A systematic review and meta-analysis of the treatment for Barrett's esophagus

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CRD summary
This review concluded that pharmacological therapy, antireflux surgery and endoscopic ablative techniques were promising in treating Barrett's oesophagus, but studies performed to date did not possess adequate power to assess reduction and prevention of progression to adenocarcinoma. The conclusions reflected the results presented, but due to potential sources of bias (language, publication and reviewer error) their reliability is uncertain.

Authors' objectives
To evaluate different treatment modalities for Barrett's oesophagus.

Searching
PubMed, EMBASE (both from 1980) and The Cochrane Library (2008, Issue 1) were searched for articles published in English. Search terms were reported and search filters used. Bibliographies of relevant studies and recent review articles were also searched.

Study selection
Randomised controlled trials (RCTs) of Barrett's oesophagus patients were eligible for inclusion. Barrett's oesophagus had to be validated by pathology review and patients had to be randomised to two or more treatment arms for inclusion. Primary outcome variables had to include at least one of the following: significantly reduced acid reflux; regression based on endoscopic or histological evaluation; area or length of regression; and risk of progression to oesophageal adenocarcinoma.

The interventions in the included studies were medical, surgical, omeprazole, ranitidine, photodynamic therapy, proton pump inhibitors, argon plasma coagulation and multipolar electrocoagulation. Median age ranged from 43 to 67.3 years. Most patients were male. In most studies most patients' histology was intestinal metaplasia (others had low grade dysplasia and high grade dysplasia).

It was not clear how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using the Jadad scale to evaluate RCTs in terms of randomisation, blinding, withdrawals and dropouts and give a quality score out of 5. Allocation concealment was assessed using Cochrane Collaboration criteria.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
When the same therapies and outcomes were described in more than one study, odds ratios and corresponding 95% confidence intervals (CIs) were calculated for the study outcome. Authors were contacted for additional data where necessary.

Two reviewers independently performed data extraction.

Methods of synthesis
Studies were presented in a narrative synthesis presented by types of intervention. Where outcomes for the same comparison were available in more than one study, pooling was considered. Odds ratios and 95% CIs were pooled in a fixed-effect meta analysis (unless $I^2$ exceeded 50%, in which case a random-effects model was used). Statistical heterogeneity was assessed using the $I^2$ statistic. If studies were considered clinically heterogeneous in terms of study population and therapeutic modalities, pooling was not implemented and results of subgroup analyses or descriptive
statistics were used.

Results of the review
Twelve RCTs were included in the review (n=at least 747). Jadad scores were 2 in seven RCTs, 3 in three RCTs, 4 in one RCT and 5 in one RCT. Allocation concealment was through sealed envelopes in five of 12 RCTs and unclear in the remainder.

Medical versus surgical (one RCT): Oesophagitis and stricture was higher with medical treatment than surgical treatment (p<0.05) and no patients demonstrated complete regression of intestinal metaplasia. There was a significant decrease in the length of the Barrett's segment (p<0.05) and length of time with a pH less than 4 (p<0.05). A higher incidence of dysplasia de novo was found in the medical group (20% versus 2%, p<0.05). There was no difference between treatments with respect to malignancy.

Proton pump inhibitors versus H2 receptor antagonists (one RCT): Only omeprazole was associated with a statistically significant regression in Barrett's oesophagus in length (6.4%) and area (7.9%) compared to ranitidine. There was a significant difference in the regression of area of Barrett's oesophagus between the two drugs (p=0.02).

Photodynamic therapy versus proton pump inhibitors (two RCTs reported in three publications): One trial reported a significantly greater decrease in Barrett's oesophagus area with photodynamic therapy (30% versus 0%, p<0.001) in patients with low grade dysplasia. Persistent low grade dysplasia was found in 12 patients in the omeprazole group (p<0.001). Another trial found photodynamic therapy was superior to omeprazole in terms of ablation (52% version 7%, p<0.0001) and progression to cancer (13% versus 29%, p=0.006). After five years, occurrence of cancer was significantly lower in the photodynamic therapy group (15% versus 29%, p=0.027) and had a longer time to progression with photodynamic therapy (p=0.004). Common photodynamic therapy-related side effects were photosensitivity reactions, oesophageal strictures and chest pain.

Argon plasma coagulation versus surveillance (two RCTs): One RCT reported complete regression in 55% of patients with argon plasma coagulation and 15% of surveillance patients (p<0.05). Another study reported complete regression in eight of 20 argon plasma coagulation patients versus three of 20 surveillance patients at five-year follow-up (p>0.05). One study showed minor side effects in argon plasma coagulation patients, but no serious complication; the other study found late oesophageal strictures in two patients.

Argon plasma coagulation versus photodynamic therapy (four RCTs, three included in meta-analysis): Argon plasma coagulation was associated with greater incidence of complete ablation than photodynamic therapy (59% versus 27.5%, odds ratio 3.46, 95% CI: 1.67 to 7.81, p=0.0008; three RCTs). Complications with either treatment were limited and usually mild. There was no statistical heterogeneity ($I^2=0$).

Argon plasma coagulation versus multipolar electrocoagulation (two RCTs): There was no significant difference in the incidence of histologically complete reversal of Barrett's oesophagus with argon plasma coagulation compared to multipolar electrocoagulation (odds ratio 2.01, 95% CI: 0.77 to 5.23, p=0.15; two RCTs). No severe treatment-related complications were reported in either trial. There was no statistical heterogeneity ($I^2=0$).

Authors' conclusions
Pharmacological therapy, antireflux surgery and endoscopic ablative techniques were promising in terms of treating Barrett's oesophagus, but studies carried out to date did not possess adequate power to assess reduction and prevention of progression to adenocarcinoma.

CRD commentary
The review question was supported by inclusion criteria for study design, participants and outcomes. Relevant databases were searched; searches were restricted to published English-language articles, so the review may have been susceptible to language and publication biases. Data extraction was performed in duplicate, which reduced the possibility of reviewer error and bias; similar steps were not reported for study selection or validity assessment. Validity of the included studies was assessed and quality taken into consideration in the report. Clinical and statistical heterogeneity was taken into account and decisions on whether to perform narrative synthesis or meta-analysis appeared to be appropriate. The authors conclusions reflected the results presented, but there were possible sources of bias in the...
review so the reliability of the conclusions is unclear.

**Implications of the review for practice and research**

**Practice**: The authors stated that ablative therapy may be considered in patients with high grade dysplasia or intramucosal carcinoma and those who might prefer a non-surgical approach.

**Research**: The authors stated that future studies should be RCTs with rigorous methodology, standardised endpoints for treatment modality and a long follow-up period. The endpoint should be progression to cancer and the natural history of Barrett's oesophagus. Markers for cancer risk, level of acid suppression required for treatment, maintenance of neosquamous epithelium and definitive treatment protocol should be addressed.

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