Interventions for growth failure in childhood Crohn's disease (Review)

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[Intervention Review]

Interventions for growth failure in childhood Crohn's disease

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ABSTRACT

Background

Crohn's disease in childhood is a chronic relapsing condition. Fifteen to forty per cent of children with Crohn's disease have growth retardation (Griffiths 1993a). Some treatment modalities including corticosteroids have been implicated in growth failure but it is thought mainly to be secondary to uncontrolled disease activity (Motil 1993; Markowitz 1993). Growth is fundamental to the practice of pediatrics, so by taking growth as the primary outcome measure we address issues important to both patients, their families and pediatricians.

Objectives

To evaluate the effectiveness of the different modalities available for the treatment of childhood Crohn's disease with regard to the reversal of growth failure and the promotion of normal growth.

Search methods

Searches were made of the following databases using the Collaborative Review Group Search Strategy: EMBASE (1984-2004), MEDLINE (1966-2004), The Cochrane Central Register of Controlled Trials, The Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialized Trials Register and the Science Citation Index. Abstracts from the major gastrointestinal research meetings and references from published articles were also reviewed.

Selection criteria

Randomized controlled trials pertaining to children less than 18 years of age with Crohn's disease were selected. Those with growth as an outcome measure were included in the review.

Data collection and analysis

Data extraction and assessment of the methodological quality of each trial was independently reviewed by two reviewers. Only one good quality randomized controlled trial was included in the review and therefore no statistical analysis was possible.

Main results

Three randomized controlled trials were identified. One was of good methodological quality (Markowitz 2000). This study looked at the use of 6-mercaptopurine (6-MP) as a steroid sparing agent. No difference in linear growth was observed between the intervention and placebo groups, although the total steroid dose received over the 18 month follow up period was reduced in the group receiving 6-MP. The two remaining randomized controlled trials (Sanderson 1987; Thomas 1993a) consider the use of enteral feeding versus corticosteroids for induction of remission, with height velocity standard deviation score at 6 months as an outcome measure. Although of less rigorous methodological quality, the results of these studies are discussed in detail in the review. In both studies height velocity standard deviation scores were significantly increased in the enteral feeding group compared with the corticosteroid group.

Authors' conclusions

In addition to these randomized controlled trials, a body of lower quality evidence does exist relevant to two other important interventions; the use of supplemental enteral nutrition (Morin 1980; Belli 1988; Israel 1995) and the judicious use of surgical interventions in pre-pubertal children with refractory disease (Alperstein 1985; Lipson 1990; McLain 1990). Newer treatments, such as infliximab, are now becoming more widely used and may offer advantages in promoting growth. These effects are as yet unstudied. This review highlights the need for large, multi centre studies of the different treatment options in paediatric Crohn's disease and the importance of standardised measurements of growth, such as height velocity standard deviation scores and height standard deviation scores as outcome measures.

PLAIN LANGUAGE SUMMARY

Interventions for growth failure in childhood Crohn's disease

Growth failure occurs in 15-40% of children with Crohn's disease. Growth in affected children is influenced by the disease process itself and by some treatments. Management in children differs from that in adults because of the required emphasis on achieving optimum growth and pubertal development. The aim of this review was to evaluate the effectiveness of various treatments for growth failure in childhood Crohn's disease. Three randomized controlled trials were identified. One trial did not show any benefit for linear growth with 6-mercaptopurine treatment compared to placebo among children being treated with steroids. The other two trials looked at nutritional treatment (elemental feedings) versus steroids (prednisolone). Both trials showed a statistically significant benefit for height velocity standard deviation scores with nutritional treatment. However, these results need to be confirmed by large, multi-centre, randomized controlled trials of therapeutic interventions in pre-pubertal children with Crohn's disease. These trials should use growth as an outcome measure. In conclusion, more research is needed to identify effective treatments for growth failure in childhood Crohn's disease.

BACKGROUND

Crohn's disease in childhood is a chronic relapsing condition for which growth is an important measure of disease severity and can be used to monitor the success of medical treatments and nutritional or surgical interventions. Growth is fundamental to the practice of pediatrics, so by taking growth as the primary outcome we address core issues that are important to, both patients, their families and pediatricians.

Growth failure affects 15-40% of children with Crohn's disease (Griffiths 1993a; Motil 1993). Variation in the reported prevalence of growth failure may be due to the study population (population based versus tertiary referral centre), definition of growth failure and age of children included in study. One small study showed these children did achieve normal adult height (Ferguson 1994) but other work has suggested that up to 25% of patients will ultimately not achieve their full adult growth potential (Hildebrand 1994; Buller 2000). Growth failure is at least twice as common in Crohn's disease compared to ulcerative colitis. This is most likely to be a consequence of the disease process rather than the unwanted effects of therapy (Markowitz 1993; Motil 1993).

Poor nutrition and malabsorption were thought to be the major causes of growth failure in Crohn's disease. We know from earlier work that children with active Crohn's disease have low serum insulin-like growth factor I (IGF-I) levels. IGF-I is a polypeptide which acts as a stimulus to growth by mediating the anabolic ef-

fects of growth hormone. However, levels of growth hormone itself are not suppressed (Thomas 1993b; Akobeng 2002; Beattie 1998; Kirschner 1986). There is now evidence that the inflammatory process itself is also responsible for poor growth via direct suppression of IGF-I at the hepatocyte level. Inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are increased in Crohn's disease and have been shown to suppress IGF-I concentrations in animal models allowing for the confounding effect of nutrition (Murch 1991; De Benedetti 1997; Ballinger 2000). Treatments aimed at reversing growth failure need to address nutrition and also target the underlying inflammatory process.

Definitions of growth failure often used include: "height below the third percentile", "velocity of linear growth and of weight gain below the third percentile", "bone age retarded by 2 years" (Belli 1988) and "height velocity less than third percentile for age and bone age greater than 2 standard deviations below chronological age" (Polk 1992) and "no signs of puberty" (Morin 1980). Outcome measures of growth can also vary between studies, with some papers comparing change in height standard deviation score (SDS) or Z score, whilst others look at change in height velocity. Pubertal staging of children is also very important as declining height velocities may be a reflection of post-pubertal status and not disease activity. Any intervention to reverse growth failure should be initiated well before completion of puberty. Tanner staging (1-5) should be quoted for all children included in any analysis of growth failure (Walker-Smith 1996).

Quality of life issues are becoming increasingly recognized as important outcome measures (Akobeng 1999). In pediatrics, growth is integral to quality of life as growth failure and developmental delay can have devastating psychological consequences for children. This is especially pertinent to adolescents who make up a large percentage of pediatric Crohn's disease patients.

The need to promote growth and development has long been recognised in pediatric Crohn's disease and many studies have looked at growth as an outcome measure, albeit as a secondary outcome. Many therapies have been shown to be effective in reducing inflammatory markers, symptomatology or the Pediatric Crohn's Disease Activity Index (Hyams 1991) with variable effectiveness on reversal of growth failure.

Potential interventions

Medical interventions:

One of the main stays of medical treatment for Crohn's disease has been the use of corticosteroids, the adverse effects of which include inhibition of growth. Studies on the use of steroids have commented on this undesirable effect whilst also commenting on their efficacy in lowering disease activity. However, growth suppression secondary to sub-optimal control of disease may be more important for growth failure than the adverse effects of corticosteroid usage (Motil 1993).

Traditionally, the use of the immunosuppressive azathioprine and it's analogues, 6-mercaptopurine and thioguanine, has been reserved for severe refractory disease but more recent studies have shown early azathioprine usage can prevent relapse and can be used as a steroid sparing agent (Markowitz 2000). Pooled adult data provides an odds ratio of 2.16 (95% CI 1.35 - 3.47) for maintenance of remission with azathioprine (Pearson 1998). Theoretically, a longer period of remission combined with decreased steroid use should have a beneficial effect on growth, although this has not been prospectively studied. Markowitz 2000 did demonstrate a steroid sparing effect in a pediatric population, with significant improvement in the rate of remission. However, linear growth did not differ over the follow-up period.

5-ASA compounds are widely used in maintenance therapy in Crohn's disease but with little evidence supporting their use (Akobeng 2005). There is much stronger evidence for their efficacy in ulcerative colitis (Sutherland 2006). Their role in promotion of growth is, therefore, probably negligible (Griffiths 1993b).

A variety of immuno modulating agents such as cyclosporine A, tacrolimus, infliximab, mycophenolate, methotrexate and thalidomide are currently in use in childhood Crohn's disease. Their use has usually been confined to patients with refractory disease.

More recently, the use of infliximab, a chimeric monoclonal antibody to TNF-α has become accepted practice in the management of refractory disease. Studies have shown good efficacy although more long term follow-up data are not yet available (Hyams 2000; Kugathasan 2000; Stephens 2003; Baldassano 2003). Small amounts of growth data are now emerging with encouraging results (Cezard 2003).

Nutritional interventions:

There has been much work on the role of enteral nutrition for the treatment of Crohn's disease in children. There have been a number of small studies which, although being underpowered to detect a difference in efficacy in acute disease compared with corticosteroids, do cite the added benefit of growth promotion (Sanderson 1987; Thomas 1993a; Papadopoulou 1995). A recent meta-analysis shows that enteral nutrition is less likely than corticosteroids to induce remission with a pooled odds ratio of 0.31 (95% CI 0.17 - 0.52), although these data are mainly from studies in adults (Zachos 2007). Enteral feeding has also been shown to improve growth in Crohn's disease after remission has been induced (Belli 1988; Wilschanski 1996). In the case of non-acceptance of enteral feeding, administration of parenteral nutrition has been shown to be effective in improving nutrition and growth (Keller 1992; Strobel 1979).

Hormonal Interventions

Growth Hormone:

Interest in growth hormone as a possible treatment for Crohn's disease in childhood has been generated by work with adult patients. Slonim 2000 randomized patients to receive growth hormone or placebo over a 16-week course, with a significant improvement in the Crohn's disease activity index seen in the intervention group. The mechanism of action is thought to be enhancement of the benefit of supplemental protein on the gut by increase in the uptake of amino acids and electrolytes, decrease in intestinal permeability and increased protein synthesis.

Testosterone:

Testosterone has been used by some in boys where there is extreme delay in puberty, although there are no randomized clinical trials of this intervention (Walker-Smith 1996).

Surgical interventions:

Correct timing of surgical interventions can also have extremely important consequences for growth promotion and pubertal development (Alperstein 1985; Davies 1990; Evans 1991; Griffiths 1991).

Although growth failure is common in pediatric Crohn's disease and many studies have commented on potential benefits of therapy on growth this approach does not appear to have been reviewed systematically. The aim of this review is to examine the evidence from randomized controlled trials of medical, nutritional and surgical interventions for the treatment of growth failure in childhood Crohn's disease.

OBJECTIVES

To evaluate the effectiveness of the different modalities for the treatment of growth failure and the promotion of normal growth in childhood Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials of any medical, nutritional or surgical intervention in childhood Crohn's disease with growth as a primary or secondary outcome measure. Studies published as abstracts only were excluded from the analysis.

Types of participants

Patients aged less than 18 years with Crohn's disease.

Types of interventions

Any recognized medical, nutritional or surgical intervention in Crohn's disease in children.

Types of outcome measures

The reversal of growth failure at any point in the course of the disease process. Growth failure will be as defined by the authors provided one of the previously mentioned definitions is applied or other appropriately used definitions are given. Reversal of growth failure will be defined as a return to normal height velocity or exhibition of catch-up growth.

Search methods for identification of studies

See: Collaborative Review Group Search Strategy
A. Electronic searching
The following electronic databases were searched for relevant studies:
1. EMBASE (1984-2004)
2. MEDLINE (1966-2004)
3. The Cochrane Central Register of Controlled Trials
4. The Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialized Trials Register
5. Science Citation Index
EMBASE and MEDLINE on OVID were searched using the following search strategy:
#1 randomized controlled trial.pt
#2 controlled clinical trial.pt
#3 clinical trial.pt
#4 research design
#5 explode "Randomized-Controlled-Trial/all subheadings"
#6 explode "Random-Allocation/all subheadings"
#7 explode "Double-Blind-Method/all subheadings"
#8 explode "Single-Blind-Method/all subheadings"
#9 explode "clinical-trial/all subheadings"
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 placebo$
#12 placebo$.ti
#13 placebo$.ab
#14 random$
#15 random$.ti
#16 random$.ab
#17 volunteer$
#18 volunteer$.ti
#19 volunteer$.ab
#20 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19

#21 singl$ or doubl$ or trebl$ or tripl$
#22 blind$ or mask$
#23 #21 or #22
#24 #21 and #22
#25 #10 or #20 or #24
#26 Limit #25 to human
#27 inflammatory bowel disease.ti
#28 inflammatory bowel disease.ab
#29 inflammatory bowel disease.tw
#30 explode "Inflammatory-Bowel-Disease/all subheadings"
#31 crohn$.ti
#32 crohn$.ab
#33 crohn$.tw
#34 explode "Crohn-Disease/all subheadings"
#35 explode "Colitis-Ulcerative/all subheadings"
#36 colitis not ischaemic
#37 colitis not infectious
#38 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or # 35 or #36 or #37
#39 #26 and #38
#40 Limit #39 to ((age=adolescent) or (age=child) or (age=child-preschool) or (age=infant) or (age=infant-newborn))
#41 growth
#42 explode "Growth-/all subheadings or Growth-Disorders/all subheadings"
#43 height
#44 explode "Body-Height/all subheadings"
#45 weight
#46 explode "Body-Weight/all subheadings"
#47 short$
#48 "short stature"
#49 thrive
#50 failure to thrive
#51 explode "Failure-To-Thrive/all subheadings"
#52 stunt$
#53 nutrit$
#54 explode "Nutrition-/all subheadings or Nutrition-Disorders/all subheadings or Enteral-Nutrition/all subheadings or Parenteral-Nutrition/all subheadings or Parenteral-Nutrition-Total/all subheadings"
#55 #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or # 49 or #55 or #51 or #52 or #53 or #54
#56 #40 and #55

Similar search strategies, modified appropriately, were used to search the other electronic databases listed above.

B. Reference Searching

The references of all identified studies were inspected for further randomized controlled trials.

C. Meeting Abstracts

A manual search of abstracts presented at major gastroenterology meetings and published in the following journals between 1990 and 2004 was performed to identify unpublished studies:

1. Gastroenterology (American Gastroenterological Association);
2. American Journal of Gastroenterology (American College of Gastroenterology);
3. Canadian Journal of Gastroenterology (Canadian Association of Gastroenterology);
4. Journal of Pediatric Gastroenterology and Nutrition (European Society of Paediatric Gastroenterology, Hepatology and Nutrition), (North American Society of Pediatric Gastroenterology, and Nutrition);
5. Gut (British Society of Gastroenterology);
6. and the Scandinavian Journal of Gastroenterology, (Nordic Gastroenterology meetings).

D. Personal Contacts

Leaders in the field were contacted to identify other studies.

Data collection and analysis

A. Selection of Trials

Two reviewers independently assessed identified studies for fulfillment of the inclusion criteria detailed above. Disagreement was resolved by consensus.

B. Quality Assessment

The methodological quality of included studies was independently assessed by two reviewers using: the scheme recommended in the Cochrane Reviewers' Handbook (Clarke 2003) and the Jadad Scale (Jadad 1998). Studies were included if they met the Cochrane Reviewers' Handbook criteria A or B and scored at least 2 points on the Jadad Scale.

C. Statistical Analysis

No statistical meta-analysis of pooled data was performed in this review as only one study of sufficient quality was identified. If in future any further randomized controlled trials are published, which meet the above criteria, the data will be analysed according to the intention-to-treat principal using the Cochrane Collaboration Review Manager software (RevMan version 4.2).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The above search strategy produced 180 non-duplicated hits. Forty-one papers were fully reviewed as they concerned either growth or nutrition or were randomized controlled trials of treatment effect. Of the 41 studies reviewed, 3 were randomized controlled trials with growth as an outcome measure (Sanderson 1987; Thomas 1993a; Markowitz 2000). One study was a good quality randomized controlled trial (Markowitz 2000) and was included

in the review. Two were not of rigorous methodological quality but are included and discussed below because they are highly relevant to the subject (Sanderson 1987; Thomas 1993a). In view of these methodological flaws, a pooled statistical analysis was not undertaken.

Risk of bias in included studies

In the Markowitz 2000 study allocation of participants to intervention or placebo was random, i.e. by the use of permuted blocks. The trial was double-blinded and allocation concealment was adequate (A). The Markowitz 2000 study was given a score of 4 on the Jadad scale. Sanderson 1987 and Thomas 1993a did not discuss the randomization process or allocation concealment (D). The authors were contacted for additional information and both studies employed appropriate methods for the randomization of patients. Both Sanderson 1987 and Thomas 1993a received a Jadad scale score of 2.

Effects of interventions

Markowitz 2000 randomized 55 children ages 13 +/- 2 years with active Crohn's disease to receive prednisone 40 mg/day plus 6-mercaptopurine (6-MP) 1.5 mg/kg/day (n = 27) or prednisone 40 mg/day and placebo (n = 28). The 6-MP dose remained unchanged for 18 months whilst the prednisone dose varied in each group according to a standardised dosing regimen depending on disease activity. The two groups were comparable in terms of age, sex, sites of disease, disease activity and enrollment (early versus late). The study was analysed on an intention-to-treat basis. The 6-MP group required significantly less steroids during the study period ($p < 0.01$), with significant improvement in days in remission ($p < 0.01$) on survival analysis. Linear growth did not differ between the two groups at the end of the 18-month study period or at 6 month intervals within this time. At 18 months the mean and standard deviation for linear growth in the intervention group was 6.8 cm (4.1) compared with 5.3 cm (4.0) in the placebo group ($p = 0.3$). However, pubertal status was not taken into account in the analysis nor were the results compared with normal growth velocities.

Thomas 1993a randomized 24 children aged less than 18 years with active Crohn's disease to receive normal diet, prednisolone 2 mg/kg/day for 2 weeks (maximum 60 mg/day), with subsequent dosage tapering depending on clinical response plus sulphasalazine 25 mg/kg or exclusive elemental feed for 4 weeks after which time normal diet was reintroduced as per a specified regimen. Twelve children were randomized to each group using sealed envelopes drawn from a box (author contacted). The characteristics (i.e. age, sex, height, weight, stunted, and wasted) of the 2 groups were compared but no comment made as to any statistically significant differences between them. Height was measured before commencing treatment and after 6 months. Height velocity standard deviation scores were calculated. The mean height velocity standard deviation score at 6 months in the enteral nutrition group was +0.32 (standard deviation = 3.32) compared with -3.1 (standard deviation = 2.8) in the steroid group ($p < 0.05$). No comment on pubertal status was made. Improvement in disease activity (increase in Lloyd-Still activity index) and duration of remission was similar in the two groups. The drop-out rate was not discussed in this paper so no comment can be made as to whether the study was analysed on an intention-to-treat basis.

Sanderson 1987 randomized 17 children aged less than 18 years with active Crohn's disease to receive either normal diet, high dose steroids, i.e. 2 IU/kg/day intra-muscular adrenocorticotrophic hormone for 5 days followed by prednisolone 2 mg/kg/day (maximum 30 mg/day) with a reducing regimen instituted after 3 weeks plus sulphasalazine 50 mg/kg/day (n = 8) or exclusive elemental feed for 6 weeks then a food reintroduction programme over 6 weeks with elemental feed being stopped completely at the end of this 12 week period (n = 9). Randomization took place by a series of sealed envelopes marked 1-20 which were opened as the next patient was diagnosed and entered into the study. The treatment allocation to each envelope was randomly generated by the researcher at the start of the study (author contacted). The characteristics (i.e. age, sex, pubertal state, disease activity, height standard deviation score, ESR, and C reactive protein or albumin concentrations) of the 2 groups at entry into the trial were statistically comparable. Two children did not complete the trial, one from each group. Height was measured on entry to the study and at 6 months. Height velocity standard deviation scores were calculated. The mean height standard deviation score at 6 months was +0.3 (standard deviation = 2.03) in the enteral nutrition group and -2.8 (standard deviation = 2.50) in the steroid group ($p < 0.05$). Results were not analysed on an intention-to-treat basis. In both groups the disease activity index (Lloyd-Still disease activity index) was significantly improved at 6 weeks
($p < 0.01$), with improvement of a similar magnitude being seen in both groups. Remission was maintained in both groups at 12 weeks at which time the enteral feed group were off treatment whereas the corticosteroid group remained on prednisolone (10 mg/kg/day). Sanderson 1987 comments that there may be confounding factors in the data such as pubertal status, disease activity, steroid dosage and energy intake.

In both the Sanderson 1987 and Thomas 1993a studies it was not possible to blind the researcher or participants to the interventions or the outcome measures because of their nature. Sanderson 1987 and Thomas 1993a used different dosage schedules for steroids and regimens for length of course of enteral feeds.

DISCUSSION

Although only the three randomized controlled trials discussed above were identified, there are other data pertaining to growth in Crohn's disease which can be extracted from cohort and case control studies.

Enteral Nutrition

A recent meta-analysis (Heuschkel 2000) looking at corticosteroids versus enteral nutrition for the treatment of acute Crohn's disease in children noted the statistically significant benefit of enteral nutrition for height velocity standard deviation scores. This outcome measure was not included in the meta-analysis because of the small number of children randomized. The studies included in the meta-analysis were of less rigorous methodological quality, mainly the studies addressed above (Sanderson 1987; Thomas 1993a) plus data from two abstracts (Seidman 1991; Seidman 1993) and a study with weight as the only outcome measure (Ruuska 1994). Two non-randomized trials were also included in the analysis (Breese 1994; Chafai 1995).

One other randomized controlled trial looking at cycles of enteral nutrition versus alternate day steroids has been published in abstract form (Seidman 1996). This study randomized 18 children to receive exclusive enteral nutrition for 4 weeks out of every 20 weeks over an 80 week study period with 19 children randomized to receive alternate day steroids (0.33 mg/kg qid). Relapse rates were improved in the enteral feed group, although this difference was not statistically significant. However, height standard deviation score was significantly improved in the enteral feed group (0.40+/-0.14 compared with -0.02+/-0.09; p = 0.02).

Papadopoulou 1995 retrospectively reviewed data on 28 children with an acute flare of Crohn's disease treated with corticosteroids using the same regimen as Thomas 1993a compared to 30 children treated with enteral nutrition. At 1 year the mean height standard deviation score for the steroid group was -0.13 compared with +0.85 for the enteral nutrition group ($p < 0.001$).

Several cohort studies and case reports have looked at the value of longer term supplementary enteral nutrition as a means of promoting growth in Crohn's disease with up to 2 years of follow up data. After 1 year Polk 1992 and Wilschanski 1996 showed significantly improved height velocities ($p < 0.001$ in both studies) for a combined group of 30 children with Crohn's disease receiving supplemental enteral nutrition compared with those receiving standard medical therapy. Belli 1988, Israel 1995 and Morin 1980 showed improved growth in case reports of children receiving long term enteral nutrition. Cosgrove 1997 and Israel 1995 also reported the advantages of gastrostomy placement in combination with supplemental feeding in childhood Crohn's disease.

Two types of enteral feed are available: elemental and polymeric. In a recent randomized controlled trial Ludvigsson 2004 found no difference in efficacy for induction of remission between the two enteral feeds, but a slight advantage with polymeric feed with respect to weight gain. Height was not studied (Ludvigsson 2004).

Parenteral Nutrition

Layden 1976 and Strobel 1979 report 18 cases of improved growth after the introduction of parenteral nutrition for growth failure in Crohn's disease, although no statistical conclusions can be drawn from these data. Parenteral nutrition in the pre-operative period improved post-operative growth for up to a year in 8 children after elective surgery (Lake 1985). However the control group were children undergoing emergency surgery for obstruction, so it is difficult to draw any definite conclusions.

Steroids

Studies in other pediatric specialities show growth suppression at dosages equivalent to 4-6 mg/kg of prednisolone per day (Hyams 1988). However, as stated earlier sub-optimal disease control may be a much more powerful suppressor of growth than steroid treatment (Motil 1993). In this study 65% of 34 children prospectively followed over 3 years received oral prednisolone. When compared with the 35% who did not, there was no significant difference between short and long term measures of growth. Although a tendency to an inverse relationship between length of steroid use and height velocity was noted, this was a weak association ($r = -0.16$). Griffiths 1993a retrospectively reviewed growth data on 100 children with Crohn's disease and concluded that, after adjusting for severity of symptoms, steroid administration was not a significant predictor of height velocity. Kundhal 2001 looked at budesonide as an alternative steroid preparation and failed to show any significant benefit for growth in the 32 children studied. A correlation between poor disease control and poor growth was also noted.

Surgery

A number a retrospective reviews appear in the literature concerning the timing of surgery and the beneficial effect of surgery on growth. Alperstein 1985 reviewed the effect of surgery on 26 children with Crohn's disease, of whom 14 were pre-pubertal (i.e. Tanner stage 1, 13 of those having a growth velocity of less than 5 cm/year). Eleven of these 13 children achieved an increase in height velocity after surgery, with 9 showing a height velocity of greater than 5 cm/year. Davies 1990 noted a similar trend to increased height velocity in the first year after surgery for 40 children with Crohn's disease. These children were older, having a mean age of at least 12.1 years at the time of operation. McLain 1990 showed increased growth in 19 children after surgical resection, with half of the pubertal children (7/12) also seeing some benefit. Lipson 1990 and Griffiths 1991 showed good benefit for growth in pre pubertal children.

Infliximab

In the last 5 years infliximab has become a widely accepted treatment for children with severe, refractory Crohn's, especially fistulizing disease. Several studies have reported good efficacy but it's use is not without potential serious adverse effects including anaphylaxis and long-term data are not yet available. One study

so far has looked at growth as an outcome measure. Cezard 2003 prospectively followed 21 children with severe Crohn's disease. Growth data were reported on the 10 pre-pubertal children within the study group. Height standard deviation scores were recorded 1 year prior the treatment (mean -0.45) and after treatment (mean +0.5; p = 0.004). These results are encouraging, especially in this severely ill group where growth may be more affected. Further studies, with greater numbers of patients, are needed to establish the size of the effect.

AUTHORS' CONCLUSIONS

Implications for practice

Although there are no good quality randomized controlled trials pertaining to growth in childhood Crohn's disease, a body of low quality evidence does exist relevant to two very important interventions; the use of enteral nutrition and the judicious use of surgical interventions in pre pubertal children with refractory disease. Although conflicting evidence exists as to the effectiveness of enteral nutrition compared to corticosteroids for inducing remission, low quality evidence suggests benefit of the nutritional approach in the pediatric population. There is no hard evidence on which to make recommendations for clinical practice.

Implications for research

This review highlights the need for large, multi centre, randomized controlled trials in this important area of Crohn's disease, using growth as an outcome measure. Of note there are no randomized controlled trials of enteral nutrition versus placebo. A definitive study looking at enteral nutrition versus corticosteroids in pediatric practice would be important. Further trials comparing supplemental nutrition with conventional nutritional advice in steroid treated patients would also be of interest. Where enteral feeds and corticosteroids are used there is great variation in length of treatment courses, type of feed used and dose of corticosteroids because of a lack good quality evidence on which to base practice. Further studies are needed to establish guidelines and to look at the effect of the newer immuno-modulating and biological agents, which are now being used in childhood Crohn's disease. Future trials should employ appropriate assessment of linear growth such as height standard deviation scores and height velocity standard deviation scores.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Markowitz 2000

Methods	Double-blind, randomized, placebo controlled, intention-to-treat basis
Participants	55 children age < 18 years with Crohn's disease
Interventions	6-mercaptopurine and prednisone verses placebo and prednisone
Outcomes	Cumulative prednisone dose, length of remission and linear growth
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sanderson 1987

Methods	Randomized controlled trial
Participants	15 children age < 18 with Crohn's disease
Interventions	Elemental diet verses high dose steroids and sulphasalazine
Outcomes	Height velocity standard deviation score
Notes	Dose of steroid - 2 IU/kg/day intra-muscular adrenocorticotrophic hormone for 5 days and then prednisolone 2 mg/kg/day (max 30 mg/day), sulphasalazine 50 mg/kg/day

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Thomas 1993a

Methods	Randomized controlled trial
Participants	24 children age < 18 with Crohn's disease
Interventions	Elemental diet verses prednisolone and sulphasalazine

Thomas 1993a (*Continued*)

Outcomes	Height velocity standard deviation score
Notes	Dose of prednisolone 2 mg/kg/day (max 60 mg/day), tapered after 2 weeks depending on response plus sulphasalazine 25 mg/kg/day

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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

Study	Reason for exclusion
Akobeng 2000	Small amount of data pertaining to weight only
Akobeng 2002	Only 4 week follow-up, unable to comment on growth
Alperstein 1985	Retrospective review
Baldassano 2003	No data pertaining to height
Belli 1988	Cohort series
Campieri 1997	Adult data only
Cezard 2003	Cohort study
Davies 1990	Retrospective review
Escher 2004	No data pertaining to height
Gassull 2002	Adult data only
Gaya 1999	Descriptive data only
Gorard 1993	Adult data only
Griffiths 1993b	No data pertaining to height
Israel 1995	Not a randomized controlled trial
Khoshoo 1996	Data on weight only

(*Continued*)

Kugathasan 2000	No growth data
Kundhal 2001	Retrospective data
Kundhal 2003	No growth data
Lake 1985	Cohort series
Layden 1976	Case report
Levine 2003	No data pertaining to height
Lipson 1990	Cohort series
Ludvigsson 2004	No data pertaining to height
Mahdi 1996	No growth data
McLain 1990	Retrospective review
Morin 1980	Case reports
Motil 1993	Cohort series
Nicholls 1994	No growth data
Papadopoulou 1995	Cohort series
Polk 1992	Case series
Royall 1995	Adult data
Ruuska 1994	Data on weight only
Seidman 1996	Abstract only
Sentongo 2000	Descriptive data only
Stober 1983	No data pertaining to height
Strobel 1979	Case series
Thomas 1993b	Same data as included study
Wilschanski 1996	Case control study
Zoli 1997	Adult data

DATA AND ANALYSES

Comparison 1. 6-mercaptopurine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Linear growth	1	55	Mean Difference (IV, Fixed, 95% CI)	1.5 [-0.64, 3.64]

Comparison 2. Elemental feed versus prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Height velocity standard deviation scores	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

WHAT'S NEW

Last assessed as up-to-date: 15 May 2005.

Date	Event	Description
17 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 3, 2005

Date	Event	Description
16 May 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Newby EA: Literature search, Critical appraisal of evidence, Author

Sawczenko A: Design of database for references

Thomas AG: Critical appraisal of evidence

Wilson D: Critical appraisal of evidence

DECLARATIONS OF INTEREST

AG Thomas is the author of a manuscript that was included in this review.

INDEX TERMS

Medical Subject Headings (MeSH)

6-Mercaptopurine [therapeutic use]; Adrenal Cortex Hormones [therapeutic use]; Antimetabolites [therapeutic use]; Crohn Disease [complications; *therapy]; Enteral Nutrition; Growth Disorders [etiology; *therapy]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans