Update on nutritional status, body composition and growth in paediatric inflammatory bowel disease

Rebecca J Hill

Rebecca J Hill, Children’s Nutrition Research Centre, Queensland Children’s Medical Research Institute, The University of Queensland, Herston, Qld 4029, Australia
Rebecca J Hill, School of Medicine, The University of Queensland, Herston, Qld 4029, Australia

Author contributions: Hill RJ was solely responsible for all facets of manuscript writing and preparation.

Supported by Hill RJ in receipt of the Reginald Ferguson Research Fellowship in Gastroenterology, The University of Queensland

Correspondence to: Rebecca J Hill, PhD, Children’s Nutrition Research Centre, Queensland Children’s Medical Research Institute, The University of Queensland, Old Milk Kitchen, Cnr Fourth and Back Rds, Herston, Qld 4029, Australia. rj.hill@uq.edu.au
Telephone: +61-7-33655351 Fax: +61-7-33464684
Received: September 27, 2013 Revised: December 2, 2013
Accepted: February 20, 2014
Published online: March 28, 2014

Abstract

Growth and nutritional status are important issues in paediatric inflammatory bowel disease (IBD). While linear growth is easy to assess, nutritional status is more complicated, with reports often compromised by the use of simple measures, such as weight and the body mass index, to assess nutritional status rather than more appropriate and sophisticated techniques to measure body composition. This review is an update on what is currently known about nutritional status as determined by body composition in paediatric IBD. Further, this review will focus on the impact of biologics on growth in paediatric IBD. Significant lean mass deficits have been reported in children with IBD compared with controls, and there is evidence these deficits persist over time. Furthermore, data imply that gender differences exist in body composition, both at diagnosis and in response to treatment. With respect to growth improvements following treatment with biologics, there are conflicting data. While some studies report enhancement of growth, others do not. The relationship between disease severity, impaired growth and the requirement for biologics needs to be considered when interpreting these data. However, key features associated with improvements in growth appear to be successful clinical response to treatment, patients in early stages of puberty, and the presence of growth failure at the onset of treatment.

Key words: Crohn’s disease; Ulcerative colitis; Lean mass; Pubertal status; Infliximab; Inflammatory bowel disease

Core tip: Assessing body composition gives a much better indication of nutritional status than measures of anthropometry, such as BMI. In children with IBD, significant and persistent deficits in lean mass, suggestive of compromised nutritional status, have been reported, both at diagnosis and following treatment. Data pertaining to body composition in response to biologics is lacking, and data concerning growth improvements is controversial. However, evidence suggests that the key components associated with linear growth improvements when treating with biologics are (1) successful clinical response to treatment; (2) patients in early stages of puberty; and (3) the presence of growth failure at the onset of treatment.

Hill RJ. Update on nutritional status, body composition and growth in paediatric inflammatory bowel disease. World J Gastroenterol 2014; 20(12): 3191-3197 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i12/3191.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i12.3191
INTRODUCTION

Treatment considerations for paediatric patients with inflammatory bowel disease (IBD) are two-fold. Firstly, to achieve optimal disease control and attain remission, and secondly, to promote growth and progression through puberty. Often, when the first consideration is achieved, the latter will follow.

Growth failure and delayed puberty have long been associated with paediatric IBD, and is more prevalent in Crohn’s disease (CD) than ulcerative colitis (UC)\(^1\). Malnutrition has long been described as a factor contributing to growth impairment. The development of malnutrition in this cohort is multifactorial, being influenced by enteric nutrient losses, suboptimum intake, malabsorption of nutrients, and increased energy needs\(^3\). However, while linear growth is straight forward to measure, and it is clear patients with CD are more prone to growth failure than UC, assessing malnutrition is more complex, with many results limited by crude measures of weight and body mass index (BMI) as proxy measures of malnutrition. Both these measures give little information about what is actually happening in the compartments of the body, and as such, increases in these parameters may not be representative of improved nutritional status.

Assessing body composition, that is, fat mass and lean mass at its most basic, gives a much better indication of nutritional status than anthropometry. With this in mind, growth and nutritional status in paediatric patients with IBD should be considered in terms of body composition, rather than simple anthropometric changes. This review is an update on what is currently known about nutritional status as determined by body composition in paediatric IBD. Further, as there have been several recent reviews about the prevalence and mechanisms of growth failure in IBD\(^1\) this review will focus on the impact of biologies on growth in paediatric IBD. Suitable research studies were identified from the literature by searching PubMed. Key words used to search included: IBD; body composition; nutritional status; growth; child; adolescent; infliximab. Relevant studies were also identified from the reference lists of search results.

NUTRITIONAL STATUS AS DETERMINED BY MEASURES OF BODY COMPOSITION

The techniques reported in the literature to measure body composition in IBD have paralleled the technical advancements in the field and become increasing more sophisticated and, therefore, accurate. Early work utilized anthropometry, such as measurements of skinfold thickness and body circumferences, which are proxy methods at best, and are less accurate than other methods like bioelectrical impedance (BIA), isotope dilution, total body potassium and dual energy X-ray absorptiometry (DXA).

**IBD compared with normative data or controls**

There is general consensus in the literature that lean mass is reduced in children with IBD compared with controls. Boot et al\(^8\) reported reduced lean mass Z-scores in a cohort of 55 children with IBD, and this reduction persisted over two years of measurement. Similarly, Sylvester et al\(^9\) also found persistence of significantly lower lean mass Z-scores over two years in patients with CD, and these remained lower than controls even after adjustment for height. Werkstetter et al\(^1\) found significantly reduced lean mass in children with well controlled IBD compared with controls, as indicated by reduced phase angle Z-scores measured by BIA. Our group\(^5\) has detailed significant reductions in body cell mass Z-scores (the metabolically active component of lean mass; adjusted for height) in patients with UC having repeated measures of total body potassium over three years. Lean mass adjusted for age and lean mass adjusted for height was shown by Burnham et al\(^8\) to be significantly lower in children with CD than controls, and in a regression model including height, age, Tanner stage and race, CD was associated with a 6% reduction in lean mass. Further, concurrent increases in fat and lean mass were reported in control subjects, whereas no relationship was found in those with CD; that is, increases in fat mass were not associated with increases in lean in children with CD. Azcue et al\(^8\) report body composition comparisons between patients with CD, healthy controls, and patients with Anorexia Nervosa, however, the different techniques used to calculate fat and lean mass, and the potential errors associated with this, limit the interpretation of these data. They do suggest that their finding of an elevated ECW:ICW ratio in CD compared with control subjects is indicative of protein-energy malnutrition, which in turn, is representative of lean mass deficits.

Despite consensus with respect to lean mass reductions in IBD, not all studies are in agreement with respect to fat mass. Boot et al\(^8\) suggest proportional reductions in lean and fat mass, as shown by percentage body fat that did not differ significantly from zero in their combined IBD cohort. In contrast, in an all CD cohort Burnham et al\(^8\) report fat mass adjusted for age and fat mass adjusted for height was not significantly different from controls. Similarly, in 42 children with CD weight gain over a two-year period was explained by gains in fat mass\(^8\).

Several studies highlight the ineffectiveness of BMI to determine nutritional status, as compared with body composition, in this cohort. Our group\(^5\) have recently shown normal BMI Z-scores in patients with UC, where body cell mass Z-scores were significantly reduced. Sylvester et al\(^9\) found children with CD had lean Z-scores consistently below the mean of healthy controls over two years, despite increases in BMI after 1 year that made them comparable to healthy children. In the study of Thayu et al\(^11\), changes in body composition were not reflected by changes in BMI, shown by normalisation of BMI in the face of continued significant deficits in lean mass at follow-up for female patients with CD compared with controls. While easy to calculate, BMI is of little value in determining nutritional status in children with IBD.
Gender differences in body composition

Several studies have detailed gender differences in body composition in patients with IBD, and further, have shown different treatment effects with respect to influence on nutritional status between genders. Dung et al. [11] report significantly higher percentage body fat in girls with CD compared with boys, and Sentongo et al. [13] detail girls with CD have significantly higher percentage body fat (approximately 6%) than controls, while boys were not different. However, for any given age, this study found significantly reduced lean mass in both the boys and girls with CD, which was associated with disease activity.

Work by Thayu et al. [14, 15] is somewhat in disagreement with the body composition patterns described above. In contrast to the studies of Dung et al. [11] and Sentongo et al. [13], Thayu’s group studied incident CD within two weeks of diagnosis, and report body composition at diagnosis [14] and changes over time in response to treatment [15] in the same cohort. At diagnosis, girls with CD displayed a decrease in both lean and fat mass compared with controls (wasting), while boys displayed reductions in lean mass, with relative preservation of fat mass (cachexia). After adjustment for race, Tanner stage, age and fat mass for height Z-scores, deficits in lean mass remained significant in both genders compared with controls, but were more pronounced in the girls with CD compared with boys, and within the girls, in the girls diagnosed during adolescence. Interestingly, body composition was not associated with disease activity, however, there were correlations with inflammatory markers. A subset of this cohort was followed for 24-63 mo, and in boys the body composition pattern changed from cachexia to one of normalised lean mass, but excess fat mass compared with controls. In girls, wasting at baseline developed into cachexia at long term follow-up, illustrated by continued deficits in lean mass, but normalisation of fat mass compared with controls.

An important consideration when interpreting these data detailing gender differences in body composition is the differential timing of peak height velocity between girls and boys [13] and the changes in body composition that are associated. Gender differences may in part be explained by the timing of onset of disease in relation to the occurrence of peak height velocity [13], which in normal developing children, occurs earlier in girls than boys.

Effects of treatment on body composition

Data describing treatment effects of medications for IBD is somewhat confounded by disease severity. For example, disease activity was correlated with greater lean mass deficits in the study of Burnham et al. [11], and there was a trend for use of corticosteroids to be associated with lean mass reduction, which may simply be a result of increased corticosteroid use with more severe disease. The same study found mesalamine was predictive of lean mass for height Z-score less than -1.00, and the authors suggest this is indicative of upper gastrointestinal disease, which is associated with more micronutrient deficiencies, and hence, may compromise nutritional status.

Nonetheless, Thayu et al. [13] described determinants of change in body composition during follow-up of their CD cohort. Medications included corticosteroids, methotrexate, 6-mercaptopurine, azathioprine, infliximab and enteral nutrition (not exclusive). In their model of predictors, greater improvements in lean mass for height Z-scores were associated with concurrent infliximab, while greater increases in fat for height Z-scores were associated with cumulative corticosteroid dose and methotrexate. Interestingly, high dose corticosteroid therapy has been shown to significantly increase whole body protein breakdown and loss, even in the short term, in children with CD and this may influence lean body mass acquisition in the long term [6]. This potentially explains the persistent deficits in lean mass over time described by Thayu et al. [13] and Sylvester et al. [9].

Body composition in response to nutritional therapy

The early study of Lin et al. [13] combined measures of subscapular and triceps skinfold thickness, mid arm circumference, CT scanning of the thigh, and creatine excretion to investigate truncal and extremity body composition in children with both CD and UC combined. Normative data were not reported, nor were measures converted to Z-scores, but rather, their work investigated change in response to two durations of parenteral nutrition. Both short term (ST; 5 wk) and long term (LT; 10 wk) parenteral nutrition were associated with reduced disease activity and significant increases in weight, muscle mass, and truncal fat. Further, height was significantly increased at 50-d post cessation of ST nutrition and at cessation of LT, however, the relevance of this is limited as only absolute heights were given and not Z-scores (no control group). It is, therefore, unknown whether the increase in height was simply a reflection of normal growth, as opposed to increased growth, as there was no comparison group. With respect to extremity composition, increases in fat were more pronounced in the arms and increases in muscle were more pronounced in the legs, with changes more apparent with longer parenteral nutrition.

Investigating two types of exclusive enteral nutrition (EEN), Khoshoo et al. [18] also showed improved body composition and decreased disease activity. Fourteen children with CD increased weight, lean mass (BIA) and triceps skinfold thickness after both three and six weeks of EEN compared to baseline. Similarly, Azcue et al. [19] showed improvements in weight, percentage ideal body weight and absolute values of lean mass in children with CD on EEN. EEN was compared to corticosteroids and both groups significantly increased in the aforementioned parameters. In an age and Tanner stage matched subgroup of ten males, height was shown to significantly increase in the EEN group compared with the corticosteroid group. Interestingly, in both groups percentage of lean mass did not change significantly over the three months of treatment, but percentage fat mass did, with a trend to greater increase in the corticosteroid group.
This finding is perplexing, as for percentage fat mass to increase there would need to be a decrease in percentage lean mass. However, as previously mentioned several different body composition techniques, of varying accuracy and sophistication, were used to measure each component, and as there is error and assumptions inherent in different techniques, this questions the validity of their body composition component data comparisons. For example, Boost et al. have shown that BIA overestimates fat mass compared with DXA as the standard in a cohort of IBD patients. They also found greater differences between the two methods when DXA determined bone mass and lean tissue mass were added together and compared with lean mass by BIA. Further, Sentongo et al. have shown significant differences between lean and fat mass predicted from skinfold thickness compared with assessment by DXA.

**GROWTH IN THE ERA OF BIOLOGICS**

In the era of biologics, initial investigations into the efficacy and safety of their use in paediatrics are now evolving into interest in their ability to promote growth (Table 1) and improve nutritional status, although data predominantly investigate weight or BMI change and data on body composition are scarce. In three retrospective studies, weight following infliximab therapy was shown to increase, but no significant changes in linear growth were reported. Afzal et al.[20] reviewed the case notes of 24 children and detailed growth parameters 6 mo prior to the first infusion of infliximab, at the time of first infusion, and 6 mo post third infusion. All children were on concomitant immunosuppression and while weight Z-score significantly improved from initial dose of infliximab to 6 mo post, no significant change in height Z-score was found between time points. Similarly, Smitsky et al.[23] reported a significant improvement in BMI Z-score and a trend to improvement in weight Z-score at 1 year after starting infliximab in a cohort of 16 patients, however, height Z-scores were not different. Diamanti et al.[20] retrospectively evaluated 28 patients and divided them into groups according to therapy so as to compare combined infliximab, mesalazine and azathioprine, with mesalazine and azathioprine only. Significant increases in weight and BMI between baseline and follow-up (median 10 mo) were reported for the infliximab group, however, height was not found to be different in either treatment group.

Pfefferkorn et al.[24] described the relationship between growth and current treatment options in children remaining in Tanner stages 1-3 over 2 years. Thirty-six percent of their cohort received infliximab and no significant differences in height velocity Z-scores were found at one or two years follow-up. More frequent doses of infliximab were reported in children receiving early and sustained corticosteroid use, and this association persisted over the two-years-of-follow-up.

In contrast, other studies have reported resumption of normal linear growth following treatment with biologics.[23-29]. In a small number of patients with CD ($n = 6$) who were refractory to conventional therapy (corticosteroids and/or azathioprine) and had growth impairment (at least -1.00 change in Z-score for height), de Ridder et al.[25] described recommencement of normal linear growth velocity in half their retrospectively studied cohort. Borrelli et al.[23] prospectively studied 18 children with severe CD and reported both significantly increased weight and height Z-scores at 6 mo post induction regimen. Following the three induction infusions, endoscopic and histologic scores were significantly decreased. Clinical remission was achieved in 10 patients and inflammatory remission in 12 patients, and eight patients who had achieved both clinical and inflammatory remission had retreatment with infliximab beyond the induction regimen. When examining retreated patients compared with the 10 who only completed induction therapy, it was shown that the significant improvements in weight and height Z-scores remained only in the retreated group. It is interesting to note that mean height Z-scores were indicative of growth failure in the retreated group (-1.15), whereas they were not in the induction group (-0.86).

Further, all patients in the retreated group displayed clinical and inflammatory remission post induction therapy. Hyams et al.[26] studied only patients who clinically responded to induction with infliximab in their randomised controlled trial of two different dosage regimens. Height Z-scores were determined only in those patients with greater than a 1 year delay in bone age, and at both wk 30 and 50 height Z-scores were significantly improved.

Pubertal progression and skeletal maturation are important considerations when evaluating the impact of therapies on growth. Both these parameters were taken into account by Walters et al.[27] in their retrospective investigation of growth during the first year of infliximab therapy. A bone age correction factor was applied to Z-score calculations for those children with a delay and patients were grouped according to pubertal status (Tanner stages 1-3 vs Tanner stages 4-5). All 27 patients with growth assessed established at least a partial response to the induction regimen, and mean height Z-score had decreased over the period from diagnosis to infliximab induction, even with the use of other conventional therapies. Height and height velocity Z-scores were subsequently found to improve only in those patients in early puberty, however, all children showed significant improvement in weight. Improvements in height velocity, weight and BMI were significantly greater in those children exhibiting complete symptomatic remission as opposed to partial. Similar results with respect to pubertal status and clinical response were reported in the retrospective study of Malik et al.[29]. Height velocity Z-scores accounted for pubertal status, and height and height velocity Z-scores significantly improved over the first 6-mo of treatment, with height Z-scores additionally showing significant increases 12-mo from baseline. Clinical responders showed significant improvements in height velocity. In a prospective study of children with severe refractory or corticosteroid dependent CD, ten children who had not completed pubertal growth showed significant improvement in height Z-score.
### Table 1  Summary of studies investigating the impact of biologics on linear growth

| Ref.         | Study type and biologic | Subjects and medication at baseline | Growth failure | Pubertal status data | Measurement times | Remission achieved | Linear growth outcomes |
|--------------|-------------------------|-------------------------------------|----------------|----------------------|-------------------|--------------------|------------------------|
| Afzal et al\(^{[a]}\) | Retrospective; infliximab | n = 24; median age: 10.3 yr; All concomitant immunosuppression | No | Data not given | T0; T + 6; T + 6 post 3rd infusion | n = 17 clinical remission | No sig Δ ht Z at T + 6 |
| Diamant \(n = 28\); mean age: 13 yr in infliximab, 5-ASA and azathioprine (Group A: n = 14); 14 yr in 5-ASA and azathioprine (Group B: n = 14) | Retrospective; infliximab | Data not given | Data not given | T0; T + 12 | Clinical remission in group A | No sig Δ HV Z at 10 mo post for either group |
| Sinitsky et al\(^{[a]}\) | Retrospective; infliximab | n = 16; mean age 13.0 yr; n = 2 concomitant MTX; n = 1 6-MP; n = 1 tacrolimus; n = 8 5-ASA; n = 14 azathioprine; n = 7 corticosteroid | No | Data not given | T0; T + 12 | n = 10 clinical remission | No sig Δ ht Z at T + 12 |
| Pfefferkorn et al\(^{[a]}\) | Prospective; infliximab | Subgroup n = 34 commencing infliximab during first year of study; mean age: data not given; concomitant medication: data not given | No | Tanner 1-3 | Dx; T + 12; T + 24 | Data not given | No sig Δ HV Z at T + 12; No sig difference HV Z at T + 24 between infliximab ≥ 1 yr, vs < 1 yr or no infliximab |
| Borrelli et al\(^{[a]}\) | Prospective; infliximab | n = 18; median age: 13 yr; n = 18 concomitant azathioprine; n = 15 mesalamine; n = 13 corticosteroids | Yes in retreated group only | Tanner 1-3 | T0; T + 6 | After induction n = 10 clinical remission; n = 12 inflammatory remission. n = 8 were retreated | Sig ↑ ht Z from T0 to T + 12 in retreated group only; Note: all in retreated group had achieved clinical and inflammatory remission |
| Cezard et al\(^{[a]}\) | Prospective; infliximab | Subgroup n = 10; mean age: data not given; concomitant medication: data not given | Yes | Data not given | T-12; T + 12 | Data not given | Sig ↑ HV Z at T + 12 |
| de Ridder et al\(^{[a]}\) | Retrospective; infliximab | Subgroup n = 10; median age: 13 yr; n = 3 no change | Yes | Data not given | T0; T + 12 | Data not given | No sig Δ HT Z at T + 6 |
| Hyams et al\(^{[a]}\) | Prospective; randomized to 8 or 12 weekly infusions | n = 103; mean age: 13.3 yr; however, ht Z only assessed in those with > 1 yr delay skeletal maturation (n = not reported); n = 93 concomitant 6-MP/azathioprine; n = 9 MTX; n = 56 5-ASA; n = 36 corticosteroids | Yes | Tanner 1-3 | T0; week 10; week 54 | 3 clinical remission | Sig ↑ ht Z from T0 to weeks 30 and 54 |
| Malik et al\(^{[a]}\) | Retrospective; adalimumab | n = 36; median age: 14.7 yr; of these, n = 33 prior infliximab (n = 7 non-responders; n = 16 loss of clinical response; n = 11 allergic reaction); n = 33 concomitant immunosuppression; n = 15 corticosteroids | No | Tanner 1-3 | T0; T + 6; n = 11 T + 12 | n = 28 clinical remission | Sig ↑ ht Z and HV at T + 6 for whole group, those in clinical remission, Tanner 1-3, immunosuppression, allergic reaction to infliximab; no sig changes for group followed to T + 12; independent of corticosteroid use |
| Malik et al\(^{[a]}\) | Retrospective; infliximab | n = 28; median age: 13.1 yr; n = 17 concomitant 5-ASA, n = 13 azathioprine; n = 13 MTX; n = 12 corticosteroids | Yes | Tanner 1-3 | T - 6; T0; T + 6; T + 12 | n = 21 clinical response; n = 10 clinical remission | Sig ↑ ht Z from T0 to T + 6, and T + 6 to T + 12 for whole group; Sig ↑ HV from T0 to T + 6 for whole group, clinical responders, Tanner 1-3, no corticosteroids, MTX throughout |

**Note:** All in retreated group

\[^{[a]}\] Ref.
in the year after treatment compared to the year before\(^1\). In the whole group of 21 children, 90% achieve complete remission.

A further study by Malik et al\(^{[20,21]}\) detailed the effects of a different biologic on growth in children with CD, namely adalimumab. Their cohort comprised mainly of children (34 out of 36) who had previously been treated with infliximab but were either unresponsive, lost clinical response or had an allergic reaction. Both height Z-score and height velocity significantly improved over 6 mo, however, this increase was significant only in the group who achieved clinical remission. Further, height Z-score did not show significant change in those patients who were either unresponsive or lost clinical response to infliximab, but was only apparent in those with an allergic reaction to infliximab. Linear growth was also related to stage of puberty, with only those in the early stages of puberty (Tanner 1-3) showing significant increases in height Z-score and median height velocity, and while use of corticosteroids did not impact improvements in height, those on concurrent immunosuppression displayed significant improvement as opposed to those who were not.

In summary, growth deficits are a marker of more severe disease\(^1\), as is use of biologics\(^{[30]}\). Hence, the relationship between treatment with infliximab and growth promotion seems multifactorial. From the data reviewed herein, features associated with improvements in growth with use of biologics appear to relate to clinical response to treatment, stage of puberty, and presence of growth failure. Evidence suggests that clinical response is important for improving growth and while limited data exist, this is probably related to mucosal healing\(^2\). It is also apparent, and not surprising, that children late in puberty do not respond with linear growth improvement. This may have been a factor associated with the studies not showing improvement in height at pubertal status was either not assessed\(^{[20,21]}\), or indicated to be in the later stages\(^{[30]}\). Better growth response is also seen in those patients who are suffering from growth failure prior to treatment, with studies showing no improvement involving a cohort where growth was not impaired\(^{[30,21]}\). The study of Diamanti et al\(^{[30]}\) is limited by the authors only looking at change in actual height values, with both genders grouped together, and no information on pubertal status. Hence, it is difficult to determine at what stage their patients are with respect to pubertal progression and peak height velocity.

### CONCLUSION

Nutritional status, as indicated by compromised body composition (that is, reduced lean mass), is present in children with IBD and persists over time, irrespective of treatment. Further, alterations in body composition are expressed differently between boys and girls, and in response to treatment. Reports suggest girls present with wasting which morphs into cachexia with treatment. In contrast, boys present with cachexia, with resolution of lean mass with treatment, and excess of fat mass. It must be noted that literature in this area is relatively limited, and more studies are needed, particularly addressing responses to treatment.

As with compromised nutritional status, growth deficits are reported in children with IBD. Data are promising with respect to improvements in linear growth as a result of treatment with biologics, however, it is clear that further research is necessary in this area as the majority of studies conducted are retrospective in nature and subject numbers are small. Key features associated with improvements in growth appear to be successful clinical response to treatment, patients in early stages of puberty, thereby allowing a greater window of opportunity for growth potential, and the presence of growth failure at the onset of treatment, again allowing for greater growth potential. An area that is lacking for evidence is the impact of biologics on body composition, and more data are warranted in this area.

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P-Reviewers: Ciccone MM, Capasso R, Hokama A
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