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Glutamine for induction of remission in Crohn's disease (Review)

Akobeng AK, Elawad M, Gordon M



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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	4
OBJECTIVES	4
METHODS	4
RESULTS	6
Figure 1.	7
Figure 2.	9
Figure 3.	10
Figure 4.	10
Figure 5.	11
DISCUSSION	11
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	12
REFERENCES	12
CHARACTERISTICS OF STUDIES	14
DATA AND ANALYSES	18
Analysis 1.1. Comparison 1 Glutamine-enriched diet versus standard diet, Outcome 1 Clinical remission.	18
Analysis 1.2. Comparison 1 Glutamine-enriched diet versus standard diet, Outcome 2 Intestinal permeability.	19
Analysis 1.3. Comparison 1 Glutamine-enriched diet versus standard diet, Outcome 3 Central catheter infections.	19
APPENDICES	19
CONTRIBUTIONS OF AUTHORS	20
DECLARATIONS OF INTEREST	20
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	20

Glutamine for induction of remission in Crohn's disease

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ABSTRACT

Background

Crohn's disease is a chronic relapsing condition of the alimentary tract with a high morbidity secondary to bowel inflammation. Glutamine plays a key role in maintaining the integrity of the intestinal mucosa and has been shown to reduce inflammation and disease activity in experimental models of Crohn's disease.

Objectives

To evaluate the efficacy and safety of glutamine supplementation for induction of remission in Crohn's disease.

Search methods

We searched the following databases from inception to November 15, 2015: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane IBD Group Specialised Register. Study references were also searched for additional trials. There were no language restrictions.

Selection criteria

Randomised controlled trials (RCTs) that compared glutamine supplementation administered by any route to a placebo, active comparator or no intervention in people with active Crohn's disease were considered for inclusion.

Data collection and analysis

Two authors independently extracted data and assessed the methodological quality of the included studies. The Cochrane risk of bias tool was used to assess methodological quality. The primary outcome measure was clinical or endoscopic remission. Secondary outcomes included intestinal permeability, clinical response, quality of life, growth in children and adverse events. Risk ratios and 95% confidence intervals were calculated for dichotomous outcomes. The overall quality of the evidence supporting the primary outcome was evaluated using the GRADE criteria.

Main results

Two small RCTs (total 42 patients) met the inclusion criteria and were included in the review. One study (18 patients) compared four weeks of treatment with a glutamine-enriched polymeric diet (42% amino acid composition) to a standard polymeric diet (4% amino acid composition) with low glutamine content in paediatric patients (< 18 years of age) with active Crohn's disease. The other study (24 patients) compared glutamine-supplemented total parenteral nutrition to non-supplemented total parenteral nutrition in adult

patients (> 18 years of age) with acute exacerbation of inflammatory bowel disease. The paediatric study was rated as low risk of bias. The study in adult patients was rated as unclear risk of bias for blinding and low risk of bias for all other items. It was not possible to pool data for meta-analysis because of significant differences in study populations, nature of interventions, and the way outcomes were assessed. Data from one study showed no statistically significant difference in clinical remission rates at four weeks. Forty-four per cent (4/9) of patients who received a glutamine-enriched polymeric diet achieved remission compared to 56% (5/9) of patients who received a standard low-glutamine polymeric diet (RR 0.80, 95% CI 0.31 to 2.04). A GRADE analysis indicated that the overall quality of evidence for this outcome was low due to serious imprecision (9 events). In both included studies, no statistically significant changes in intestinal permeability were found between patients who received glutamine supplementation and those who did not. Neither study reported on clinical response, quality of life or growth in children. Adverse event data were not well documented. There were no serious adverse events in the paediatric study. The study in adult patients reported three central catheter infections with positive blood cultures in the glutamine group compared to none in the control group (RR 7.00, 95% CI 0.40 to 122.44).

Authors' conclusions

Currently there is insufficient evidence to allow firm conclusions regarding the efficacy and safety of glutamine for induction of remission in Crohn's disease. Data from two small studies suggest that glutamine supplementation may not be beneficial in active Crohn's disease but these results need to be interpreted with caution as they are based on small numbers of patients. This review highlights the need for adequately powered randomised controlled trials to investigate the efficacy and safety of glutamine for induction of remission in Crohn's disease.

PLAIN LANGUAGE SUMMARY

Glutamine for treatment of active Crohn's disease

What is Crohn's disease?

Crohn's disease is a chronic inflammatory disorder of the intestines which has periods of inactivity and periods when it flares up. Crohn's disease can affect any part of the digestive tract, from the mouth to the anus. The most common symptoms of the disease include abdominal pain, non-bloody diarrhoea and weight loss. When people with Crohn's disease are experiencing symptoms of the disease it is said to be 'active'; periods when the symptoms stop are called 'remission'.

What is glutamine?

Glutamine is an amino acid that plays a key role in maintaining the integrity of the intestinal mucosa (lining of the intestines) and has been shown to reduce inflammation and disease activity in animal models of Crohn's disease. It has therefore been suggested that glutamine may reduce intestinal inflammation in people with Crohn's disease.

What did the researchers investigate?

The researchers investigated whether glutamine is effective for inducing remission in people with active Crohn's disease and whether this treatment causes any harms (side effects). The researchers searched the medical literature up to November 15, 2015.

What did the researchers find?

The researchers identified two randomised controlled trials (total 42 participants) that investigated the role of glutamine for the treatment of active Crohn's disease. One study (18 patients) compared four weeks of treatment with a glutamine-enriched polymeric diet (42% amino acid composition) to a standard polymeric diet (4% amino acid composition) with low glutamine content in paediatric patients (< 18 years of age) with active Crohn's disease. Participants were encouraged to consume the diet orally. If this was not possible the diet was administered via a fine-bore nasogastric tube. The other study (24 participants) compared glutamine-supplemented total parenteral nutrition (TPN) to non-supplemented TPN in adult patients (> 18 years of age) with sudden worsening of inflammatory bowel disease. The TPN diet was administered intravenously via a central catheter (a thin tube) for at least one week. Both studies were generally high quality. Neither study demonstrated any beneficial effects for glutamine. Side effects were not well documented in the two studies. There were no serious side effects noted in the paediatric study. The study in adult patients reported three central catheter-related blood infections in the glutamine group compared to none in the non-glutamine control group. Currently, there is insufficient evidence to allow any firm conclusions regarding the effectiveness and harms of glutamine for the treatment of active Crohn's disease.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Glutamine-enriched polymeric diet versus standard low-glutamine polymeric diet for induction of remission in Crohn's disease						
Patient or population: Childen (<6 years old)with active Crohn's disease						
Settings: Hospital						
Intervention: Glutamine-enriched polymeric diet						
Comparison: Standard low-glutamine polymeric diet						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Glutamine-enriched polymeric diet				
Induction of remission at 4 weeks	555 per 1000 ¹	444 per 1000 (172 to 1132)	RR 0.80 (0.31 to 2.04)	18 (1 study)	⊕⊕○○ low ²	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio.						
GRADE Working Group grades of evidence						
High quality: Further research is very unlikely to change our confidence in the estimate of effect.						
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.						
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.						
Very low quality: We are very uncertain about the estimate.						

¹ The control group estimate comes from the control arm of the included study on children with active Crohn's disease.

² Downgraded two levels due to small sample size and low event rates resulting in serious imprecision (9 events).

BACKGROUND

Crohn's disease is a chronic relapsing inflammatory condition of the alimentary tract characterised by gut mucosal inflammation, enhanced pro-inflammatory cytokine activity, increased gut permeability and poor nutrition secondary to decreased intake and to increased catabolic losses (Katz 1989). Glutamine, a conditionally essential amino acid in catabolic states, is the principal respiratory substrate for enterocytes (Windmueller 1978). It is known to play a key role in maintaining the integrity of the intestinal mucosa. Glutamine supplementation has been shown to reduce intestinal permeability (Hond 1999), prevent mucosal atrophy and maintain gut integrity (Van der Hurst 1993). It spares mobilisation of glutamine from skeletal muscle and thereby improves nitrogen balance (Stehle 1989).

Protein turnover is increased in active Crohn's disease (Thomas 1992), and subjects are in a state of catabolism (Kangas 1986). Low plasma glutamine levels have been described in patients with Crohn's disease (Thomas 1991). This may be due to enhanced utilisation of glutamine by the diseased intestinal mucosa (Lacey 1990). The body's requirement for glutamine may exceed the supply causing a state of glutamine deficiency. This nature of conditional essentialness has been demonstrated in other catabolic states such as burns, trauma and sepsis (Hall 1996).

In experimental animal models of Crohn's disease, glutamine supplementation prevented macroscopic ileitis and increased intestinal glutathione status (Sido 2006), reduced inflammation, prevented weight loss, improved nitrogen balance and reduced disease activity (Fox 1988). Glutamine has been shown to reduce bacterial translocation in an animal model (Fujita 2005), which may have important implications in the setting of gut mucosal inflammation as seen in Crohn's disease. In vitro, glutamine reduces the production of the pro-inflammatory cytokines interleukin-6 and interleukin-8, and enhances the production of the anti-inflammatory cytokine, interleukin-10 in human intestinal mucosa (Coeffier 2003). Down-regulation of chemokines by glutamine could also contribute to its therapeutic potential by reducing intestinal inflammation during critical illnesses (Marion 2004).

Considering that glutamine may have positive nutritional, metabolic and immunologic benefits with respect to Crohn's disease, it has been trialled for the treatment of people with the disease (Akobeng 2000). The aim of this systematic review is to summarise the current evidence on the use of glutamine for induction of remission in Crohn's disease.

OBJECTIVES

1. To evaluate the effectiveness of glutamine supplementation for induction of remission in Crohn's disease.
2. To evaluate adverse events associated with glutamine supplementation in Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials were considered for inclusion.

Types of participants

Patients of any age with active Crohn's disease were considered for inclusion. Crohn's disease should have been diagnosed by conventional clinical, radiographic, endoscopic and histological criteria. Active disease should have been defined using a recognised Crohn's disease activity index.

Types of interventions

Randomised controlled trials where glutamine was administered by any route and compared to placebo, an active comparator, or a no intervention control group were considered for inclusion.

Types of outcome measures

The primary outcome was clinical or endoscopic remission as defined by the primary studies. Secondary outcomes included clinical response as defined by the primary studies, improvement in intestinal permeability, quality of life, growth in children, and adverse events.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases from inception to November 15, 2015:

1. MEDLINE;
2. EMBASE;
3. Cochrane Central Register of Controlled Trials; and
4. The Cochrane IBD Group Specialised Register.

There were no language restrictions. The search strategy is reported in Appendix 1.

Searching other resources

Reference lists from retrieved articles were inspected to identify additional citations that may have been missed by the electronic searches.

Data collection and analysis

Selection of studies

The search results were independently screened by two authors (MG and ME) to identify potentially relevant studies. Two authors (MG and ME), after reading the full texts, independently assessed the eligibility of all trials identified using the pre-specified eligibility criteria stated above. Disagreement among authors was resolved by discussion and agreement was reached by consensus.

Data extraction and management

A data extraction form was developed and used to extract information on relevant features and results of included studies. The form was based on the Cochrane checklist of items to consider for data extraction (Higgins 2011a). Two authors (ME and MG) independently extracted and recorded data on the predefined checklist. Extracted data included the following items:

- A. Methods (methods of randomisation, allocation concealment, blinding, inclusion and exclusion criteria, definition of outcomes);
- B. Participants (number, age, gender, disease activity, concurrent medication);
- C. Interventions (formulation, dose, frequency, duration, method of administration); and
- D. Outcomes (clinical remission, intestinal permeability, adverse events) and time of assessment.

Assessment of risk of bias in included studies

ME and MG independently assessed the methodological quality of each included study using the Cochrane risk of bias tool (Higgins 2011b). The study features assessed included:

- a. Random sequence generation;
- b. Allocation concealment;
- c. Blinding of participants and personnel;
- d. Blinding of outcome assessment;
- e. Completeness of outcome data;
- f. Selective reporting; and
- g. Other sources of bias.

We rated each of these factors as 'low risk', 'high risk' or 'unclear risk' of bias.

The overall quality of the evidence supporting the primary outcome was assessed using the GRADE criteria (Guyatt 2008; Schunemann 2011). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect reflects the item being assessed. Randomised trials start as high quality evidence, but may be downgraded due to: risk of bias (methodological quality), indirectness of evidence, unexplained heterogeneity, imprecision (sparse data) and publication bias. The overall quality of the evidence for each outcome was determined after considering each of these factors and graded as:

- High: further research is very unlikely to change confidence in the estimate of effect;
- Moderate: further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate;
- Low: further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; and
- Very low: any estimate of effect is very uncertain.

Measures of treatment effect

The Cochrane Collaboration Review Manager (RevMan) software (version 5.3) was used for data analysis. We calculated the risk ratio and corresponding 95% confidence interval (95% CI) for dichotomous outcomes using a fixed-effect model. We calculated the mean difference (MD) and corresponding 95% CI for continuous outcomes measured using the same units. We planned to calculate the standardised mean difference (SMD) and corresponding 95% CI for continuous outcomes where different scales were used to evaluate the same outcome.

Unit of analysis issues

If any trial had multiple treatment groups, the 'shared' comparison group was to be divided by the number of treatment groups, and comparisons between each treatment group and the split comparison group were to be treated as independent comparisons.

Dealing with missing data

Data were analysed according to the intention-to-treat principle. Patients with final missing outcomes were assumed to be treatment failures. A sensitivity analysis was planned to assess the impact on the results of the assumption of treatment failure when data were missing.

Assessment of heterogeneity

We planned to assess heterogeneity by visually inspecting forest plots and by calculating the Chi² test of heterogeneity. A P value of < 0.10 was considered statistically significant. The I² statistic was to be calculated to quantify the effect of heterogeneity (Higgins 2003).

An I² value of:

- < 25% denotes low heterogeneity;
- ≥ 50% denotes moderate heterogeneity; and
- ≥ 75% denotes high heterogeneity.

We planned to use a random-effects model in situations of unexplained heterogeneity. When significant heterogeneity was identified, we planned to examine the included studies for sources of both clinical and methodological heterogeneity. We planned to

explore potential explanations for heterogeneity using sensitivity analysis.

Assessment of reporting biases

If there was an appropriate number of studies in a pooled analysis (i.e. > 10 studies), we planned to investigate potential publication bias using funnel plots (trial effects versus trial size).

Data synthesis

Studies were to be pooled for meta-analyses when the interventions, patient groups, outcome measures, and timing of outcome assessment were sufficiently similar (to be determined by consensus).

Subgroup analysis and investigation of heterogeneity

The following pre-specified subgroup analyses were planned:

- a. route of glutamine supplementation;
- b. duration of treatment;
- c. duration of disease; and
- d. disease location (pure colonic disease versus small bowel involvement).

Sensitivity analysis

Sensitivity analyses were to be conducted based on the following:
a. only including patients whose outcome is known (i.e. number of patients who completed the study used as denominator);
b. random-effects versus fixed-effect models; and
c. study quality.

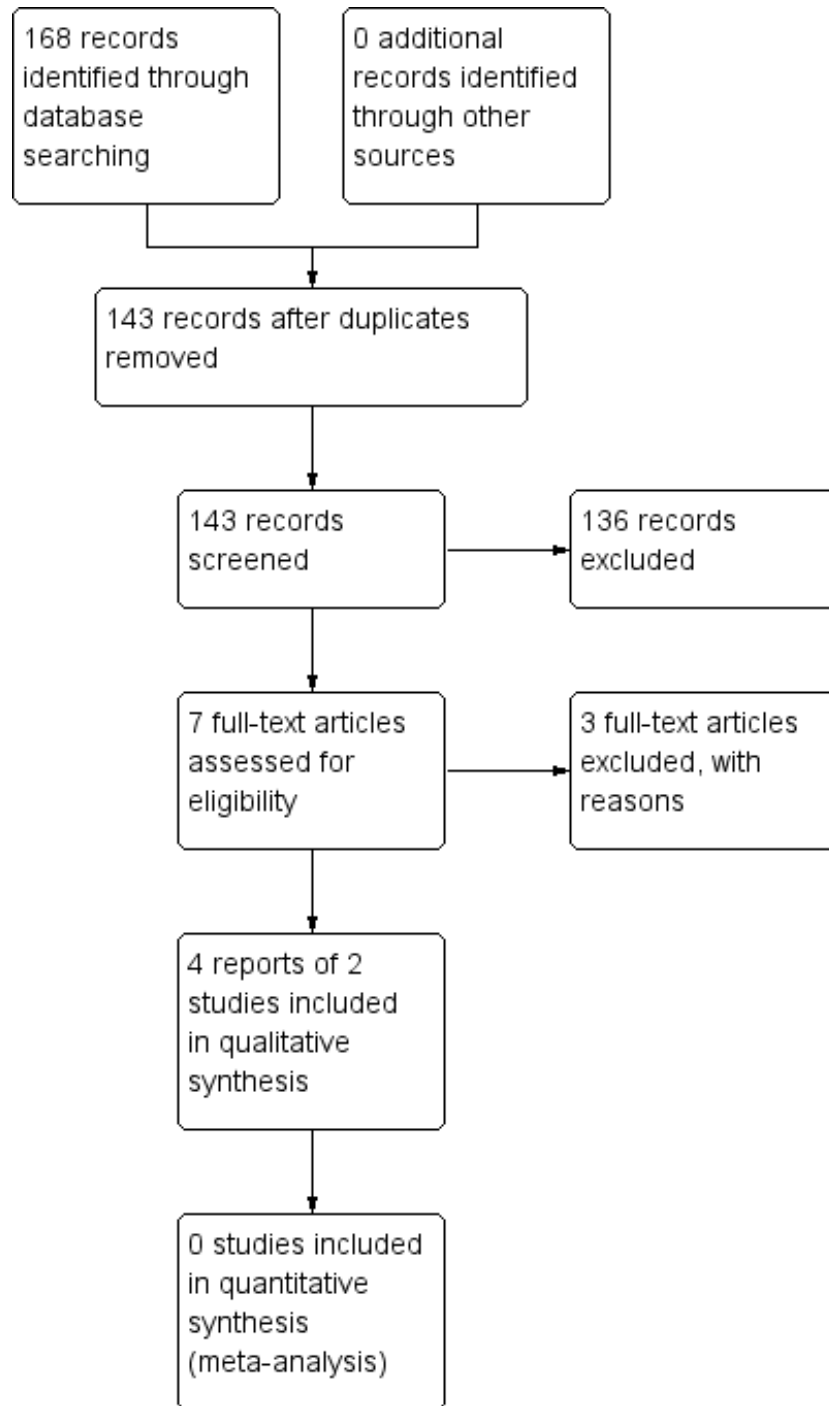
R E S U L T S

Description of studies

Results of the search

A literature search conducted on November 15, 2015 identified 168 records. After duplicates were removed, a total of 143 records remained for review of titles and abstracts. Two authors (AA and MG) independently reviewed the titles and abstracts of these trials and seven records were selected for full text review (see [Figure 1](#)). Three articles were excluded (See: [Characteristics of excluded studies](#)). Four reports of two trials (total of 42 patients) met the pre-defined inclusion criteria and were included in the review ([Akobeng 2000](#); [Ockenga 2005](#)).

Figure 1. Study flow diagram.



Included studies

[Akobeng 2000](#) was a double-blind randomised controlled trial conducted at a single centre in the UK. This study randomised 18 patients (< 16 years old) with active Crohn's disease, defined by a Paediatric Crohn's Disease Activity Index (PCDAI) of > 12. Participants received either a standard polymeric diet with a low glutamine content (4% of amino acid composition) or a glutamine-enriched polymeric diet (42% of amino acid composition) for four weeks as primary therapy for active Crohn's disease. The two diets were isocaloric and isonitrogenous with an identical essential amino acid profile. Patients were encouraged to consume the diet orally. If this was not possible the diet was administered via a fine-bore nasogastric tube. The primary study outcome was clinical remission at four weeks, defined as a PCDAI < 10. Secondary outcomes included changes in clinical and laboratory parameters of disease activity after four weeks. Exclusion criteria included treatment at entry with prednisolone at doses higher than 5 mg/day, and treatment with immunosuppressive agents. The use of concurrent medications was not reported. Two patients, both from the glutamine-enriched diet group, were withdrawn from the trial because of non-tolerance of the diet. Analysis of remission rates was performed on an intention-to-treat basis. Data from the same trial on intestinal permeability and serum antioxidant concentrations were published separately ([Akobeng 2000a](#); [Akobeng 2007](#)). [Ockenga 2005](#) was a randomised controlled trial conducted at a single centre in Germany. The study randomised 24 adults (> 18 years of age) with acute exacerbation of inflammatory bowel disease (19 Crohn's disease, 5 ulcerative colitis) who were being considered for total parenteral nutrition (TPN). Patients in the glutamine group received 0.3 g/kg/day alanyl-glutamine (resulting in 0.2 g/kg/day glutamine) which was added to 1.2 g/kg/day of standard amino-acid solution. Patients in the control group received 1.5 g/kg/day amino acids in a standard solution which did not contain glutamine. The study investigators, patients, nurses, and primary physicians were unaware of treatment assignment. Exclusion criteria included non consent, receipt of TPN within two weeks of entry, pregnancy, and renal failure. All patients were

treated with mesalazine (dosage not specified). Ten patients in the glutamine group received prednisolone (mean dose 0.85 mg/kg/day $\pm$ 0.66), whilst 12 patients in the control group received prednisolone (mean dose 0.73 mg/kg/day $\pm$ 0.20). One patient in the glutamine group was treated with azathioprine compared to three patients in the control group. TPN was administered for at least one week. The primary study outcomes were glutamine plasma concentrations and intestinal permeability after one week. Secondary outcomes included protein catabolism, disease activity measured by the Crohn's Disease Activity Index (CDAI), infectious complications, and duration of TPN.

See the [Characteristics of included studies](#) table for further information on the included studies.

Risk of bias in included studies

Both included studies used computer-generated randomisation codes and sealed opaque envelopes for allocation concealment and were rated as low risk of bias for these items. The [Akobeng 2000](#) study was rated as low risk of bias for participants and personnel and for outcome assessors. The study double-blind and the two diets were not distinguishable in appearance, smell, or taste and the randomisation code was not broken until the study was completed. There were no drop-outs in [Akobeng 2000](#) and the study was rated as low risk of bias for incomplete outcome data. [Akobeng 2000](#) reported on all pre-specified outcomes and was rated as low risk of bias for selective outcome reporting. There did not appear to be any other apparent sources of bias and [Akobeng 2000](#) was rated as low risk of other sources of bias. The [Ockenga 2005](#) study did not describe methods for blinding of participants and personnel, and for blinding of outcome assessment and was rated as unclear risk of bias for these items. Intestinal permeability data were available for 14 of 19 patients with Crohn's disease in the [Ockenga 2005](#) study. Incomplete outcomes data was judged to be at low risk of bias. [Ockenga 2005](#) reported on all pre-specified outcomes and was rated as low risk of bias for selective outcome reporting. There did not appear to be any other apparent sources of bias and [Ockenga 2005](#) was rated as low risk of bias for other sources of bias. The risk of bias assessment is summarised in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Akobeng 2000							
Ockenga 2005							

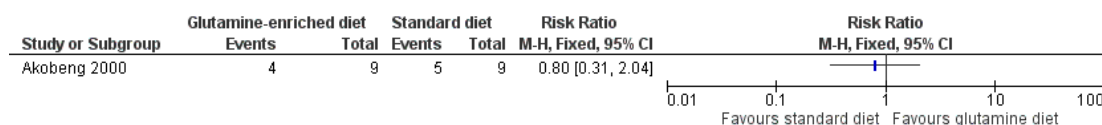
Effects of interventions

See: [Summary of findings for the main comparison](#)

See [Summary of findings for the main comparison](#)

Clinical remission: One study investigated this outcome ([Akobeng 2000](#)). There was no statistically significant difference in remission rates between patients who received the glutamine-enriched diet compared to those who received a standard low glutamine diet. Forty-four per cent (4/9) of patients who received the glutamine-enriched diet achieved clinical remission (PCDAI <10) after 4 weeks compared to 56% (5/9) of those who received the standard low glutamine diet (RR 0.80, 95% CI 0.31 to 2.04; See [Figure 3](#)). A GRADE analysis indicated that the overall quality of evidence for this outcome was low due to serious imprecision (9 events, see [Summary of findings for the main comparison](#)).

Figure 3. Forest plot of comparison: I Glutamine-enriched diet versus standard diet, outcome: I.1 Clinical remission.



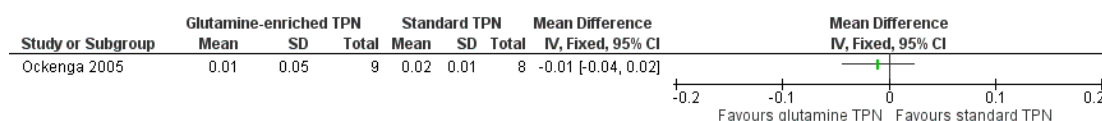
Endoscopic remission: None of the included studies reported on this outcome.

Clinical response: None of the included studies reported on this outcome.

Intestinal permeability: Both trials investigated this outcome. In [Akobeng 2000](#) the mean lactulose/mannitol permeability ratio decreased from 0.103 to 0.037 in the standard diet group ($P = 0.012$) after 4 weeks, and reduced from 0.068 to 0.043 in the glutamine-supplemented group ($P = 0.058$). There was no statis-

tically significant difference between the two groups with regard to changes in lactulose/mannitol permeability ratios ($P = 0.239$). In [Ockenga 2005](#), the mean lactulose/xylose ratio at baseline was 0.042 ± 0.03 with no difference between patients with Crohn's disease or ulcerative colitis (0.043 ± 0.038 versus 0.040 ± 0.027 , $P > 0.05$). After one week, changes in lactulose/xylose permeability ratio were not significantly different in patients who received glutamine compared to those who did not receive glutamine (MD -0.01, 95% CI -0.04 to 0.02; See [Figure 4](#)).

Figure 4. Forest plot of comparison: I Glutamine-enriched diet versus standard diet, outcome: I.2 Intestinal permeability.



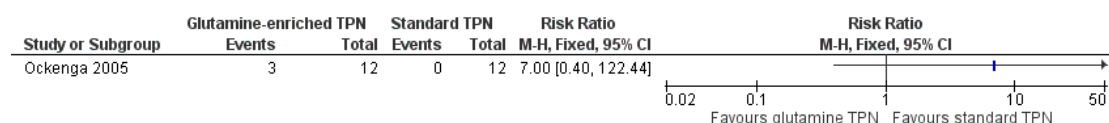
Quality of life: None of the included studies reported on this outcome.

Growth in children: None of the included studies reported on this outcome.

Adverse events: The stated purpose of [Akobeng 2000](#) was to compare the efficacy of the glutamine-enriched diet with a standard low-glutamine diet for the treatment of active Crohn's disease.

No specific adverse event outcomes were reported but the authors have confirmed that no serious adverse events were noted in either group (Akobeng, personal communication). In Ockenga 2005, three central catheter infections with positive blood cultures were diagnosed in the glutamine group compared to none in the control group (RR 7.00, 95% CI 0.04 to 124.44; See Figure 5).

Figure 5. Forest plot of comparison: I Glutamine-enriched diet versus standard diet, outcome: I.3 Central catheter infections.



Other outcomes: Both studies evaluated changes in measures of disease activity or symptoms. In Akobeng 2000, reduction in mean PCDAI was significantly higher in the control group compared to the glutamine-enriched group after four weeks but there were no statistically significant differences in changes in platelet count, orosomucoid, or weight. In Ockenga 2005, glutamine supplementation was not associated with any statistically significant changes in CDAI, white cell count, frequency of diarrhoea, pain, or extraintestinal symptoms. Ockenga 2005 also reported that the length of hospital stay did not differ significantly between patients who received glutamine and those who did not. Akobeng 2000 investigated changes in plasma antioxidant concentration. After 4 weeks, there were no statistically significant differences between patients who received the glutamine-enriched diet compared to those who received a standard diet with regard to changes in plasma concentrations of selenium ($P = 0.076$), urate ($P = 0.053$), glutathione ($P = 0.815$), vitamin E ($P = 0.245$), vitamin C ($P = 0.639$), and malondialdehyde ($P = 0.190$). There was however a statistically significant increase in the mean vitamin A level in the standard diet group compared to the glutamine-enriched diet group ($P = 0.018$). In Ockenga 2005, plasma concentrations of glutamine did not change significantly in either group throughout the study.

DISCUSSION

Summary of main results

Glutamine, the principal respiratory substrate for enterocytes is known to be important for maintenance of intestinal metabolism, structure and function. It has therefore been suggested that it may facilitate the induction of remission in people with Crohn's disease. We have found no evidence in this review to suggest that glutamine

supplementation provides any benefit in the treatment of active Crohn's disease.

Two trials were included in the review (Akobeng 2000; Ockenga 2005). The study populations, nature of interventions, and the way outcomes were assessed differed between the two studies and it was not possible to pool data for meta-analysis. Akobeng 2000 found no statistically significant difference in clinical remission rates between patients who were supplemented with glutamine and those who were not. Neither study demonstrated any significant changes in intestinal permeability between patients supplemented with glutamine and those who were not. In Akobeng 2000, the reduction in mean PCDAI was significantly higher in patients who received a standard low glutamine diet compared to those who received the glutamine-enriched diet. In Ockenga 2005, glutamine supplementation was not associated with any statistically significant differences in CDAI, white cell count, frequency of diarrhoea, pain, extraintestinal symptoms or length of hospital stay. Neither study reported data on endoscopic remission, clinical response, or quality of life.

Adverse event data were not well documented in the included studies. Akobeng 2000 did not report on any specific adverse event outcomes. However, the authors have confirmed that no serious adverse events were noted in either group. Ockenga 2005 reported that three catheter infections with positive blood cultures were diagnosed in the glutamine group compared to none in the control group. Ockenga 2005 did not report on any other adverse events.

Overall completeness and applicability of evidence

The results of this systematic review, which are applicable to patients with active Crohn's disease, should be interpreted with caution. Although the results of the included studies did not support

the hypothesis that glutamine supplementation may be useful in active Crohn's disease, both studies were limited by small sample sizes and serious imprecision. For the primary outcome, induction of clinical remission, the point estimate of the risk ratio (0.80) suggests that patients who received the glutamine-enriched polymeric diet were 20% less likely to enter remission compared to patients who received the standard low-glutamine diet. However, the 95% confidence interval includes both a reduction in likelihood of remission of about 70%, and a two fold increase in the likelihood of remission (95% CI 0.31 to 2.04). Larger trials are required to determine if glutamine provides any benefit for induction of remission in Crohn's disease.

Quality of the evidence

The Akobeng 2000 study was judged to be at low risk of bias. Ockenga 2005 did not describe the methods used for blinding of participants and personnel, or for blinding of outcome assessment and was rated as unclear risk of bias for these domains. Ockenga 2005 was rated as low risk of bias for the other items. The GRADE rating for the evidence supporting the primary outcome (clinical remission) was low because the small sample size and low event rates resulted in serious imprecision.

Potential biases in the review process

A comprehensive literature search was performed to reduce potential bias and identify all eligible studies. Two review authors independently assessed studies for inclusion, extracted data and rated study quality. There are limitations to this review. The two included studies were small and it was not possible to pool data for meta-analysis because of significant differences in the study populations, nature of interventions, and the way outcomes were assessed.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other published systematic reviews that assess the efficacy and safety of glutamine in active Crohn's disease.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is insufficient evidence to allow firm conclusions regarding the efficacy and safety of glutamine for induction of remission in Crohn's disease. Data from two small studies suggest that glutamine supplementation may not be beneficial in active Crohn's disease but these results need to be interpreted with caution as they are based on small numbers of patients.

Implications for research

This review highlights the need for high quality, adequately powered randomised controlled trials to investigate the efficacy and safety of glutamine for induction of remission in Crohn's disease.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akobeng 2000

Methods	Randomised, double blind, single centre trial	
Participants	Patients (aged 6-16 years) with active Crohn's disease defined as a paediatric Crohn's disease activity index (PCDAI) higher than 12 (N=18) Exclusion criteria included treatment at entry with prednisolone at doses higher than 5 mg/day, treatment with immunosuppressive drugs, and unwillingness to provide informed consent	
Interventions	Exclusive glutamine-enriched polymeric diet (42% of amino acid composition) [n=9] for 4 weeks Exclusive standard low glutamine polymeric diet (4% of amino acid composition) [n=9] for 4 weeks	
Outcomes	Primary outcome: clinical remission at 4 weeks defined as a PCDAI < 10 Secondary outcomes: changes in PCDAI, changes in inflammatory markers, intestinal permeability, serum antioxidant concentrations	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Assignments in opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind; the two diets were not distinguishable in appearance, smell, or taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Codes were not broken until the study was completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data reported
Selective reporting (reporting bias)	Low risk	All outcomes specified in the methods section reported on in the results
Other bias	Low risk	None apparent

Ockenga 2005

Methods	Randomised, blinded, single centre	
Participants	Adults with acute exacerbation of inflammatory bowel disease (19 Crohn's disease, 5 ulcerative colitis) who were being considered for TPN (N=24) Exclusion criteria included: not consenting to the study, on TPN within 2 weeks before study, being pregnant, having renal failure	
Interventions	TPN with 1.5g/kg body weight of a standard amino acid [n=12] for at least 1 week TPN with 1.2 g/kg body weight of a standard amino acid and 0.3 g/kg L-alanine-L-glutamine [n=12] for at least one week	
Outcomes	Primary outcomes: Glutamine plasma concentrations, intestinal permeability Secondary outcomes: disease activity, infectious complications, duration of TPN	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment groups generated by random order sequence
Allocation concealment (selection bias)	Low risk	Assignments in sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors say it was blinded but unclear how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intestinal permeability data were available for 14 of 19 patients with Crohn's disease
Selective reporting (reporting bias)	Low risk	All outcomes specified in the methods section reported on in the results
Other bias	Low risk	None apparent

TPN: total parenteral nutrition.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Benjamin 2011	Participants did not have active disease
Coeffier 2010	Review article
Hond 1999	Participants did not have active disease

DATA AND ANALYSES

Comparison 1. Glutamine-enriched diet versus standard diet

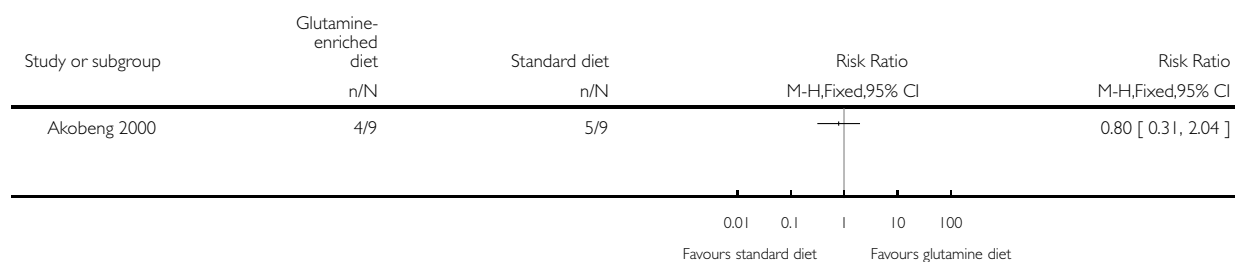
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Intestinal permeability	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Central catheter infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Glutamine-enriched diet versus standard diet, Outcome 1 Clinical remission.

Review: Glutamine for induction of remission in Crohn's disease

Comparison: 1 Glutamine-enriched diet versus standard diet

Outcome: 1 Clinical remission

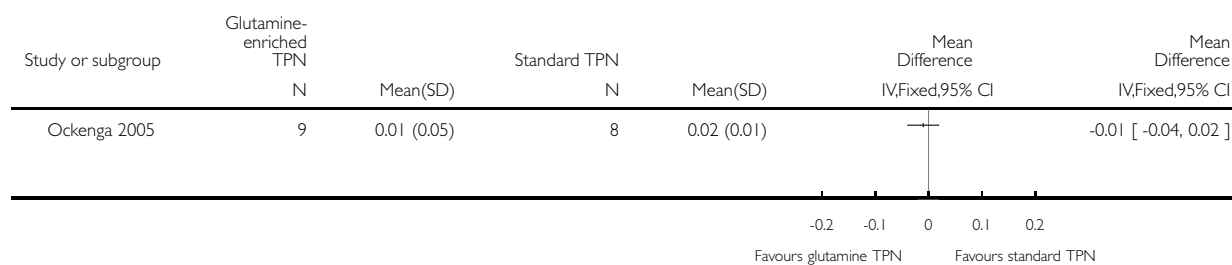


Analysis 1.2. Comparison 1 Glutamine-enriched diet versus standard diet, Outcome 2 Intestinal permeability.

Review: Glutamine for induction of remission in Crohn's disease

Comparison: 1 Glutamine-enriched diet versus standard diet

Outcome: 2 Intestinal permeability

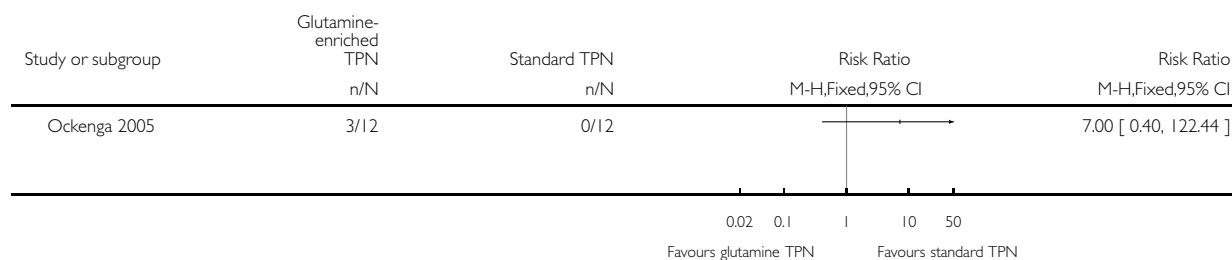


Analysis 1.3. Comparison 1 Glutamine-enriched diet versus standard diet, Outcome 3 Central catheter infections.

Review: Glutamine for induction of remission in Crohn's disease

Comparison: 1 Glutamine-enriched diet versus standard diet

Outcome: 3 Central catheter infections



APPENDICES

Appendix I. Search strategy

PubMed

1. Crohn* disease
2. Crohn disease (MeSH)
3. Regional enteritis
4. Ileitis
5. Ileitis (MeSH)
6. Inflammatory bowel disease
7. Inflammatory bowel diseases (MeSH)
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. Glutamine
10. 8 AND 9

EMBASE

1. crohn disease.mp. or crohn disease/
2. crohn's disease.mp. or crohn's disease
3. ileitis.mp. or ileitis/
4. inflammatory bowel disease.mp. or enteritis/ or inflammatory bowel disease
5. 1 or 2 or 3 or 4
6. Glutamine/ or glutamine.mp.
7. 5 and 6

Cochrane Central Register of Controlled Trials

1. Crohn's disease
2. Crohn disease
3. inflammatory bowel disease
4. 1 or 2 or 3
5. glutamine
6. 4 and 5

CONTRIBUTIONS OF AUTHORS

- AA conceived and coordinated the review, helped develop the protocol, searched for and screened studies, performed data entry and data analysis, and helped write the review text.
- ME searched for and screened studies, performed data extraction, assessed study quality, checked data and helped write the review text.
- MG searched for and screened studies, performed data extraction, assessed study quality, checked data and helped write the review text.

DECLARATIONS OF INTEREST

Dr. AK Akobeng was one of the lead investigators for a randomised controlled trial that investigated the role of enteral glutamine in childhood Crohn's disease. Dr Akobeng has no known financial activities to declare.

Mamoun Elawad: None known.

Morris Gordon has received a travel grants from Vifor / Warner Chilcott (DDW 2013), Ferring / Danone (Advances in IBD 2014), Tillotts (Advances in IBD 2015) to attend gastroenterology conferences and travel grants from Abbot Nutrition, Clinova, Biogai, and Danone for attending meetings to present research. All of these activities are outside the submitted work.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to contact leaders in the field to identify applicable studies. This was not undertaken. In line with current Cochrane Collaboration recommendations, we assessed the methodological quality of each included study using the risk of bias tool ([Higgins 2011b](#)) instead of the Jadad scale mentioned in the original protocol. We also assessed the quality of the overall evidence supporting the primary outcome using the GRADE approach ([Guyatt 2008](#); [Schunemann 2011](#)). In addition to the outcomes pre-specified in the protocol, we also reported on other outcomes mentioned in the included primary studies.