



Evidence-Based Care Guideline

Management of Pediatric Moderate / Severe Inflammatory Bowel Disease (IBD): Specific medication recommendations and related interventions^a

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This guideline is subdivided into selected medication options, such that the following will be addressed:

- recommended care prior to treatment
- induction and maintenance with the following medications
 - 6-mercaptopurine (6-MP) or azathioprine (AZA) (Imuran®/Azasan®) with or without prednisone
 - OR
 - methotrexate (MTX) OR
 - infliximab (Remicade®)
- other treatment related interventions
- patient / family education.

Target Population

Children 0 to 22 years of age diagnosed with Inflammatory Bowel Disease (IBD) [either Crohn's Disease (CD) or Ulcerative Colitis (UC)].

Target Users

Include but are not limited to (in alphabetical order):

- clinicians caring for patients diagnosed with IBD
- patient care staff, including:
 - nurse practitioners
 - nurses
- patients and families
- physicians in training
- primary care providers.

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Guideline 29, pages 1-29, April 5, 2007.

Introduction

References in parentheses () Evidence strengths in [] (See last page for definitions)

Inflammatory bowel disease (Crohn's Disease and Ulcerative Colitis) is a chronic illness that primarily affects young adults, but also occurs in children presenting commonly with abdominal pain, diarrhea and growth failure. IBD is characterized by periodic exacerbations that can be physically and socially disabling. Estimated prevalence rates for IBD range from 80 to 150 cases per 100,000 population. For IBD, there are uncertainties regarding etiology, diagnosis, management and prognosis. A research agenda is included at the end of this guideline.

Etiology

There is considerable uncertainty regarding the cause or causes of IBD. One hypothesis is that inappropriate immune responses leading to gastrointestinal injury are mediated by genetic and/or environmental factors.

Guideline Recommendations

Prior to treatment

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

Note 1: The physician global assessment (PGA) includes four categories: quiescent, mild, moderate and severe disease activity. See [Appendix 1A](#), CCHMC IBD Physician Follow-up visit form (*Local Consensus [E]*).

Note 2: Other helpful clinic forms capturing various IBD assessment components include: [Appendix 1B](#), [Appendix 1C](#), [Appendix 1D](#), [Appendix 1E](#), [Appendix 1F](#) (*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 1999 [O]*, *Hyams 1991 [O]*).

Note 1: See PCDAI tool in [Appendix 2a](#).

Note 2: The PCDAI was validated against the PGA (Hyams 2005 [O], Otley 1999 [O], Hyams 1991 [O]). The PCDAI was used in many pediatric treatment trials (Kundhal 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](#) 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 2004 [S,E]). See [Appendix 3](#).

Note 1: Live virus vaccines are contraindicated in patients receiving prednisone and/or any of the following (6-MP, AZA, 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 (Appendix). For a list of treatment related side effects and costs of treatment, see [Appendix 4](#) and [Appendix 5](#).

(6-MP or AZA) with or without prednisone
(see [Appendix 6](#) 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 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 2004 [M], Sandborn 2004 [M], Ardizzone 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 2000 [C], Dubinsky 2000 [D], Local Consensus [E]).
6. It is recommended that thiopurine methyltransferase (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 2000 [C], Dubinsky 2000 [D], Local Consensus [E]).
7. It is recommended that 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](#) 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 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 site,
<http://centerlink/Portal/DesktopDefault.aspx?l=2579>

9. It is recommended that alanine aminotransferase (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, and
- 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 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,
<http://centerlink/Portal/DesktopDefault.aspx?l=2579>.

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
- azathioprine (AZA) 1 to 2.5 mg / kg / day P.O. (*Pearson 2004 [M]*, *Sandborn 2004 [M]*, *Vilien 2004 [B]*, *Markowitz 2000 [B]*, *Hawthorne 1992 [B]*).

Note 1: No controlled trials of steroids versus placebo have been performed in children with CD (*Escher 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 2007 [M]*, *Malchow 1984 [A]*, *Singleton 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 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 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 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 2000 [M]*, *Johnson 2006 [B]*, *Afzal 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 2000 [C]*, *Dubinsky 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 2000 [C]*, *Dubinsky 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 1993 [D], Beattie 1996 [O], Local Consensus [E]).

Note 1: No controlled trials of steroids versus placebo have been performed in children with UC (Escher 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 2007 [M], Malchow 1984 [A], Singleton 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 2005 [A], Levine 2002 [A], Pruitt 2002 [A], Safdi 1997 [B], Kam 1996 [B]).

14. It is recommended that prednisone be discontinued within 3 months of being initiated in patients with CD / UC (Munkholm 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 2004 [M], Present 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 (number needed to treat [NNT] = 7) (Pearson 2004 [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% CI^b 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 2004 [M]). For definitions / use of odds ratios see <http://www.jr2.ox.ac.uk/bandolier/band25/b25-6.html>.

^b 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 (number needed to harm [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 2004 [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 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 advanced 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 leukopenia (Lowry 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 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 6-thioguanine (6TG) levels be used to adjust 6-MP or AZA dosing, such that:

- if the 6TG level is below 235 pmol / 8×10^8 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 / 8×10^8 erythrocytes, it is less likely that increasing the dose of 6-MP or AZA will be beneficial, relative to the risk of leukopenia (*Gupta 2001 [C]*, *Dubinsky 2000 [D]*).
- if the 6TG level is greater than 400 pmol / 8×10^8 erythrocytes, alternative therapies including methotrexate or infliximab may be considered (*Goldenberg 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 2001 [C]*, *Dubinsky 2000 [D]*).

Note 2: The likelihood ratio (LR) for remission with a 6TG level greater than 235 pmol / 8×10^8 erythrocytes is approximately 2 (*Gupta 2001 [C]*, *Dubinsky 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 2004 [M]*)

Methotrexate (MTX)

(see [Appendix 7](#) 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 2005 [M]*, *Feagan 2000 [B]*, *Mack 1998 [C]*, *Lichtenstein 2006a [S,E]*, *Lichtenstein 2006b [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 2006a [S,E]*, *Lichtenstein 2006b [S,E]*)

MTX: Safety Monitoring

See [Appendix 4](#) 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 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 2003 [S]).
28. It is recommended that the possibility of MTX induced renal toxicity be monitored by measurement of serum BUN and creatinine at least every 3 months (Izzedine 2005 [S], Local Consensus [E]).

MTX: Dosing

29. It is recommended that MTX at 15mg/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 (Alfadhi 2005 [M], Lichtenstein 2006a [S,E], Lichtenstein 2006b [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 1995 [A], Feagan 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, (number needed to harm (NNH = 7) (Feagan 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 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 2003 [B], Stephens 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 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 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 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 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 advanced to the maximum dose which is not associated with leukopenia;
 - 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 leukopenia;
 - if WBC is abnormal, consider that potential interaction with other medications, may be contributing to leukopenia.

(Lowry 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 at: <http://centerlink/Portal/DesktopDefault.aspx?l=2579>

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 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 GI side effects.

Infliximab

(see Appendix 8 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 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 2006 [M])

Infliximab: Safety Monitoring

See [Appendix 4](#) and [Appendix 5](#) 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, PPD, chest x-ray and consider urine histoplasmosis antigen when risk higher (see Note 2 below) (*Mow 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: OH, IN, KY, TN, MO, AR, IL, MS, IA, AL; or endemic regions: WV, VA, AK, KS, LA, OK, NB, TX; or in low endemic regions: AZ, UT, central-southern CA, southern NM, Southern NV
- 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 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 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 RR 1.99, 95% CI 1.65, 2.41; NNT = 4, 95% CI 2.5, 3.9) (*Lawson 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 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 2004 [A], Hanauer 2002 [A], Arnott 2003 [C], Hlavaty 2005 [D], Baert 2003 [D], Parsi 2002 [D], Vermeire 2002 [D]*).

Future Research Agenda

1. Does initiation of 6-MP at diagnosis in children with moderate to severe CD / UC lead to a higher duration of steroid free remission?
2. Does dosing 6-MP in children based on 6TG level lead to a higher duration of steroid free remission?
3. Does 6-MP maintenance therapy in children reduce the frequency of surgeries in CD / UC?
4. Does 6-MP improve quality of life in children with CD / UC?

Appendix 1A: Physician global assessment as captured in CCHMC IBD Physician Follow-up Visit form

Follow Up Physician (version 3-19-07) be aware most current versions of these forms are found within active IBD clinic documentation

Follow-Up Visit (Physician)

Diagnosis

- Ulcerative Colitis
- Crohn's Disease
- Indeterminate Colitis

Changed since last visit:

- Diagnosis: No Yes
 Extent of Disease: No Yes
 Crohn's Phenotype: No Yes

If Yes, document

Nutrition/Growth

Wt _____ kg _____ % ile HT _____ cm _____ % ile BMI _____ %ile

HT velocity _____ cm/yr

O₂ SAT _____ T _____ °C Oral Rectal Axillary _____

Electronic Manual BP _____ HR _____ RR _____

Cuff	Position	Location	Activity
<input type="checkbox"/> Neonate <input type="checkbox"/> Adult	<input type="checkbox"/> Sit	<input type="checkbox"/> R Arm	<input type="checkbox"/> Quiet
<input type="checkbox"/> Infant <input type="checkbox"/> Small	<input type="checkbox"/> Stand	<input type="checkbox"/> L Arm	<input type="checkbox"/> Cry
<input type="checkbox"/> Child <input type="checkbox"/> Medium	<input type="checkbox"/> Supine	<input type="checkbox"/> _____	<input type="checkbox"/> _____
<input type="checkbox"/> Thigh <input type="checkbox"/> Large	<input type="checkbox"/> Held	<input type="checkbox"/> _____	

Signature/Credentials

Interval History

Since last visit:

- Hospitalized: No Yes If Yes, documented Reviewed patient/family form
- Surgery: No Yes If Yes, documented Reviewed phone calls
- Diagnostic studies:* No Yes Reviewed labs/studies*
- If Yes, check all that apply: Diagnostic Imaging EGD Colonoscopy
- Sigmoidoscopy Capsule Endoscopy

Clinical course for the last 6-12 months (Check one) Patient followed for <6 months

Quiescent (continuously asymptomatic) Mild symptoms (no steroids) Exacerbations & remissions Chronically active (moderate or severe)

Comments:

Review of Systems

Physical Examination

Growth: < 1 channel decrease ≥1, < 2 channel decrease ≥ 2 channel decrease

Tanner Stage: Stage I Stage II Stage III Stage IV Stage V Not assessed (N/A)

**Abdominal Mass None Questionable Definite Definite & Tender

*Abdominal Tenderness No Yes

**Perianal Disease No Yes Not assessed (N/A) If Yes, check all that apply:

Asymptomatic Tags Inflamed Tags Fissures Indolent Fistula Active Fistula Abscess

* Extraintestinal Manifestations (currently) No Yes If Yes, check all that apply:

Fever > 38.5 for 3 days in the past week Aphthous Ulcers Arthritis Uveitis Erythema Nodosa Pyoderma Gangenosum

Renal Stones Arthralgia PSC Other (Specify: _____)

Constitutional	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A	Cardiovascular	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A
HEENT	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A	Gastrointestinal	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A
Lymphatics	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A	Rectal Exam	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A
Respiratory	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A	Neurologic	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A
GU	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	<input type="checkbox"/> N/A				

Comment if Abnormal:

Physician Global Assessment

Disease Activity Quiescent Mild Moderate Severe Comments:

Annuals (Check yes if needed)

- DEXA No Yes
- Eye Exam No Yes
- Flu Shot No Yes

Plan

- Labs/Diagnostic Studies (see order sheet) Nutritional Counseling Medication Changes (see MedRec)
- Psychology Referral Social Services Referral Other:

Printed Name _____

Signature _____

Date _____

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Appendix 1B: Diagnosis workup documentation on CCHMC IBD form

Diagnosis -Significant Event Template.doc (version 3-15-07)

be aware most current versions of these forms are found within active IBD clinic documentation



Date of diagnosis: _____

Type of disease

- UC IC CD
- proctitis
- left-sided
- extensive
- pancolitis

- Inflammatory
- Strictureing
- Fistulizing
- Perianal Disease

IBD Serologies (circle + or -)

- ASCA + -
- pANCA + -
- ompC + -
- CBir + -

At Diagnosis:

EGD _____

Colonoscopy _____

UGI/SBFT _____

CT scan _____

Endoscopic/Radiographic

- mouth esophagus stomach duodenum
- jejunum ileum cecum ascending colon
- transverse colon descending colon sigmoid colon
- rectum

Dates

Hospitalizations					
Procedures	Date	Date	Date	Date	Date
Colonoscopy					
EGD					
Capsule EGD					
Other					

Extraintestinal complications

- uveitis episcleritis PSC kidney stones arthritis sacroileitis erythema nodosum
- pyoderma gangrenosum Other: _____

Medication

TPMT

- Genotype** (circle one)
- TPMT*H/TPMT*H
 - TPMT*H/TPMT*L
 - TPMT*L/TPMT*L

- Level**
- Normal/ High
 - Intermediate
 - Low

- Varicella Titer**
- Positive
 - Negative
 - Unknown

Serious Adverse Event (medication discontinued)

Date :

- 5-ASAs**
- Allergy
- diarrhea
- bloody diarrhea
- renal toxicity
- other

Date :

- 6-MP, AZA**
- allergy
- pancreatitis
- marrow suppression
- hepatitis
- other

Date :

- MTX**
- allergy
- marrow suppression
- hepatotoxicity
- GI symptoms
- other

Date :

- infliximab**
- allergy
- infusion reaction
- infection
- serum sickness
- failure
- other

Date :

- metronidazole**
- allergy
- GI symptoms
- neuropathy
- other

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Appendix 1C: HBI and Abbreviated PCDAI assessments from patient as captured in CCHMC IBD clinic form Follow-Up Visit (Patient*)

* HBI * Abbreviated PCDAI

* For patients who are 9 years of age or older

<p>Reason for Today's Visit</p> <p>What is the reason for your visit today?</p> <p><input type="checkbox"/> Routine Follow-Up <input type="checkbox"/> Sick Visit</p>	<p>What is your major concern today?</p> <p>_____</p> <p>_____</p>	<p>Patient Template (version 3-20-07) be aware most current versions of these forms are found within active IBD clinic documentation</p>																													
<p>Patient Global Assessment</p>																															
<p>*General Well-Being</p> <p><input type="checkbox"/> Very Well <input type="checkbox"/> Alright <input type="checkbox"/> Poor <input type="checkbox"/> Very Poor <input type="checkbox"/> Terrible</p> <p>Use the following scales to rate how you feel overall:</p> <p style="text-align: center;">BEST WORST</p> <p style="text-align: center;">Today (circle rating) <table border="1" style="display: inline-table; text-align: center; width: 150px;"><tr><td>10</td><td>9</td><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td></tr></table></p> <p style="text-align: center;">The best I have felt in my life (circle rating) <table border="1" style="display: inline-table; text-align: center; width: 150px;"><tr><td>10</td><td>9</td><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td></tr></table></p> <p style="text-align: center;">How confident are you in managing your disease? (circle rating)</p> <p style="text-align: center;">VERY CONFIDENT NOT CONFIDENT</p> <p style="text-align: center;"><table border="1" style="display: inline-table; text-align: center; width: 150px;"><tr><td>10</td><td>9</td><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td></tr></table></p>	10	9	8	7	6	5	4	3	2	1	10	9	8	7	6	5	4	3	2	1	10	9	8	7	6	5	4	3	2	1	<p>Please use this space to add any comments you may have about your answers</p>
10	9	8	7	6	5	4	3	2	1																						
10	9	8	7	6	5	4	3	2	1																						
10	9	8	7	6	5	4	3	2	1																						
<p>Recent History (1 week before this visit)</p> <p>In the past week, please rate the following::</p> <p>**Abdominal Pain <input type="checkbox"/> None <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe</p> <p>*Stools (bowel movements) Average number of stools per day: _____</p> <p>Most stools are: <input type="checkbox"/> formed (solid) <input type="checkbox"/> partially formed (loose) <input type="checkbox"/> liquid (watery)</p> <p>Average number of liquid (watery) stools per day (0 if none): _____</p> <p>How many stools have blood in them? <input type="checkbox"/> none <input type="checkbox"/> less than half <input type="checkbox"/> more than half</p> <p>If stools have blood, it is usually: <input type="checkbox"/> small amount <input type="checkbox"/> large amount</p> <p>Nighttime diarrhea (wake up at night with diarrhea): <input type="checkbox"/> yes <input type="checkbox"/> no</p> <p>*Limitations in Daily Activities <input type="checkbox"/> None <input type="checkbox"/> Occasionally <input type="checkbox"/> Frequently</p> <p>How often do you miss school? <input type="checkbox"/> None <input type="checkbox"/> Occasionally <input type="checkbox"/> Frequently <input type="checkbox"/> All the time <input type="checkbox"/> Not Applicable</p>			<p>Please use this space to add any comments you may have about your answers</p>																												

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**Appendix 1D: HBI and Abbreviated PCDAI assessments from parent as captured in CCHMC IBD clinic form
Follow-Up Visit (Parent*)**

* HBI * Abbreviated PCDAI * Please fill out if the patient is younger than 9 years of age

Family Template (version 3-20-07) be aware most current versions of these forms are found within active IBD clinic documentation

To Be Filled Out by Parent	Reason for Today's Visit																														
	What is the reason for your child's visit today? <input type="checkbox"/> Routine Follow-Up <input type="checkbox"/> Sick Visit	What is your major concern today? _____ _____																													
To Be Filled Out by Parent	Patient Global Assessment		Please use this space to add any comments you may have about your answers																												
	*General Well-Being <input type="checkbox"/> Very Well <input type="checkbox"/> Alright <input type="checkbox"/> Poor <input type="checkbox"/> Very Poor <input type="checkbox"/> Terrible																														
To Be Filled Out by Parent	Use the following scales to rate how your child feels overall:		Please use this space to add any comments you may have about your answers																												
	<p style="text-align: center;"> BEST WORST <table border="1" style="margin: auto; text-align: center;"> <tr> <td>10</td><td>9</td><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td> </tr> </table> Today (circle rating) </p> <p style="text-align: center;"> BEST WORST <table border="1" style="margin: auto; text-align: center;"> <tr> <td>10</td><td>9</td><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td> </tr> </table> The best your child has felt in their life (circle rating) </p> <p style="text-align: center;"> How confident are you in managing your child's care? VERY CONFIDENT NOT CONFIDENT <table border="1" style="margin: auto; text-align: center;"> <tr> <td>10</td><td>9</td><td>8</td><td>7</td><td>6</td><td>5</td><td>4</td><td>3</td><td>2</td><td>1</td> </tr> </table> (circle rating) </p>			10	9	8	7	6	5	4	3	2	1	10	9	8	7	6	5	4	3	2	1	10	9	8	7	6	5	4	3
10	9	8	7	6	5	4	3	2	1																						
10	9	8	7	6	5	4	3	2	1																						
10	9	8	7	6	5	4	3	2	1																						
To Be Filled Out by Parent/Patient	Recent History (1 week before this visit)		Please use this space to add any comments you may have about your answers																												
	In the past week, please rate the following for you/your child: **Abdominal Pain <input type="checkbox"/> None <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe *Stools (bowel movements) Average number of stools per day: _____ Most stools are: <input type="checkbox"/> formed (solid) <input type="checkbox"/> partially formed (loose) <input type="checkbox"/> liquid (watery) Average number of liquid (watery) stools per day (0 if none): _____ How many stools have blood in them? <input type="checkbox"/> none <input type="checkbox"/> less than half <input type="checkbox"/> more than half If stools have blood, it is usually: <input type="checkbox"/> small amount <input type="checkbox"/> large amount Nighttime diarrhea (wake up at night with diarrhea): <input type="checkbox"/> yes <input type="checkbox"/> no *Limitations in Daily Activities <input type="checkbox"/> None <input type="checkbox"/> Occasionally <input type="checkbox"/> Frequently How often do you miss school? <input type="checkbox"/> None <input type="checkbox"/> Occasionally <input type="checkbox"/> Frequently <input type="checkbox"/> All the time <input type="checkbox"/> Not Applicable																														

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Appendix 1E: Nursing and Discharge documentation on CCHMC IBD clinic form

Follow-up Nurse Discharge (version 3-15-07)
 be aware most current versions of these forms are found within active IBD clinic

Follow-Up Visit(Nursing / Discharge)

TO BE FILLED OUT BY NURSING ON DAY OF VISIT

DEVELOPMENT: <input type="checkbox"/> Age Appropriate			NUTRITION SCREENING		
DELAYS: <input type="checkbox"/> Motor <input type="checkbox"/> Cognitive <input type="checkbox"/> Speech <input type="checkbox"/> Other		FUNCTION: <input type="checkbox"/> Independent <input type="checkbox"/> Assisted <input type="checkbox"/> Dependent <input type="checkbox"/> Other		THERAPIES: <input type="checkbox"/> PT _____ <input type="checkbox"/> OT _____ <input type="checkbox"/> Speech _____ <input type="checkbox"/> Early Intervention _____ <input type="checkbox"/> Other _____	
PSYCHOLOGICAL: <input type="checkbox"/> Cooperative <input type="checkbox"/> Quiet <input type="checkbox"/> Interactive <input type="checkbox"/> Anxious <input type="checkbox"/> Smiling <input type="checkbox"/> Fussy <input type="checkbox"/> Playing <input type="checkbox"/> Sleeping <input type="checkbox"/> Emotional Concerns <input type="checkbox"/> Alert <input type="checkbox"/> Uncooperative			SOCIAL: <input type="checkbox"/> Home with _____ <input type="checkbox"/> Daycare _____ <input type="checkbox"/> School/Work <input type="checkbox"/> Attendance <input type="checkbox"/> Home School <input type="checkbox"/> Individual Education Plan (IEP) <input type="checkbox"/> Activities _____ <input type="checkbox"/> Financial Issues <input type="checkbox"/> Transportation Issues <input type="checkbox"/> Tobacco Use/Exposure		
CULTURAL/SPIRITUAL <input type="checkbox"/> None Related to Care			Key Satisfactory: Voluntary: wt. gain, At Risk: Involuntary: stable wt. or wt. loss 1-9% In Failure: wt. loss ≥ 10%		
PAIN <input type="checkbox"/> Yes <input type="checkbox"/> No Site _____ Onset _____					
PAIN TYPE (✓) <input type="checkbox"/> Current <input type="checkbox"/> Chronic <input type="checkbox"/> Intermittent <input type="checkbox"/> Procedural		DURATION (✓) <input type="checkbox"/> Constant <input type="checkbox"/> Intermittent <input type="checkbox"/> Other		QUALITY (✓) <input type="checkbox"/> Sharp <input type="checkbox"/> Throbbing <input type="checkbox"/> Aching <input type="checkbox"/> Dull <input type="checkbox"/> Burning <input type="checkbox"/> Spasm <input type="checkbox"/> Other <input type="checkbox"/> Unable to Describe	
		SCALES/SCORES (✓) <input type="checkbox"/> NIPS <input type="checkbox"/> CHEOPS <input type="checkbox"/> OUCHER <input type="checkbox"/> VAS <input type="checkbox"/> Unable to score: <input type="checkbox"/> Neurological <input type="checkbox"/> Developmental <input type="checkbox"/> Behavioral		INTERVENTION (*Also Complete All Education Sections Below) Intervention _____ Education* _____	
Comments:				REASSESSMENT <input type="checkbox"/> Situationally Inappropriate <input type="checkbox"/> Unable to Assess <input type="checkbox"/> Score _____ <input type="checkbox"/> Home Management Discussed <input type="checkbox"/> Intervention Education* <input type="checkbox"/> Medications <input type="checkbox"/> Continue Current Treatment Plan <input type="checkbox"/> Distraction <input type="checkbox"/> Non Pharmacological <input type="checkbox"/> Child Life <input type="checkbox"/> Relaxation Techniques <input type="checkbox"/> Directed To _____ <input type="checkbox"/> Referred To _____	
EDUCATION <input type="checkbox"/> None Indicated <input type="checkbox"/> Yes <input type="checkbox"/> Per _____					
READINESS TO LEARN		BARRIERS TO LEARNING		METHOD	
Learner #1: _____		#1 #2 <input type="checkbox"/> None <input type="checkbox"/> Distraction <input type="checkbox"/> Cognitive <input type="checkbox"/> Physical <input type="checkbox"/> Emotional <input type="checkbox"/> Cultural/Spiritual <input type="checkbox"/> Language <input type="checkbox"/> Other		Pref. Actual <input type="checkbox"/> Verbal <input type="checkbox"/> Demo <input type="checkbox"/> Written <input type="checkbox"/> Audio/Visual <input type="checkbox"/> Health Topic <input type="checkbox"/> Visual Aid <input type="checkbox"/> Other	
Learner #2: _____					
#1 #2 <input type="checkbox"/> Attentive <input type="checkbox"/> Denies Need <input type="checkbox"/> Uncooperative <input type="checkbox"/> Other					
EVALUATION: <input type="checkbox"/> Return Demonstration <input type="checkbox"/> Verbalizes Understanding <input type="checkbox"/> Reinforcement Needed <input type="checkbox"/> Instructed to Call With Questions					
EDUCATION: _____ _____ _____ _____ _____ _____ _____ _____					
SIGNATURE/CREDENTIALS: _____					

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Appendix 1F: Infliximab Dosing and Reaction CCHMC documentation form
Infliximab Therapy

Infliximab Template 3-15-07.doc be aware most current versions of these forms are found within active IBD clinic documentation

To Be Filled Out By GI Nursing Prior to Visit	Dose (5 – 10 mg/kg)		→	For Induction Dose #1 Only:		
	<input type="checkbox"/> Induction Dose #1 (0 weeks) <input type="checkbox"/> Induction Dose #2 (2 weeks) <input type="checkbox"/> Induction Dose #3 (6 weeks) <input type="checkbox"/> Maintenance Dose (8-12 wks)	Dose _____ _____ _____		PPD <input type="checkbox"/> Pos <input type="checkbox"/> Neg <input type="checkbox"/> N/D CXR <input type="checkbox"/> Pos <input type="checkbox"/> Neg <input type="checkbox"/> N/D Risk factors for Histoplasmosis? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, was Histo Ag done? <input type="checkbox"/> Yes <input type="checkbox"/> No Result _____		
	Concomitant Immunomodulators (mg)					
<input type="checkbox"/> 6-MP <input type="checkbox"/> Azathioprine <input type="checkbox"/> Methotrexate <input type="checkbox"/> None		Dose _____ _____ _____				
To Be Filled Out By Nursing Prior to Infusion	Interval Problems Related to Infliximab					
	<input type="checkbox"/> Unable to Reach Family prior to Infusion* <input type="checkbox"/> Yes – Call Fellow or Attending <input type="checkbox"/> No	If Yes, check all that apply: <input type="checkbox"/> Delayed hypersensitivity (Rash, Urticaria, Myalgias, Flu-like symptoms, Joint Stiffness, Headache) <input type="checkbox"/> Infection <input type="checkbox"/> Exposure to Tuberculosis <input type="checkbox"/> Exposure to Histoplasmosis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Abscess <input type="checkbox"/> Other _____				
	Pre-Treatment for Prior Infusion Reaction/Prolonged Interval Between Infusions: (Previous reaction/delayed reaction/> 6 months since last infusion)					
	<input type="checkbox"/> Yes <input type="checkbox"/> No Pre-Treatment indicated	If Yes, see order sheet, check all that apply and give dose: <input type="checkbox"/> Prednisone ___ x ___ day <input type="checkbox"/> Antihistamine (Zyrtec®) ___ x ___ days <input type="checkbox"/> Hydrocortisone (IV)** <input type="checkbox"/> Solumedrol (IV)**				
To Be Filled out by Nursing on Day of Infusion	Pre-Infusion Vital Signs					
	Wt _____ % _____ Ht _____ % _____ BMI _____ % _____ Temp _____ HR _____ RR _____ BP _____					
	Adverse Events					
	Adverse Event <input type="checkbox"/> No <input type="checkbox"/> Yes If No, Requires Nurse Signature _____	Nurse: _____ Signature: _____				
	If Yes, Adverse Event _____ Requires Physician/NP Signature _____	<input type="checkbox"/> Infusion Reactions <input type="checkbox"/> Mild – Flushing, Dizziness, Headache, Diaphoresis, Nausea, Palpitations <input type="checkbox"/> Moderate – Chest Discomfort, SOB, ↑↓ BP (> 20), Fever, Palpitations, Urticaria <input type="checkbox"/> Severe – ↑↑ BP (> 40), fever with rigors, chest discomfort, SOB w/ wheezing, Stridor, Flushing				
	Comment: _____	<input type="checkbox"/> Treatment During Infusion <input type="checkbox"/> No Intervention <input type="checkbox"/> Oxygen (O ₂ saturation _____) <input type="checkbox"/> Diphenhydramine _____ <input type="checkbox"/> Acetaminophen _____ <input type="checkbox"/> Hydrocortisone _____ <input type="checkbox"/> Epinephrine (SQ) _____ <input type="checkbox"/> Fluid Bolus _____ <input type="checkbox"/> Slowed infusion <input type="checkbox"/> Stopped infusion If Infusion Stopped , Infusion Restarted? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Other _____		<input type="checkbox"/> Recommended pre-treatment for next infusion: <input type="checkbox"/> Antihistamine <input type="checkbox"/> Prednisone <input type="checkbox"/> Hydrocortisone <input type="checkbox"/> Solumedrol (IV)		
Physician/NP: _____ Signature: _____						

* To Be Filled out by Nursing on Day of Infusion **See Order Sheet
 ***** PLEASE FAX COMPLETED FORM TO MICHELLE WHITT @ 636-7805 *****

Appendix 2A: Assessment Tool: Pediatric Crohn's Disease Activity Index (PCDAI)

As originally developed by (Hyams 1991 [O])

History (Recall = 1week)**1. Abdominal pain:**

- None (0)
 Mild- Brief, does not interfere with activities (5)
 Mod / severe – Daily, longer lasting, affects activities, nocturnal 1 (10)

2. Stools (per day):

- 0-1 liquid stools, no blood (0)
 Up to 2 semi-formed w/ small blood, or 2-5 liquid (5)
 Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea (10)

Patient Functioning, General Well-being (Recall = 1 week)

3. Activities: No limitation of activities, well (0)
 Occasional difficulty in maintaining age appropriate activities, below par (5)
 Frequent limitation of activity, very poor (10)

Laboratory**4. HCT (%)**

Age < 10 yrs:

- ≥ 33 (0)
 28-32 (2.5)
 < 28 (5)

Age 11 – 18 Female

- ≥ 34 (0)
 29-33 (2.5)
 < 29 (5)

Age 11 – 14 Male:

- ≥ 35 (0)
 30-34 (2.5)
 < 30 (5)

Age 15 – 18 Male:

- ≥ 37 (0)
 32-36 (2.5)
 < 32 (5)

5. ESR (mm / hr):

- < 20 (0)
 20-50 (2.5)
 > 50 (5)

6. Albumin (g / dL):

- ≥ 3.5 (0)
 3.1-3.4 (5)
 ≤ 3.0 (10)

Examination**7. Weight:**

- Weight gain or voluntary weight stable / loss (0)
 Involuntary weight stable, weight loss 1-9% (5)
 Weight loss $\geq 10\%$ (10)

8. Height:

- Height velocity $\geq -1SD$ (0)
 Height velocity < -1SD, > -2SD (5)
 Height velocity $\leq -2SD$ (10)
 Tenderness, involuntary guarding, definite mass (10)

9. Abdomen:

- No tenderness, no mass (0)
 Tenderness, or mass without tenderness (5)

10. Perirectal disease:

- None, asymptomatic tags (0)
 1-2 indolent fistula, scant drainage, no tenderness (5)
 Active fistula, drainage, tenderness, or abscess (10)

11. Extra-intestinal manifestations:

(Fever $\geq 38.5 \geq 3$ days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)

- None (0) One (5) \geq Two (10)

Total Score: _____

Level of CD disease severity level by PCDAI scores: quiescent 10 or less; mild 11-29; moderate to severe 30 or higher

Appendix 2B: Pediatric Ulcerative Colitis Activity Index (PUCAI)

Used by permission from developer: Ann Griffiths, MD, publication pending.

COMPLETE THIS SECTION FOR A PATIENT DIAGNOSED WITH ULCERATIVE COLITIS - PUCAI®

1. Abdominal Pain

- No pain ⁽⁰⁾
- Pain can be ignored ⁽⁵⁾
- Pain cannot be ignored ⁽¹⁰⁾

4. Number of stools per 24 hours

- 0-2 ⁽⁰⁾
- 3-5 ⁽⁵⁾
- 6-8 ⁽¹⁰⁾
- >8 ⁽¹⁵⁾

2. Rectal bleeding

- None ⁽⁰⁾
- Small amount only, in less than 50% of stools ⁽¹⁰⁾
- Small amount with most stools ⁽²⁰⁾
- Large amount (>50% of the stool content) ⁽³⁰⁾

5. Nocturnal bowel movement (any diarrhea episode causing waking)

- No ⁽⁰⁾
- Yes ⁽¹⁰⁾

3. Stool consistency of most stools

- Formed ⁽⁰⁾
- Partially formed ⁽⁵⁾
- Completely unformed ⁽¹⁰⁾

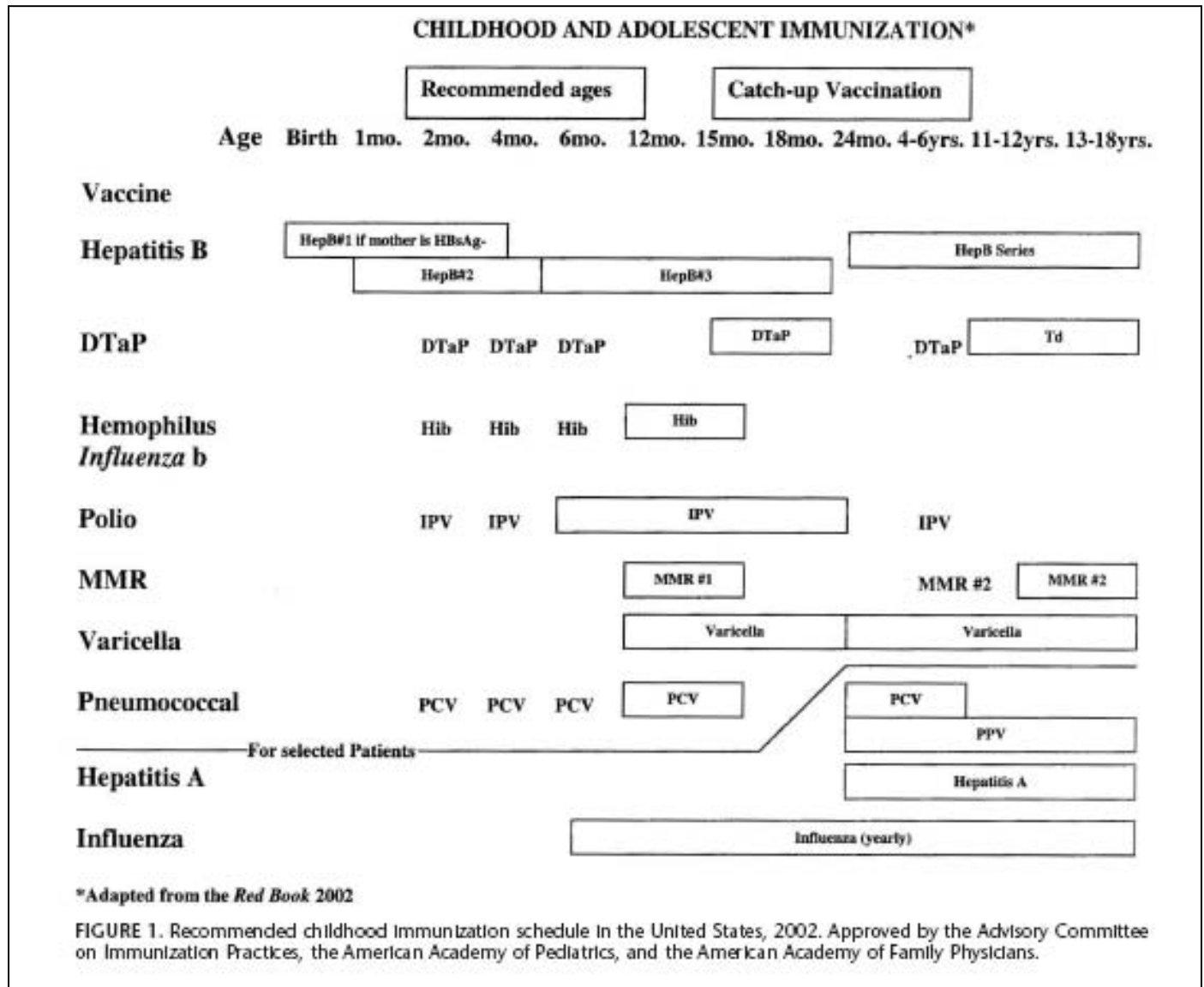
6. Activity level

- No limitation of activity ⁽⁰⁾
- Occasional limitation of activity ⁽⁵⁾
- Severe restricted activity ⁽¹⁰⁾

SUM OF PUCAI (0-85)

Appendix 3: Graphic display of recommended Childhood and Adolescent Immunizations

Sands, B. E.; Cuffari, C.; Katz, J.; Kugathasan, S.; Onken, J.; Vitek, C.; and Orenstein, W.: Guidelines for immunizations in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, 10(5): 677-92, 2004, [S, E]



Appendix 4: Table of treatment dosing, indications, side effects, costs of treatment for various medications

Generic Medication Name (trade)	Effective Daily Dose of Medication (route(s))	Indications for Use (see guideline text for details)	Risk of Side Effects	Cost to Patient \$ = <100 \$\$ = 100-600 \$\$\$ =1500-1600	References
Prednisone	1 mg / kg / day (max 40 to 60 mg / day), (oral), weaning down over 4 to 8 wks	<u>Induction</u> of remission for moderate to severe CD or UC	Leukopenia, acne, skin rash, itching, ecchymosis, moon face, headache, HTN, depression, nausea / vomiting epigastric pain, polyuria, back pain, arthritis / arthralgia, growth failure	\$	(Markowitz 2000 [B], Singleton 1979 [C])
6-MP (6-mercaptopurine) (Purinethol)	0.75–1.5 mg / kg / day (oral - tablet) (lack of available oral liquid formulation)	<u>Check TMPT activity</u> <u>Induction</u> CD / UC (yet slow in action) <u>Maintenance</u> CD / UC	Leukopenia in 10%; Gastrointestinal (nausea, vomiting), flu-like symptoms (myalgia, headache, diarrhea) that characteristically occur after 2–3 weeks and cease rapidly when the drug is withdrawn. Elevated ALT > 2x normal; (13.7 & 21%); pancreatitis. Independent risk of non-Hodgkin's lymphoma, relative risk is 4.18 (95% CI = 2.07, 7.51). NNH = 300 (95% CI = 160-1000).	\$	(Kandiel 2005 [M], Sandborn 2004 [M], Pearson 1995 [M], Markowitz 2000 [B], Present 1980 [B], Colombel 2000 [C], Dubinsky 2000 [D], Kirschner 1998 [D])
AZA (azathioprine) (Imuran®) (Azasan®)	1.5–2.5 mg / kg / day (oral)	<u>Check TMPT activity</u> <u>Induction</u> CD / UC <u>Maintenance</u> CD / UC	Leukopenia in 10%; skin rash, itching, acne, depression, anorexia, epigastric pain, arthritis / arthralgia, gastrointestinal (nausea, vomiting), flu-like symptoms (myalgia, headache, diarrhea) pancreatitis that characteristically occur after 2–3 weeks and cease rapidly when the drug is withdrawn. Elevated ALT > 2x normal; (13.7 & 21%; independent risk of non-Hodgkin's lymphoma, relative risk is 4.18 (95% CI 2.07, 7.51). NNH = 300 (95% CI 160, 1000).	\$ to \$\$	(Kandiel 2005 [M], Sandborn 2004 [M], Pearson 1995 [M], Hawthorne 1992 [B], Singleton 1979 [C], Kirschner 1998 [D])
Mesalamine (Asacol, 5-ASA Sulfasalazine (Azulfidine®))	Delayed-release 50 to 100 mg / kg / day (maximum dose range of 2.4 to 4.8 grams / day) (oral)	<u>Induction</u> CD/UC <u>Maintenance</u> CD / UC	Headache, diarrhea, exacerbation of colitis, renal dysfunction, leukopenia, (reversible azospermia azulfidine only)	\$	(Griffiths 1993 [D], Beattie 1996 [O])
Colazal (balsalazide disodium, a pro-drug that in the colon produces mesalamine (5-ASA))	2250 mg three times daily (oral)	<u>Induction</u> CD/UC <u>Maintenance</u> CD / UC	Abdominal pain, diarrhea, renal dysfunction	\$\$	(Kruis 2001 [A], Green 1998a [B], Green 1998b [B])
Methotrexate (MTX)	15 mg / m ² / week (subcutaneously) up to 25 mg per week (subcutaneously) for 12-16 weeks as tolerated	<u>Induction</u> CD <u>Maintenance</u> CD	Teratogenic, leukopenia, hepatotoxicity, nephrotoxicity <i>Use of Folic Acid 1 mg/day PO will reduce GI side effects.</i> Concomitant use of methotrexate and trimethoprim-sulfa has been associated with bone marrow suppression.	\$ to \$\$	(Alfadhli 2005 [M], Feagan 1995 [A], Kurnik 2003 [B], Feagan 2000 [B], Stephens 2005 [C], Mack 1998 [C], Lichtenstein 2006a [S,E], Lichtenstein 2006b [S,E])
Infliximab (Remicade®)	5mg / kg IV (at 2 wks, 6 wks, and every 8 wks thereafter).	<u>Induction</u> CD / UC <u>Maintenance</u> CD / UC	Mild bacterial infection (most common: respiratory tract infections and UTI), Serious infection (pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection), Infusion reaction – anaphylaxis, human anti-chimeric antibodies (HACA) to infliximab. Also see Appendix 5	\$\$\$	(Lawson 2006 [M], Probert 2003 [B], Geborek 2005 [C], Friesen 2004 [D], Krishnan 2004 [O], Khanna 2004 [S], FDA Committee AA 2003 [E])

Appendix 5: Infliximab (Remicade®) Side effects

Side effect (<i>Lawson 2006 [M], Probert 2003 [B], Geborek 2005 [C], Friesen 2004 [D], Krishnan 2004 [O], Khanna 2004 [S], FDA Committee AA 2003 [E]</i>)	Risk in CD patients receiving infliximab	Risk in CD patients not receiving infliximab	NNH (Number Needed to Harm) / level of risk
Mild bacterial infection (treated with outpatient antibiotics and/or temporary withdrawal of drug)	36%	26%	None calculated as no published significant increase in risk was identified for any of these side effects.
Serious infection (hospitalization or parenteral antibiotics)	6.2% (CD & Rheumatoid Arthritis combined)	6.8% (CD & Rheumatoid Arthritis combined)	
	5.2% (CD only)	1.8% (CD only)	
Infusion reaction – (anaphylaxis) (<i>Friesen 2004 [D]</i>)	8%		
Infusion reaction – (characterized by headache, dizziness, nausea, injection-site irritation, flushing, chest pain, dyspnoea, and pruritus) (<i>Hanauer 2002 [A]</i>)	4-6%	3%	
Delayed hypersensitivity	Case reports of serum sickness		
HACA* to infliximab	10%		
Solid tumors	No increased risk		
Non-specific lymphoma	Risk is increased approximately 5 to 10 fold (1/200) compared to the overall population risk (approximately 1/1000).		
Hepatosplenic lymphoma	Risk is uncertain, but likely increased in children and young adults receiving both 6-MP or AZA and infliximab. There is no appropriate comparison group receiving infliximab alone. Assuming that there have been approximately 10,000 exposures among children and young adults and 12 cases of HTSL (assumes that only 50% of cases have been reported) then risk is approximately 1 case for every 1,000 children treated.		

HACA = human anti-chimeric antibodies

