

Management Challenges in Adolescents with Crohn's Disease- Current Practice

Yair Kasirer¹, Liron Birimberg-Schwartz¹, Shelly Ben Harush Negari² and Dan Turner^{1,3*}

¹The Juliet Keidan Institute of Pediatric Gastroenterology, Shaare Zedek Medical Center, Jerusalem, Israel

²Adolescence Medicine Unit, Shaare Zedek Medical Center, Jerusalem, Israel

³The Hebrew University of Jerusalem, Israel

*Corresponding author: Dan Turner, The Juliet Keidan Institute of Pediatric Gastroenterology, Hepatology and Nutrition Shaare Zedek Medical Center, The Hebrew University, P.O.B. 3235, Jerusalem 91031, Israel, Tel: +972-50-8685841; Fax: +972-2-6555756; E-mail: turnerd@szmc.org.il

Received date: February 21, 2017; Accepted date: March 23, 2017; Published date: March 28, 2017

Copyright: © 2017 Kasirer Y. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

The incidence and prevalence of Crohn's disease (CD) in adolescents is rising. The clinical course differs in several aspects from that of adults. Pediatric-onset disease is more extensive and its course is somewhat more aggressive. In addition to the common manifestation of CD, adolescents with CD may present with pubertal delay, growth retardation and osteopenia. These unique aspects of adolescence CD should impact the treatment paradigm. In cases of growth impairment and osteopenia, treatment should be intensive aiming at promoting complete mucosal healing and, in turn, improved growth and bone formation. The use of enteral nutrition should be thus encouraged both for induction and maintenance of remission. However, adolescent CD carries implications that go beyond the physical manifestations of the disease. Children diagnosed with IBD are at increased risk of emotional distress and decreased social functioning. The use of support groups and other psychosocial interventions is advocated as a mean to enhance coping skills and improve quality of life. Half of adolescents are non-compliant with the recommended treatment hence, a particular emphasis should be placed on engaging the adolescent in the treatment plan, using several intervention strategies. Adolescence is a time of dynamic physical changes and growth along with emotional maturation. This review highlights some of the unique aspects that should come into play while managing CD during this sensitive period of life.

Keywords: Adolescence; Crohn's disease; Pediatric onset; Intestinal resection; Growth impairment

Introduction

Inflammatory bowel diseases (IBD) can present during childhood and adolescence in up to 25% of cases [1]. In a multicenter pediatric registry, the mean age at diagnosis of Crohn's disease (CD) has been found to be 10.3 years; 15% were diagnosed before six years of age, 48% between 6-12 years, and 37% thereafter [2]. The incidence of CD in adolescents appears to be increasing worldwide reaching 2.5-11.4 per 100,000 [3], with a prevalence of 58/100,000 [4]. Although the basic pathophysiology and response to treatments are similar, pediatric onset CD differs in several aspects from adult onset disease. In addition, adolescence is a time of dynamic physical changes and growth along with emotional maturation. Clinicians should be aware of the bidirectional influence between these changes and IBD and be ready to incorporate them in the decision making process. This review focuses on some of the unique aspects that should come into play while managing adolescent CD.

Pediatric vs. Adult Onset Crohn's Disease

Compared to adult onset disease, studies have shown a predilection for CD over UC in children with a ratio of 2.8:1, and only pediatric onset CD is characterized by male predominance [5]. The likelihood for isolated colonic CD increases in younger age [6]. Children suffer more frequently from extensive disease, a condition prone to less favorable outcome, including a greater propensity for disease extension [7-9]. The cumulative risk of progression to complicated CD (i.e.

fistulizing or stricturing disease) is similar to adults but naturally occurs at a younger age. By the age of 30 years, the risk of having undergone an intestinal resection is $48 \pm 5\%$ and $14 \pm 2\%$ in pediatric and adult onset CD, respectively [9]. Extensive CD (ileocolonic and upper gastrointestinal involvement) is seen in 43% of pediatric patients compared with <10% in adults and extensive colitis is twice as common in children with UC [7]. The more aggressive disease course may be partially explained by the higher genetic exertion associated with early onset IBD [10,11]. The Montreal classification of CD separated pediatric onset CD (A1 ≤ 16 years) from the adult onset forms) A2 17-40 years; A3 >40 years). However, serologic [12] and clinical [12,13] evidence suggests that pediatric CD is comprised of two further distinguishable groups: early and late onset. Accordingly, a pediatric modification of the Montreal classification, termed the Paris classification, brings these factors into consideration and subdivides the Montreal A1 classification into A1a (0-9 years) and A1b (10 -16 years) [14], while acknowledging that further division of infantile IBD (0-2 years) may be appropriate in the future. Acknowledging the more frequent proximal gastrointestinal involvement in children, the Paris classification separates the original L4 (upper gastrointestinal) into L4a (proximal to the ligament of Treitz) and L4b (proximal to the 2/3 of the ileum). The new classification also highlights growth as another unique aspect of pediatric CD, denoting the presence of growth failure as G1 versus G0.

Growth

Depending on the definition used, growth failure at diagnosis has been described in 4 to 38% of CD children whereas growth velocity may be reduced in up to 88% of CD children [15] and may be the

presenting sign of the disease [16]. In addition to malnutrition, pro-inflammatory cytokines impair growth by imposing growth hormone resistance [17,18]. Prolonged steroid treatment compounds these disease-related factors by disrupting the metabolic processes essential for growth. However, short courses of steroids do not seem to affect long term growth.

All children should have regular measurements of body weight, height, and pubertal status at each clinic visit. Growth impairment is best described in terms of "height velocity", expressed as growth in cm/year, over a period of 6-12 months, transformed into standard deviation score, or z-score [19].

Improving growth necessitates a combined approach in providing adequate nutrition and aggressively controlling mucosal inflammation. The delayed bone age in many children with CD enables some degree of catch-up growth, but final adult height may still be impaired if mucosal healing is not achieved [20]. Catch up growth requires ~120% of the recommended daily caloric allowance [16]. In general, any treatment capable of inducing mucosal healing has also a positive effect on growth by suppressing circulating cytokines. Exclusive Enteral Nutrition (EEN) improves growth by mediating mucosal healing and down-regulating proinflammatory cytokines such as IL-6 and TNF, potent inhibitors of IGF-1 [21]. Regardless of the induction treatment, supplemental enteral nutrition is indicated in all children with malnutrition or linear growth failure [22]. Walters et al. [23] demonstrated that the positive effect of infliximab on growth is apparent only until the early stages of puberty (i.e. Tanner growing stages, 2-3 in girls and 3-4 in boys), emphasizing the need for timely and aggressive treatment in patients approaching puberty. There is no firm evidence to suggest that thiopurines facilitate growth [24]. A retrospective cohort study showed catch-up growth when methotrexate was administered to children who failed previous thiopurine treatment [25]. Nonetheless, anti-TNF biologics are the most effective drugs to induce mucosal healing and therefore also improving growth [26]. Early use of steroid sparing immunomodulators is indicated and in severe cases, anti-TNF- α therapy may be prescribed as the first drug of choice [26]. Timely referral for surgery has been also found to induce strong catch-up growth in medically-refractory CD [27]. It is currently not recommended to treat children with CD with growth hormone for inducing growth although endocrinology consultation should be sought in severe cases as CD and growth hormone deficiency may rarely coexist.

Treatment Paradigm - Pediatric Considerations

A full description of the philosophy and controversies of treating CD is beyond the scope of this review and can be found elsewhere [22]. Although in most part, the management of adolescent CD is similar to adults, there are several unique aspects to management that should be highlighted. Studies of infliximab [28,29], thiopurines [30,31], and nutritional therapy [32] often show a better response to therapy in children than similar studies in adults. The more favorable outcome merely reflects a shorter duration of disease in the included children; it has been repeatedly shown that shorter disease duration is associated with a better response to therapy [33]. Similarly, studies [34], suggest that a more intensified "top-down" approach may be associated with a more favorable outcomes in some. There is little doubt nowadays that biologics are more effective than thiopurines or methotrexate and all are superior to 5-ASA that are as effective as placebo for maintaining remission in CD [22]. Adults who have risk

variables indicative of high risk for future complicated disease such as fistulizing, stenotic or perianal disease and extensive inflammation, especially in the presence of severe colonic involvement, are treated via the top down approach. High risk children are judged by the same parameters but also by the presence of severe osteopenia and significant growth delay [22]. Regardless of the initial choice of treatment, rapid treatment escalation should be considered if the mucosal inflammation has not been sufficiently controlled after a short trial-run, a relatively new notion termed "treat-to-target" [35]. This should be especially true in children who have many future disease years ahead and given their typical extensive disease.

Corticosteroids vs. Exclusive Enteral Nutrition (EEN)

Corticosteroids are highly effective in inducing remission in CD but their use is heralded by multiple side effects, some of which are particularly problematic in adolescents: cosmetic changes, negative effect on bone and growth and mood changes. The use of corticosteroids does not often attain mucosal healing, which is required for growth acceleration and bone formation [36,37]; even the locally active budesonide may still impair growth [38].

EEN requires the consumption of formulated food exclusively for 6-10 weeks; it seems that the type of formula, whether elemental or polymeric, is not associated with the outcome [32]. Unlike in adults where steroids may be more effective than nutritional treatment, in children the two treatments seem equipotent for inducing remission [39]. Furthermore, EEN may lead to bone formation and restoration of growth. Therefore, EEN is recommended as the first line therapy to induce remission in children with active luminal CD [22]. With an appropriate multidisciplinary support, many children and adolescents will agree to drink polymeric formula without the need for placement of a nasogastric tube.

Balancing Lymphoma Risk Associated with Thiopurines in Pediatric CD

While thiopurines are associated with a 4-fold increased risk for non-Hodgkin's lymphoma [40,41], this risk is age-dependent; the risk for lymphoma is greatest in those older than 65 years of age, and low in those younger than 20 years of age [41,42]. It must also be emphasized that effective thiopurines use may reduce the inflammation-associated adenocarcinoma in both the large and small bowel [43]. Taken together, it may be concluded that the benefit of thiopurine treatment in children outweighs the general risk of lymphoma in children. However, in addition to the general lymphoma risk, over 40 cases of aggressive and otherwise extremely rare, hepatosplenic T-cell lymphoma have been identified in those treated with thiopurines, many of whom as combination therapy with anti-TNF [44]. A recent meta-analysis show a numerical benefit of adding thiopurines to infliximab, although the difference missed statistical significance (OR: 1.73 (95% CI 0.97, 3.07)) [45]. However, since the vast majority of hepatosplenic T-cell lymphoma patients were young males (age range 12-40 years) some pediatric gastroenterologists refrain from combining thiopurines with anti-TNF and prescribe either anti-TNF monotherapy or combination with low dose methotrexate. Others advocate adding thiopurines for a short period of several months, especially in girls, and in those who are at risk of severe disease [44].

Bone Health

Any degree of osteopenia has been reported in up to 70% of children with CD [46] but significant osteopenia (i.e. z score below -2) in 25% [47,48]. Attaining high peak bone mass during childhood is the most significant determinant, besides genetics, in reducing the risk of fractures in old age [49]. The etiology of low bone mineral density (BMD) in CD is multifactorial of which the negative effect of circulating pro-inflammatory cytokines (e.g. IL-1, IL-6 and TNF- α) is probably the most important, just like with growth [50,51]. Other contributing factors include chronic use of corticosteroids, malnutrition and low intake of vitamin D and calcium. DEXA (dual x-ray absorptiometry) is considered the gold standard for measuring bone mass, but this should utilize pediatric software and age-appropriate nomograms corrected for height and possibly also for bone age (i.e. using z-score rather than t-score as done in adults). To date, only several studies investigated the impact of therapies on BMD in pediatric CD. A prospective study that followed 58 children with CD for two years did not show significant improvement in BMD despite increased height z-score and reduced disease activity [52]. Anti-TNF therapy and EEN showed rapid improvement of serum bone markers in children with CD [53-56]. Numerous studies showed that physical activity especially weight bearing exercise promotes cortical bone acquisition [57-59]. Vitamin D status should be monitored and supplemented as needed. The rare use of bisphosphonates should be reserved to those with pathological fractures in consultation with endocrinologist.

Puberty

Brain et al. [60] reported a mean delay in pubertal onset of 1.5 years for girls and 0.8 years for boys with CD. Menarche occurred after the age of 16 years in 73% of females whose disease onset preceded puberty, especially in those with frequent relapses. The inflammatory process and malnutrition both contribute to hypogonadism leading to pubertal delay. Therefore, just as with growth and bone, the optimal management for pubertal delay involves caloric supplementation and aiming at mucosal healing achieved by medical or surgical interventions [61]. Data from other chronic inflammatory disease suggest that treatment with sex hormones can accelerate puberty in affected patients [62]. Treating pubertal delay is a tradeoff between the need to reduce the psychosocial implication of pubertal delay and reduced growth potential due to the associated closure of the epiphysis. A multidisciplinary approach with a pediatric endocrinologist is mandatory for optimizing management.

The Effects of CD and Treatment on Adolescent Developmental Stages

It is imperative for clinicians who care for adolescents to understand their developmental, psychological and educational needs and consult an adolescent medicine physician when needed. In the early adolescence stages (ages 10-13 years) the interest in family activities is reduced and the adolescent seeks social support from peers. The brain develops during adolescence from caudal to frontal direction and thus the ability for long term planning, which is dependent on the frontal lobe, is not well developed. This fact explains the need for immediate satisfaction and difficulty in accepting the limitations induced by the illness and its treatment. Delayed puberty and impaired growth further affects the self-esteem of the adolescent.

Mid adolescence (ages 14-16 years) is characterized by decreased interest in parental activity and increased conflicts due to reduced acceptance of authority. The adolescent, who feels omnipotent and invulnerable, seeks independence while the parents, who were accustomed to taking care of their ill child, often find it hard to provide the space for independence. An adolescent with chronic illness can express risk behaviors such as by stopping medical treatment. Peer group activity is dominant during mid-adolescence. Members of the group define their dress, moral and cultural codes in accord with the group. The ill adolescent may find the illness, recurrent medical treatments and clinic visit to interfere with their ability to integrate with the team.

During late adolescence (ages 17-21 years) intimate relationships replace some of the peer group activity. The illness and disturbed body image can affect the confidence to endeavor in romantic relationships. It is recommended that pediatric gastroenterologists see adolescent patients without their caregivers, providing them with opportunity to discuss concerns in private. It is imperative to assure confidentiality that will provide the adolescent the sufficient confidence in the discussion.

Psychological Issues

Children with IBD may be at risk for stress, social strain and even isolation, blame, altered self-image and psychiatric sequelae [63-69]. The altered quality of life of children with IBD can affect the entire family who often lack the appropriate strategies to deal with this complicated reality [65]. In a qualitative study, children with IBD expressed concerns related to symptoms and treatments, vulnerability, lack of control, and perceived the 'self' negatively [63]. Adolescents with IBD demonstrate higher levels of internalizing disorders (anxiety and depression). The rate of depression may be as high as 25% and it is often under-recognized both by parents and health care professionals. Anxiety and depression appear to be risk factors for early recurrence of the disease and adversely affect the disease course [70].

Despite the overwhelming evidence that show impaired quality of life, increased anger, fear and embarrassment in patients with IBD [71], data to guide treatment is sparse. Referral for cognitive behavioral therapy has been shown to be especially effective in improving depressive symptoms and functioning in children with IBD [72]. In our unit we run a support group guided by experienced psychologists with particular experience with IBD. The support group offers children and their families the opportunity to share their strengths, experiences, knowledge and enhance their coping skills with the disease. Following participation in our support groups, the participants reported better quality of life and improved coping mechanisms with the disease-related symptoms (data not published). Several websites provide opportunities for social interaction (e.g. www.cffa.org, www.myibdu.org, and www.ibdsf.com).

Adherence to Therapy

Non adherence in pediatric IBD patients is high, in the range of 38%-66%, especially in adolescents [73-75]. Adherence is affected by doctor-patient relationship, treatment duration, number of prescribed medications and doses per day, adverse effects of the medications, and symptoms disappearance. In the clinical setting, the most efficient way to evaluate adherence is simply asking the child how often they missed a medication. The successful clinician will gradually build trust with the adolescent by providing supportive guidance without being

judgmental. Other effective measures to improve adherence are simplifying the treatment regimen, providing a written treatment plan and educating the adolescent about effective organizational strategies. Adolescents often wish to have a greater role in the decision making process. The interested reader is referred to an excellent review on adherence in pediatric IBD by Hommel et al. [76].

Transition of Care

The period of transition and transfer may be associated with poorer health outcomes. Gradual encouragement of the adolescent to gain knowledge about the management of his/her illness and assuming increased responsibility is the mainstay of transition. A recent study found that self-assessed ability to perform self-management tasks related to IBD seems to improve with age, but not with disease duration. The timing of the transition should be tailored to the needs of the patient and the local practice. The pediatric gastroenterologist should prepare a detailed summary of the clinical history, including the original reports of all tests in order to minimize repeating procedures by the adult physicians. At least one joint pediatric- adult care visit should be scheduled before the transfer to introduce the adolescent and the new team in a secure environment. However, two joint clinics may be preferred- one in the pediatric facility and one in the adult facility.

Summary

Treating adolescents with CD requires understanding of the unique aspects of this sensitive age. While many of the concepts discussed herein are also relevant to adolescents with UC, still growth impairment, osteopenia, delayed puberty and malnutrition are much less common than in CD. This review highlighted the main physical and psychosocial challenges apparent in adolescence, and suggested management considerations to address these challenges.

Conflict of Interests

Last 3 years DT received consultation fee, research grant, royalties, or honorarium from Janssen, MSD, Pfizer, Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, Abbvie, Takeda, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health, Shire; The other authors have no relevant conflicts to report

References

1. Kelsen J, Baldassano RN (2008) Inflammatory bowel disease: the difference between children and adults. *Inflamm Bowel Dis* 14 Suppl 2: S9-11.
2. Heyman MB, Kirschner BS, Gold BD, Ferry G, Baldassano R, et al. (2005) Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 146: 35-40.
3. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, et al. (2011) Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 17: 423-439.
4. Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, et al. (2007) The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol* 5: 1424-1429.
5. Gupta N, Bostrom AG, Kirschner BS, Ferry GD, Winter HS, et al. (2007) Gender differences in presentation and course of disease in pediatric patients with Crohn disease. *Pediatrics* 120: e1418-1425.

6. Levine A (2009) Pediatric inflammatory bowel disease: is it different? *Dig Dis* 27: 212-214.
7. Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, et al. (2008) Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 135: 1114-1122.
8. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, et al. (2008) Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 135: 1106-1113.
9. Pigneur B, Seksik P, Viola S, Viala J, Beaugerie L, et al. (2010) Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 16: 953-961.
10. Kugathasan S, Baldassano RN, Bradfield JP, Sleiman PM, Imielinski M, et al. (2008) Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet* 40: 1211-1215.
11. Imielinski M, Baldassano RN, Griffiths A, Russell RK, Annesse V, et al. (2009) Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet* 41: 1335-1340.
12. Markowitz J, Kugathasan S, Dubinsky M, Mei L, Crandall W, et al. (2009) Age of diagnosis influences serologic responses in children with Crohn's disease: a possible clue to etiology? *Inflamm Bowel Dis* 15: 714-719.
13. Meinzer U, Idestrom M, Alberti C, Peuchmaur M, Belarbi N, et al. (2005) Ileal involvement is age dependent in pediatric Crohn's disease. *Inflamm Bowel Dis* 11: 639-644.
14. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, et al. (2011) Pediatric modification of the Montreal classification for inflammatory bowel disease: The Paris classification. *Inflamm Bowel Dis* 17: 1314-1321.
15. Ley D, Duhamel A, Behal H, Vasseur F, Sarter H, et al. (2016) Growth Pattern in Paediatric Crohn Disease Is Related to Inflammatory Status. *J Pediatr Gastroenterol Nutr* 63: 637-643.
16. Gasparetto M, Guariso G (2014) Crohn's disease and growth deficiency in children and adolescents. *World J Gastroenterol* 20: 13219-13233.
17. Tenore A, Berman WF, Parks JS, Bongiovanni AM (1977) Basal and stimulated serum growth hormone concentrations in inflammatory bowel disease. *J Clin Endocrinol Metab* 44: 622-628.
18. Kirschner BS, Sutton MM (1986) Somatomedin-C levels in growth-impaired children and adolescents with chronic inflammatory bowel disease. *Gastroenterology* 91: 830-836.
19. Tanner JM, Davies PS (1985) Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr* 107: 317-329.
20. Sawczenko A, Ballinger AB, Croft NM, Sanderson IR, Savage MO (2003) Adult height in patients with early onset of Crohn's disease. *Gut* 52: 454-455.
21. Fell JM, Paintin M, Arnaud-Battandier F, Beattie RM, Hollis A, et al. (2000) Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Aliment Pharmacol Ther* 14: 281-289.
22. Rummelle FM, Veres G, Kolho KL, Griffiths A, Levine A, et al. (2014) Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis* 8: 1179-1207.
23. Walters TD, Gilman AR, Griffiths AM (2007) Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. *Inflamm Bowel Dis* 13: 424-430.
24. Walters TD, Griffiths AM (2009) Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol* 6: 513-523.
25. Turner D, Grossman AB, Rosh J, Kugathasan S, Gilman AR, et al. (2007) Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. *Am J Gastroenterol* 102: 2804-2812.
26. Walters TD, Kim MO, Denson LA, Griffiths AM, Dubinsky M, et al. (2014) Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease. *Gastroenterology* 146: 383-391.
27. Lipson AB, Savage MO, Davies PS, Bassett K, Shand WS, et al. (1990) Acceleration of linear growth following intestinal resection for Crohn disease. *Eur J Pediatr* 149: 687-690.

27. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, et al. (2007) Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 132: 863-873.
28. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LE, Schreiber S, et al. (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 359: 1541-1549.
29. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F (2000) A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 119: 895-902.
30. Candy S, Wright J, Gerber M, Adams G, Gerig M (1995) A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 37: 674-678.
31. Zachos M, Tondeur M, Griffiths AM (2007) Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* CD000542.
32. Markowitz J (2009) Early inflammatory bowel disease: different treatment response to specific or all medications? *Dig Dis* 27: 358-365.
33. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, et al. (2008) Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 371: 660-667.
34. Reinink AR, Lee TC, Higgins PD (2016) Endoscopic Mucosal Healing Predicts Favorable Clinical Outcomes in Inflammatory Bowel Disease: A Meta-analysis. *Inflamm Bowel Dis* 22: 1859-1869.
35. Beattie RM, Nicholls SW, Domizio P, Williams CB, Walker-Smith JA (1996) Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. *J Pediatr Gastroenterol Nutr* 22: 373-379.
36. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, et al. (2006) Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 4: 744-753.
37. Kundhal P, Zachos M, Holmes JL, Griffiths AM (2001) Controlled ileal release budesonide in pediatric Crohn disease: efficacy and effect on growth. *J Pediatr Gastroenterol Nutr* 33: 75-80.
38. Berni Canani R, Terrin G, Borrelli O, Romano MT, Manguso F, et al. (2006) Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. *Dig Liver Dis* 38: 381-387.
39. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD (2005) Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 54: 1121-1125.
40. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lemann M, et al. (2009) Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 374: 1617-1625.
41. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE (2009) Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 7: 874-881.
42. Armstrong RG, West J, Card TR (2010) Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. *Am J Gastroenterol* 105: 1604-1609.
43. Cozijnsen MA, Escher JC, Griffiths A, Turner D, de Ridder L (2015) Benefits and risks of combining anti-tumor necrosis factor with immunomodulator therapy in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 21: 951-961.
44. Jones JL, Kaplan GG, Peyrin-Biroulet L, Baidoo L, Devlin S, et al. (2015) Effects of Concomitant Immunomodulator Therapy on Efficacy and Safety of Anti-Tumor Necrosis Factor Therapy for Crohn's Disease: A Meta-analysis of Placebo-controlled Trials. *Clin Gastroenterol Hepatol* 13: 2233-40 e1-2.
45. Cowan FJ, Warner JT, Dunstan FD, Evans WD, Gregory JW, et al. (1997) Inflammatory bowel disease and predisposition to osteopenia. *Arch Dis Child* 76: 325-329.
46. Lopes LH, Sdepanian VL, Szejnfeld VL, de Moraes MB, Fagundes-Neto U (2008) Risk factors for low bone mineral density in children and adolescents with inflammatory bowel disease. *Dig Dis Sci* 53: 2746-2753.
47. Semeao EJ, Jawad AF, Zemel BS, Neiswender KM, Piccoli DA, et al. (1999) Bone mineral density in children and young adults with Crohn's disease. *Inflamm Bowel Dis* 5: 161-166.
48. Bradney M, Karlsson MK, Duan Y, Stuckey S, Bass S, et al. (2000) Heterogeneity in the growth of the axial and appendicular skeleton in boys: implications for the pathogenesis of bone fragility in men. *J Bone Miner Res* 15: 1871-1878.
49. Varghese S, Wyzga N, Griffiths AM, Sylvester FA (2002) Effects of serum from children with newly diagnosed Crohn disease on primary cultures of rat osteoblasts. *J Pediatr Gastroenterol Nutr* 35: 641-648.
50. Sylvester FA, Wyzga N, Hyams JS, Gronowicz GA (2002) Effect of Crohn's disease on bone metabolism in vitro: a role for interleukin-6. *J Bone Miner Res* 17: 695-702.
51. Sylvester FA, Wyzga N, Hyams JS, Davis PM, Lerer T, et al. (2007) Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. *Inflamm Bowel Dis* 13: 42-50.
52. Franchimont N, Putzeys V, Collette J, Vermeire S, Rutgeerts P, et al. (2004) Rapid improvement of bone metabolism after infliximab treatment in Crohn's disease. *Aliment Pharmacol Ther* 20: 607-614.
53. Thayu M, Leonard MB, Hyams JS, Crandall WV, Kugathasan S, et al. (2008) Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. *Clin Gastroenterol Hepatol* 6: 1378-1384.
54. Ryan BM, Russel MG, Schurgers L, Wichers M, Sijbrandij J, et al. (2004) Effect of antitumour necrosis factor-alpha therapy on bone turnover in patients with active Crohn's disease: a prospective study. *Aliment Pharmacol Ther* 20: 851-857.
55. Miheller P, Muzes G, Racz K, Blazovits A, Lakatos P, et al. (2007) Changes of OPG and RANKL concentrations in Crohn's disease after infliximab therapy. *Inflamm Bowel Dis* 13: 1379-1384.
56. Whitten KE, Leach ST, Bohane TD, Woodhead HJ, Day AS (2010) Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol* 45: 399-405.
57. Robinson RJ, Krzywicki T, Almond L, al-Azzawi F, Abrams K, et al. (1998) Effect of a low-impact exercise program on bone mineral density in Crohn's disease: a randomized controlled trial. *Gastroenterology* 115: 36-41.
58. Bass SL, Saxon L, Daly RM, Turner CH, Robling AG, et al. (2002) The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players. *J Bone Miner Res* 17: 2274-2280.
59. Brain CE, Savage MO (1994) Growth and puberty in chronic inflammatory bowel disease. *Baillieres Clin Gastroenterol* 8: 83-100.
60. Ballinger AB, Savage MO, Sanderson IR (2003) Delayed puberty associated with inflammatory bowel disease. *Pediatr Res* 53: 205-210.
61. Landon C, Rosenfeld RG (1984) Short stature and pubertal delay in male adolescents with cystic fibrosis. Androgen treatment. *Am J Dis Child* 138: 388-391.
62. Nicholas DB, Otley A, Smith C, Avolio J, Munk M, et al. (2007) Challenges and strategies of children and adolescents with inflammatory bowel disease: A qualitative examination. *Health Qual Life Outcomes* 5: 28.
63. Bruce T (1986) Emotional sequelae of chronic inflammatory bowel disease in children and adolescents. *Clin Gastroenterol* 15: 89-104.
64. Engstrom I (1991) Parental distress and social interaction in families with children with inflammatory bowel disease. *J Am Acad Child Adolesc Psychiatry* 30: 904-912.
65. Engstrom I (1999) Inflammatory bowel disease in children and adolescents: mental health and family functioning. *J Pediatr Gastroenterol Nutr* 28: S28-33.

-
66. Tojek TM, Lumley MA, Corlis M, Ondersma S, Tolia V (2002) Maternal correlates of health status in adolescents with inflammatory bowel disease. *J Psychosom Res* 52: 173-179.
 67. Maunder R, Esplen MJ (1999) Facilitating adjustment to inflammatory bowel disease: a model of psychosocial intervention in non-psychiatric patients. *Psychother Psychosom* 68: 230-240.
 68. De Boer M, Grootenhuis M, Derkx B, Last B (2005) Health-related quality of life and psychosocial functioning of adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 11: 400-406.
 69. Mittermaier C, Dejaco C, Waldhoer T, Oefflerbauer-Ernst A, Miehsler W, et al. (2004) Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Med* 66: 79-84.
 70. Wolfe BJ, Sirois FM (2008) Beyond standard quality of life measures: the subjective experiences of living with inflammatory bowel disease. *Qual Life Res* 17: 877-886.
 71. Rufo PA, Denson LA, Sylvester FA, Szigethy E, Sathya P, et al. (2012) Health supervision in the management of children and adolescents with IBD: NASPGHAN recommendations. *J Pediatr Gastroenterol Nutr* 55: 93-108.
 72. Hommel KA, Davis CM, Baldassano RN (2008) Medication adherence and quality of life in pediatric inflammatory bowel disease. *J Pediatr Psychol* 33: 867-874.
 73. Hommel KA, Davis CM, Baldassano RN (2009) Objective versus subjective assessment of oral medication adherence in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 15: 589-593.
 74. Mackner LM, Crandall WV (2005) Oral medication adherence in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 11: 1006-1012.
 75. Hommel KA, Denson LA, Crandall WV, Mackner LM (2008) Behavioral Functioning and Treatment Adherence in Pediatric Inflammatory Bowel Disease: Review and Recommendations for Practice. *Gastroenterol Hepatol (N Y)* 4: 785.
 76. Whitfield EP, Fredericks EM, Eder SJ, Shpeen BH, Adler J (2015) Transition readiness in pediatric patients with inflammatory bowel disease: patient survey of self-management skills. *J Pediatr Gastroenterol Nutr* 60: 36-41.