Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression

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CRD summary
This review assessed intravenous corticosteroid (IVCS) therapy in patients with exacerbations of severe ulcerative colitis and predictors of response. The colectomy rate has remained stable and is not related to IVCS dosage or use of cyclosporine. Predictors of therapy failure were identified. Limitations in the reporting of the review process and the lack of a formal validity assessment undermine the reliability of these findings.

Authors' objectives
To review the short-term outcomes in patients treated with intravenous corticosteroids (IVCS) for exacerbations of ulcerative colitis (UC), and to identify predictor variables associated with the response to or failure of treatment.

Searching
MEDLINE, EMBASE, the Cochrane CENTRAL Register (Issue 2, 2006) and ACP Journal Club were searched for studies published between January 1974 and January 2006; the search terms were reported. The references of identified studies were screened and a personal library was searched. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Prospective and retrospective studies were eligible for inclusion. Where stated, the included studies were retrospective and prospective cohort studies and randomised controlled trials (RCTs).

Specific interventions included in the review
Studies of IVCS, with or without cyclosporine, were eligible for inclusion. Where stated, the IVCS evaluated in the included studies were methylprednisolone, hydrocortisone and betamethasone. Daily dosages varied between the studies. Infliximab was also administered in some studies.

Participants included in the review
Studies of adult or paediatric patients with UC admitted for a first or subsequent exacerbation of UC, with symptoms severe enough to warrant IVCS, were eligible for inclusion. Studies that evaluated other patient subgroups where the full cohort of patients receiving IVCS was not described were excluded from the review. The majority of the studies were performed in adults with only severe UC; a small number of studies evaluated both moderate and severe UC patients. Disease severity was assessed using different classifications and indices.

Outcomes assessed in the review
Studies had to report a short-term outcome and/or predictors of response to treatment to be eligible for inclusion; short-term was defined as any time during the same admission. The primary end point of interest was colectomy rate, but all end points that were clearly defined were eligible. Other outcomes reported were clinical improvement, number of days to improvement, death, composite of colectomy or death, need for further medical therapy, and a clinical and endoscopic score.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion in the review. Any disagreements were arbitrated by a third reviewer.

Assessment of study quality
A systematic validity assessment was not applied to the included studies on the grounds that there was a lack of
consensus on how to assess the validity of observational studies.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Data were extracted for colectomy rate, response to IVCS, administration of and response to cyclosporine, time to evaluation of need for colectomy and death. The dose of IVCS was extracted and standardised as a methylprednisolone equivalent using a mean adult weight of 70 kg, giving a mean dosage of 68 mg (range: 40 to 100).

**Methods of synthesis**
How were the studies combined?
A meta-regression was performed to determine the relationship between colectomy rates over time and IVCS dose, whilst controlling for potential sources of heterogeneity. Where appropriate, pooled estimates with 95% confidence intervals (CIs) were calculated. Predictors of IVCS failure were tabulated and described in a narrative summary.

How were differences between studies investigated?
Sensitivity analyses were performed on the following clinically important factors: year of publication, IVCS dose, the time at which need for colectomy was evaluated, cyclosporine use, disease severity of the patients and study design. Factors shown to be important were subsequently controlled for in the meta-regression.

**Results of the review**
Thirty-two studies were included in the review. Twenty-nine studies (n=1,991) reported short-term outcomes: 14 retrospective cohorts (n=1,145), 6 prospective cohorts (n=427), 5 RCTs (n=149) and 4 studies of unspecified design (n=270). Nineteen studies (number of patients not available) reported predictors of therapy failure.

**Colectomy rate.**
Overall, 27% of patients required a colectomy (95% CI: 26, 28) and 1% of patients died (95% CI: 0.7, 1.5). The subgroup analysis showed that study design (p=0.9), time at which colectomy rate was evaluated (p=0.13), cyclosporine use (p=1) and IVCS dose (p=0.98) were not significant sources of heterogeneity. Studies that only included patients with severe UC had a significantly higher colectomy rate compared with studies including moderately active patients (p=0.003).

The meta-regression analysis suggested that no significant change has occurred in colectomy rate over the past 30 years (p=0.8). In the multivariate meta-regression model, none of the sources of potential heterogeneity were statistically significant: IVCS dosage (p=0.9), time to colectomy evaluation (p=0.58) and disease severity (p=0.62).

**Predictive factors.**
Twenty-two predictive factors of IVCS failure were identified. The factors replicated across numerous studies were disease extent (5 studies), temperature (7 studies), pulse rate (7 studies), stool frequency (12 studies), C-reactive protein (7 studies), albumin (9 studies) and radiologic assessment (6 studies). Three studies went on to attempt to use the identified variables to develop predictive indices.

**Authors' conclusions**
Colectomy rates in UC attacks warranting IVCS therapy have remained stable over the past 30 years. Some clinical predictors of response to therapy have been identified; however, there is insufficient information at present to determine the optimum treatment sequence of calcineurin inhibitors, infliximab and colectomy.

**CRD commentary**
The review addressed a somewhat broad research question, which led to the wide variation in included study designs, populations, interventions and outcomes. Several relevant sources were searched for eligible studies; however, there does not appear to have been any attempt to locate unpublished material and a potentially relevant study published in abstract form only was excluded, suggesting that publication bias cannot be ruled out. Methods were used to minimise the potential for reviewer error and bias when selecting studies for inclusion, but there was insufficient reporting of the data extraction to rule out reviewer error or bias. A systematic evaluation of validity was not performed; the authors stated this was because of a lack of consensus on how to assess the validity of observational studies. Further detail on study design would give more strength to the validity and reliability of the review findings.

Based on the information presented, the use of meta-regression and a narrative synthesis was appropriate for the data, and heterogeneity was suitably explored and controlled for in the analysis. Limitations in the reporting of the review process and the use of observational studies with insufficient reporting of aspects of validity may undermine the reliability of the review findings.

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

Practice: The authors stated that there is no evidence to support increasing the IVCS dose beyond 60 mg/day methylprednisolone. Various clinical variables at the third day of IVCS use may aid decisions on second-line treatment.

Research: The authors stated the need for prospective cohort studies validating and comparing the three main predictive indices of treatment failure; further research evaluating second-line medical therapies such as infliximab or calcineurin inhibitors; and studies systematically evaluating steroid responsiveness from genetic, serologic or faecal markers.

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