Systematic Review of the Evidence Base for the Medical Treatment of Paediatric Inflammatory Bowel Disease

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ABSTRACT

Objective: To systematically review the evidence base for the medical (pharmaceutical and nutritional) treatment of paediatric inflammatory bowel disease.

Methods: Key clinical questions were formulated regarding different treatment modalities used in the treatment of paediatric (not adult-onset) IBD, in particular the induction and maintenance of remission in Crohn disease and ulcerative colitis. Electronic searches were performed from January 1966 to December 2006, using the electronic search strategy of the Cochrane IBD group. Details of papers were entered on a dedicated database, reviewed in abstract form, and disseminated in full for appraisal. Clinical guidelines were appraised using the AGREE instrument and all other relevant papers were appraised using Scottish Intercollegiate Guidelines Network methodology, with evidence levels given to all papers.

Results: A total of 6285 papers were identified, of which 1255 involved children; these were entered on the database. After critical appraisal, only 103 publications met our criteria as evidence on medical treatment of paediatric IBD. We identified 3 clinical guidelines, 1 systematic review, and 16 randomised controlled trials; all were of variable quality, with none getting the highest methodological scores.

Conclusions: This is the first comprehensive review of the evidence base for the treatment of paediatric IBD, highlighting the paucity of trials of high methodological quality. As a result, the development of clinical guidelines for managing children and young people with IBD must be consensus based, informed by the best-available evidence from the paediatric literature and high-quality data from the adult IBD literature, together with the clinical expertise and multidisciplinary experience of paediatric IBD experts.

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Crohn disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC) together form inflammatory bowel disease (IBD), a common and chronic cause of morbidity in children and teenagers. The aims of treatment of IBD in childhood and adolescence are to induce remission of disease activity, maintain remission, prevent relapse, normalise growth and development, and restore a normal quality of life without adverse effects of either disease or therapy. In textbooks, CD is noted as manifesting during childhood or adolescence in up to 25% of patients (1) and UC manifests before 20 years of age in between 15% and 40% of all patients (2). Recent evidence from Scotland would suggest that 50% of IBD cases present in children and adolescents (3), confirming the need for paediatric multidisciplinary teams with appropriate training, expertise, and experience for the management of IBD in these children and teenagers. In a prospective survey of cases of newly diagnosed children younger than 16 years of age in the United Kingdom during a 13-month period in 1998, 33% of children received care only from adult services (4). During that time period, many children were seen by general paediatricians with help from adult services; for example, only 50% of children in Scotland had any involvement in 1998/1999 with a paediatric gastroenterology, hepatology, and nutrition service (4). The presence of evidence-based clinical guidelines, presenting age-appropriate data from a large number of systematic reviews, meta-analyses, and well-designed randomised controlled trials (RCT) of therapy, would be of inestimable benefit in the management of children and teenagers with IBD, particularly if they are not being seen or are rarely seen by relevant specialist paediatric IBD teams.

The lack of availability of both evidence-based clinical guidelines and methodologically sound RCT of treatment modalities for paediatric IBD is widely known to be a problem, including to the IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition (BSPGHAN). In their review of the best-available evidence for the treatment of IBD in childhood, Escher et al (5) were able to find only 1 placebo-controlled RCT in children with IBD. Others have also recently reviewed treatment options for paediatric IBD (6–8). The BSPGHAN IBD Working Group therefore wished to construct a methodologically robust, consensus-based clinical guideline for the treatment of paediatric IBD, comprising the best-available evidence

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from the paediatric literature, relevant methodologically high- quality data from the adult IBD literature, together with clinical expertise from multidisciplinary paediatric IBD specialists. The authors' aim for the first phase of this process was to produce a systematic review of the evidence base available for the treatment of paediatric IBD, with the evidence on the therapies appraised in a critical manner.

METHODS

Clinical Questions

The key clinical question was ''What is the evidence for this therapy in the treatment of paediatric IBD?'' with treatment modalities confined to medical and nutritional treatment, and excluding surgical treatment. The following specific subquestions were also to be answered:

- Does this therapy induce remission in children younger than 18 years with CD compared to placebo or other therapies?
- Does this therapy maintain remission in children younger than 18 years with CD compared to other therapies or placebo?
- Does this therapy induce remission in children younger than 18 years with UC compared to placebo or other therapies?
- Does this therapy maintain remission in children younger than 18 years with UC compared to placebo or other therapies?
- Is there any harm associated with this therapy in the management of paediatric IBD?
- Does this therapy affect bone health in children younger than 18 years with IBD?

Approach to Evidence Review

Clinical guidelines were assessed by a subgroup (D.C.W., A.G.T.). Medication or nutritional therapies were divided into categories and reviewed by a further 7 subgroups: immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, ciclosporin, tacrolimus, thalidomide, mycophenolate [M.S.M., M.E., S.H.M., D.C.W.]); 5-aminosalicylate acid (5-ASA) preparations and sulphasalazine (N.M.C., A.S., D.C.W.); corticosteroids (J.M.E.F., R.M.B.); biological agents (A.K.A., B.K.S., B.K.S., D.C.W.); antibiotics, antituberculous therapy, and probiotics (S.G.M., E.N., D.C.); nutrition (enteral nutrition [EN], parenteral nutrition [PN], and fish oil [D.C.W., A.G.T.]); and other treatment modalities (those not covered in previous 6 categories by D.C.W., A.G.T.).

Inclusion Criteria

To obtain the maximal clinical material for review, the inclusion criteria involved any of the following studies for the treatment of paediatric IBD: clinical guidelines, systematic reviews and meta-analyses, RCT, other controlled trials, cohort studies, case-control studies, case series, and expert opinion (including letters and narrative review). Paediatric therapy statements from the European Crohn's and Colitis Organisation (ECCO) consensus on diagnosis and management of CD (9–11) were noted.

It was not our aim to perform a comprehensive literature search for all of the evidence for treatment of adult IBD, but relevant adult data from reviews of treatment of IBD in the Cochrane Library to the end of 2006, statements from ECCO on diagnosis and management of CD (9–11), the British Society of Gastroenterology guidelines for the management of IBD in adults (12), and other major systematic reviews or meta-analyses were reviewed. Reviews of the IBD group of the Cochrane Collaboration are highlighted in the discussion of each treatment modality.

Electronic Searches

The electronic search strategy of the Cochrane IBD group was used (*www.mrw.interscience.wiley.com/cochrane_clsysrev_crglist_fs.html*). A hierarchy of material was searched, with the initial search being for clinical guidelines, systematic reviews, RCTs, cohort studies, and case-control studies. For completeness of the evidence review, the search was extended to surveys, letters, narrative reviews, case series, and case reports. Repeated searches were performed during a period of time, with electronic searches made in November 2001, August 2004, January 2007, and May 2007. MEDLINE was searched from 1950 to December 2006 and Embase from 1980 to December 2006 (A.G.T., E.N.). Successive issues of the Cochrane Library up to 2007, issue 2, were searched for reviews on CD, UC, and IBD (E.N., D.C.W.).

Hand Searching and Other Sources

Hand searching was performed for RCTs of the treatment of paediatric IBD only. These were searched from 1996 to 2006 and represented the meeting abstracts (relevant journal) from BSPGHAN (*Archives of Disease of Childhood*, A.G.T.), European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (*Journal of Pediatric Gastroenterology and Nutrition*, S.G.M.), North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (*Journal of Pediatric Gastroenterology and Nutrition*, D.C.), Digestive Disease Week (*Gastroenterology*, N.M.C.) and United European Gastroenterology Week (*Gut*, S.H.M.). Relevant papers from reference lists and from the personal collections of IBD working group members were also used to complete the literature search.

Processing of Literature

Details of all papers were entered on a dedicated database (A.S.). All abstracts obtained from the electronic searches were reviewed in abstract form to obtain those relevant to treatment of paediatric IBD and to our key questions. This was performed by 2 members of the group, with any disagreement enlisting the help of a third member, all of whom were trained in critical appraisal (E.N., A.G.T., D.C.W.). We only reviewed the English language literature. Full papers were then distributed to the 8 subgroups for critical appraisal. These papers were reviewed in all 8 subgroups for relevance to key clinical questions and for appropriate study design. After this, the included papers were critically appraised using predetermined criteria (see below). All of the papers were reviewed by at least 2 members of the subgroup, with any disagreement resolved by other working group members, up to the whole group if necessary. Papers that had been received but were judged as either irrelevant or of inappropriate design were excluded, and each subgroup kept a list of excluded studies. Examples of excluded studies were those that had been identified in the initial search including the methodology filter of age younger than 18 years but contained either only adult data or where it was impossible to separate out the adult and paediatric combined data.

Critical Appraisal

Clinical guidelines were appraised using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (13). After analysis of each document using the 23 key items organised in 6 domains of the AGREE appraisal instrument, an overall assessment is given as to whether the guidelines under consideration are

recommended for use in practice. There are 4 choices: ''strongly recommend,'' ''recommend (with provisos or alterations),'' ''would not recommend,'' or ''unsure.''

Full copies of all of the papers were then obtained and critically appraised using the Scottish Intercollegiate Guidelines Network (SIGN; *www.sign.ac.uk*) methodology (14,15) by at least 2 appraisers in the other 8 subgroups. A third appraiser was consulted if agreement could not be reached. In this appraisal, SIGN checklists on methodology were used for systematic reviews and meta-analyses (defined as evidence level of 1), RCTs (defined as evidence level of 1), cohort studies (defined as evidence level of 2), and case-control studies (defined as evidence level of 2). Studies of evidence levels 1 and 2 were further appraised on their methodological quality as ++, +, or − (14,15). All of the other observational evidence (defined as case series, surveys, and case reports) that contained relevant clinical details and outcome data (benefit, harm) and had been subject to the peer review process was given an evidence level of 3. Narrative reviews and statements from expert groups that did not have a strict guide to methodology were given an evidence level of 4, as were letters to journals that contained relevant clinical details and outcome data (benefit, harm) but had not been subject to the peer review process. The included evidence was constructed into an evidence table for each subgroup; studies that were excluded were noted for each evidence table.

Manuscript Preparation

The writing group consisted of Drs Akobeng, Croft, Fell, Mitton, Thomas, and Wilson, and was led by Dr Wilson.

RESULTS

A total of 6285 papers were identified, of which 1255 were on children; these were entered into the database. After critical appraisal, only 103 publications met our criteria as evidence on medical and nutritional treatment of paediatric IBD. Within this number, we identified only 3 clinical guidelines, 1 systematic review, and 16 RCT; all of them were of variable quality and none obtained the highest methodological scores.

Clinical Guidelines

There are no published European or North American guidelines specifically for managing children and young people with IBD. We reviewed 3 clinical guidelines: the section on CD in children and adolescents of the ECCO consensus on diagnosis and management of CD (11) and Japanese guidelines on the treatment of children with UC (16) and CD (17). After analysis of each document using the 23 key items organised in 6 domains of the AGREE appraisal instrument, none were strongly recommended for use in practice, being either recommended with provisos and alterations (11) or not recommended (16,17). The lack of relevant guidelines with appropriate methodology resulted in our comprehensively reviewing all of the remaining evidence.

Immunomodulators

There are 26 publications on immunomodulator usage included in evidence Tables 1 and 2. There have been 13 publications (Table 1) on use of azathioprine and 6-mercaptopurine (6-MP), namely 1 RCT (18; evidence level (EL) 1-), 1 cohort study (19; EL2+), 2 questionnaire surveys (20,21; EL3), and 9 case series (22–30; EL3). There have been 6 case series (31–36; EL3) of cyclosporin usage, 2 case series, and 1 case report (37–39; EL3) of topical or oral tacrolimus usage, 2 case series (40,41; EL3) of methotrexate usage, and 1 case series (42; EL3) and 1 letter (43; EL4) concerning thalidomide usage (Table 2). There are no reports of mycophenolate usage.

Induction of Remission in IBD

There were no paediatric studies that specifically addressed the possible role of azathioprine and 6-MP in the treatment of active CD. A small case series reported the use of low dose (3 mg/kg) intravenous azathioprine to aid speed of time to remission in 3 children with severe colitis—1 each of CD, UC, and IC (22).

Cyclosporin usage (Table 2) to induce remission was analysed in 6 case series, 3 of UC (31,32,34; total of 19 children), 2 of CD (33,35; total of 20 children), and 1 mixed (36; 6 children). Although described as having random allocation, no details of randomisation are given by Nicholls et al (35), and a personal communication from a member of the research team casts doubt on randomisation having been performed, so this has been treated as a case series (following guidance from SIGN).

There have been 3 case series or reports (37–39) of tacrolimus usage to induce remission in severe oral or perianal CD, 2 topical and 1 oral (Table 2).

There have been 2 case series of methotrexate usage to induce remission in CD (40,41; 14 and 61 children, respectively) (Table 2). Nine of 14 showed clinical and haematological response within 4 weeks in the first series, and methotrexate improved the patients' condition or induced a remission in 49 of 61 (80%) patients in the second.

There is 1 case series and 1 letter concerning thalidomide usage to induce remission in refractory CD (42,43; 4 children).

Maintenance of Remission in IBD

In a RCT of 55 children with newly diagnosed moderate-to-severe CD who were randomised to receive an initial course of prednisone and either 6-MP or placebo, follow-up lasted for 18 months (18). No difference in remission rate was noted between the treatment groups (both 89%). Those taking 6-MP had a reduced total duration of corticosteroid usage, and their cumulative steroid dose received was also less. Only 9% of the 6-MP group relapsed during the study period compared with 47% of the controls. This trial was not sufficiently powered and may have failed to identify a significant effect on remission rates.

In a retrospective cohort study from 3 centres in the Netherlands, median maintenance of first remission in patients with CD was longer in steroid-treated patients who received azathioprine from the outset compared with those who did not. (19). There were 8 published case series reporting the authors' experience with azathioprine or 6-MP in children with relatively troublesome IBD (both UC and CD) (24–30). The authors merely indicated that in their experience the agents were ''generally well tolerated and useful,'' while in some cases quantifying corticosteroid usage. In 1 retrospective review the use of 6-MP or azathioprine for perianal CD was examined (27). There is 1 case series and 1 letter concerning thalidomide usage to maintain remission in refractory CD (42,43; 4 children).

Methotrexate was evaluated in 1 series from 3 French centres (41); methotrexate was given to 61 children with active CD either because of nonresponse to or relapse on azathioprine (n = 42) or azathioprine intolerance/toxicity (n = 19). Methotrexate had improved the patients' condition or induced a remission in 49 (80%). Complete remission was observed in 39%, 49%, and 45% at 3, 6, and 12 months, respectively.

TABLE 1. Evidence table for azathioprine and 6-MP use in paediatric IBD

Author/year (ref)	Methodology	Evidence level	Subjects	Intervention	Outcome	Comment
Markowitz et al, 1993 (20)	Expert opinion	3	Questionnaire to members of NASPGHAN	None	Use of azathioprine and 6-MP was common for intractable IBD and steroid-dependent disease	
Markowitz et al, 2002 (21)	Expert opinion	3	Questionnaire to members of NASPGHAN	None	Substantial increase in azathioprine and 6-MP use between 1990 and 2000, particularly in early disease	
Markowitz et al, 2000 (18)	RCT	1-	Moderate/severe active CD (55)	Routine use of 6-MP (1.5 mg/kg) from presentation	Use of 6-MP was associated with reduced prednisone usage and a reduction in relapse rate for 18 mo	Small number of participants; only 32/55 completed study; lack of clarity on data analysis for subjects withdrawing early
Casson et al, 1999 (22)	Case series	3	Acute fulminant colitis: UC (1), CD (1), IC (1)	IV azathioprine (single dose 3 mg/kg)	All 3 achieved remission and were then maintained on oral azathioprine	Only 3 subjects; uncontrolled
Papp et al, 1974 (23)	Case series	3	Poorly controlled CD (6)	Azathioprine (2 mg/kg)	For 13–39 mo follow-up clinical benefits seen, although 1 patient died	Small numbers of subjects; uncontrolled
Kader et al, 1999 (24)	Case series	3	Active UC (20)	Treated with azathioprine or 6-MP	Steroids were discontinued in 12/16 with steroid-dependent disease	Small numbers (20); retrospective
Markowitz et al, 1990 (25)	Case series	3	CD (36)	> 6 mo of 6-MP	6-MP reduced disease activity, prednisone usage, and frequency of perianal fistulas and abscesses	Retrospective study comparing patient data before and after commencing 6-MP
Verhave et al, 1990 (26)	Case series	3	CD (12), UC (9)	Azathioprine (2 mg/kg)	Reported benefit after 3 mo with reduced steroid usage	Only 21 subjects; uncontrolled
Jeshion et al, 2000 (27)	Case series	3	CD (20) with perianal disease	Treated with azathioprine or 6-MP for >6 mo	15 improved	Retrospective; uncontrolled
Fuentes et al, 2003 (28)	Case series	3	IBD (107)	Treated with high-dose azathioprine (3 mg/kg)	Only 2 had to discontinue treatment due to adverse effects	Retrospective; uncontrolled
Kirschner, 1998 (29)	Case series	3	CD (66), UC (28)	Treated with azathioprine or 6-MP	17 discontinued medication (hypersensitivity, pancreatitis, GI intolerance); in 78 continuing treatment, mean daily prednisolone dose reduced from 24.6 to 8.3 mg	Retrospective; uncontrolled
Barnes et al, 2004 (30)	Case series	3	IBD (120)	Treated with azathioprine or 6-MP	Improvement associated with pattern of low CRP despite minor ESR increase, and elevation of MCV	Retrospective, uncontrolled
Jaspers et al, 2006 (19)	Retrospective cohort	2+	CD (72)	Treated with azathioprine	Maintenance of remission was longer in those receiving azathioprine from time of diagnosis	Uncontrolled

CD = Crohn disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; IBD = inflammatory bowel disease; IC = indeterminate colitis; IV = intravenous; MCV = mean corpuscular volume; 6-MP = 6-mercaptopurine; NASPGHAN = North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition; RCT = randomised clinical trial; UC = ulcerative colitis.

TABLE 2. Evidence table for cyclosporine, tacrolimus, and methotrexate use in paediatric IBD

Author/year (ref)	Methodology	Evidence level	Subjects	Intervention	Outcome	Comment
Treem et al, 1995 (31)	Case series	3	Severe acute UC (14), unresponsive to bowel rest, TPN, and methylprednisolone	Oral cyclosporine 4.6–9.6 mg · kg^{-1} day^{-1}, adjusted for trough 150–300 ng/mL	11/14 responded in 2–9 days; 2/11 required surgery by 20 days, and 7 subsequently required surgery by 1 y	May prevent need for emergency colectomy and allow nutritional and psychological preparation for elective procedure
Benkov et al, 1994 (32)	Case series	3	Severe, treatment-resistant UC (5)	IV followed by oral cyclosporine	Only 1 responded, all 5 requiring surgery	1 patient with significant hypertension
Mahdi et al, 1996 (33)	Case series	3	Crohn colitis (10) unresponsive to methylprednisolone + TPN	Induction of remission with IV then oral cyclosporine, maintained with 6-MP	Response in 7/10, overall reduction of PCDAI (mean 55→ 19) by 2 wk; 3 nonresponders and 3 relapsers required surgery	Adverse effects included hypertension, hirsutism, and tremors
Hyams and Treem, 1989 (34)	Case series	3	2 adolescents with fulminant UC	Oral cyclosporine	Remission within 5 days	Both sustained remission for 8–12 mo
Nicholls et al, 1994 (35)	Case series	3	Newly diagnosed or relapsed CD (10)	Oral cyclosporine (10 cases) versus conventional therapy (14)	Worse clinical response to cyclosporine compared to conventional therapy, similar histological changes at 8 wk	Not recommended as initial therapy for CD
Ramakrisha et al, 1996 (36)	Case series	3	Severe UC or CD (6)	IV cyclosporine followed by oral (7 also received azathioprine/6-MP)	7/8 showed rapid clinical response, but 3 of these needed colectomy by 1 y; 4/8 in remission 2–5 y, off cycA.	
Casson et al, 2000 (37)	Case series	3	Treatment-resistant oral or perianal CD (8)	Topical tacrolimus	7/8 improved within 6 wk, healing within 1–6 mo	Rebound worsening on stopping treatment in 2/8
Russell et al, 2001 (38)	Case report	3	Treatment-resistant oral CD	Topical tacrolimus	Marked clinical improvement, but significant systemic absorption	Patient developed shingles
Bousvaros et al, 2000 (39)	Case series	3	14 children with treatment-nonresponsive UC and CD colitis	Oral tacrolimus (0.1 mg/kg bd)	1 withdrew, 9/13 responded, of whom 4 required surgery within 1 y	Potential to delay but not prevent surgery in severe UC in 50% of initial responders
Mack et al, 1998 (40)	Case series	3	CD unresponsive to 6-MP and steroids (14)	Low-dose weekly SC methotrexate	9/14 showed improvement; treatment stopped in 4—adverse effects or electively	One patient died with acute onset illness (also receiving steroids)
Ulhen et al, 2006 (41)	Case series	3	CD (61) in whom azathioprine either failed or was not tolerated	Weekly methotrexate SC or IM 17 mg/m^2	MTX was associated with remission in 39%, 49%, and 45% at 3, 6, and 12 mo; MTX discontinued in 10% due to poor tolerance	Retrospective; uncontrolled
Facchini et al, 2001 (42)	Case series	3	Refractory CD (3) with steroid dependency or resistance	Thalidomide 1.5–2.0 mg · kg^{-1} day^{-1}	No relapses in minimum 19 mo follow-up	Retrospective; also 2 males age >18 y in series
Odeka and Miller, 1997 (43)	Case (letter)	4	Oral CD refractory to azathioprine and steroid dependent	Thalidomide 100 mg	Remission of oral CD	

CD = Crohn disease; IBD = inflammatory bowel disease; IM = intramuscular; IV = intravenous; 6-MP = 6-mercaptopurine; MTX = methotrexate; PCDAI = Pediatric Crohn's Disease Activity Index; SC = subcutaneous; TPN = total parenteral nutrition; UC = ulcerative colitis;

Harm

In the RCT of 6-MP in CD, no growth disadvantage was identified amongst patients taking steroids, but the small number of subjects (n = 55) and the relatively short duration of the study (18 months) could have concealed any benefit (18). A rapid response to topical tacrolimus was noted in a 15-year-old with severe oral CD, but there was significant systemic absorption and treatment was complicated by shingles (38). Adverse reactions were observed in 14 of 61 patients (24%) receiving methotrexate (41), requiring discontinuation in 6 (10%). There are no published studies regarding risk of malignancy and immunosuppressant usage in patients with paediatric IBD.

Bone Health

No study reported bone health as an outcome.

5-Aminosalicylate Acid Preparations and Sulphasalazine

There are 13 publications on mesalazine and sulphasalazine usage included in evidence Table 3. There were 3 RCT (44–46; EL1-) involving 102 patients and a cohort study (47; EL2-) of 153 patients. An additional 147 patients were reported in 9 case series (48–56; EL3).

Induction of Remission in CD

There is 1 small RCT examining the effect of mesalazine against placebo for small bowel CD after 1, 2, and 3 months of therapy (44). Six of 14 children enrolled in the study completed it. A total of 40% improved with mesalazine compared with 20% with placebo.

Maintenance of Remission in CD

There is no evidence for the use of aminosalicylates for the maintenance of remission in CD in children.

Induction of Remission in UC

Two RCTs (45,46) were identified in children. Ferry et al compared orally administered olsalazine ($30\,mg\ kg^{-1}\cdot day^{-1}$) against sulphasalazine ($60\,mg \cdot kg^{-1}\cdot day^{-1}$) in 59 children (45). There was a nonsignificant trend in favour of sulphasalazine, comparing remission rates after 3 months of monotherapy (79% vs 50%). No difference in adverse effects was noted and all of these were reported to be minor. Odera et al reported in 29 patients that either ASA or hydrocortisone enemas resulted in a higher remission rate than placebo for isolated left-sided colitis (46).

Maintenance of Remission in UC

There is no evidence for the use of aminosalicylates for the maintenance of remission in UC in children.

Harm

Although adverse effects were reported in many of the paediatric studies (eg, diarrhoea, skin rash, neutropaenia), only 1 case series specifically investigated the risk of renal adverse effects and found none (55).

Bone Health

No study reported bone health as an outcome.

Corticosteroids

There are 33 publications on corticosteroid usage included in evidence Table 4. Apart from 1 small RCT that compared different enema regimens to placebo (46; EL1), none of the other RCTs have been placebo controlled (57, EL1+; 58–62, EL1-). In these 7 RCTs (all in CD), prednisolone has been used as standard therapy in 6 and oral methyl prednisolone in 1 (57), against which other treatments were tested (EN in 4 [57–60], azathioprine in 1 [18], and budesonide in 2 [61,62]). There was 1 meta-analysis comparing EN with corticosteroids in children with CD (63; EL1-).

The other papers identified have focused on different aspects of corticosteroid therapy in both UC and CD. There were 2 large case series that reported the natural history of 97 children with UC (64, EL3) and 109 with CD (65; EL3). These provided information on outcome at 1 year following various treatments including corticosteroids in most cases. Further case series reported children with CD and UC treated with prednisolone (66; EL3); children with CD treated with budesonide (67–70; EL3), EN (35,71,73; EL3), or azathioprine (25; EL3); and children with UC (72; EL3) treated with prednisolone. A further set of 12 reports focused on pharmacokinetics (74,75; EL3) and the potential adverse effects of corticosteroids (76–85; EL3) on growth, metabolism, bone health, ocular pressure, and intracranial hypertension.

Induction of Remission in CD

All but 1 (57) of the RCTs comparing EN with corticosteroids to induce remission in intestinal CD were of poor methodological quality (58–60), as is the systematic review on the subject (63). The 2 RCTs comparing corticosteroids with budesonide (61,62) were also of poor methodological quality. There are no RCT comparing dosage regimens or weaning regimens, although a dose of prednisolone of 1 to $2\,mg \cdot kg^{-1}\ day^{-1}$, or budesonide of 9 mg is adopted in nearly all of the studies. These doses have been found to induce remission in the reported case series.

Maintenance of Remission in CD

Steroid dependence at 1 year of 31% has been reported in 1 series (65), in which 81% of cases had received immunomodulatory therapy and 28% received infliximab.

Induction of Remission in UC

There was 1 small RCT into different enema regimens (hydrocortisone, 5-ASA or placebo), which included 10 cases with UC (46). Otherwise, there are no RCTs on corticosteroid use in UC to attain remission; however, in 2 series (totalling almost 100 cases) remission was obtained with prednisolone or methyl-prednisolone doses of 1 to $2\,mg \cdot kg^{-1}\ day^{-1}$ before tapering (64,73). In 1 of these series (64), corticosteroids were avoided in 21% of cases only in the first year after diagnosis.

Maintenance of Remission in UC

Steroid dependence at 1 year of 45% has been reported in 1 series (64), in which 61% of patients had also received azathioprine or 6-MP.

TABLE 3. Evidence table for aminosalicylate use in paediatric IBD

Author/year (ref)	Study	Evidence level	n	Outcomes measured	Effect size	*P*	Notes	Efficacy	Dose	Adverse effects
Griffiths, 1993 (44)	RCT	1-	6 (14)	Mesalazine for small bowel CD; relapse at 1, 2, 3 mo		NS		40% improved with ''mesalazine'' and up to 20% with placebo	50 mg · kg^{-1} day^{-1} Pentasa	None reported
Ferry et al, 1993 (45)	RCT	1-	56 (59)	PCDAI on olsalazine vs sulphasalazine in UC	Remission at 1 mo: olsalazine 13/30 and sulphasalazine 21/29	0.034		Olsalazine 50% improved; sulphasalazine 79% improved	Olsalazine 30 mg/kg/day (max 2 g) sulphasalazine 60 mg · kg^{-1} day^{-1}	No major; minor effects with olsalazine (39%) and sulphasalzine (46%)
Odera et al, 1986 (46)	RCT	1-	29	5-ASA vs hydrocortisone vs placebo enemas for UC and IC	Clinical and histological remission and need for oral 5-ASA	<0.05 (placebo vs 5-ASA or hydrocortisone)	Only abstract in English	3/10 placebo, 6/9 5-ASA, and 5/11 efficacy	1g 5-ASA vs 25 mg hydrocortisone	
Koutras et al, 1985 (55)	Case series	3-	13				Description of renal effects in 13 5-ASA vs 13 not taking 5-ASA			No evidence of renal risk
Christensen et al, 1993 (48)	Case series	3	9	5-ASA in plasma and faecal water			Description of bioavailability		Pentasa 1 g/day, sulphasalzine max 2 g/day	
Barden et al, 1989 (49)	Case series	3	45				Case series describing mesalazine (Asacol) in those intolerant to sulphasalazine		1–1.5 g · mg^{-1} day^{-1} of sulphasalazine; mesalazine 800 mg/day	2/45 had neutropaenia and 1/45 had rash
Bondesen et al, 1986 (50)	Case series	3	19		Recovery of sulphasalzine in faeces and plasma concentration		Kinetics in children with UC		Sulphasalzine 50 mg/kg	
Clarke et al, 1982 (51)	Series	3	24	Pharmcakinetics and acetylator status	No efficacy data			Not examined	Range 20–100 mg/kg	Not related to dose, acetylator status, or serum concentration

Leickly et al, 1986 (52)	Case report	3	1			Case report about IgG			
Tolia et al, 1989 (53)	Case series	3	5	Pharmacokinetic data		CD and UC; 3/5 weaned off steroids; plasma and urinary levels similar to adult	400–1200 tds		2/5 had diarrhoea and stopped medication (but sounds like disease process not drug)
Goldstein et al, 1979 (54)	Case series	3	15	Sulphasalazine levels	Serum levels		40–70 mg · kg^{-1} day^{-1}		Looked at acetylator status
D'Agata et al, 1996 (47)	Cohort	2-	153	Eudragit 5-ASA, adverse effects, tolerance		Retrospective, 10-y experience	Not studied	30–50 mg/kg	5.2 (8/152) diarrhoea the main one, no renal/hepatic/ rash/dyscrasia
Wiersma, et al 2004 (56)	Case series	3	16	Pharmacokinetic data on mesalazine UC/CD	No efficacy data			20 mg/kg mesalazine)	

5-ASA = 5-aminosalicylate acid; CD = Crohn disease; IBD = inflammatory bowel disease; IgG = immunoglobulin G; PCDAI = Pediatric Crohn's Disease Activity Index; RCT = randomised controlled trial; UC = ulcerative colitis;

TABLE 4. Evidence table for corticosteroid use in paediatric IBD

Author/year (ref)	Study type	Evidence level	Population	Outcomes measured	Effect size	CI/*P*	Comments
EN vs steroids							
Heuschkel et al, 2000 (63)	Meta-analysis (CD)	1-	147 randomised cases	Remission rate		CS vs EN NS	Inadequate power, contains abstracts of RCT
Sanderson et al, 1987 (58)	RCT (CD)	1-	CD: EN (Flexical) 8; steroids 8	Decrease in Lloyd Still Disease Activity Index, growth (SDS) 6 mo	EN 0.3, CS −2.8	NS/$P < 0.05$	Steroid treatment: ACTH 2 IU · kg^{-1} day^{-1} for 5 days then prednisone 2 mg/kg max 30; small no.
Ruuska et al, 1994 (59)	RCT (CD)	1-	CD: prednisolone 9, polymeric diet 10	Decrease in PCDAI: prednisolone 45−14, EN 45−12	NS (small no.)	NS	Prednisolone dose 1.5–60 mg/kg
Thomas et al, 1993 (60)	RCT (CD)	1-	CD: prednisolone 12, elemental diet 12	Increase in LSI, growth at 6 mo; prednisolone z −3.1, elemental z 0.32	NS	NS	Prednisolone 2 mg/kg up to 60
Borrelli et al, 2006 (57)	RCT (CD)	1+	CD: CS 18, polymeric diet 19	Remission (PCDAI≤10), Mucosal healing	Steroid remission 67%, diet remission 79%, Steroid healing 33%, diet healing 74%	95% CI 44%–85%, 95% CI 56%–84%, $P = 0.4$, $P < 0.05$	Polymeric diet (Modulen IBD) 10 wk CS: oral methyl prednisolone 1.6 mg · kg^{-1} day^{-1} 4 wk, then 6-wk taper, Study powered for 50% difference between groups
Budesonide vs prednisolone							
Levine et al, 2003 (61)	RCT (CD)	1-	Mild/moderate CD (PCDAI 12.5–40; 58% ileocaecal, 27% ileocolonic, 15% colitis): budesonide 19, prednisolone 14	Remission at 12 wk (steroid-related adverse events as secondary measure)	Remission 12 wk: budesonide 47%, prednisolone 50%, Adverse effects: budesonide 32%, prednisolone 71%	NS, $P < 0.05$	Prednisolone dose 40 mg/day, taper from 2 wk; budesonide dose 9 mg/day for 8 wk, then taper (stop after 10 wk); nonblinded study
Escher, 2004 (62)	RCT (CD)	1-	Ileal and/or ascending colon CD: budesonide 22 (9 mg for 8 wk, then 6 mg), prednisolone (1 mg/kg for 4 wk, then taper)	Remission (adverse effects)	Budesonide remission 55%, prednisolone remission 71%	NS; difference −16%; 95% CI 45−13	Failed to recruit planned 120 cases, thus study terminated early; fewer side effects with budesonide; morning cortisol levels higher with budesonide
Azathioprine							
Markowitz et al, 2000 (18)	RCT (CD)	1-	CD: 6-MP 27, controls (prednisolone) 28	Relapse rate 18 mo; remission at 1 mo; pred nisolone use	Prednisolone 47%, 6-MP 9%, 6-MP 93%, prednisolone 79%	$P < 0.001$, NS, NS, $P < 0.001$	Prednisolone dose 1 mg/kg; max dose 40 mg for 1 mo, then taper
Enema							
Odera et al, 1986 (46)	RCT	1-	IC 19, UC 10, enema treatment, 9 (4 UC), 5-ASA 1 g/day, 10 (3 UC) hydrocortisone 25 mg, 10 (3 UC) placebo	Remission	5-ASA and hydrocortisone better than placebo	$P < 0.05$	Italian paper, English abstract; small no., predominance of IC
Registry: natural history of CD, UC							
Markowitz et al, 2006 (65)	Series	3	CD n = 109, from multicentre observational register	Short-term outcome: off prednisolone, not requiring infliximab or surgery at 3 mo; long-term outcome: discontinued steroids by 3−6 mo and off steroids at 1 y	60% short-term (3 mo) steroid responders; 61% had good long -term response to CS at 1 y, but 73% were on concomitant immunomodulatory therapy		Moderate/severe disease treated with prednisolone or methyl prednisolone at 1–2 mg · kg^{-1} day^{-1}, By 1 y, 81% received immunomodulatory treatment (28% received infliximab)

	Hyams et al, 2006 (64)	Series	3	UC n = 97, from a multicentre observational register	Short-term outcome: Inactive, moderate, or severe disease at 3 mo after CS therapy; long-term outcome: CS responsive+ inactive/mild disease within 3–6 mo and off CS for remainder of year 1	60% inactive disease at 3 mo (but 36% of these still taking CS), 50% CS responsive (45% CS dependent)		77/97 received CSs (typically prednisolone or methyl prednisolone) 1–2 mg · kg^{-1} day^{-1}; of those who received CSs concomitant medicines: azathioprine/6-MP 61%, 5-ASA 86%
	Tung et al, 2006 (66)	Series	3	CD (<19 y) n = 50, UC n = 36; population-based cohort observational study	Short-term outcome: remission at 30 days after steroid therapy; long-term outcome: maintenance of remission 1 y after steroid treatment complete	CD: 62% remission at 30 days, UC: 50% remission at 30 days; CD prolonged response 42%, UC prolonged response 57%	95% CI 41–80, 95% CI 23–77, 95% CI 23–63, 95% CI 29–82	Population cohort <19 y at diagnosis from 1940–2001; no CS dosage data provided
EN vs steroids: other studies								
	Papadopoulou et al, 1997 (71)	Cohort (CD)	2-	CD: prednisolone 18, EN 25	Remission, response, relapse, growth	Pred nisolone remission rate 64%		Retrospective; prednisolone 2–60 mg, halved every 2–4 wk to 5–10 mg, then stop; bias is study design against pred nisolone (more relapsed cases)
	Nicholls et al (35)	Series	3	CD: prednisolone 4, EN 10, cyclosporine 10	Fall in LSI	Cyclosporine response 67%; EN, prednisolone response 93%	NS difference in 2 treatments	Prednisolone dose 1–2 mg/kg; ??tapering; populations receiving different treatments differed more small bowel disease with prednisolone/EN group than cyclosporine, thus potential major bias at randomisation in this ''RCT''
	Faure et al, 1998 (74)	Series	3	CD 12: methyl prednisolone vs prednisolone				Pharmacokinetics
	Berni Canani, 2006 (73)	Series	3	CD: steroids 10, polymeric diet 12, semi-elemental diet 13, elemental diet 12	Remission rate; duration of remission	EN 86.5%, CS 90%	NS difference in treatments	CS treatment: methylprednisolone 1–2 mg · kg^{-1} day^{-1} max 40 mg for 4 wk, then taper; treatments nonrandomised
CD: budesonide; other studies								
	Kundhal et al, 2001 (67)	Series	3	CD: budesonide 32, ileum 23, ileocaecal 9	No useful remission rate			Acute dose 9 mg budesonide; maintenance 6 mg (variable acute courses)
	Levine et al, 2002 (68)	Case note review	3	Mild/moderate CD (not excluding distal colonic disease): budesonide 62, prednisolone 58	Remission	Budesonide 48%, prednisolone 77%	$P < 0.001$	Budesonide dose 0.45 mg · kg^{-1} day^{-1}, max 9 mg; prednisolone 2 mg · kg^{-1} day^{-1}, max 40 mg for at least 2 wk, Report adverse effect of benign intracranial hypertension with budesonide
	Lundin et al, 2003 (69)	Series	3	8 children (pharmacokinetic study)	Pharmacokinetics			Budesonide dose 9 mg in children >20 kg
	Dilger et al, 2006 (70)	Series	3	12 CD (pharmacokinetic/pharmacodynamic study)				Budesonide dose 9 mg/day

(continued)

TABLE 4. (*Continued*)

Author/year (ref)	Study type	Evidence level	Population	Outcomes measured	Effect size	CI/*P*	Comments
CD: azathioprine/ 6-MP; other studies							
Markowitz, 1990 (25)	Case series	3					Prednisolone use down with 6-MP use
UC: other studies							
Beattie et al, 1996 (72)	Series	3	20 UC	Colitis symptom score	Prednisolone 1–2 mg/kg tapering		
Milov et al, 1988 (75)	Single case	3					Steroid kinetics
Steroid adverse effects							
Tripathi et al, 1992 (76)	Survey	3	Steroids 54: CD 37, UC 17	Ocular pressure increase with steroids		$P<0.001$	
Tripathi et al, 1992 (77)	Survey	3	IBD 58: CD 38, UC 20; controls 58	Ocular complications or steroids			
Levine et al, 2001 (78)	Series	3	3 cases	Benign intracranial hypertension			Description of adverse events
Ucchida et al, 2006 (79)	Series	3	23 children with UC undergoing colectomy	Severe steroid-related complications	Osteoporosis 36%, glaucoma 32%, cataract 25%, hypertension 11%, growth retardation 50%	Compared with adult controls: $P=0.027$, $P=0.002$, $P=0.013$, NS, $P<0.0001$	In children a 100% risk of major steroid-related complication with a dose of glucocorticoids/ body weight of >300 mg/kg
Growth							
Motil et al, 1993 (80)	Cohort	2-	Growth in IBD (69 cases 49% CD, 51% UC)	Survey of growth			Growth suppression related to poor disease control rather than steroid dosage
Metabolism							
Azcue et al, 1997 (81)	Cohort	2-	24 ileocolonic CD, 12 EN, 12 prednisolone treated (19 malnourished, 22 healthy controls)	Energy expenditure and body composition	Prednisolone increases all body compartments (height unchanged) EN significantly greater increase in intracellular water and lean body mass	$P<0.05$	Prednisolone dose 1 mg · kg^{-1} day^{-1} for 1 mo, then taper 5 mg/week for 2 mo
Bone							
Boot et al, 1998 (82)	Survey	3	22 CD, 33 UC; 34 boys, ages 4–18 y	BMD reduced relative to Dutch reference; CD BMD less than UC; lower BMD with greater steroid use			
Gokhale et al, 1998 (83)	Survey (cross-sectional)	3	n = 99, IBD children	BMD reduced; effect greater with CD than UC; effect greater with increased steroid dose			
Cowan et al, 1997 (84)	Survey	3	CD 21, UC 11, controls 58	BMC reduced with IBD; effect greater with those who receive steroids (but no dose effect found)	41% with IBD 1SD or more reduced	$P<0.05$; $P<0.005$	Not clear whether effect is result of steroids or marker of worse disease
Walther et al, 2006 (85)	Survey	3	IBD n = 90; 34 steroid naïve, 53 steroid treated, 3 not known	BMD, BMAD	Osteoporosis (BMAD-SDS <2) girls 8%, boys 20%; steroid naïve 12%, steroid treated 11%		Limited data on steroid treatment exposure

ACTH = adrenocorticotropic hormone; BMAD = bone mineral apparent density; BMD = bone mineral density; CI = confidence interval; CS = corticosteroid; EN = enteral nutrition; IBD = inflammatory bowel disease; IC = indeterminate colitis; 6-MP = 6-mercaptopurine; NS = nonsignificant; PCDAI = Pediatric Crohn's Disease Activity Index; RCT = randomised controlled trial; SDS = standard deviation score.

Harm

Numerous adverse effects of corticosteroids have been reported in the context of IBD treatment, either as case series (76–85) or as individual cases within RCTs. These effects include raised ocular pressure, cataract, intracranial hypertension, infections, altered mood, and changes in cosmetic appearance. One RCT that compared prednisolone to budesonide failed to achieve the planned recruitment to investigate its primary outcome measures of remission, but as a secondary outcome measure reported reduced facial adverse effects and less cortisol suppression with budesonide (62). Two RCTs comparing corticosteroids with EN have described worsened short-term growth on corticosteroids (58,60).

Bone Health

The potential harmful effects of corticosteroids on bone health have also been explored in 4 case series (270 IBD cases treated with corticosteroids) (82–85). Although bone mineralisation was reduced in children with IBD, the studies were unable to distinguish conclusively between the effects of the underlying disease and the effects of therapy.

Biological Agents

Sixteen publications on biological therapy usage are included in evidence Table 5. There were 13 publications on the use of infliximab; 7 cohort or open-label studies (86–92 and 98; EL2-)—from which 1 cohort of 9 children with UC had both induction (87) and maintenance (98) of remission of UC described—and 5 case series (93–97; EL3). Three other biological agents have been studied in case series or reports, namely adalimumab (99; EL3), anti-CD25 (100; EL3), and CDP571 (101; EL3).

Induction of Remission in CD

There was an apparent benefit for children treated with infliximab (5 or 10 mg/kg) with medically refractory CD and also fistulising intestinal CD (86,88,89,91–95,97) in case series and cohort studies. In 1 prospective study, 3 consecutive infusions were given at 0, 15, and 45 days to children with refractory and/or fistulating disease and 19 of 21 went into complete remission by day 45 (86). In this study, all perianal fistulas (n = 12) had closed by day 90. In a prospective cohort study, Borrelli et al found infliximab to be effective in inducing remission, healing gut inflammatory lesions, and promoting growth (91).

There is a single case report (99) of a teenage girl with refractory CD and intolerant of infliximab who entered remission on adalimumab and has had 12 fortnightly doses, remaining in remission at week 22. There is a case series of 20 children with CD who received a single dose of CDP571 (101). At week 2, 30% were in remission.

Maintenance of Remission in CD

There have been no formal paediatric studies assessing the efficacy of infliximab for maintaining remission in CD. One prospective study (88) looked at the long-term (1 year) impact of remission induced by 3 infliximab infusions. It found that the effect was transitory, with 90% having frequent relapses despite immunosupression. In a retrospective study, 29% of 88 patients with CD who received between 1 and 17 infusions of infliximab during a median time period of 4 months were found to be in remission after 90 days (97).

Induction of Remission in UC

There have been 2 retrospective cohort studies of infliximab involving 23 children (87,90) and 1 case series involving 12 children (96). There is a case series of 4 children given anti-CD25 for fulminant UC who were then treated with intravenous cyclosporin or tacrolimus (100). None required colectomy within 60 days; 2 later relapsed after cyclosporin withdrawal and underwent elective colectomy.

Maintenance of Remission in UC

There was 1 retrospective cohort with follow-up of all patients for 26 to 38 months (98). Nine children with UC had infliximab to induce remission for UC (87); 7 responded and had a total of 33 infusions. Five of 7 maintained response and 2 required colectomy.

Harm

In the small total number of cases so far reported, a small number of adverse events have been reported. Hyams et al (93) reported adverse events—erythema, facial swelling, and dyspnoea—in 3 children. Serrano et al (94) reported 1 patient who developed *Staphylococcus aureus* septicaemia associated with septic arthritis and osteomyelitis. Cezard et al (88), in a retrospective cohort study, reported 1 case of anaphylactic reaction to medication and 1 case of catheter-related sepsis, 6 patients developed anti-nuclear antibodies, and 2 developed anti-DNA antibodies.

Bone Health

No study reported bone health as an outcome.

Antibiotics, Antituberculous Therapy, and Probiotics

There were no publications on antibiotic usage, antituberculous therapy, or probiotics that met the inclusion criteria, therefore, there is no evidence table.

Nutrition (Enteral Nutrition, Parenteral Nutrition, and Fish Oil)

There are 27 publications included in the evidence Table 6. There has been 1 systematic review of RCT of EN versus corticosteroids (63; EL1-). It contained 3 RCT (58–60; EL1-); since then, there has been 1 additional RCT of EN versus corticosteroids (57; EL1+). There have been 4 RCT of EN strategies, with both arms of the study receiving EN (102 [EL1+]; 103–105 [EL 1-]) There was 1 RCT of the addition of n3-fatty acid or olive oil placebo to mesalazine to maintain remission in CD (106; EL1-). There were no RCTs of the use of PN. There have been 5 cohort studies, 2 of supplemental EN (107 [EL2+]; 108 [EL2-]), and 1 each of EN or prednisolone (71; EL2-), intermittent EN (109; EL2-), and PN (110; EL2-). There have been 11 case series, 5 of EN for remission in CD (35,73,111–113; EL3), 1 of long-term EN (114; EL3), 1 of supplemental EN (115; EL3), 1 of intermittent EN (116; EL3), 1 of oral or rectal *N*-acetyl glucosamine as a nutritional substrate (117; EL3), and 2 of PN (118,119; EL3). There has been 1 case report of a significant adverse event during EN (120; EL3).

TABLE 5. Evidence table for biological agent use in paediatric IBD

Author/year (ref)	Study type	Evidence level	Population	Outcomes measured	Effect size	CI/*P*	Comments
Hyams et al, 2000 (93)	Case series (IFX)	3	Children with CD, n = 19	PCDAI and physician global assessment after 4 wk of infusion	Mean PCDAI decreased from 42.1 ± 13.7 to 10.0 ± 5.6	$P < 0.0001$	
Serrano et al, 2001 (94)	Case series (IFX)	3	Children with CD, n = 15	''Clinical improvement''	''All patients experienced subjective clinical improvements''		
Kugathasan et al, 2000 (86)	Cohort (prospective) (IFX)	2-	Children with CD, n = 15	''Clinical response'' and clinical remission as defined by PCDAI ≤15	10 of 15 children in remission at 10 wk		
Mamula et al, 2002 (87)	Cohort (IFX)	2-	Children with UC, n = 9	Clinical response as measured by the Lichtiger colitis activity index score and by PGA	Median Lichtiger score decreased from 11 before infusion to 1 at 2 wk; 7/9 had decreased activity as measured by PGA		Retrospective
Mamula et al, 2004 (98)	Cohort (IFX)	2-	Children with UC, (n = 9; same as ref [89])		All studied for at least 2 y; 7/9 responded to induction; 33 infusions for 26–36 mo; 5 had sustained response, 2 had colectomy		Retrospective
Cezard et al, 2003 (88)	Prospective, uncontrolled (IFX)	2-	Children with CD; n = 21	Clinical remission as defined by Harvey-Bradshaw index	19 of 21 children were in remission on day 45; all perianal fistulas (n = 12) healed by day 90		
Lionetti et al, 2003 (95)	Case series (IFX)	3	Children with CD; n = 22	Improvement in PCDAI	Significant reduction in PCDAI score at 4 and 18 wk; complete closure of fistulas achieved in 7/13 children		
Baldassano et al, 2003 (89)	Prospective cohort (IFX)	2-	Children with CD; n = 21	Improvement in PCDAI, clinical response, clinical remission	All patients achieved improvement in PCDAI; 100% achieved clinical response; 48% achieved clinical remission		
Russell and Katz, 2004 (90)	Open-label prospective (IFX)	2-	Children with UC; n = 14	Clinical response as measured by Lichtiger colitis activity index score	9/14 had clinical response		
Eidelwein et al, 2005 (96)	Case series (IFX)	3	Children with UC; n = 12	Clinical response	9 patients had clinical response		
Borrelli et al, 2004 (91)	Prospective, uncontrolled (IFX)	2-	Children with CD	Clinical remission defined as PCDAI ≤10 and inflammatory remission defined as decrease in both endoscopic and histological scores by ≥50%	10/18 patients achieved clinical remission; 12/18 achieved inflammatory remission		
Lamireau et al, 2004 (97)	Case series (IFX)	3	Children with CD who received 1–17 infliximab infusions for median period of 4 mo	Clinical remission as defined by Harvey-Bradshaw index	29% of 88 patients were in remission at 90 days		
de Ridder et al, 2004 (92)	Prospective, uncontrolled (IFX)	2-	30 children with active CD (with or without fistulas)	Clinical response was defined as good if PCDAI ≤10 or showed decline of ≥20 points; in fistulous disease, response was considered good if fistula closure or cessation of drainage was maintained for >4 wk by physical exam	6/13 patients with refractory disease without fistulas showed long term response; 9/16 patients with draining fistulas achieved closure of fistulas or nondraining fistulas		
Mian and Baron, 2005 (99)	Case report on adalimumab (40 mg SC every 2 wk)	3		Corticosteroids weaned and in remission at wk 22			
Schwarzer et al, 2005 (100)	Case series (n = 4) on anti-CD25 in fulminant UC	3		All had ''rapid clinical improvement''			
Mamula et al, 2004 (101)	Case series (n = 20) on anti-TNF CDP571 (single IV dose)	3		6/20 in remission at wk 2	Remission defined as PCDAI <15		

CD = Crohn disease; CI = confidence interval; IBD = inflammatory bowel disease; IFX = infliximab; IV = intravenous; PCDAI = Pediatric Crohn's Disease Activity Index; PGA = physician global assessment; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis.

TABLE 6. Evidence table for EN, PN, and fish oil therapies in paediatric IBD

Author/year (ref)	Study type	Evidence level	Population	Outomes measured	Effect size	CI/*P*	Comments
Heuschkel et al, 2000 (63)	Systematic review	1-	5 RCTs (2 abstracts) of EN vs steroids; n = 147 children with CD	Remission	RR 0.95	(0.67–1.34)	No quality assessment; n = 60 in published RCTs, remainder from abstracts; less than own sample size calculation (n = 182)
Johnson et al, 2006 (102)	RCT	1+	Total EN vs partial; n = 50 children with CD	Remission (PCDAI <10)	42% vs 15%	0.035	Power calculation n = 50; analysis with ITT
Akobeng et al, 2000 (103)	RCT	1-	Polymeric diet with or without glutamine; n = 18 children with CD	Remission (PCDAI)	56% vs 44%	*P* = 0.5, no CI	No randomisation details, no sample size, small no.
Khoshoo et al, 1996 (104)	RCT	1-	Peptide diets of high vs low fat; n = 16 children with CD	PCDAI response	Total group result only	—	No randomisation details, no concealment, no blinding, no ITT, no sample size
Thomas et al, 1993 (60)	RCT	1-	Elemental diet vs steroids; n = 24 children with CD	Activity (Lloyd-Still score)	No difference	Not given	No randomisation details, no concealment, no blinding, no ITT, no sample size
Ruuska et al, 1994 (59)	RCT	1-	Polymeric diet vs steroids; n = 19 children with CD	PCDAI response	No difference	Not given	
Nicholls et al, 1994 (35)	Case series	3	Cyclosporine vs conventional treatment (nutrition, 5-ASA, or steroids); n = 24 children with CD	Response in activity (Lloyd-Still score)	67% improved vs 93%	Not given	No randomisation details, treat as case series (member of research team doubts randomisation done)
Ludvigsson et al, 2004 (105)	RCT	1-	Elemental diet vs polymeric; n = 37 children with CD	Remission (PCDAI)	69% improved vs 82%	*P* = 0.44, no CI	No a priori sample size, small no. (would need n = 171 to reject null hypothesis)
Romano et al, 2005 (106)	RCT	1-	Mesalazine ± n3 fatty acids; n = 38 children with CD	Maintainence of remission (relapse = PCDAI >20)	61% relapsed vs 95%	0.0016	No randomisation details, no concealment, no blinding, no ITT, no sample size
Borrelli et al, 2006 (57)	RCT	1+	Polymeric diet vs steroids; n = 37 children with CD	Remission (PCDAI <10)	79% vs 67%	0.4	Powered on mucosal healing rather than clinical efficacy
Sanderson et al, 1987 (58)	RCT	1-	Elemental diet vs steroids; n = 17 children with small bowel CD	Response in activity (Lloyd-Still score); linear growth	No direct comparison	Decreased score ($P < 0.01$) in both	No randomisation details, no concealment, no blinding, no ITT, no sample size
Wilschanski et al, 1996 (107)	Cohort	2+	47 children with CD and in remission by EN; 28 took supplementary NG feeds, 19 did not	Maintenance of remission (PCDAI <20)	Relapse rate at 1 y 43% vs 79%	<0.02	
Aiges et al, 1989 (115)	Case series	3	Overnight supplemental NG enteral feeds; n = 8 children with CD and growth failure	Growth			8 given overnight NG tube feeding; 4 controls (did not consent to diet)
Polk et al, 1992 (116)	Case series	3	Intermittent NG enteral feeds; n = 6 children with CD, Tanner stage 1–2	Growth		Weight increased ($P < 0.02$); height velocity increased ($P < 0.001$)	
Belli et al, 1988 (109)	Cohort	2-	Intermittent elemental EN; n = 12 children with growth failure and CD	CDAI, weight, height, and prednisolone intake when on intermittent enteral feeds		Increased height ($P < 0.01$); increased weight ($P < 0.01$); decreased CDAI ($P < 0.05$); decreased prednisolone intake ($P < 0.05$)	8 given diet; 4 controls (did not consent to diet)
Israel and Hassall, 1995 (108)	Cohort	2-	20 children with CD and growth failure; 16 had GT	Growth on supplemental NG or GT feeds (>6 mo)			Retrospective
Fell et al, 2000 (112)	Case series	3	29 children with CD given polymeric feed	Remission (PCDAI <10) at 8 wk	23 (79%) gained remission		
Morin et al, 1980 (113)	Case series	3	4 children with CD and growth failure; 6/52 exclusive enteral NG feeds	Growth		Increased height and weight ($P < 0.02$)	
Layden et al, 1976 (118)	Case series	3	4 children with CD and growth arrest given TPN	Growth			

(*continued*)

TABLE 6. (*Continued*)

Author/year (ref)	Study type	Evidence level	Population	Outomes measured	Effect size	CI/*P*	Comments
Lake et al, 1985 (110)	Cohort	2-	Preop children with CD given TPN	Growth on TPN in preop period		Increased growth velocity ($P < 0.02$)	4 cases, 4 controls in retrospective cohort
Strobel et al, 1979 (119)	Case series	3	12 children and 5 young adults with CD treated with home TPN	Maintenance of remission, weight and height increase, and catch-up growth on TPN			4 had increase in height, 10 showed catch-up growth
Navarro et al, 1982 (114)	Case series	3	Exclusive then long-term supplemental EN in 17 children with CD				Descriptive study
Papadopoulou et al, 1995 (71)	Cohort	2-	36 children with CD given elemental feed (19) or prednisolone (17)	Response in activity (Lloyd-Still score)	83% remission with EN, 64% with steroids		Retrospective
Salvatore, 2000 (117)	Case series	3	21 children with CD or UC given oral (12) or rectal (9) nutritional substrate				Remission undefined; descriptive study; given *N*-acetyl glucosamine
Afzal et al, 2005 (111)	Case series	3	2 polymeric diets, different fat blends; n = 65 children with CD	Remission (PCDAI <20)	50 (67%) gained remission		Analysis dependent on disease site (ileal vs ileocolonic vs colonic)
Berni Canani et al, 2006 (73)	Case series	3	47 children with CD: 10 steroids, 12 polymeric EN, 13 semielemental EN, 12 elemental EN	Remission rate	EN 87%, steroids 90% (NS)		Steroids: methyl prednisolone
Afzal et al, 2002 (120)	Case report	3	Refeeding syndrome during EN treatment of CD				

5-ASA = 5-aminosalicylate; EN = enteral nutrition; GT = gastrostomy tube; IBD = inflammatory bowel disease; ITT = intention to treat; NG = nasogastric; NS = nonsignificant; PCDAI = Pediatric Crohn's Disease Activity Index; PN = parenteral nutrition; RCT = randomised controlled trial; RR =; TPN = total parenteral nutrition; UC = ulcerative colitis.

Induction of Remission in CD

The systematic review of RCT of EN versus corticosteroids for induction of remission of CD in paediatric patients was of low quality (63). It comprised 147 children: 60 from 3 small RCTs (58–60) and 87 from 2 abstracts of RCT; 2 nonrandomised trials containing 47 more children were also added to the analysis. A further RCT of EN versus corticosteroids for induction of remission of CD in paediatric patients was of better methodological quality and comprised 37 children (57). All of the trials showed roughly equivalent remission rates, slightly favouring corticosteroids.

The 4 RCTs of differing EN strategies to induce remission showed the superiority of total EN as opposed to partial EN in the only appropriately powered trial (102; $P < 0.04$), but no benefit of the addition of glutamine to polymeric EN (103), no benefit of altered fat composition in EN (104), and no benefit for elemental as opposed to polymeric feed (105) in studies of low power.

Maintenance of Remission in CD

There was significant benefit from the addition of n3-fatty acid to mesalazine to maintain remission in CD in an RCT of low methodological quality and at high risk for bias (106).

Induction of Remission in UC

The only data in UC were 2 of 12 children in a series from a pilot trial when given an oral nutritional substrate (*N*-acetyl glucosamine); both improved.

Maintenance of Remission in UC

There are no relevant studies.

Harm

The only serious adverse event reported with EN, PN, or fish oil was a case of refeeding syndrome during EN therapy to induce remission in CD (120).

Bone Health

None of the studies reported this as a primary or well-defined secondary outcome.

Other Treatment Modalities

There were no publications on other treatment modalities that met the inclusion criteria, therefore, there is no evidence table.

DISCUSSION

We have rigorously searched the available literature for relevant evidence on the treatment of paediatric IBD to January 1, 2007. The results are disappointing, with a lack of high-quality evidence. There are no methodologically robust clinical guidelines and no systematic reviews nor RCTs that can meet the highest methodological criteria, in this case those of the SIGN. Only a handful of RCT and cohort studies were well conducted with a low risk of bias in the results (EL1+ or EL2+, respectively). By contrast, there is evidence of high quality for the treatment of adult IBD, including Cochrane reviews and other systematic reviews, some of which may combine both adult and paediatric evidence. Paediatric practitioners emphasize that there are important

differences in terms of managing children and adults with IBD, given the differences in relative physiology, pharmacokinetics, and pharmacodynamics, and the relevant aims for treatment. In paediatric IBD, treatment aims include restoration of normal growth, normal progression through the pubertal stages, achievement of full educational potential, restoration of normal lifestyle, and prevention of harm (both physical and psychological). Given the profound effects of proinflammatory cytokines on growth and pubertal development, we may need to aim for not just clinical remission, radiological remission, remission of serology, and other biological markers but also for mucosal remission. For all of these reasons, extrapolated data from the adult IBD literature alone is insufficient to guide treatment of paediatric IBD. Although limited in terms of the quality of the methodology, the enclosed evidence base of management of paediatric IBD does provide much important information for paediatric IBD teams and includes some highly influential publications that have helped to advance paediatric IBD care.

Clinical Guidelines

There are no clinical guidelines available that can be strongly recommended for use in clinical paediatric IBD practice. Given the lack of available high-quality evidence, a strict clinical guideline based on both systematic reviews and large, robustly designed and clinically appropriate RCTs is many years away. This comprehensive evidence review has therefore led to our present consensus guideline document (see pp. S1–S13). In this accompanying guideline, a small number of the BSPGHAN IBD Working Group reviewed this paediatric evidence base, together with the ECCO consensus on diagnosis and management of CD (9–11, which is on adult CD except for a brief section on paediatric CD) and the British Society of Gastroenterology guidelines for the management of IBD in adults (12). The draft guideline was sent to all of the members of BSPGHAN (a multidisciplinary group) and to lay/patient/family groups interested in paediatric IBD, and the responses were evaluated. It was recirculated a second time and consensus was achieved.

Immunomodulators

With just 1 RCT, there is little reliable evidence regarding the use of these agents in childhood IBD, despite the marked current increase in their use (21). Current practice is based on adult practice, and tending towards earlier use of azathioprine/6-MP, possibly even as first-line agents. Methotrexate is used as a second-line immunomodulator in the event of intolerance to or failure of azathioprine/6-MP. By contrast, use of cyclosporine and tacrolimus remains limited to children with complex and treatment-resistant disease. Cyclosporin has a limited role as the therapy of last resort after failure of conventional treatment in refractory or fulminant UC, potentially allowing deferral of operation until the patient is physically and psychologically better prepared for surgery.

Cochrane and Other Significant Reviews of Management of Adult Inflammatory Bowel Disease

Using data of studies in adults with IBD, a meta-analysis has confirmed the role of azathioprine/6-MP in maintaining long-term disease remission in adults (121). A Cochrane review has also done so and has supported their steroid-sparing benefit (122). However, it takes at least 17 weeks for effectiveness to manifest (123).

There have been several studies of methotrexate therapy in treatment-resistant CD in adults, including 3 randomized placebo-controlled trials. A Cochrane review supports the findings that weekly injections of 25 mg of methotrexate intramuscularly may induce remission and steroid withdrawal in patients with refractory CD (124). There is limited evidence that cyclosporin is more effective than standard treatment alone for severe UC (125). The use of low-dose oral cyclosporin for the treatment of chronic active CD is not justified (126).

5-Aminosalicylate Acid Preparations and Sulphasalazine

The quality of available evidence is poor. Oral 5-ASA and sulphasalazine at a dose of 50 to 100 $mg \cdot kg^{-1}$ day^{-1} appear to be safe and effective in the induction and maintenance of remission of active UC. Topical 5-ASA may be used for left-sided or distal UC. There is no adequate evidence for or against the use of 5-ASA in childhood CD.

Cochrane and Other Significant Reviews of Management of Adult Inflammatory Bowel Disease

There have been 3 Cochrane reviews of aminosalicylate usage (127–129). For the treatment of active UC, 5-ASA is superior to placebo, with a probable dose response trend. Thus higher doses may be of benefit in this situation. There is a trend to benefit of oral 5-ASA preparations (both in terms of efficacy and minimising side effects) over sulfasalazine. However, considering their relative costs, a clinical advantage to using the newer 5-ASA preparations in place of sulphasalazine appears unlikely (127). ASA can be used for the prevention of relapses in UC. 5-ASA is superior to placebo but slightly inferior to sulphasalazine (128). There is no evidence for using 5-ASA in the maintenance of medically induced remission in CD (129).

Corticosteroids

Corticosteroids are widely used as primary therapy for induction of remission in children with IBD. There are, however, concerns regarding toxicity, such as the suppression of linear growth, that are of particular relevance to paediatric practice. The quality of available evidence is poor. Corticosteroids appear to induce clinical remission in childhood CD and UC. Rectal therapy can be used for distal disease. There is a risk of osteopenia with corticosteroid usage plus other toxicities, including obesity, striae, susceptibility to infection, and mood disturbance.

Cochrane and Other Significant Reviews of Management of Adult Inflammatory Bowel Disease

There have been 3 Cochrane reviews of corticosteroid usage in adult patients (130–132). Corticosteroid therapy is more effective than EN for remission of active CD (130). There is no evidence for using either prednisolone (131) or budesonide (132) in the maintenance of medically induced remission in CD.

Biological Agents

There is a lack of good-quality studies on the use of infliximab and adalimumab in paediatric IBD. A single-dose intravenous infusion of 5 mg/kg of infliximab has been shown to lead to improvements in symptoms in children with active CD and in some children with UC refractory to conventional medical therapy. For perianal fistulating and/or severe refractory CD, 3 doses of 5 mg/kg have been shown to induce remission. The effect may be transitory, with most patients relapsing by 1 year. Adverse events in

these studies were rare but occasionally serious, especially risk of sepsis. Recent reports suggest that infliximab may be associated with an increased risk of hepatosplenic T cell lymphoma (HSTCL). Eight cases of HSTCL in young patients using infliximab to treat IBD were reported to the Food and Drug Administration between 1998 and October 2006 (133). Interestingly, all 8 patients were receiving concomitant treatment with azathioprine or 6-MP. Whilst definite evidence on the association between the development of lymphoma and the use of infliximab in CD disease is lacking (134), there may be a small risk (about 8/10,000), especially in patients treated with a combination of infliximab and purine analogues (135). This has been a cause of great concern to paediatric gastroenterologists, together with reports of HSTCL in young patients with IBD treated with adalimumab (Abbott Laboratories, unpublished observation) and of occurrences of demyelination, toxic retinopathy, and cancers that reversed on cessation of biological therapy. It is vital that the risk of rare but serious adverse events be discussed with children and their families before initiating the use of biological agents, and that an exit strategy for future cessation of biological therapy be discussed. The use of written informed consent is now common amongst BSPGHAN members, together with the provision of detailed written summaries of benefits and risks of biological therapy in paediatric IBD.

Cochrane and Other Significant Reviews of Management of Adult Inflammatory Bowel Disease

There have been 2 Cochrane reviews of infliximab usage in adult patients (136,137). Infliximab has been shown to be effective in the induction of remission in adults with CD (136) and more recently in adults with UC (137).

In an RCT, infliximab was shown to be effective in the maintenance of remission in adults with CD (138). For clinical practice in the United Kingdom, the National Institute of Clinical Excellence has issued its guidance on the use of infliximab in CD in adults (*www.nice.org.uk*, guideline no. 40). It recommends that infliximab use be reserved for patients with severe disease that is unresponsive to conventional therapy and for whom surgery is inappropriate.

Antibiotics, Antituberculous Therapy, and Probiotics

Despite the widespread use of antibiotics and probiotics by paediatric gastroenterologists and families, there was no paediatric literature available for either.

Cochrane and Other Significant Reviews of Management of Adult Inflammatory Bowel Disease

There have been 2 essentially negative Cochrane reviews (139,140); the first concluded that the use of antituberculous therapy cannot be recommended on the basis of the available evidence (139). A second review (140) concluded that there was no evidence to suggest that probiotics are beneficial for the maintenance of remission in CD.

Nutrition (Enteral Nutrition, Parenteral Nutrition, and Fish Oil)

EN is regarded as the primary therapy for induction of remission of CD by paediatric gastroenterologists in the United Kingdom and Europe, but less so by paediatric gastroenterologists elsewhere and by adult gastroenterologists in the United Kingdom and elsewhere. PN is usually used as supportive therapy during acute severe exacerbations of IBD, or else when CD is complicated by short gut syndrome or extensive enterocutaneous fistulae. Fish oil preparations are usually purchased by families as supportive complementary/alternative therapy for IBD in their children. Of note, there are no RCTs of EN versus placebo; 4 are of EN versus steroids and 4 are of 1 EN regimen against another. Many of the practical aspects of EN administration, such as duration of feed administration or food reintroduction regimen, have yet to be subjected to primary analysis by RCT. There are no RCTs of PN usage nor of use of fish oil in induction of remission in paediatric IBD.

The systematic review of RCT of EN versus corticosteroids in paediatric patients was of low quality (63). It comprised 147 children in 3 small RCTs and 2 abstracts of RCTs; of these, only 60 children were from fully published articles and the remainder from 2 abstracts. Neither abstract has been converted to an original article in more than 10 years, so it is doubtful that either ever will be. The authors calculated that a sample size of 182 children was needed to demonstrate a treatment effect of 20%. There is a need for a definitive well-conducted RCT, rather than the lumping of small and heterogeneous studies together in a meta-analysis. Mucosal remission may be important in the restoration of growth in paediatric IBD, with return of proinflammatory cytokines towards normal levels. Mucosal rather than clinical remission was used as the primary outcome to generate sample size in 1 RCT of EN versus corticosteroids (57), and was significantly more likely at 10 weeks in children taking polymeric formula. There was no difference in clinical outcome.

From these studies, EN appears to be safe and effective in the induction of remission of CD and is almost as effective as corticosteroids, with none of the steroid-associated toxicities during treatment.

Cochrane and Other Significant Reviews of Management of Adult Inflammatory Bowel Disease

There has been 1 Cochrane review (130), which showed that corticosteroids were more effective at inducing remission of CD than EN; however enteral feeding ''allows improved nutritional status and growth.'' Two of the 16 studies included were paediatric studies.

Other Treatment Modalities

Many drugs and nutritional and complementary/alternative therapies beyond those described in the 6 treatment groups above are used by physicians and families in paediatric IBD, but we could find no relevant publications.

Cochrane and Other Significant Reviews of Management of Adult Inflammatory Bowel Disease

No relevant reviews were discovered.

CONCLUSIONS

With our systematic literature search ending on January 1, 2007, there have been significant recent additions to the paediatric and combined paediatric and adult literature. These include an RCT of infliximab usage in children with CD (141) and an open-label

study of natalizumab usage in children with CD (142). There are new or updated Cochrane reviews of combined paediatric and adult interventions, such as those for fish oil (143) and enteral nutrition (144), respectively. Many gaps still exist in areas that are generating high-quality adult data but as yet no paediatric data, such as antituberculous therapy for CD (145) and either the induction or maintenance of remission in CD using adalimumab (146,147).

This exercise has identified significant gaps in the literature on the treatment of paediatric IBD, which suggests the need for a rolling programme of clinically relevant, methodologically robust, and well-performed and well-presented RCTs of treatment. Although attention will inevitably concentrate on the newer agents, such as biological therapies, there is a great need to evaluate traditional and useful agents, such as the immunomodulators azathioprine and methotrexate. Consideration of clinically relevant outcomes is needed; for example, restoration of normal growth is vital in paediatric IBD, yet this has not been the primary outcome of any study to date (148). The publication of the first Consolidated Standards of Reporting Trials (better known as CONSORT) statement was in 1996 (149), with revision in 2001 (150), yet RCTs in paediatric IBD continue to be designed and their results disseminated despite failing to meet the agreed-upon methodological and presentation criteria. Of the 16 RCTs in this evidence base, many have obvious methodological flaws (no or inadequate randomisation details, no concealment details, no sample size calculation, no intention-to-treat analysis) and few have a CONSORT-type flow diagram of subject progress through the RCT.

The present review has directly led to the construction of a methodologically robust, consensus-based clinical guideline on the treatment of paediatric IBD (see pp. S1–S13), comprising the best-available evidence from the paediatric literature (including the use of this evidence-based review), relevant methodologically high-quality data from the adult IBD literature, together with the clinical expertise and experience of multidisciplinary teams that manage paediatric IBD in children and teenagers. The content of evidence-based practice is controversial to some, and we agree with Glasziou (151) that what we need is evidence-*informed* practice, with wisdom derived from clinical expertise and experience, in this case in the treatment of paediatric IBD.

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