem to promote elongation of Barrett’s oesophagus, which was an initial fear following reports of hypergastrinaemia caused by proton pump inhibitors. 29 However, case reports have speculated about a possible link between use of proton pump inhibitors and intestinal infections—especially Clostridium difficile—deficiencies of nutrients like folate and vitamin B 12, and osteoporosis. Proton pump inhibitors also reduce the effectiveness of clopidogrel, and co-administration of the two drugs should be avoided if possible.

Some practitioners have attempted to reduce costs and potential for side effects of proton pump inhibitors by treating patients who have gastro-oesophageal reflux disease with on demand medication. 30 However, this approach might be the worst of all options because intermittent treatment could in fact increase the risk of Barrett’s oesophagus and adenocarcinoma. Partial treatment might prevent the oesophagitis from healing completely and might also conceivably regulate the inflammation sufficiently for the metaplastic Barrett’s cells at the ulcer base, which can tolerate a low pH, to colonise the residual ulcerated oesophageal mucosa. 30 31 Selective mechanisms that allow Barrett’s cells to grow preferentially in low inflammatory conditions when compared with native oesophageal squamous cells have already been demonstrated. 31 Detecting significant differences between interventions for relatively rare outcomes in Barrett’s oesophagus such as adenocarcinoma would need a controlled study with a very large number of subjects. Future developments in linking routine clinical data with research in the community could potentially facilitate this type of large scale study. A large randomised trial in secondary care, AspECT, —is currently evaluating the long
term value of low dose (20 mg) esomeprazole (a proton pump inhibitor) compared with high dose (80 mg) esomeprazole, either with or without aspirin. Aspirin is arguably the best drug to prevent cancer of the gastrointestinal tract, such as cancers of the colon, stomach, and oesophagus. So far 2513 patients have been recruited into the AspECT trial, and an interim analysis in one large centre has found a low rate of major side effects, suggesting that any interaction between esomeprazole and aspirin is acceptable.

**Nissen fundoplication**

Moderately sized randomised controlled trials have shown that surgical repair of the oesophageal sphincter by buttressing the stomach onto the oesophagus (fundoplication) offers good symptom control in patients with severe reflux disease and Barrett’s oesophagus. In addition, this approach might be cheaper than proton pump inhibitors when drug use over many years is anticipated. Other randomised trials have confirmed that surgery controls reflux more completely than does medical therapy.

Furthermore, fundoplication may prevent all constituents of the refluxate from entering the oesophagus, in particular the contents of the duodenum such as bile. Evidence from case series has suggested that these agents may not be suppressed by proton pump inhibitor therapy.

**Newer endoscopic therapies**

Endoscopic mucosal resection for the eradication of early cancers (by definition confined to the mucosal lining) is highly effective—five year survival is 98% in patients with early adenocarcinoma confined to the mucosa and high grade dysplasia. The type of epithelium that re-grows is in part determined by the depth of injury that occurs as a consequence of treatment. In order to ensure squamous cell regeneration as opposed to recurrence of Barrett’s oesophagus, some of the superficial squamous lined ducts of the oesophageal mucous glands must survive.

Photodynamic therapy comprises systemic administration of photosensitising agents that are retained selectively in malignant tissue. When exposed to appropriate wavelength laser light, a cytotoxic reaction occurs that causes cellular destruction. The strongest evidence for the effectiveness of photodynamic therapy comes from the five year follow-up of a randomised, multicentre, multinational, pathology blinded trial that evaluated the usefulness of the technique to eradicate dysplasia. Photodynamic therapy was significantly more effective at eradicating high grade dysplasia than omeprazole only (odds ratio 2.4±0.7) and reduced the likelihood of developing cancer by half, with a significantly longer time to progression in the photodynamic therapy group compared with the omeprazole group. It may be necessary to repeat ablation at intervals, and patients treated this way should remain in lifelong surveillance.

A further randomised trial compared thermal ablation and argon plasma coagulation with surveillance in 40 patients who had undergone surgical reflux control. Significant reversal of Barrett’s oesophagus occurred in patients treated with argon plasma coagulation ablation (63% v 15% in patients under surveillance (odds ratio 4.1±1.2)). Most recently, a randomised trial of radiofrequency ablation showed that this strategy is very effective in ablating both non-dysplastic and dysplastic Barrett’s oesophagus, with complete eradication in 90.5% and 81.0% of cases, respectively. The immediate side effects of ablation are minor retrosternal discomfort in 30% of patients, but full functional activity is possible in almost all patients. Stricture, bleeding, and perforation occur in 10%, 1%, and less than 1% of patients, respectively.

Recently published National Institute of Health and Clinical Excellence guidelines from the UK recommend that clinicians consider offering endoscopic ablative therapy as an alternative to oesophagectomy for people with high grade dysplasia and intramucosal cancer, according to individual patient preferences and their suitability for the procedure. National Institute of Health and Clinical Excellence guidelines consider endoscopic therapy—especially endoscopic resection and radiofrequency ablation—to be particularly suitable for patients who are considered unsuitable for surgery and those who do not wish to undergo oesophagectomy.

**What does the future hold?**

Consensus has not yet been reached on the value of either tissue or blood biomarkers to stratify patients with Barrett’s oesophagus in terms of risk of developing cancer. However, researchers hope that data from genome-wide association studies may assist with the understanding of the inherited basis of Barrett’s oesophagus and its progression. Such knowledge might allow patient centred stratification of already known risk factors such as ethnicity, gender, and mucosal phenotype and facilitate individual tailoring of management. In fact, diagnosis and stratification may very well move to another level when the first genome-wide assessment study of Barrett’s oesophagus is published in 2011. Several genetic consortiums are being set up to replicate these genetic data once published and validate them for clinical use. Perhaps the largest in Europe is the Esophageal Adenocarcinoma Genetic LinkagE (EAGLE) consortium, which incorporates both the Chemoprevention Of Premalignant Intestinal Neoplasia (ChOPIN) trial and the Inherited Predisposition of Oesophageal Diseases (IPOD) study.

**Conclusion**

From diagnosis through to management of all stages of Barrett’s oesophagus, early prompt action is important. Expert consensus and evidence based guidelines recommend that for patients with Barrett’s oesophagus confirmed on histology, two yearly endoscopic surveillance is warranted along with either medical or surgical treatment to prevent gastric reflux. In patients with confirmed dysplasia, ablation therapy should be considered with endoscopic resection either alone or coupled with ablation therapy. For patients with non-dysplastic disease, the risk-benefit equation for ablation therapy has not yet determined and stratification of the likelihood of progression should be undertaken using conventional histological and endoscopic criteria. A large specialist and patient international consensus on the management of high grade dysplasia (Barrett’s Dysplasia and Cancer Taskforce (BAD CAT)) is due in 2011, and the National Institute of Health and Clinical Excellence has published management guidelines this year. In the meantime patients with Barrett’s oesophagus are strongly recommended to join patient support organisations with expertise in this disease, such as Fight Oesophageal Reflux Together (FORT), so they can be helped to have an informed opinion of their options at each stage in the pathway.

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Tips for non-specialists

Who should be referred for routine endoscopy?

Patients with reflux for more than five years and who are aged over 50 years.1,2

What are the alarm symptoms for immediate referral for endoscopy?

Dysphagia.1,2
Weight loss.1,2
Vomiting blood.1,2
Anaemia.1,2

What other comorbid diseases should be screened for?

Ischaemic heart disease.1,2
Hypercholesterolaemia.1,2

What is the best treatment approach for patients diagnosed with Barrett’s oesophagus?

90% can be managed by acid suppression therapy.1,4,5
5% may benefit from Nissen fundoplication.1,4,5
5% may develop oesophageal adenocarcinoma after at least 15 years.1,3,5

What dose of proton pump inhibitors should be used?

Use the lowest effective dose that suppresses symptoms so that heartburn occurs less than once a week.1,6,5

When should patients be reviewed?

Primary care physician—Dose of proton pump inhibitors should be reviewed annually, and healthy living messages—such as maintaining a low fat diet, exercising, and maintaining a BMI of less than 30—should be reinforced regularly

Secondary care physician—Patients should be reviewed endoscopically every two years in the UK and every three years elsewhere (because of higher incidence of cancer in the UK).1

Additional educational resources

For healthcare professionals

- CORE (www.corecharity.org.uk)—Charity specifically geared towards funding research into gastrointestinal diseases
- National Institute for Health and Clinical Excellence (www.nice.org.uk)—National body providing evidence based guidance on specific diseases and conditions
- Barrett’s Dysplasia and Cancer Taskforce (www.worldgastroenterology.org/international-consensus-of-management-of-dysplastic-barretts-and-cancer.html)—Taskforce producing evidence based guidelines for best clinical and cost effective management of high grade dysplasia and early mucosal cancer in Barrett’s oesophagus

For patients

- Oesophageal Patients Association (www.opa.org.uk)—Largest patients’ support group dedicated to oesophageal cancer
- Patient UK (www.patient.co.uk)—Comprehensive source of health and disease information for patients
- Fight Oesophageal Reflux Together (refluxhelp.org)—Largest UK patient support group, with online resources
- American College of Gastroenterology (www.acg.gi.org/patients/patientinfo/barrett.aspx)—Patient information on Barrett’s oesophagus from one of the largest clinical organisations dealing with digestive care
- MacMillan Cancer Support and Cancer Backup (www.macmillan.org.uk/Cancerinformation/Cancertypes/Gulleteosophasus/Pre-cancerousconditions/Barrettsoesophagus.aspx)—Patient information from one of the largest cancer patient information websites
- British Society of Gastroenterology (www.bsg.org.uk/patients/patients/general/oesophageal-cancer.html)—Patient information from one of the largest gastroenterology organisations in Europe

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Figures

Fig 1 The standard and alternative models of progression of Barrett’s oesophagus to adenocarcinoma of the oesophagus. The standard pathway to cancer is through the oesophagitis-metaplasia-dysplasia-adenocarcinoma sequence. Recently, however, it has been recognised that submucosal glands can also develop into metaplastic cells (alternative pathway A). In addition, squamous oesophagitis can conceivably develop directly into adenocarcinoma via “microscopic metaplasia” without apparently transitioning through endoscopically evident metaplasia (alternative pathway B). The column on the left shows the environmental factors that help facilitate progression of the Barrett’s oesophagus. The column on the right shows the genetic (blue) and epigenetic (red) changes in the evolution of cancer. APC, adenomatous polyposis coli gene

Fig 2 Endoscopic image of Barrett’s oesophagus. The two pictures are from the same patient but were taken five seconds apart. The panel on the right shows correct air insufflation during endoscopy, whereas the panel on the left shows the oesophagus suboptimally distended. As a consequence, the picture on the left may be misdiagnosed by inexperienced endoscopists as a hiatal hernia, because the folds in the oesophageal lining extend to the gastro-oesophageal junction (broken arrow). The panel on the right indicates circumferential Barrett’s oesophagus, which can easily be seen above the folds of the hiatal hernia (solid arrow). Pictures taken with full informed written consent