



Nutritional Management of Inflammatory Bowel Disease: Exclusive Enteral Nutrition Beyond Paediatrics

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Abstract

Exclusive enteral nutrition is first-line induction therapy for paediatric Crohn's disease and is not offered as sole primary therapy to most adults. The pooled evidence explains why, and also complicates the explanation. Across eight trials in 223 participants, remission on enteral nutrition was 50 per cent against 72 per cent on corticosteroids, a risk ratio of 0.77 (95% CI 0.58 to 1.03) with substantial heterogeneity. Splitting by age reverses the direction: adults 45 against 73 per cent, giving 0.65 (0.52 to 0.82), and children 83 against 61 per cent, giving 1.35 (0.92 to 1.97). The complication is what happens when withdrawals for tube intolerance and unpalatable formula are removed. On per-protocol analysis the adult deficit narrows to 0.82 (0.70 to 0.95) and the paediatric advantage becomes significant at 1.43 (1.03 to 1.97). Adults were nearly three times more likely to withdraw for adverse events, at 2.95 (1.02 to 8.48), while adverse events themselves did not differ. The adult result is therefore consistent with a tolerability problem rather than a different biology, and no trial has separated the two. Every estimate in the review is rated very low quality.

Keywords: Crohn's disease; Exclusive enteral nutrition; Corticosteroids; Adherence; Evidence quality

Introduction

Exclusive enteral nutrition, in which all nourishment is taken as a liquid formula for a defined induction period, occupies an unusual position in gastroenterology. In children with active Crohn's disease it is recommended as first-line induction therapy [1,2]. In adults with the same disease it is not offered as sole primary therapy in most settings, and corticosteroids are preferred [1,3].

The conventional explanation is that adults do worse on it. The pooled data support that statement as written, but the same analysis offers a second explanation that is difficult to distinguish from the first, and the two carry different implications for practice [3,4].

This review examines what the randomised evidence shows by age group, what happens to that difference when

non-adherence is accounted for, and what has not been tested.

Objective

This review sets out to establish four things from the published literature. First, what the pooled comparison against corticosteroids shows overall. Second, how the result differs between adults and children. Third, how much of the adult deficit survives an analysis restricted to those who completed the intervention. And fourth, what the quality of the underlying evidence permits anyone to conclude.

Literature Review

What the pooled comparison shows: A systematic review pooled eight trials with 223 participants comparing enteral nutrition against corticosteroids for inducing remission in active Crohn's disease [3]. On intention to treat, 50 per cent (111 of 223) entered remission on enteral nutrition against 72 per cent (133 of 186) on steroids, a risk ratio of 0.77 (95% CI 0.58 to 1.03), with statistically significant heterogeneity at an I-squared of 67 per cent [3]. The overall estimate therefore does not exclude equivalence, and the heterogeneity is the signal that something inside the pooled group differs [3].

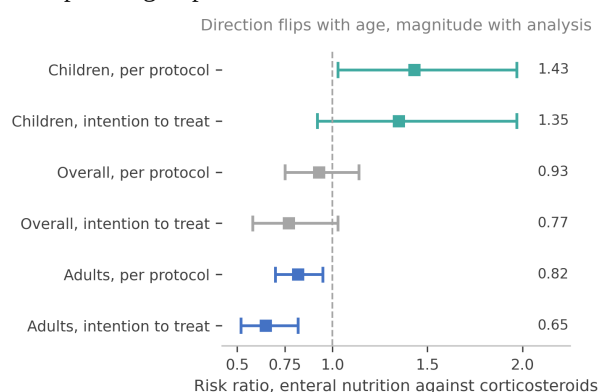


Figure 1: Remission on enteral nutrition against corticosteroids, by group and analysis [3]

Age reverses the direction: Subgroup analysis by age found a significant difference favouring steroids in adults but not in children [3]. Among adults, 45 per cent (87 of 194) entered remission on enteral nutrition against 73 per cent (116 of 158) on steroids, a risk ratio of 0.65 (0.52 to 0.82) with heterogeneity falling to 36 per cent [3]. Among children, 83 per cent (24 of 29) against 61 per cent (17 of 28) gave 1.35 (0.92 to 1.97), heterogeneity 14 per cent [3]. Splitting the pool resolved most of the heterogeneity, which is what one expects when a subgroup boundary corresponds to something real [3].

Table 1: Remission rates and risk ratios as published, all rated very low quality [3]

Analysis and group	Enteral	Steroids	Risk ratio
ITT, overall	50%	72%	0.77 (0.58-1.03) [3]
ITT, adults	45%	73%	0.65 (0.52-0.82) [3]
ITT, children	83%	61%	1.35 (0.92-1.97) [3]
Per protocol, overall	—	—	0.93 (0.75-1.14) [3]
Per protocol, adults	58%	73%	0.82 (0.70-0.95) [3]
Per protocol, children	89%	61%	1.43 (1.03-1.97) [3]

The honest complication: Treatment failures in these trials were frequently not failures of the intervention but refusals of it, with dropouts attributed to poor acceptance of a nasogastric tube and unpalatable formulations [3]. When a per-protocol analysis accounted for those withdrawals, the overall difference disappeared at 0.93 (0.75 to 1.14), the adult deficit narrowed to 0.82 (0.70 to 0.95), and the paediatric advantage crossed into

significance at 1.43 (1.03 to 1.97) [3]. The adult numerator did not change; the denominator fell from 194 to 149, moving the rate from 45 to 58 per cent (Figure 2) [3].

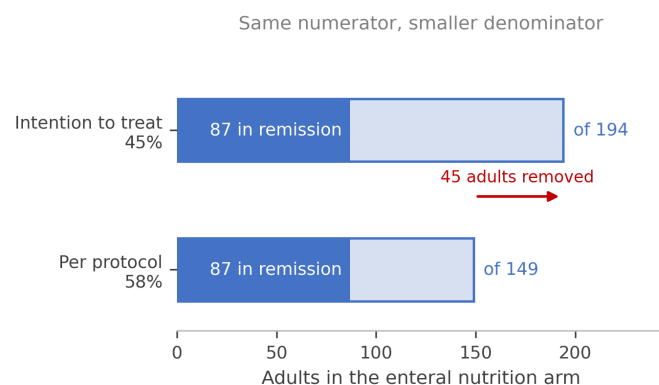


Figure 2: What per-protocol analysis changes in the adult arm [3]

Tolerating it, not its safety: Adverse events did not differ between enteral nutrition and steroids, at a risk ratio of 1.39 (0.62 to 3.11) [3]. Withdrawals attributable to adverse events did, at 2.95 (1.02 to 8.48), with events in the enteral group including heartburn, flatulence and diarrhoea [3]. That pairing is informative: the intervention is not more harmful, it is harder to stay on (Figure 4) [3]. A treatment whose measured disadvantage is concentrated in withdrawal rather than in harm or in failure among completers is describing an adherence problem [3,4].

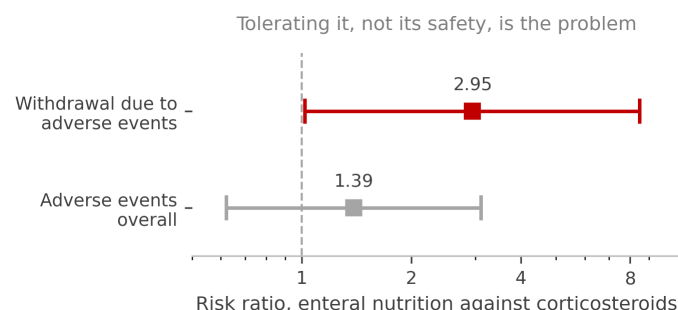


Figure 4: Adverse events and withdrawals attributable to them [3]

Two readings of the same gap: The adult deficit is compatible with two accounts. Adults may respond less well to the same intervention, or adults may be less able to complete it, with the observed gap arising from the difference in completion. The per-protocol result is consistent with the second and does not establish it, because excluding withdrawals breaks randomisation and the completers may differ from the withdrawers in ways that also predict remission [3]. No trial in the review was designed to separate the two, and the review's own recommendation was that further research is required to confirm the superiority of corticosteroids over enteral nutrition in adults (Figure 6) [3].

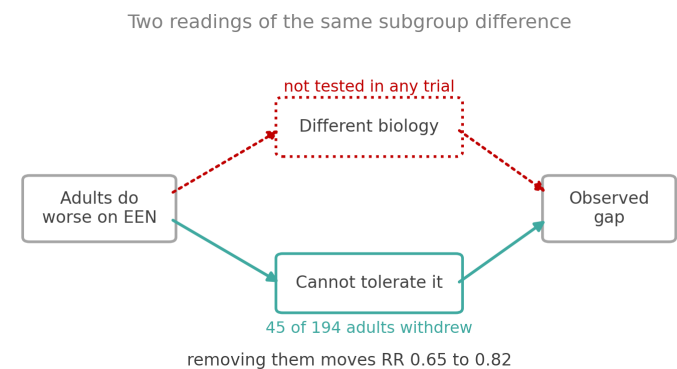


Figure 6: Two accounts of the adult deficit, one of them untested [3]

How much the paediatric result rests on: The paediatric subgroup comprised 29 children on enteral nutrition and 28 on steroids, 57 patients in total, against 352 adults across the two arms [3]. The recommendation that has reshaped paediatric practice therefore rests on a smaller randomised base than the recommendation it displaced, and its confidence interval on intention to treat includes no effect (Figure 3) [1,3]. That is not an argument against the practice, which has other support including growth and steroid avoidance, but it is a reason not to describe the paediatric evidence as strong [1,2,3].

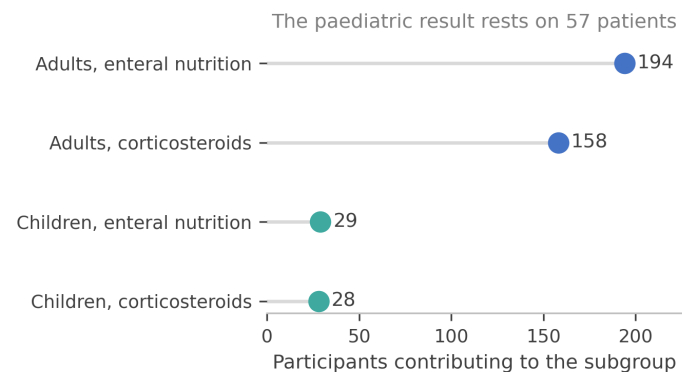


Figure 3: Participants contributing to each age subgroup [3]

Formula composition does not explain it: A separate pooled analysis of eleven trials in 378 adults and children found no difference between elemental and non-elemental feeds, with 64 per cent (134 of 210) entering remission against 62 per cent (105 of 168), a risk ratio of 1.02 (0.88 to 1.18) and no detectable heterogeneity [3]. Adverse events and withdrawals also did not differ between formula types, at 1.00 (0.63 to 1.60) and 1.29 (0.80 to 2.09) [3]. Analyses by fat content found no difference between higher and lower fat formulas at 1.03 (0.85 to 1.26), though very low fat and very low long-chain triglyceride content showed higher remission rates [3]. The practical implication is that palatability can be optimised without an efficacy penalty, since composition is not carrying the effect [3].

What the quality rating permits: Every estimate cited above is rated very low quality under the review's own appraisal (Figure 5) [3]. That rating applies equally to the adult result used to withhold the therapy and to the paediatric result used to recommend it, which is an asymmetry in how the same evidence is treated rather than in the evidence itself [1,3]. Very low

quality means the true effect may differ substantially from the estimate, so neither the adult nor the paediatric figure should be quoted as a settled quantity [3,5].

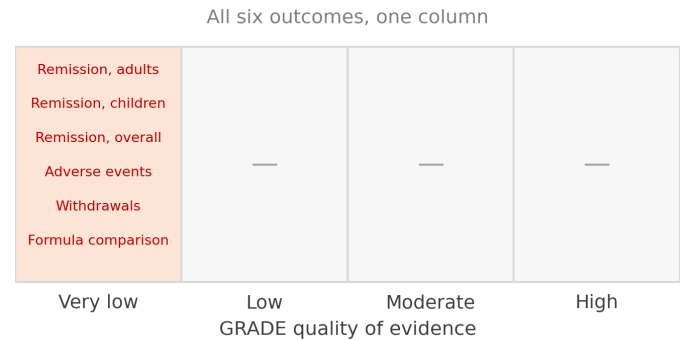


Figure 5: Quality rating of every pooled outcome in the review [3]

Table 2: What the pooled evidence answers and how firmly [3]

Question	Status in the reviewed evidence
Do adults do worse on ITT?	Yes, RR 0.65 (0.52-0.82) [3]
Does the deficit survive per protocol?	Narrows to 0.82 (0.70-0.95) [3]
Is it more harmful than steroids?	No difference, 1.39 (0.62-3.11) [3]
Is it harder to stay on?	Yes, 2.95 (1.02-8.48) [3]
Does formula type matter?	No, 1.02 (0.88-1.18) [3]
Is any of it high quality?	No, all very low [3]

Guidance and the adult gap: Society guidance recommends enteral nutrition as first-line induction in children and does not recommend it as sole primary therapy for most adults, while noting it may be considered where steroids are to be avoided or where a patient can comply [1,2,6]. The reviewed evidence supports that division of practice, and the review authors added that adults who can comply with tube feeding or find the formulations palatable, or in whom steroid effects are better avoided, are candidates for it [3]. The guidance is therefore narrower than a reading of the adult risk ratio alone would suggest [1,3,6].

Where the mechanism argument sits: Interest in enteral nutrition has been sustained by work on how it acts, including effects on the intestinal microbial community and on mucosal healing, and by food-based regimens designed to reproduce its effects without the formula [7,8,9]. Those lines of work address plausibility and acceptability rather than the adult efficacy question, and they do not alter the pooled estimates reported here [3,7]. A food-based approach that removes the palatability obstacle would, if it worked, test the tolerability account directly, which is the reason it matters to the argument of this review [8,9].

Table 3: Why single figures from this literature mislead

Source of variation	Consequence for comparison
Analysis population	RR 0.65 or 0.82 in adults [3]
Age subgroup	Direction of effect reverses [3]
Withdrawal handling	Drives the overall estimate [3]

Quality rating	Very low for every outcome [3]
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Where the paediatric position came from: Consensus guidance for children with Crohn’s disease places exclusive enteral nutrition alongside corticosteroids as a first-line induction option, and systematic review of the paediatric literature supports that placement [11,33]. The individual trials underlying the paediatric subgroup are small and were conducted across several decades and formulations [12,13,14]. One compared a polymeric diet directly with corticosteroids in children and reported mucosal outcomes as well as clinical ones, which is the comparison most often cited when the paediatric preference is justified [12,13]. The adult trials in the same pooled analysis used different formulations, different delivery routes and different remission definitions [15,16,17].

Why adults withdraw: The reasons recorded for withdrawal in the enteral arms were unpalatability of the formula and intolerance of the nasogastric tube, not clinical deterioration [3]. Reviews of adherence in this setting identify the same determinants and note that they are properties of the delivery rather than of the therapy [18,19]. That distinction is what makes the adult result difficult to read as a biological finding: a treatment that works when taken and is frequently not taken produces a low intention-to-treat estimate without any difference in mechanism [3,18,19].

Attempts to make it tolerable: Partial enteral nutrition combined with a restricted table diet has been studied as a way to retain some of the effect while reducing the burden, and food-based regimens designed to reproduce the exclusion properties of formula have been developed on the same reasoning [21,28]. These are responses to the adherence problem rather than to any doubt about the underlying effect, and they change the intervention enough that their results do not transfer back to the exclusive regimen [21,28].

The adult literature outside randomised trials: Cohort and observational work in adults reports use in complicated disease, in stricturing and fistulating presentations, and as a bridge to surgery, generally with more favourable results than the randomised comparison against corticosteroids [20,22,23,30]. Those series select patients who accepted and completed the regimen, so they describe what the therapy achieves in adherent adults rather than what it achieves on assignment [22,23]. Read that way the two literatures are compatible: the pooled trial estimate answers a question about assignment and the cohorts answer one about completion [3,23].

The perioperative case is different: Use before surgery has been examined as a way to improve nutritional state and reduce postoperative complications rather than to induce remission, and surgical guidance addresses it in that role [24,25]. The endpoint is not remission, the duration is defined by the operating date rather than by response, and adherence is easier to sustain over a

short fixed course [24,25]. This is the adult indication with the least dependence on the disputed induction evidence [24,25].

What the mechanism work shows: Exclusive enteral nutrition produces extensive change in the intestinal microbial community and in markers of immune regulation, and these have been characterised in paediatric cohorts [26,27]. The direction of compositional change is not what would be predicted from a diet regarded as healthy, which is one reason the mechanism is not straightforwardly attributable to improved nutrition [26,27,28]. Meta-analysis of mucosal healing alongside microbiota signatures reports more favourable mucosal outcomes with enteral nutrition than with steroids in children, on an objective endpoint rather than a symptom score [29].

What the adult guidance says: European clinical nutrition guidance for inflammatory bowel disease does not recommend exclusive enteral nutrition as first-line induction in adults and positions it for patients in whom corticosteroids are unsuitable, declined or poorly tolerated [31]. National gastroenterology guidance takes a similar position [32]. Critical appraisals of the adult evidence reach the same place by a different route, arguing that the intention-to-treat estimate understates efficacy while correctly describing effectiveness as delivered [34]. Guidance and appraisal therefore agree on the recommendation while disagreeing about what the number means [31,32,34].

Beyond induction: Enteral nutrition has also been examined for maintaining remission rather than inducing it, and that literature is separate, smaller and similarly limited by tolerance over longer periods [10]. Results from induction trials should not be carried across to maintenance, since the duration over which adherence must hold differs by an order of magnitude [10,18].

Method

This is a narrative review of published literature. Sources were assembled by searching the indexed literature for randomised trials, systematic reviews and society guidance concerning exclusive enteral nutrition as induction therapy in Crohn’s disease, giving precedence to pooled randomised evidence reporting results separately by age [3].

Effect estimates are reproduced as their authors published them, with the interval and the quality rating attached. Where intention-to-treat and per-protocol analyses of the same comparison differ, both are given, because the difference between them is the subject of this review rather than an inconvenience in it [3].

No new patient data were collected and no search protocol was registered, so this is not a systematic review. Induction regimens are described as the interventions the trials tested, not as recommendations for any individual.

Concluding Remarks

The statement that adults respond less well to exclusive enteral nutrition is supported on intention to treat and weakens considerably when non-adherence is accounted for. Withdrawal for adverse events was almost three times more common while adverse events themselves were not, which locates the adult disadvantage in staying on the treatment rather than in the treatment failing.

That distinction has a practical consequence. If the adult gap is biological, formula and delivery improvements will not close it. If it is a tolerability gap, they may. The finding that formula composition does not affect remission rates means palatability can be pursued without an efficacy cost, which makes the question worth resolving rather than merely interesting.

Resolving it requires a trial that removes the adherence obstacle rather than adjusting for it after the fact, and that reports adults separately with a clinical endpoint. Until then the defensible position is the one the guidance already takes, which offers the therapy to adults able and willing to complete it while not relying on it as sole primary therapy for the rest.

Study Limitations

The pooled adult and paediatric subgroups are small, and the paediatric estimate rests on 57 patients. Every outcome is rated very low quality, so the point estimates should not be treated as stable. Per-protocol analysis breaks randomisation and its results are presented here as a comparison rather than as an unbiased estimate. Trials span several decades, during which induction alternatives and disease classification both changed, and the reviewed evidence concerns Crohn's disease rather than inflammatory bowel disease as a whole.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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