Systematic review on drug and diet-induced endoscopic remission in Crohn's disease

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CRD summary
The authors concluded that treatments for Crohn’s disease appeared to improve endoscopic outcomes, but that the prognostic significance of such outcomes required prospective evaluation. Due to methodological problems in the review, in particular heterogeneity between the studies and use of indirect comparisons, these conclusions may not be reliable.

Authors' objectives
To determine the rate of endoscopic remission associated with different therapies for Crohn’s disease, and evaluate the prognostic value of endoscopy for Crohn’s disease.

Searching
MEDLINE and The Cochrane Library were searched for papers published up to January 2008. Search terms were reported. Reference lists of retrieved studies and reviews were checked. The search was restricted to published studies.

Study selection
Studies of patients treated for Crohn’s disease who received endoscopic evaluation before and after a predetermined therapy were eligible for inclusion. Studies were excluded if they were concerned solely with fistulising, upper digestive or perineal disease or with preventing recurrence. Studies of combined treatments or of unconventional treatment given to fewer than 10 patients were excluded, as were case reports. Outcomes of interest were endoscopic changes and/or mucosal healing and their relationship with clinical remission (prognostic value).

Participants in the included studies had colon and/or ileal Crohn’s disease, and in most cases had surgery. Most studies were restricted to adults; some were restricted to children. The proportion of males ranged from 25% to 77%. Clinical inclusion criteria varied widely. Interventions included enteric diet, infliximab, corticosteroids and azathioprine (commonly with steroid induction). Drug regimens and treatment duration varied widely. Comparison groups received different interventions, different regimens of the same intervention or placebo. About half of the studies used Crohn’s Disease Endoscopic Index of Severity (CDEIS) or a four-point severity score to assess endoscopic outcomes; the rest of the studies used different scores and/or subjective measures. The definition of endoscopic remission varied widely and about half of the studies provided no definition. Study measures of clinical remission (where defined) included quality of life, weight and height. Duration of follow-up varied from two to 96 weeks.

Two reviewers analysed study abstracts for relevance.

Assessment of study quality
The reviewers stated that study validity was assessed using the CONSORT scale for controlled studies and the STROBE scale for observational studies. (These are guidelines for the quality of reporting of trials). Points were allocated for adequate description of quality components, up to a maximum of 40 points. Studies were classified as high quality (over 30 points), medium quality (20 to 30 points) and low quality (less than 20 points).

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

Data extraction
Event rates and mean changes from baseline scores were extracted for each study group and expressed as a percentage and standard error (based on the published standard deviation) or as a median and range. Where data were reported separately for the ileum and colon, a mean was calculated. According to the time between initial and follow-up endoscopy, data were categorised as short term (two to six weeks), medium term (six to 12 weeks) or long term (over 12 weeks). Endoscopic remission was defined as mucosal healing or as per the primary study; if necessary, the reviewers defined this outcome using descriptive data available (for example, marked or complete improvement).
Data were extracted independently by two reviewers. Differences were resolved by consensus.

Methods of synthesis
It appeared that data were grouped by intervention and pooled across studies (regardless of the comparator) to calculate pooled mean change and 95% confidence interval (CI) for each outcome. The reviewers stated that a fixed model was used.

The significance of differences between groups was tested with the $\chi^2$ test. Two analyses were conducted using alternative definitions of remission (ulcer-free or variously defined) for the outcome of endoscopic remission. Subgroup analysis was conducted by study design and quality and duration of follow-up. The relationship between endoscopic outcomes and clinical remission was investigated with weighted linear regression.

Results of the review
Twenty-four studies were included in the review (n=981): eight randomised controlled trials (RCTs, n=370); 11 controlled trials (n=489); and five observational studies (n=122). Quality scores ranged from 29 to 38 for RCTs, nine to 29 for controlled trials and 20 to 23 for observational studies.

Endoscopic remission: Mean rate of endoscopic remission (defined as no ulceration) with corticosteroids was 17% (95% CI 12% to 22%; n=212), which was significantly higher than placebo ($p=0.02$). The equivalent rate with enteric diet therapy was 43% (95% CI 33% to 52%; n=100) and was similar with infliximab, at 44% (95% CI 35% to 53%; n=107); both were significantly superior to corticosteroids ($p=0.0001$). Mean rate of endoscopic remission (variously defined) with azathioprine was 54% (95% CI 38% to 69%; n=137).

Endoscopic improvement: The mean reduction in CDEIS (Crohn's Disease Endoscopic Index of Severity) with corticosteroids was 46% (95% CI 39% to 53%; n=204) and with infliximab was 70% (95% CI 62% to 78%; n=121). The mean reduction on a four-point severity score with enteric diet therapy was 63% (95% CI 53% to 72%; n=91). When data were pooled across scoring tools, corticosteroids were significantly superior to placebo (45% versus 12%, $p=0.0008$). Enteric diets and infliximab did not differ significantly, but both were significantly superior to corticosteroids (61% $p=0.01$ for enteric diets and 70%, $p<0.0001$ for infliximab).

No statistically significant relationship was found between endoscopic and clinical remission (only one study reported this outcome). There was some evidence of a correlation between endoscopic improvement and clinical remission. Subgroup analyses had inconclusive findings. Other data were reported in the review, including 95% CIs for all outcomes.

Authors' conclusions
Current treatments for Crohn’s disease appeared to improve endoscopic outcomes, but the prognostic significance of such outcomes required prospective evaluation.

CRD commentary
The objectives and inclusion criteria of the review were clear. However, the questions raised about the clinical relevance of endoscopic outcomes cast some doubt on the clinical value of the review findings. Relevant sources were searched for studies, but the restriction to published studies meant that some studies may have been missed. Publication bias was not formally assessed. It was not stated whether there was any restriction by language. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently extract the data; it was unclear whether this also applied to validity assessment. The validity assessment tools used were designed only to address study reporting (as opposed to study conduct) and the summary quality scores were difficult to interpret. The statistical methods used to combine data did not appear reliable, as they utilised indirect comparisons between heterogeneous populations and used widely differing outcome measures. The authors acknowledged the problems associated with heterogeneity between the studies and conducted some subgroup and sensitivity analyses, but did not formally quantify statistical heterogeneity. Total sample numbers were reported, but it was unclear which (or how
many) studies were included in the pooled analyses. Sample numbers overall were low. Due to methodological problems in the review, in particular heterogeneity between the studies and the use of indirect comparisons, the authors’ conclusions may not be reliable.

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

**Practice:** The authors stated that some therapies in use at the time of the review appeared to improve mucosal healing and that endoscopic improvement may be associated with better prognosis.

**Research:** The authors stated that RCTs were needed to assess whether endoscopic remission should be a goal and/or gold standard of treatment for Crohn’s disease and to determine the optimum timing for endoscopy. They noted that a clear definition of endoscopic outcomes was required.

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