



Complete Summary

GUIDELINE TITLE

Evidence-based care guideline for management of pediatric moderate/severe inflammatory bowel disease (IBD).

BIBLIOGRAPHIC SOURCE(S)

IBD Guideline Team, Cincinnati Children's Hospital Medical Center. Evidence-based care guideline for the management of pediatric moderate/severe inflammatory bowel disease (IBD). Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2007 Apr 5. 29 p. (Guideline; no. 29). [66 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Inflammatory bowel disease (Crohn's disease or ulcerative colitis)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Patients
Physician Assistants
Physicians
Students

GUIDELINE OBJECTIVE(S)

To provide an evidence based guideline for management of pediatric moderate/severe inflammatory bowel disease

TARGET POPULATION

Children 0-22 years of age diagnosed with inflammatory bowel disease (IBD) (either Crohn's disease or ulcerative colitis)

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment

1. Determine severity of disease using physician global assessment (PGA), Pediatric Crohn's Disease Activity Index (PCDAI)
2. Determine thiopurine methyl transferase (TPMT) genotype
3. Physical examination and history
4. Pre-treatment complete blood count (CBC) alanine aminotransferase (ALT), amylase, and lipase levels
5. Post-treatment monitoring of white blood cell (WBC) counts, ALT, serum blood urea nitrogen, and creatine levels
6. Monitoring of 6-thioguanine (6TG) levels

Management/Treatment

1. Corticosteroids (prednisone, mesalamine)
2. Azathioprine (AZA)
3. 6-Mercaptopurine (6-MP)

Note: Not recommended in inflammatory bowel disease (IBD) patients who are doing well

4. Methotrexate (MTX)
5. Infliximab (with or without benadryl and acetaminophen prophylactic premedication plus tuberculosis evaluation prior to treatment)

6. Combination therapy (6-MP or AZA or MTX plus infliximab)
7. Immunizations (in accordance with guidelines from American Academy of Pediatrics and American Academy of Family Physicians)
8. Patient and family education
9. Folic acid supplements (in patients on MTX)

MAJOR OUTCOMES CONSIDERED

- Percent of patients in clinical remission
- Quality of life
- Nutrition and growth
- Adverse effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

To select evidence for critical appraisal by the group for the development of this guideline, the Medline, EmBase and the Cochrane databases were searched for dates of January 1970 to September 2005 to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to inflammatory bowel disease (IBD) (see Appendix 9 of the original guideline document) and employing a combination of Boolean searching on human-indexed thesaurus terms (Medical Subject Heading [MeSH] headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms.

The citations were reduced by eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles and adult literature were identified.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines have been reviewed and approved by clinical experts not involved in the development process, senior management, other appropriate hospital committees, and other individuals as appropriate to their intended purposes.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is followed by an evidence classification (A-X) identifying the type of supporting evidence. Definitions for the types of evidence are presented at the end of the "Major Recommendations" field.

Prior to Treatment

1. It is recommended that clinicians use a physician global assessment (PGA) to determine disease severity for pediatric Crohn's disease (CD) or ulcerative colitis (UC) (Local Consensus [E]).

Note 1: The PGA includes four categories: quiescent, mild, moderate, and severe disease activity. See Appendix 1A in the original guideline document, Cincinnati Children's Hospital and Medical Center (CCHMC) inflammatory bowel disease (IBD) Physician Follow-up visit form (Local Consensus [E]).

Note 2: Other helpful clinic forms capturing various inflammatory bowel disease (IBD) assessment components include: Appendix 1B, Appendix 1C, Appendix 1D, Appendix 1E, Appendix 1F in the original guideline document (Local Consensus [E]).

Note 3: CD patients with mild disease as indicated by history and physical, but who have significant growth failure are placed in the moderate disease severity category (Local Consensus [E]).

2. It is recommended that clinicians consider using the Pediatric Crohn's Disease Activity Index (PCDAI) as another measure of disease severity in making CD treatment decisions (Otley et al., 1999 [O]; Hyams et al., 1991 [O]).

Note 1: See PCDAI tool in Appendix 2a in the original guideline document.

Note 2: The PCDAI was validated against the PGA (Hyams et al., 2005 [O]; Otley et al., 1999 [O]; Hyams et al., 1991 [O]). The PCDAI was used in many pediatric treatment trials (Kundhal et al., 2003 [O]).

Note 3: The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a recently reported pediatric disease activity tool for UC that is pending publication. See Appendix 2b in the original guideline document used with permission.

3. It is recommended that immunizations be given in accordance with the American Academy of Pediatrics and American Academy of Family Physicians recommendations (Sands et al., "Guidelines," 2004 [S,E]). See Appendix 3 in the original guideline document.

Note 1: Live virus vaccines are contraindicated in patients receiving prednisone and/or any of the following (6-mercaptopurine [6-MP], azathioprine [AZA], methotrexate [MTX], infliximab) for treatment of IBD.

Note 2: To the extent that children with IBD have some degree of immunosuppression, the severity of infection with vaccine-preventable diseases may be increased.

Medications

Each section below refers to a specific medication algorithm (see Appendices 6, 7, and 8 in the original guideline document). For a list of treatment related side

effects and costs of treatment, see Appendix 4 and Appendix 5 in the original guideline document.

(6-MP or AZA) With or Without Prednisone (see Appendix 6 in the original guideline document for summarized algorithm)

6-MP or AZA: Indications/Contraindications

4. It is recommended that the following indications be considered for use of 6-MP or AZA:
 - For *induction of remission* in children with moderate/severe CD (per PGA or PCDAI score ≥ 30) who have thiopurine methyltransferase (TPMT) genotype that is consistent with some TPMT activity
 - For *induction of remission* in children with moderate/severe CD or UC who have TPMT genotype that is consistent with some TPMT activity, who have not received 6-MP or AZA initially and who are steroid-dependent/refractory, defined as:
 - Have not achieved remission after one month of prednisone alone or
 - Have not tapered off prednisone after three months or
 - Have received more than one course of steroids in one year and/or
 - Have failed or cannot tolerate 5-aminosalicylates (i.e., mesalamine recommendation #13 for specific dosing).
 - For *induction of remission* in children with moderate/severe CD or UC who have failed or cannot tolerate 5-aminosalicylates (i.e., mesalamine recommendation #12 for specific dosing).
 - For *maintenance therapy* in children with moderate/severe CD/UC

(Pearson et al., 2000 [M]; Sandborn et al., 2004 [M]; Ardizzone et al., 2006 [B], Local Consensus [E])

5. It is recommended that the following contraindications be considered by the clinician in deciding to use 6-MP or AZA for the treatment of CD/UC:
 - TPMT genotype that is consistent with absent TPMT activity (Colombel et al., 2000 [C]; Dubinsky et al., 2000 [D]; Local Consensus [E]).
6. It is recommended that TPMT genotype or phenotype be determined prior to initiation of 6-MP or AZA. See specific recommendations below for dosing based on TPMT genotype/phenotype (Colombel et al., 2000 [C]; Dubinsky et al., 2000 [D], Local Consensus [E]).
7. It is recommended that complete blood count (CBC), alanine aminotransferase (ALT), amylase, and lipase levels be obtained prior to initiation of 6-MP or AZA (Local Consensus [E]).

Note: Monitoring of these labs is done to recognize the possibility of medication toxicity (see recommended frequencies under the safety monitoring sections of each medication).

6-MP or AZA: Safety Monitoring

See Appendix 4 in the original guideline document for list of treatment related side effects and costs of treatment.

8. It is recommended that white blood count (WBC) be reviewed by the physician
- 2, 4, 8 and 12 weeks after initiation of 6-MP or AZA
 - After each dosage change of 6-MP or AZA
 - Thereafter, if WBC is >3500 cells/mm³ every 3 months as part of maintenance therapy safety monitoring (Kirschner et al., 1998 [D], Local Consensus [E]).

Note 1: See below for 6-MP or AZA dosing recommendations influenced by WBC.

Note 2: Normal values for WBC may be found on the CCHMC CenterLink Lab Information sit.

9. It is recommended that ALT be measured:
- At 2, 4, 8 , and 12 weeks after initiation of 6-MP or AZA
 - After each dosage change of 6-MP or AZA
 - Thereafter, if ALT levels are less than three-fold greater than normal, repeat in one month
 - If ALT levels normal, repeat every 3 months as part of maintenance therapy safety monitoring (Local Consensus [E]).

Note 1: If ALT is less than three-fold greater than normal, ALT will often spontaneously return to normal.

Note 2: Approximately 14% of children receiving 6-MP or AZA for CD will experience ALT two-fold greater than normal (Kirschner et al., 1998 [D], Local Consensus [E]).

Note 3: See below for 6-MP or AZA dosing recommendations influenced by ALT.

Note 4: Normal values for ALT may be found on the CCHMC CenterLink Lab Information site.

6-MP or AZA: Dosing

10. It is recommended that for *induction of remission* in children with moderate/severe CD that the following medication combinations be used:
- Prednisone 1 to 1.5 mg/kg/day by mouth (P.O.) and
 - 6-MP 0.75 to 1.5 mg/kg/day P.O. or
 - AZA 1 to 2.5 mg/kg/day P.O. (Pearson et al., 2000 [M]; Sandborn et al., 2004 [M]; Vilien et al., 2004 [B]; Markowitz et al., 2000 [B]; Hawthorne et al., 1992 [B]).

Note 1: No controlled trials of steroids versus placebo have been performed in children with CD (Escher et al., 2003 [S]). The recommended daily maximum dose range of prednisone is 40 to 60 mg. Higher doses of

prednisone are associated with greater side effects without increased benefit (Turner et al., 2007 [M]; Malchow et al., 1984 [A]; Singleton et al., 1979 [C], Local Consensus [E]).

Note 2: It is expected that 80% of patients will achieve a clinically important remission (PCDAI \leq 10 or PGA at the quiescent level) within four weeks of initiation of the first course of prednisone. Initiating 6-MP or AZA concurrently with prednisone may allow safe discontinuation of prednisone (Markowitz et al., 2000 [B]).

Note 3: Approximately five adult patients with CD need to be treated with 6-MP or AZA to induce remission in one patient (number needed to treat [NNT] = 5) (Sandborn et al., 2004 [M]). See <http://www.cebm.net/nnts.asp> for definitions and use of NNT, NNH.

Note 4: Approximately 14 adult patients with CD need to be treated with 6-MP or AZA as induction therapy to experience one patient with medication side effects (number needed to harm [NNH] = 14). The most common adverse effects are allergic reactions (2.3%) such as fever and/or rash and arthritis, leukopenia (1.4%), pancreatitis (1.4%), and nausea (1.4%) (Sandborn et al., 2004 [M]).

Note 5: Enteral nutritional therapy, sometimes given by nasogastric tube, may be offered to all patients with active CD as a steroid sparing option for induction of remission. Improving nutritional status is associated with improvement in CD symptoms and improvement in response to other therapeutic measures. Moreover, exclusive enteral liquid nutrition for a period of 4 to 6 weeks is as effective as corticosteroids in inducing remission in 42% to 80% of pediatric CD patients with mild to moderate disease activity. (Heuschkel et al., 2000 [M]; Johnson et al., 2006 [B]; Afzal et al., 2005 [C])

11. It is recommended for *induction of remission* in children with moderate/severe CD or UC who have TPMT genotype associated with intermediate TPMT activity (10% of the population), that
 - 6-MP be started at 0.75 to 1 mg/kg/day P.O. and then advanced over 4 weeks to 1.5 mg/kg/day P.O.
 - AZA be started at 1.5 mg/kg/day P.O. and then advanced over 4 weeks to 2.5 mg/kg/day P.O. while monitoring WBC and ALT as recommended below (Colombel et al., 2000 [C]; Dubinsky et al., 2000 [D]; Local Consensus [E]).
12. It is recommended for *induction of remission* in children with moderate/severe CD or UC who have TPMT genotype associated with normal to high TPMT activity (89% of the population), that
 - 6-MP be started at 1.5 mg/kg/day P.O. or
 - AZA be started at 2.5 mg/kg/day P.O. (Colombel et al., 2000 [C]; Dubinsky et al., 2000 [D], Local Consensus [E]).
13. It is recommended that prednisone 1 mg/kg/day P.O. and delayed-release mesalamine 50 to 100 mg/kg/day P.O. (maximum dose range of 2.4 to 4.8 grams) be used for *induction of remission* in children with moderate/severe UC (Griffiths et al., 1993 [D]; Beattie et al., 1996 [O], Local Consensus [E]).

Note 1: No controlled trials of steroids versus placebo have been performed in children with UC (Escher et al., 2003 [S]). The recommended daily maximum dose range of prednisone is 40 to 60 mg P.O. Higher doses of prednisone are associated with greater side effects without increased benefit (Turner et al., 2007 [M]; Malchow et al., 1984 [A]; Singleton et al., 1979 [C], Local Consensus [E]).

Note 2: For children with distal UC, consider mesalamine enemas or suppositories and/or balsalazide disodium (pro-drug that are enzymatically cleaved in the colon to produce mesalamine (Marteau et al., 2005 [A]; Levine et al., 2002 [A]; Pruitt et al., 2002 [A]; Safdi et al., 1997 [B]; Kam et al., 1996 [B]).

14. It is recommended that prednisone be discontinued within 3 months of being initiated in patients with CD/UC (Munkholm et al., 1994 [C]).
15. It is recommended that 6-MP or AZA be continued for *maintenance therapy* at the same dose that was used for induction of remission (Pearson et al., 2000 [M]; Present et al., 1980 [B]).

Note 1: See efficacy monitoring for dosing adjustments based on 6-thioguanine (6TG) levels.

Note 2: Approximately seven adult patients with CD need to be treated with AZA at doses of 2 mg/kg/day P.O. to maintain remission in one patient (NNT = 7) (Pearson et al., 2000 [M]).

Note 3: When the maintenance therapy data were analyzed for the effect of AZA dose (range 1 to 2.5 mg/kg/day P.O.), the Peto odds ratio (OR) for response increased from 1.2 (95% confidence interval [CI] ,0.6, 2.41) at 1 mg/kg/day to 3.17 (95% CI 1.33, 7.59) at 2 mg/kg/day, to 4.13 (95% CI 1.59, 10.71) at 2.5 mg/kg/day (Pearson et al., 2000 [M]). For definitions/use of odds ratios see <http://www.jr2.ox.ac.uk/bandolier/band25/b25-6.html>.

(95% CI: 95% Confidence Interval expresses the uncertainty (precision) of a measured value; it is the range of values within which we can be 95% sure that the true value lies. A study with a larger sample size will generate more precise measurements, resulting in a narrower confidence interval)

Note 4: Approximately 19 adult patients with CD need to be treated with 6-MP or AZA as maintenance therapy to experience medication side effects in one patient (NNH = 19). Discontinuation of 6-MP or AZA due to adverse effects was noted in 5.8% of patients, and 1.3% of patients receiving placebo. Common events associated with discontinuation include pancreatitis, leukopenia, nausea, allergy, and infection (Pearson et al., 2000 [M])

Note 5: It is expected that remission while receiving 6-MP or AZA will be maintained in 50% of adult patients with UC for at least 2 years and in 50% of adult patients with CD for at least 1 year. Relapse may be anticipated in 50% of adult patients in whom azathioprine is withdrawn after 42 months of continuous therapy (Lemann et al., 2005 [B]).

16. It is recommended that WBC levels be used to adjust 6-MP dosing such that:
- If WBC is less than 3000 cells/mm³, consider discontinuing 6-MP until leukopenia resolves; when leukopenia resolves, consider restarting 6-MP at 50% of the previous dose, and then slowly advancing to the maximum dose which is not associated with leukopenia.
 - If WBC is between 3000 and 3500 cells/mm³, consider decreasing dosage of 6-MP to 50% of the previous dose, and then slowly advancing to the maximum dose which is not associated with leukopenia.
 - If WBC is between 3000 and 3500 cells/mm³, consider that potential interaction with other medications, particularly mesalamine or azulfidine, may be contributing to leucopenia.

(Lowry et al., 2001 [C])

Note 1: Approximately 10% of children receiving 6-MP or AZA for CD will experience leukopenia (WBC <3500, cells/mm³) (Kirschner, 1998 [D]).

17. It is recommended that ALT levels be used to adjust 6-MP dosing, such that:
- If ALT levels are more than 10-fold greater than normal, discontinue 6-MP until signs of hepatotoxicity have subsided. Then attempt to slowly advance the dose of 6MP to the highest appropriate dose which does not cause ALT elevation.
 - If ALT levels are more than three-fold greater than normal, but less than 10-fold greater than normal, consider drug interactions that may account for hepatotoxicity, reduce the dose of 6-MP to 50% of the previous dose, and repeat ALT in one month.
 - If ALT levels are abnormal that consideration be given to other etiologies of increased ALT.

(Local Consensus [E])

Note: There is insufficient evidence to support routine monitoring of amylase and lipase in IBD patients who are doing well.

6-MP or AZA: Efficacy Monitoring

Adequate clinical response to 6-MP or AZA can be defined as a decreased physician global assessment to the quiescent or mild level.

18. It is recommended that if after at least three months of 6-MP or AZA therapy children with CD or UC have not had an adequate clinical response, that 6-thioguanine (6TG) levels be obtained. This will confirm compliance, and determine whether the 6TG level is in the target range (Goldenberg, Rawsthorne, & Bernstein, 2004 [C], Local Consensus [E]).
19. It is recommended, that in children with CD or UC who have not responded to 6-MP or AZA treatment, that 6TG levels be used to adjust 6-MP or AZA dosing, such that:
- If the 6TG level is below 235 pmol/8 x 10⁸ erythrocytes, it may be useful to incrementally increase the dose of:
 - 6-MP up to 2.5 mg/kg/day or
 - AZA up to 4 mg/kg/day.

- If the 6TG level is between 236 and 400 pmol/8 x 10⁸ erythrocytes, it is less likely that increasing the dose of 6-MP or AZA will be beneficial, relative to the risk of leukopenia (Gupta, Gokhale, & Kirschner, 2001 [C]; Dubinsky et al., 2000 [D]).
- If the 6TG level is greater than 400 pmol/8 x 10⁸ erythrocytes, alternative therapies including methotrexate or infliximab may be considered (Goldenberg, Rawsthorne, & Bernstein, 2004 [C], Local Consensus [E]).

Note 1: Erythrocyte levels of 6TG correlate with clinical response to 6-MP and AZA. Erythrocyte levels of 6TG vary widely among patients because of differences in drug metabolism and effects of concurrent medications (Gupta, Gokhale & Kirschner, 2001 [C]; Dubinsky et al., 2000 [D]).

Note 2: The likelihood ratio (LR) for remission with a 6TG level greater than 235 pmol/8 x 10⁸ erythrocytes is approximately 2 (Gupta, Gokhale, & Kirschner, 2001 [C]; Dubinsky et al., 2000 [D]). For definitions/use of likelihood ratios, see http://www.cebm.net/likelihood_ratios.asp.

6-MP or AZA: Adjunct Therapy/Other Treatment-Related Interventions/Education

20. It is recommended that antibiotic prophylaxis for *Pneumocystis carinii* pneumonia (PCP) is not routinely required for IBD patients who are receiving only 6-MP and steroids (Local Consensus [E])
21. It is recommended that patients and families of children receiving 6-MP or AZA receive education regarding signs and symptoms of pancreatitis and to report any signs or symptoms of possible infections to their physician (Local Consensus [E]).

Note: Approximately 1.4% of IBD patients will develop symptoms of pancreatitis while receiving 6-MP (Sandborn et al., 2004 [M])

Methotrexate (MTX) (See Appendix 7 in the original guideline document for summarized algorithm.)

MTX: Indications/Contraindications

22. It is recommended that the following indications for use of MTX for the treatment of CD be considered by the clinician:
 - For *induction of remission* in children with CD who
 - Do not respond to or were intolerant of induction therapy with prednisone and 6MP/AZA, or
 - As an alternative to infliximab, or
 - Are steroid-dependent/refractory, defined as:
 - a. Received more than one course of steroids in one year, or
 - b. Not achieved remission after one month of prednisone alone, or
 - c. Not tapered off prednisone after three months
 - For *maintenance therapy* in children with CD (Alfadhli, McDonald, & Feagan, 2005 [M]; Feagan et al., 2000 [B]; Mack et al., 1998 [C];

Lichtenstein et al., "Medical position statement," 2006 [S,E];
Lichtenstein et al., "Technical review," 2006 [S,E]).

Note: The currently available evidence is insufficient to support the use of MTX for the induction or maintenance of remission in patients with active UC.

23. It is recommended that the following contraindications to using MTX for the treatment of CD/UC be considered by the clinician:
- Children with CD with already abnormal liver-associated chemistries
 - Pregnant females

(Lichtenstein et al., "Medical position statement," 2006 [S,E]; Lichtenstein et al., "Technical review," 2006 [S,E])

MTX: Safety Monitoring

See Appendix 4 in the original guideline document for list of treatment related side effects and costs of treatment.

24. It is recommended that females of childbearing age be tested for pregnancy prior to initiation of MTX and be proactive in pregnancy prevention strategies, due to methotrexate's teratogenicity (Escher et al., 2003 [S]; Local Consensus [E]).
25. It is recommended that white blood count (WBC) be reviewed by the physician:
- At 2, 4, 8, 12 (up to 16) weeks after initiation of MTX
 - After each dosage change of MTX, and
 - Thereafter, if WBC is >3500 cells/mm³, every 3 months as part of maintenance therapy safety monitoring

(Kirschner, 1998 [D], Local Consensus [E])

Note: See below for MTX dosing recommendations influenced by WBC.

26. It is recommended that alanine aminotransferase (ALT) be measured:
- At 2, 4, 8, 12 (up to 16) weeks after initiation of MTX
 - After each dosage change of MTX, (Local Consensus [E])

Note: See below for MTX dosing recommendations influenced by ALT.

27. It is recommended that children with CD with persistently abnormal liver-associated chemistries either discontinue MTX therapy or be considered for a liver biopsy (Escher et al., 2003 [S]).
28. It is recommended that the possibility of MTX induced renal toxicity be monitored by measurement of serum blood urea nitrogen (BUN) and creatinine at least every 3 months (Izzedine et al., 2005 [S], Local Consensus [E]).

MTX: Dosing

29. It is recommended that MTX at 15 mg/m²/week subcutaneously up to a maximum total dose of 25 mg for 16 weeks be considered as an alternative to infliximab for induction of remission in children with CD who do not respond to induction therapy with prednisone and 6MP/AZA or who relapse after stopping prednisone (Alfadhli, McDonald, & Feagan, 2005 [M]; Lichtenstein et al., "Medical position statement," 2006 [S,E]; Lichtenstein et al., "Technical review," 2006 [S,E]).

Note 1: After 16 weeks, reduce MTX dose to 10 mg/m²/week (see maintenance recommendation below).

Note 2: There are no trials of MTX in children with CD that use contemporaneous controls.

Note 3: Approximately five adults with CD need to be treated with MTX to achieve remission in one patient (NNT = 5) (Feagan et al., 1995 [A]; Feagan et al., 2000 [B], Local Consensus [E]).

Note 4: Signs of remission in adults with CD, defined as both the absence of the need for prednisone and CDAI <150 typically occur within 4 to 6 weeks of initiating MTX.

Note 5: Reported side effects of MTX include nausea and vomiting, 40% of adults compared to 25% receiving placebo, (NNH = 7) (Feagan et al. 2000 [B]). Among adults with CD receiving 25 mg MTX subcutaneously, 17% stopped treatment because of elevated aminotransferases, skin rash, nausea, pneumonia, or optic neuritis. No increase in other drug-related adverse events was observed when MTX was compared to placebo (Feagan et al., 1995 [A]).

Note 6: Although P.O. & I.M. forms of MTX have been used in patients with CD, subcutaneous MTX is the preferred route of administration (Local Consensus [E]). There is an extremely wide range of MTX oral bioavailability among patients. Bioavailability of oral compared to subcutaneous MTX is less by a factor of 0.7 to 0.8 (Kurnik et al., 2003 [B]; Stephens et al., 2005 [C]).

Note 7: In a small open-label study of children with CD resistant to 6-MP, the response rate to MTX was approximately 50% (Mack et al., 1998 [C]).

30. It is recommended that MTX 10 mg/m²/week subcutaneously be given as maintenance therapy after successful MTX induction in CD (Feagan et al., 2000 [B]).

Note 1: Approximately three to four adults with CD need to be treated with MTX to maintain remission for at least 40 weeks in one patient (NNT = 4, 95% CI (2, 23)) (Feagan et al., 2000 [B]).

Note 2: In adults with CD that had entered remission (CDAI <150) after treatment with 25 mg of MTX once weekly for a minimum of 16 weeks, continued maintenance treatment with 15 mg of subcutaneous MTX daily was well tolerated (Feagan et al., 2000 [B]).

31. It is recommended that WBC levels be used to adjust MTX dosing such that:
- If WBC is less than 3000 cells/mm³, consider discontinuing MTX until leukopenia resolves; when leukopenia resolves, consider restarting MTX at 50% of the previous dose, and then slowly advancing to the maximum dose which is not associated with leucopenia.
 - If WBC is between 3000 and 3500 cells/mm³, consider decreasing dosage of MTX to 50% of the previous dose, and then slowly advancing to the maximum dose which is not associated with leucopenia.
 - If WBC is abnormal, consider that potential interaction with other medications, may be contributing to leukopenia.

(Lowry et al., 2001 [C], Local Consensus [E])

32. It is recommended that ALT levels be used to adjust MTX dosing, such that:
- If ALT levels are more than three-fold greater than normal, but less than 10-fold greater than normal, consider drug interactions that may account for hepatotoxicity, reduce the dose of MTX to 50% of the previous dose, and repeat ALT in two weeks.
 - If ALT levels are more than 10-fold greater than normal, discontinue MTX.
 - Consideration be given to other etiologies of increased ALT.

(Local Consensus [E])

Note: Normal values for ALT may be found on the CCHMC CenterLink Lab Information site.

MTX: Efficacy Monitoring

Adequate clinical response to MTX is defined as a decreased physician global assessment to the quiescent or mild level.

MTX: Adjunct Therapy/Other Treatment Related Interventions/Education

33. It is recommended that children receiving MTX also receive supplemental folic acid 1 mg/day P.O. (Ortiz et al., 1998 [M]).

Note 1: MTX is a structural analogue of folic acid and competitively inhibits binding of dihydrofolic acid to dihydrofolate reductase. Supplemental folic acid may reduce gastrointestinal (GI) side effects.

Infliximab (see Appendix 8 in the original guideline document for summarized algorithm)

Infliximab: Indications/Contraindications

34. It is recommended that the following indications for use of infliximab for the treatment of CD/UC be considered by the clinician:
- For *induction of remission* in children with CD who

- Do not respond to or were intolerant of induction therapy with prednisone and 6MP/AZA, or
- Relapsed during their initial course of steroids and 6-MP or AZA, or
- Have failed immunomodulator therapies 6-MP or AZA or MTX , or
- Are steroid-dependent/refractory, defined as:
 - a. Received more than one course of steroids in one year, or
 - b. Not achieved remission after one month of prednisone alone, or
 - c. Not tapered off prednisone after three months
- Have any of the following: severe colitis requiring transfusion or severe small bowel disease or draining enterocutaneous or perianal fistulas
- For *induction of remission* in children with moderate/severe UC who:
 - Are steroid dependent/refractory, or
 - Have failed immunomodulator therapies 6-MP or AZA
- For *maintenance therapy* in children with moderate/severe CD/UC

(Lawson, Thomas, & Akobeng, 2006 [M], Local Consensus [E])

35. It is recommended that the following contraindications to using infliximab for the treatment of CD/UC be considered by the clinician:

- Abscess
- Signs & symptoms of infection
- History of tuberculosis
- Histoplasmosis

(Lawson, Thomas, & Akobeng, 2006 [M])

Infliximab: Safety Monitoring

See Appendix 4 and Appendix 5 in the original guideline document for list of treatment related side effects and costs of treatment.

36. It is recommended that before infliximab treatment is started, children be evaluated for tuberculosis and histoplasmosis including history of exposure or prior symptoms, physical examination, purified protein derivative (PPD), chest x-ray, and consider urine histoplasmosis antigen when risk higher (see Note 2 below) (Mow et al., 2004 [C], Local Consensus [E]).

Note 1: Children with IBD and asymptomatic tuberculosis may be anergic. In one study of adults, 71% of patients failed to react to Candida, tetanus, or mumps.

Note 2: Histoplasmosis-associated risks:

- Living in hyperendemic state regions: Ohio, Indiana, Kentucky, Tennessee, Missouri, Arkansas, Illinois, Mississippi, Iowa, Alabama; or endemic regions: West Virginia, Virginia, Alaska, Kansas, Louisiana,

Oklahoma, Nebraska, Texas; or in low endemic regions: Arizona, Utah, central-southern California, southern New Mexico, Southern Nevada

- Living in older housing which has recently been renovated or had demolition
- Living near pigeon roosts, for example in the attic or roof areas
- Exposed to tilled farm soil
- Exposure to droppings from chickens, bats, birds (especially from old farm buildings, barns, or coops)
- Visiting caves
- In the past month, having any of the following symptoms: fever, weight loss, "flu-like illness", muscle aches, chest pain.

37. It is recommended that before infliximab treatment is initiated

- Children with CD/UC with suspected intra-abdominal abscess and/or fistulae be evaluated with abdominal contrast computed tomography (CT) (Local Consensus [E]).
- Children with CD/UC with suspected perianal abscess and/or fistulae are best be evaluated with pelvic magnetic resonance imaging (MRI) (Beets-Tan et al., 2001 [C], Local Consensus [E]).

Note: These evaluations may be important to mitigate potential complications resulting from the immunosuppressive effects of infliximab.

38. It is recommended that patients be monitored for adverse drug reactions (acute or delayed) with each infliximab infusion and prophylactic pre-medications be prescribed as indicated (Local Consensus [E]).

Note: Before each infusion, consider benadryl at standard unit based doses and acetaminophen at standard doses have been found to help reduce infusion reactions. Consider use of oral prednisone or intravenous hydrocortisone to prevent antibody formation in high risk patients (off infliximab >6 months) (Local Consensus [E]).

39. It is recommended that active, ongoing cancer surveillance be maintained during and for a period of time following infliximab therapy (Local Consensus [E]).

Note: Some combination of the following: fever, weight loss, elevation of liver function tests, hepatosplenomegaly are indications of an increased risk of hepatosplenic lymphoma requiring further clinical evaluation (Local Consensus [E]).

Infliximab: Dosing

40. It is recommended that induction of remission in children with moderate/severe CD/UC as indicated above, that infliximab 5 mg/kg intravenously (IV) be used as an initial dose followed by 5 mg/kg IV at 2 weeks, 6 weeks, and every 8 weeks thereafter (Lawson, Thomas, & Akobeng, 2006 [M], Local Consensus [E]).

Note: From data available from two adult trials with 728 participants (484 infliximab and 244 placebo), infliximab was effective in producing a clinical response (meta-analysis relative risk [RR] 1.99, 95% CI 1.65, 2.41; NNT = 4, 95% CI 2.5, 3.9) (Lawson, Thomas, & Akobeng, 2006 [M]).

41. It is recommended that if a child with CD/UC
- Fails to respond to the first infliximab 5 mg/kg IV dose or relapses on infliximab 5 mg/kg after the 2 week or six-week dose, increase subsequent doses to 10 mg/kg IV every 8 weeks, or
 - If relapses again, then consider decreasing the 10 mg/kg dosing interval to every 6 weeks and then every 4 weeks

(Local Consensus [E])

42. It is recommended that infliximab be continued for maintenance therapy in children with CD/UC at the dose and interval that was clinically safe and effective (Local Consensus [E]).

Note: If there is a loss of clinical response, consider increasing subsequent doses to 10 mg/kg every 8 weeks. If child relapses again, consider decreasing the 10 mg/kg dosing interval from every 8 weeks to every 6 weeks and then every 4 weeks.

Infliximab: Efficacy Monitoring

Adequate clinical response is defined as a decreased physician global assessment to the quiescent or mild level.

Infliximab: Adjunct Therapy/Other Treatment Related Interventions/Education

43. It is recommended that patients and families of children receiving infliximab receive education regarding signs and symptoms of delayed reactions and contraindications for receiving an infusion (Local Consensus [E]).

Combination Therapy

(6-MP or AZA or MTX) and Infliximab

44. It is recommended that children with CD/UC in remission for six months who have been on combination therapy have the immunomodulator (6-MP or AZA) withdrawn and continue infliximab alone at a regularly scheduled interval (Local Consensus [E]).

Note 1: Overall the evidence is not strong, but consistent with a greater proportion of patients achieving short term remission with combination therapy (6-MP or AZA and infliximab). The evidence for longer term efficacy and safety is equivocal, but therapy with infliximab alone seems to be at least as effective as combination therapy in producing sustained remissions. The beneficial effects of combination therapy, if they exist, seem to be restricted to CD patients without fistulae. However, each of the cases of hepatosplenic T

cell lymphoma reported to date in pediatric patients have occurred in patients on combined 6-MP or AZA or infliximab.

Note 2: There are no published randomized controlled trials (RCTs) of combination therapy compared to infliximab alone in adults or children. The primary problem in determining the effects of combination therapy on efficacy and safety is that published studies do not identify why some patients were on 6-MP, AZA (or MTX) at the initiation of infliximab and why some were not. Any effect of combination therapy is possibly confounded by unmeasured differences in these two patient populations. Emerging data suggests patients in remission after six months on combined 6-MP or AZA and infliximab may have 6-MP or AZA withdrawn without a higher rate of relapse over the next six months. (Local Consensus [E]).

Note 3: The risk of infusion reactions may be less in patients who are receiving both immunomodulators and steroids at the time of infliximab administration, but this effect may be confounded by unmeasured indications for immunomodulator/steroid treatment. Emerging data suggests that the formation of antibodies to infliximab (ATI) and the risk of infusion reactions is only slightly lower in patients on combined 6-MP or AZA or infliximab compared to infliximab alone, as long as the infliximab is administered in a regularly scheduled fashion (Sands et al., 2004 [A]; Hanauer et al., 2002 [A]; Arnott, McNeill, & Satsangi, 2003 [C]; Hlavaty et al., 2005 [D]; Baert et al., 2003 [D]; Parsi et al., 2002 [D]; Vermeire et al., 2002 [D]).

Definitions:

Evidence Grading Scale

- M: Meta-analysis
- A: Randomized controlled trial: large sample size (n >100)
- B: Randomized controlled trial: small sample size (n <100)
- C: Prospective trial or large case series
- D: Retrospective analysis
- O: Other evidence
- S: Review article
- E: Expert opinion or consensus
- F: Basic Laboratory research
- L: Legal requirement
- Q: Decision analysis
- X: No evidence

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for:

- 6-Mercaptopurine (6-MP) or azathioprine (AZA) with or without prednisone treatment
- Methotrexate treatment
- Infliximab treatment

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and classified for each recommendation (see "Major Recommendations").

Evidence Grading Scale

M: Meta-analysis
A: Randomized controlled trial: large sample size (n >100)
B: Randomized controlled trial: small sample size (n <100)
C: Prospective trial or large case series
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O: Other evidence
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F: Basic Laboratory research
L: Legal requirement
Q: Decision analysis
X: No evidence

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management and treatment of pediatric moderate/severe inflammatory bowel disease including Crohn's disease (CD), and ulcerative colitis (UC)

POTENTIAL HARMS

Adverse effects associated with treatment medications (see Appendices 4 and 5 in the original guideline document for lists of side effects)

CONTRAINDICATIONS

CONTRAINDICATIONS

- Live virus vaccines are contraindicated in patients receiving prednisone and/or any of the following (6-mercaptopurine [6-MP], azathioprine [AZA], methotrexate [MTX], infliximab) for treatment of inflammatory bowel disease (IBD).

- 6-MP or AZA is contraindicated in thiopurine methyltransferase (TPMT) genotype that is consistent with absent TPMT activity or abnormal CBC, alanine aminotranferase (ALT), amylase, and lipase levels.
- Methotrexate is contraindicated in pregnant females and children with Crohn's disease (CD) with already abnormal liver-associated chemistries.
- Contraindications to infliximab include
 - Abscess
 - Signs and symptoms of infection
 - History of tuberculosis
 - Histoplasmosis

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These recommendations result from review of literature and practices current at the time of their formulations. This Guideline does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to these recommendations is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
 Chart Documentation/Checklists/Forms
 Clinical Algorithm
 Patient Resources
 Quick Reference Guides/Physician Guides

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

IBD Guideline Team, Cincinnati Children's Hospital Medical Center. Evidence-based care guideline for the management of pediatric moderate/severe inflammatory bowel disease (IBD). Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2007 Apr 5. 29 p. (Guideline; no. 29). [66 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Apr 5

GUIDELINE DEVELOPER(S)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

GUIDELINE DEVELOPER COMMENT

As facilitated by the Health Policy & Clinical Effectiveness Department of the Cincinnati Children's Hospital Medical Center.

SOURCE(S) OF FUNDING

Cincinnati Children's Hospital Medical Center

GUIDELINE COMMITTEE

Inflammatory Bowel Disease (IBD) Guideline Team

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The guideline was developed without external funding. All Team members and Clinical Effectiveness support staff listed have declared whether they have any conflict of interest and none were identified.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the [Cincinnati Children's Hospital Medical Center](#).

Print copies: For information regarding the full-text guideline, print copies, or evidence-based practice support services contact the Children's Hospital Medical Center Health Policy and Clinical Effectiveness Department at HPCEInfo@chmcc.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Management of inflammatory bowel disease (IBD). Guideline highlights. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2006. 1 p. Electronic copies: Available in Portable Document Format (PDF) from the [Cincinnati Children's Hospital Medical Center Web site](#).

Additionally, a variety of forms and assessment tools, as well as a list of potential measures can be found in the [original guideline document](#).

PATIENT RESOURCES

The following Health Topics are available:

- Inflammatory bowel disease (IBD). Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2005 Jun. 1 p.
- Ulcerative colitis. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2005 Jun. 1 p.
- Crohn's disease. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2005 Jun. 1 p.

Electronic copies: Available from the [Cincinnati Children's Hospital Medical Center](#).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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