Supplemental Figure 1A

Cincinnati Children's Hospital Medical Center

Guideline Highlights

Management of Inflammatory Bowel Disease (IBD)

Target Population: Children 0 to 22 years of age diagnosed with IBD (either Crohn's Disease (**CD**) or Ulcerative Colitis (**UC**)).

Guideline Recommendations

Prior to Treatment

1. Use a **physician global assessment** (PGA) to determine disease severity (quiescent, mild, and moderate/severe).
2. Consider use of: Pediatric Crohn's Disease Activity Index (PCDAI) or Pediatric Ulcerative Colitis Activity Index (PUCAI)
3. Immunizations be given in accordance with the American Academy of Pediatrics and American Academy of Family Physicians recommendations Obtain

6-MP / Azathioprine(AZA) with or without prednisone *(also see the algorithm in Appendix #6 & Guideline)*

4. **Indications:**

a. *induction of remission* in children with moderate to severe (per physician global assessment) **CD** AND
- o TPMT genotype consistent with TPMT activity present
- o CBC, ALT, amylase, lipase baseline levels within appropriate limits

b. *induction of remission* in children with moderate to severe **CD** or **UC** AND
- not initially given 6-MP or AZA to induce remission, AND
- that are steroid-dependent/refractory, defined as:
  - o received more than one course of steroids in one year, or
  - o not achieved remission after one month of prednisone alone, or
  - o not tapered off prednisone after three months OR
- who have failed or cannot tolerate 5-aminosalcylates

c. ***maintenance*** *therapy* in children with moderate/severe **CD/UC**

5. **Contraindications:** TPMT genotype that is consistent with absent TPMT activity; abnormal WBC, ALT, amylase, or lipase levels
6. **Safety Monitoring:** Obtain baseline levels of: WBC, ALT, amylase, lipase; WBC & ALT at 2, 4, 8 and 12 weeks after initiation of 6-MP or AZA (& q 3 months there after) that may influence dosing changes; Do Not give live virus vaccines
7. **Dosing:** Use TPMT level or (genotype) to determine dosing as recommended in guideline. Ranges include 6-MP 0.75 to 1.5 mg / kg / day P.O. or azathioprine (AZA) 1 to 2.5 mg / kg / day P.O. Prednisone should be discontinued within 3 months of being initiated.
8. **Efficacy Monitoring:** Assess if have achieved adequate clinical response to 6-MP or AZA (defined as a decreased physician global assessment to the quiescent or mild level); if not, use 6-TG levels to further adjust dosing / continued use
9. **Adjunct Therapy / Other Treatment-Related Interventions / Education:** educate patients and families regarding signs and symptoms of pancreatitis and to report any signs or symptoms of possible infections

Methotrexate (MTX) *(also see the algorithm in Appendix #7 & Guideline)*

10. **Indications:**

a. *induction of remission* as an alternative to Infliximab in children with moderate / severe **CD** AND
- did not respond or were intolerant 6-MP/AZA to induce remission AND

that are steroid-dependent/refractory, defined as:
- o received more than one course of steroids in one year, or
- o not achieved remission after one month of prednisone alone, or
- o not tapered off prednisone after three months

b. *maintenance therapy* in children with **CD**

11. **Contraindications:** pregnant females; children with CD with already abnormal liver-associated chemistries
12. **Safety Monitoring:** Prior to MTX initiation: females of child bearing age be tested for pregnancy and be proactive in pregnancy prevention strategies; WBC & ALT at 2, 4, 8, 12 (up to 16) weeks after initiation that may influence dosing changes; Do Not give live virus vaccines
13. **Dosing:** 15mg/m2/week up to a maximum total dose of 25 mg subcutaneously, Continue for 12 - 16 weeks if labs normal
14. **Efficacy Monitoring:** Assess if have achieved adequate clinical response to MTX after 12-16 weeks of use to further adjust dosing / continued use
15. **Adjunct Therapy / Other Treatment-Related Interventions / Education:** supplemental **folic acid** 1 mg/day PO for GI side effects

Infliximab *(also see the algorithm in Appendix #8 & Guideline)*

16. **Indications:**

a. *induction of remission* in children with moderate/severe **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 / AZA, or
- have failed immunomodulator therapies 6-MP / AZA and/or MTX, or
- are steroid dependent/refractory defined as:
  - o received more than one course of steroids in one year, or
  - o not achieved remission after one month of prednisone alone, or
  - o not tapered off prednisone after three months OR
- Have any of the following: severe colitis requiring transfusion or severe small bowel disease or draining enterocutaneous or perinal fistulas

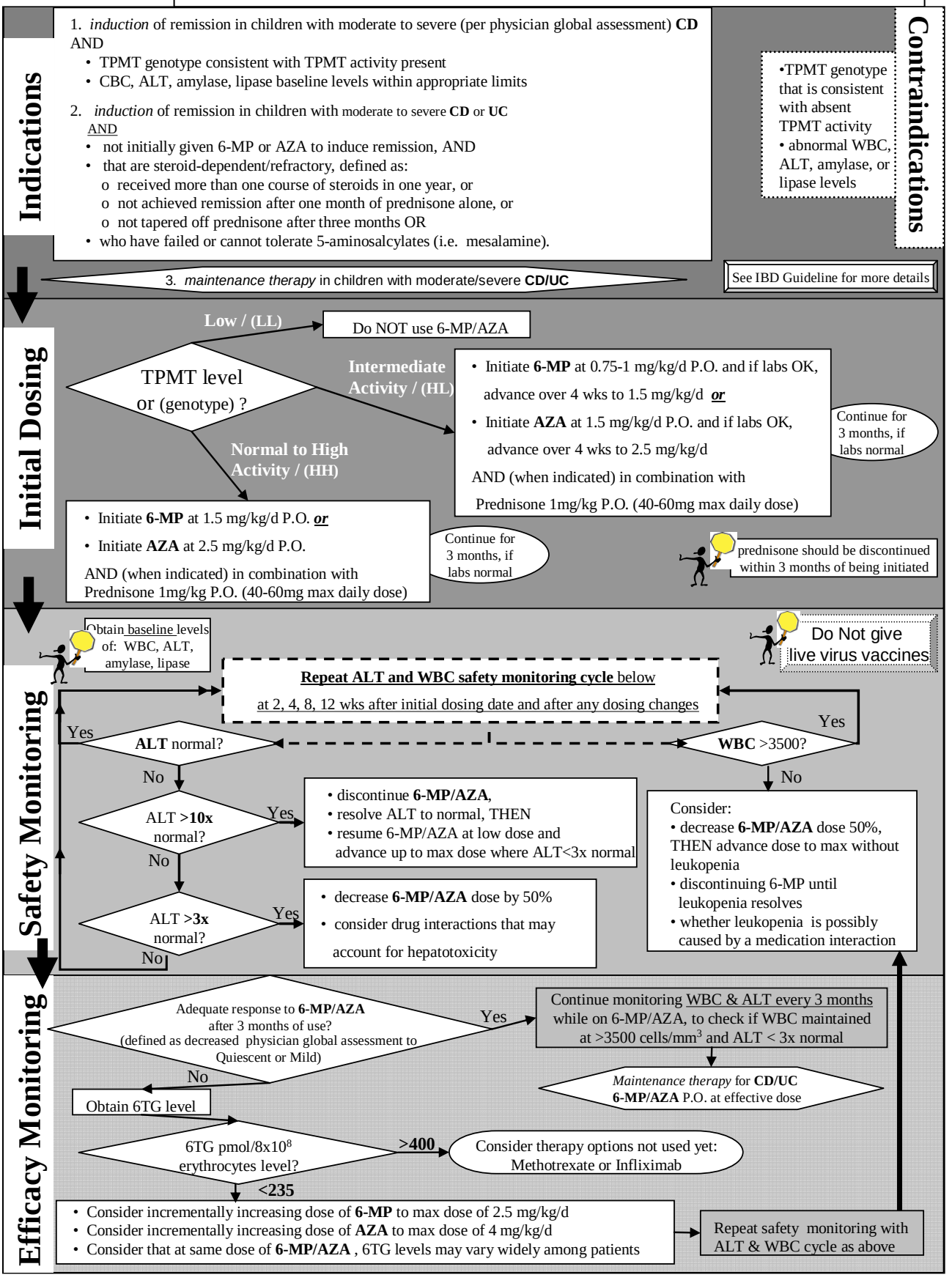
b. *induction of remission* in children with moderate/severe **UC** who:
- are steroid dependent/refractory and/or
- have failed immunomodulator therapies 6-MP / AZA

c. *maintenance therapy* in children with moderate / severe **CD / UC**

17. **Contraindications:** Abscess, Signs & symptoms of infection, Hx of Tuberculosis, Histoplasmosis
10. **Safety Monitoring:** Monitor Before Infliximab initiation: evaluate for tuberculosis and histoplasmosis WBC every 3 months while on Infliximab; If suspected intra-abdominal abscess and/or fistulae- abdominal contrast (CT); If suspected perianal abscess and/or fistulae pelvic(MRI); if infection present, DELAY the infusion; Before & during each Infliximab infusion: monitor for acute infusion reactions & allergic and anaphylaxis precautions be taken; During Infliximab therapy and for a period of time following: maintain ongoing cancer surveillance & monitor delayed hypersensitivity reactions; Do Not give live virus vaccines
18. **Dosing:** 5mg/kg at initiation, 2, and 6 weeks Intravenously; Give all 3 doses, if labs normal
19. **Efficacy Monitoring:** Assess if have achieved adequate clinical response to Infliximab after 3 doses (6 weeks of use) to further adjust dosing / continued use
20. **Adjunct Therapy / Other Treatment-Related Interventions / Education:** Consider Prophylactic Pre-Infusion Meds: Benadryl Acetaminophen (standard dosing); educate patients and families regarding delayed reactions and contraindications for receiving an infusion

See complete Evidence-Based Care Guideline for details and supporting evidence. **Adherence to recommendations is voluntary. Ultimate judgment regarding priority of any specific procedure must be made by the physician in light of the individual circumstances presented by the patient.**

Supplemental Figure 1B



Supplemental Figure 1C

Cincinnati Children's Hospital Medical Center

Infliximab Treatment Algorithm
Revision Date: 07/31/2009

Indications

1. *induction of remission* in children with moderate/severe (per physician global assessment) **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 / AZA, or
- have failed immunomodulator therapies 6-MP / AZA and/or MTX, or
- are steroid dependent/refractory defined as:
  - o received more than one course of steroids in one year, or
  - o not achieved remission after one month of prednisone alone, or
  - o not tapered off prednisone after three months OR
- have any of the following: severe colitis requiring transfusion or severe small bowel disease or draining enterocutaneous or perinal fistulas

2. *induction of remission* in children with moderate/severe **UC** who:
- are steroid dependent/refractory and/or
- have failed immunomodulator therapies 6-MP / AZA

Contraindications

- Abscess
- Signs & symptoms of infection
- Hx of Tuberculosis
- Histoplasmosis

3. *maintenance therapy* in children with moderate / severe **CD / UC**

Link to IBD Guideline for more details

Initial Dosing

Induction of remission:
Infliximab 5mg/kg at initiation, 2, and 6 weeks Intravenously

Give all 3 doses, if labs normal

Consider Prophylactic Pre-Infusion Meds:
- Benadryl (standard unit based dosing)
- Acetaminophen (standard dosing)

Safety Monitoring

Before Infliximab initiation:
- children should be evaluated for tuberculosis and histoplasmosis including history of exposure or symptoms, physical examination, PPD, chest x-ray and urine histoplasmosis antigen (see Guideline for list of histoplasmosis- and tuberculosis- associated risks to assess patient / family)

Do Not give live virus vaccines

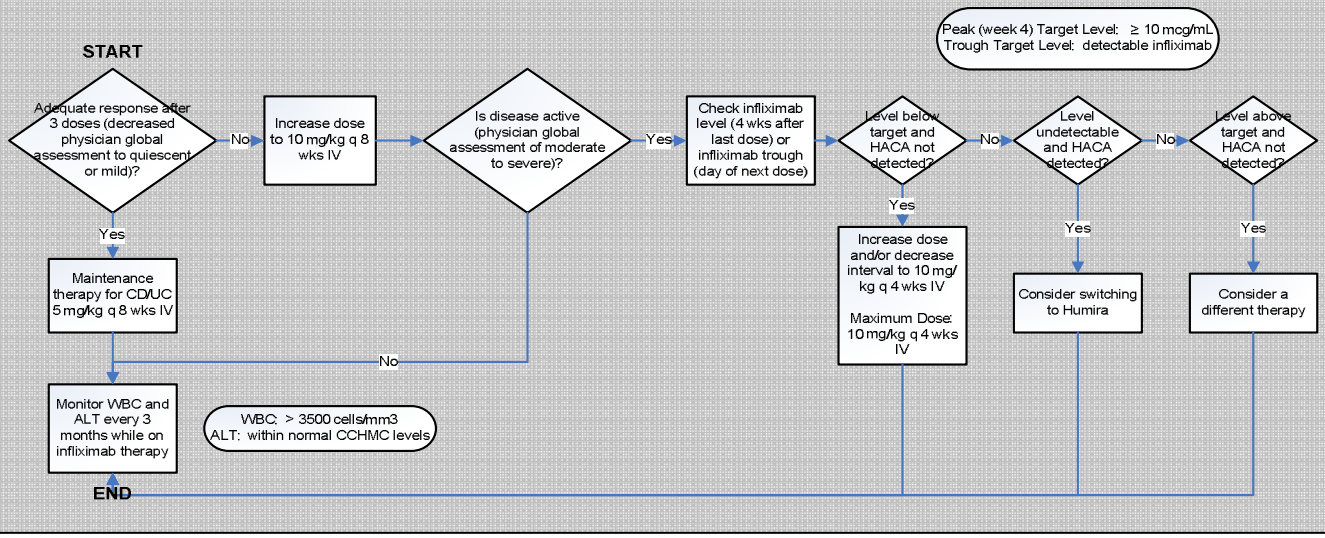
Before Infliximab initiation:
- If have suspected intra-abdominal abscess and/or fistulae evaluate with a abdominal contrast computed tomography (CT)
- If have suspected perianal abscess and/or fistulae evaluate with pelvic magnetic resonance imaging (MRI)

Before each Infliximab infusion:
- if infection present, DELAY the infusion

Before and during each Infliximab infusion:
- monitor for acute infusion reactions
- allergic and anaphylaxis precautions be taken

During Infliximab therapy and for a period of time following:
- maintain ongoing cancer surveillance
- monitor delayed hypersensitivity reactions

Efficacy Monitoring



Supplemental Figure 1D