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Management of Barrett esophagus: a practical guide for clinicians based on the BADCAT and BoB CAT recommendations

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KEY WORDS

Barrett esophagus, chemoprevention, dysplasia, endoscopy, systematic review

ABSTRACT

We undertook two of the largest evidence-based reviews in clinical medicine to assess the rationale for the management of gastroesophageal reflux disease, Barrett esophagus (BE), dysplasia, and early invasive esophageal adenocarcinoma. These reviews involved over 150 world experts in 4 continents, and over 20 000 papers were assessed. Quality assessment of the publications was made using Grading of Recommendations Assessment, Development and Evaluation, and of over 240 questions formulated, we were able to answer 30% with an agreement of at least 80%. We agreed on a unique global definition of BE meaning that the presence both of hiatus hernia endoscopically and of intestinal metaplasia histologically should be noted. In addition, we devised an escalation and deescalation pathway for the management of esophagitis, metaplasia, dysplasia, and adenocarcinoma sequence. Endoscopic resection (ER) is recommended for visible mucosal lesions. Moreover, we endorsed the early use of ablation therapy for persistent dysplasia of any degree. In this regard, ER may be both diagnostic and therapeutic and may be sufficient even in early mucosal lesions (T1m). In conclusion, fewer people should be surveyed but those that do will require more detailed mapping and endoscopic interventions than currently. In addition, patients accumulating other potentially life-threatening comorbidities should be offered cessation of surveillance. In the future, chemoprevention may be the game-changing solution but results from large randomized trials, including AspECT and BOSS, are awaited.

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Introduction Barrett esophagus (BE) is a metaplastic premalignant^{1,2} condition with inherited predisposition.^{3,4} BE is also a common condition affecting between 2% and 3% of adults in Western countries. BE is also increasingly common in the Asian continent.^{5,6} The main reason why it is important to recognize and manage BE is that it may uncommonly give rise to an esophageal adenocarcinoma (EA), which has a poor prognosis unless diagnosed early, usually at the preinvasive dysplastic stage.⁷⁻⁹ It is recognized that in the majority of cases of BE, the main initiating factor is poorly controlled gastroesophageal reflux disease (GERD).^{10,11} Therefore, the entire disease process is a continuum called the esophagitis-metaplasia-dysplasia-adenocarcinoma sequence (EMDAS).¹

The big conundrum for the management of BE is that several methods of diagnosis, monitoring, and treatment have evolved empirically without a robust evidence base.^{12,13} Consequently, there are issues with safety, efficacy, cost, and indeed patient acceptability at all stages of management. In an ideal setting, large long-term clinical trials with clinically important endpoints would be set up to achieve generalizable data for application to clinical medicine. However, with a few exceptions including the Aspirin Esomperazole Chemoprevention Trial (AspECT) and Barrett's Oesophagus Surveillance Study (BOSS) trials, there is insufficient concerted action, mainly due to funding availability, to address many of the key issues.^{10,14,15} Therefore, to address the big data needed for the clinical arena, we have

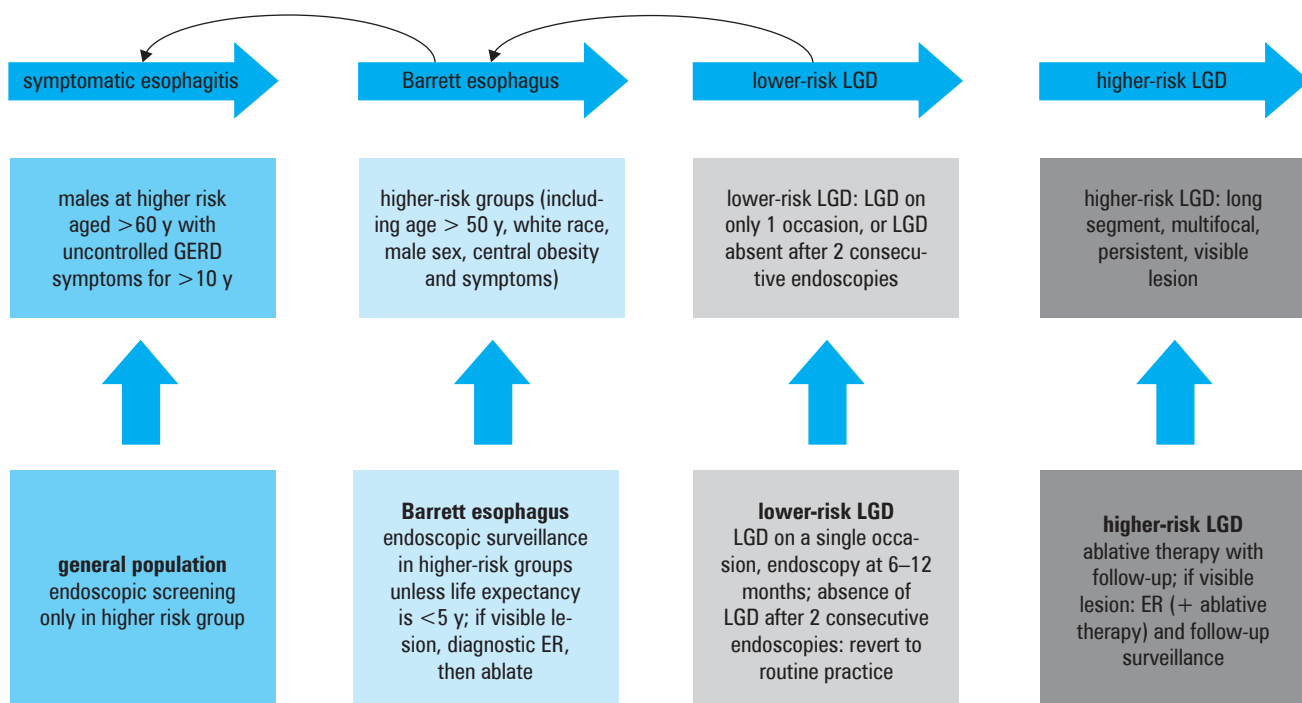


FIGURE 1 The horizontal large blue arrows represent the common stages of progression of esophageal reflux disease. The black looped arrows represent the less common stages of regression to more benign phenotypes. The smaller upper boxes represent the risk factors for progression at each stage. The larger bottom boxes represent the clinical interventions for each stage. Reproduced from Bennett et al,¹³ with consent. Abbreviations: GERD, gastroesophageal reflux disease; ER, endoscopic resection; LGD, low-grade dysplasia

devised two of the world's largest systematic reviews in clinical medicine to assess the evidence base across the entire spectrum of GERD, BE, dysplasia, and EA.

These systematic reviews are unique in several regards, including size, scope, methodology, and rigor. The Barrett's Dysplasia Cancer Task Force (BADCAT) and Benign Barrett's Cancer Task Force (BoB CAT) reviews assessed 12 500 and 20 500 publications, respectively, in comparison with conventional reviews, which may assess perhaps only a few thousand papers.^{12,13} Furthermore, we assessed a true multidisciplinary subject matter all the way from gastroenterology, gastrointestinal surgery, epidemiology, biomarkers, genomics/genetics, endoscopy, endoscopic therapy, and patient/carer support. Moreover, we used a unique methodology including an offshore web platform, which could house selected citations for review by over 100 experts from around the world who could then compose relevant questions for clinical practice and formulate the evidence base. In addition, where possible, we undertook quality evaluation of the evidence, so that the plausibility of any subsequent clinical statements could be transparently achieved.

BADCAT dealt with the rarer high-grade dysplasia and early invasive EA, whereas BoB CAT dealt with the more common benign and low-grade dysplasia. As a consequence, we achieved a global consensus of management over the entire continuum of the EMDAS.

Over 300 questions were addressed by a Delphi mechanism^{16,17} in both reviews but the evidence base was insufficient to address more than approximately one-third of them. The clinically relevant statements fell into prevention, early diagnosis, self-management, medical management, surgical management, endoscopic screening, endoscopic surveillance, endoscopic therapy,

pathological diagnosis, and staging and patient advice.

Clinically relevant guidelines **Diagnosis** BE is defined by the endoscopic presence of columnar mucosa of the esophagus. It should be stated whether intestinal metaplasia (IM) is present or absent above the gastroesophageal junction. The stipulation that IM must be present to diagnose BE has several problems. Of particular note is that the identification of IM is subject to biopsy sampling error.^{18,19} In many cases, benign BE needs just 1 expert pathologist, whereas any grade of suspected dysplasia needs 2 pathologists.²⁰ In addition, the rate of progression of IM and non-IM mucosa to dysplasia is very similar in most case series. The presence and extent of the commonly associated hiatus hernia (HH) with BE should be made to avoid a false diagnosis of BE (ie, no BE only HH in reality) or misdiagnosis of HH (ie, HH smaller than reported and a segment of BE is also present in reality).

Prevention There is a surfeit of research studies indicating that eating fresh vegetables, fruit, low-fat diets with high selenium content are associated with a lower rate of EA. However, the evidence is weak and unlikely to be applicable to the general population. Most notably, there is a lot of pressure to recommend low-dose aspirin to prevent EA.²¹⁻²³ However, again the evidence is not yet suitable for application to the general population. Data from the AspECT trial should be ready in 2017 to hopefully answer this question definitively. Obesity is a huge independent risk factor for EA, although some of this could still be due to symptom control.²⁴⁻²⁷ In addition, the length of the metaplastic segment in BE is also a strong independent factor.²⁸⁻³¹

Early diagnosis There is an abundance of advanced diagnostic endoscopic methods available. However, there is insufficient evidence to recommend them for routine use outside selected centers where ongoing evaluation of their efficacy is possible. Specifically, even advanced magnification or visualization methods with targeted biopsies should only be used in specialist centers with adequate training on their suitability.¹³

Biomarkers There were no accepted laboratory biomarkers that could improve standard histopathological methods. Interestingly, both p53 and p16 immunocytochemistry were felt to help stratify prognostication of cancer risk.³¹⁻³³

Medical management There is currently no strong evidence to recommend proton-pump inhibitors (PPIs) for the prevention of EA, although there is a strong negative association.¹³ Randomized trials, especially AspECT will report in 2017 on the value of using high-dose PPIs versus low-dose PPIs in the prevention of EA.³⁴⁻³⁶ Until then, empirical advice would be to minimize symptomatic and nonsymptomatic reflux with an effective PPI dose twice daily. If symptoms occur or endoscopic damage is apparent, higher-dose PPI therapy should be employed twice daily.

Surgical management Surgical repair of the lower esophageal sphincter cannot be recommended for cancer prevention,^{13,34} although it may be a useful option for patients who do not want to take PPIs for more than 5 years (although some patients may still require PPI therapy after such surgery). The common side effects of PPIs include diarrhea, liver toxicity, skin rashes; more recently, interference with clopidogrel activity, osteoporosis, and B₁₂ malabsorption have been also associated but remain of clinical uncertainty.

Endoscopic screening Endoscopic screening whether by endoscopic or nonendoscopic means is not recommended owing to low sensitivity and specificity. Even Markov modeling has suggested its unsuitability for routine clinical use. There is one exception where men over 60 years of age with a history of reflux of 10 years or longer are likely to have an appreciable risk of BE on endoscopy of between 20% to 50%.¹³

Endoscopic surveillance The risk of progression for average risk patients with BE is very low. We make no recommendation whether to survey or not. There will be a report on BOSS addressing this issue in 2020.¹³ Specifically, this randomized trial assesses 2-year endoscopic surveillance versus endoscopy at time of need. However, when life expectancy is less than 5 years, the risk-benefit ratio of endoscopy in elderly patients (>80 years old) becomes a vital factor.¹³ Specifically, the serious adverse complication rate of endoscopy with sedation may range from 1 in 500 to 1 in 300 individuals. In BE patients, death from other conditions

such as ischemic heart disease (IHD) and bronchopneumonia, rather than from EA, is more common, and therefore, medical management should focus on them in a holistic ethos.

Stratification When low-grade dysplasia is identified and has high-risk features such as multifocality in longer BE segments and persistence on several occasions, patients should have management intensified accordingly as they are more likely to progress. Similarly, when low-grade dysplasia is present on only one occasion and is unifocal, patients should revert to normal surveillance after a second confirmatory endoscopy (carried out within 6 to 12 months).^{13,31}

Endoscopic therapy Endoscopic resection and radio-frequency ablation should only be used where dysplasia or neoplasia is already diagnosed histologically or strongly suspected by the presence of visible irregularities in the mucosal surface.³⁶⁻⁴²

Pathological diagnosis and staging To ensure accurate reporting of BE and dysplasia, it is recommended that in benign cases there is little uncertainty in diagnosis with the reliance on only 1 trained gastrointestinal pathologist. However, when any degree of dysplasia is suspected, at least 2 trained specialist gastrointestinal pathologists are needed to ascertain the severity of the lesion. The use of pathological proformas have been recommended to ensure reproducibility of reports.^{13,18-20}

Patient advice It is important to recognize that the first clinician seeing the patient may potentially bias them to the best course of action. Therefore, it is essential that a balanced risk-benefit of both the disease progression and therapy is explained in a careful ordered sequence so as to allow reflective questioning by the patient. Patient information should be offered by mixed media including face-to-face meetings, the Internet, pamphlets, and other patients with experience via patient support groups.¹³

Conclusions In conclusion, we have achieved a worldwide definition of BE for the first time. This is important as it means that investigators can diagnose BE similarly regardless of geographic distribution. In essence, the presence of intestinal metaplasia is an important pathological feature but it is no longer an essential pathological criterion that needs to be met. In addition, we indicate that the presence and length of any HH should be noted to avoid false diagnosis of BE or misdiagnosis of HH. Specifically, failure to recognize an HH may lead to overestimation of BE or indeed a diagnosis of BE when none exists.

We have also produced a novel bidirectional escalation and deescalation pathway for the EMDAS to inform appropriate management of all stages of the disease. This means that there is now an

integrated clinical flow of management for all BE patients mitigating previous uncertainties in controversial stages, especially low-grade dysplasia.¹³

We do not recommend population screening in any cohort of patients. However, focused screening in men aged over 60 years with uncontrolled acid reflux is recommended.

Surveillance is not recommended for those whose life expectancy is less than 5 years. It is now accepted that patients with BE often have significant comorbidities, especially IHD and chest infections. Key risk factors for progression to cancer include age over 60 years, male sex, length of BE, length of BE segment, and symptom duration, frequency, and severity, as well as central obesity and tobacco smoking; therefore, these groups should take priority in any surveillance program. Overweight patients should be encouraged to lose weight (and cease tobacco use) wherever possible,⁴³ for general health reasons.

The cancer prevention value of any therapy, whether it is aspirin or PPI chemoprevention or surgical antireflux surgery, is unknown. Therefore, in this evidence, vacuum endoscopic therapy has come to the fore. In this regard, endoscopic resection is recommended for any visible nodular areas but not for benign BE without mucosal deficit. Furthermore, early prompt ablation of any persistent flat area of dysplasia, including low-grade dysplasia, is now deemed appropriate.

These recommendations have been endorsed by many gastrointestinal organisations in Europe, United Kingdom, and United States, and, most notably, by the National Institute for Health and Care Excellence. As a consequence, there are few clinical guidelines that have been so universally generalizable.

The management of gastric and gastroesophageal disease has come a long way in the last 150 years.⁴⁴ In particular, there is a better scientific basis for the construction of better trial questions.⁴⁵ However, it is clear that many of these studies still have a poor design, which results in potential bias in their findings or interpretation.⁴⁶ As to the future of gastroenterology, many more randomized clinical trials will be needed to formally ascertain strong data for clinical management options. The delineation of the genomic susceptibility and epigenetic progression has yet to break through into the identification of useful prognostic or predictive biomarkers for clinical practice.^{47,48} In the meantime, large systematic reviews such as BADCAT and BoB CAT will remain the mainstay of weighting the evidence. In the future, the role of aspirin chemoprevention in the management of BE and other gastrointestinal cancers awaits elucidation.⁴⁹

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